The Fluorinated Asymmetric Reformatsky reaction with Aromatic Ketones and Imines

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Statement of Originality

The experimental work in this thesis has been carried out by the author in the department of chemistry at the University of Leicester between October 2006 and September 2010. The work has not been submitted, and is not presently submitted, for any other degrees at this or any other university.

Signed…… Date……...

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Michal Fornalczyk

Abstract

One of the most challenging topics in organofluorine chemistry is the asymmetric introduction of fluorine atoms, difluoromethylene and trifluoromethyl groups. Outstanding progress has been made in recent years, but further developments are necessary for chiral fluorinated molecules to be increasingly used in medicinal, agricultural and material chemistry.

The enantioselective addition of the fluorinated Reformatsky reagent to aromatic aldehydes in the presence of chiral aminoalcohols to give *α*,*α*-difluoro-*β*-hydroxy esters in good enantiomeric excess is well established. However, the two step protocol is inconvenient because of the need for zinc activation, as well as the relatively high temperatures required for the generation of the fluorinated Reformatsky reagent. Consequently, a one-pot asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with benzaldehyde promoted by diethylzinc under mild reaction conditions (0 ^{o}C) has been developed. A very good yield (66 %) and enantiomeric excess (69 % ee) was obtained in the presence of the chiral ligand, *N*-methylephedrine.

The first example of the asymmetric Reformatsky reaction of ethyl iododifluoroacetate with aromatic ketones performed in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol was developed. The reaction of 2.5 equivalents of the Reformatsky reagent prepared from ethyl iododifluoroacetate and zinc dust gave good isolated yields (63-99 %) and high enantiomeric excesses (75-84 %) with a series of aromatic ketones. However, the more convenient one-step protocol at -40 ^{o}C involving activation with diethylzinc gave 62-90 % yields and even better enantiomeric excesses (81-91 %) in a shorter reaction time and with a smaller amount of the expensive ethyl iododifluoroacetate (2.0 equivalents).

The protocol of the one-step enantioselective Reformatsky reaction with ketones promoted by diethylzinc was extended to ethyl iodofluoroacetate and excellent yields (84-99 %) and enantiomeric excesses (79-95 %) were obtained. A high level of diastereomeric control was obtained in the chiral reactions with ketones with an extended aliphatic group.

The absolute configuration of the new chiral centres for the major enantiomer of the difluorinated esters, and for the major enantiomers of both diastereoisomers of monofluorinated esters obtained in the reactions performed in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol was determined to be (*S*).

A range of aromatic imines were tested in the convenient one-step asymmetric Reformatsky reaction of ethyl iododifluoroacetate and after optimisation, good enantiomeric excesses (63-68 % ee) were obtained with imines containing a methoxy group in the *ortho*-position in the presence of *N*-methylephedrine.

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Contents

Abstract		i
Acknowledgements		ii
Contents		iii
List of Abbreviations		xii
Chapter One - Introduction		
1.1	Introduction to organofluorine chemistry	1
1.2	Direct methods for the introduction of a *gem*-difluoromethyl group	3
1.2.1	Nucleophilic fluorinating reagents	3
1.2.2	Electrophilic fluorinating reagents	6
1.3	Fluorinated building blocks containing the difluoromethylene group	7
1.3.1	Reformatsky reaction of *gem*-difluorinated halogenated esters	8
1.3.2	Diastereoselective fluorinated Reformatsky reaction	14
1.3.3	Enantioselective Reformatsky reaction with aldehydes	16
1.3.4	Fluorinated aldol reaction with aldehydes and ketones	20
1.3.5	Electroreductive aldol reaction with aldehydes	24
1.3.6	Diastereoselective aldol reaction with aldehydes	24
1.3.7	Enantioselective Mukayama's aldol reaction	27
1.3.8	The reaction of trimethylsilyl-α,α-difluoroacetate ester with aldehydes	29
1.4	Enantioselective rhodium-catalysed hydrogenation of 2,2-difluoro-3-oxocarboxylates	33
1.5	Reaction of difluoroallyl moiety with carbonyl substrates	34
1.6	Conclusions and research objectives	37
1.7	References	38
Chapter Two - The Asymmetric Reformatsky reaction of Ethyl Bromodifluoroacetate with Benzaldehyde		
2.1	Introduction	42
2.2	Synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate	42
2.3	Asymmetric synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate with diethylzinc and *N*-methylephedrine	43
2.3.1	Screening different solvent systems	44

2.3.2 Screening the influence of oxygen and dimethylzinc 48
2.3.3 Investigating different ratios of the reagents 50
2.4 Conclusions 55
2.5 References 56

Chapter Three - The Asymmetric Reformatsky reaction of Ethyl Iododifluoroacetate with Ketones

3.1 Introduction 57
3.2 Optimisation of the one-step procedure using diethylzinc 57
3.3 The Reformatsky reaction with a series of ketones 66
3.4 The asymmetric Reformatsky reaction with a series of ketones 70
3.5 Determination of the absolute configuration and proposed mechanism 73
3.6 The asymmetric Reformatsky reaction using two-step protocol with zinc dust 78
3.7 Comparison between the one-step and two-step protocols 83
3.7.1 Monitoring of the Reformatsky reactions 83
3.7.2 Investigation into the active species of the Reformatsky reagent in one-step protocol using diethylzinc and traditional two step protocol with zinc dust. 85
3.8 Final optimisation studies of one-step protocol 92
3.9 Conclusions 96
3.10 References 97

Chapter Four - The Asymmetric Reformatsky reaction of Ethyl Iodofluoroacetate with Ketones

4.1 Introduction 98
4.1.1 The aldol reaction 98
4.1.2 The asymmetric Mukaiyama aldol reaction of ethyl dibromofluoroacetate 101
4.1.3 A highly diastereoselective reduction of α-fluoro-α-methyl-β-keto esters 103
4.1.4 The Reformatsky reaction of ethyl dibromofluoroacetate with diethylzinc 103
4.1.5 The Reformatsky reaction of ethyl bromoacetate and ethyl bromofluoroacetate 107

4.2 Results and discussion 109
4.2.1 The Reformatsky reaction of ethyl bromofluoroacetate and ethyl iodofluoroacetate with benzaldehyde and acetophenone 109
4.2.2 The Reformatsky reaction promoted by Wilkinson's catalyst 113
4.2.3 The Reformatsky reaction in the presence of (1*S*,2*R*)-*N*-methylephedrine 114
4.2.4 Optimisation of the asymmetric Reformatsky reaction with ethyl iodofluoroacetate 116
4.2.5 Determination of the absolute configuration 118
4.2.6 The achiral Reformatsky reaction with a series of ketones 123
4.2.7 The enantioselective Reformatsky reaction with ketones 130
4.3 Conclusions 133
4.4 References 135

Chapter Five - The Asymmetric Reformatsky reaction of Ethyl Iododifluoroacetate with Imines

5.1 Introduction 136
5.1.1 Synthesis of *α*,*α*-difluoro-*β*-amino esters 136
5.1.2 Diastereomerically controlled synthesis of *α*,*α*-difluoro-*β*-amino esters using chiral imines 139
5.1.3 Diastereomerically controlled synthesis of *α*,*α*-difluoro-*β*-amino esters using a chiral bromodifluoro ester 145
5.2 Results and discussion 147
5.2.1 Synthesis of Imines 147
5.2.2 The Reformatsky reaction with imines 149
5.2.3 The asymmetric Reformatsky reaction with ethyl iododifluoroacetate 153
5.2.4 The asymmetric Reformatsky reaction with ethyl bromodifluoroacetate 155
5.2.5 Traditional two-step Reformatsky reaction 157
5.2.6 Optimisation of the asymmetric Reformatsky reaction with ethyl iododifluoroacetate 158
5.2.7 Screening of imines 159
5.3 Conclusions 164

5.4 References 165

Chapter Six – Experimental Section

6.1 General experimental procedures 166

6.1.1 NMR Spectroscopy 166

6.1.2 Gas Chromatography 166

6.1.3 High Performance Liquid Chromatography 167

6.1.4 Mass Spectrometry 167

6.1.5 Elemental analysis 167

6.1.6 X-ray crystallography 167

6.1.7 Specific rotation 167

6.1.8 Starting materials 167

6.1.9 Separation of enantiomers of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** by ^{19}F NMR spectroscopy 168

6.1.10 Determination of conversion and separation of enantiomers of ethyl-2,2-difluoro-3-hydroxy-3-phenyl propanoate **(44)** and ethyl-2,2-difluoro-3-hydroxy-3-phenyl butanoate **(48)** by chiral GC 168

6.2 Synthetic procedures for Chapter two 169

6.2.1 Synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** 169

6.2.2 General methods for asymmetric syntheses of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** 170

6.2.3 Monitoring of the synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** by GC 172

6.3 Synthetic procedures for Chapter three 172

6.3.1 Synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **(48)** 172

6.3.2 General method for asymmetric synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **(48)** 174

6.3.3 General method for the Reformatsky reaction with ketones 177

Preparation of ethyl 3-(4-chlorophenyl)-2,2-difluoro-3-hydroxybutanoate **(51)** 177

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)butanoate **(52)** 178

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-(2-methoxyphenyl)butanoate **(53)** 178

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-phenylpentanoate **(54)** 179

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-phenylhexanoate **(55)** 179

Preparation of ethyl-2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(56)** 180

Preparation of ethyl-2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate **(57)** 180

Preparation of ethyl-2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate **(58)** 181

Preparation of (*E*)-ethyl-2,2-difluoro-3-hydroxy-3-methyl-5-phenylpent-4-enoate **(59)** 182

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-methylhexanoate **(60)** 182

Preparation of ethyl-2,2-difluoro-3-hydroxy-3,6-dimethylheptanoate **(61)** 183

Preparation of ethyl-2,2-difluoro-3-hydroxy-3,4,4-trimethylpentanoate **(62)** 183

Preparation of (*Z*)-2-(2-bromo-2,2-difluoro-1-hydroxyethylidene)-2,3-dihydro-1H-inden-1-one **(63)** 184

Preparation of ethyl-4-bromo-2,2,4,4-tetrafluoro-3,3-dihydroxybutanoate **(70)** 184

6.3.4 Determination of the absolute configuration of the new chiral centre 184

Preparation of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-propanamide **(65)** 185

Determination of the absolute configuration of the new chiral centre in ethyl-2,2-difluoro-3-hydroxy-3-phenylpentanoate **(66)** 186

Determination of the absolute configuration of the new chiral centre in ethyl-2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphtalen-1-yl)-acetate **(67)** 187

6.3.5 Monitoring of the synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **(48)** by GC. 188

6.3.6 Observation of the active species in the Reformatsky reaction by ^{19}F NMR spectroscopy 191

6.4 Synthetic Procedures for Chapter four 192

Preparation of ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate **(81)** 192

Preparation of ethyl 2-fluoro-3-hydroxy-3-phenylpropanoate **(77)** 195

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)-butanoate **(83a)** 196

Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)-butanoate **(83b)** 196

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-(2-methoxyphenyl)butanoate **(84a)** 197

Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-3-(2-methoxyphenyl)-butanoate **(84b)** 197

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-3-(4-chlorophenyl)-2-fluoro-3-hydroxy-butanoate **(85a)** 198

Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-3-(4-chlorophenyl)-2-fluoro-3-hydroxy-butanoate **(85b)** 198

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylpentanoate **(86a)** 199

Preparation of (2*R*,3*S*)/(2*S*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylpentanoate **(86b)** 199

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylhexanoate **(87a)** 200

Preparation of (2*R*,3*S*)/(2*S*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylhexanoate **(87b)** 201

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(88a)** 201

Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(88b)** 202

Preparation of ethyl-2-fluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate **(89)** 202

Preparation of ethyl-2-fluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate **(90)** 203

Determination of the absolute configuration of the new chiral centres in ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate **(81)** 204

Preparation of (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-butanamide **(82b)** 204

Preparation of (2*S*,3*R*) and (2*R*,3*S*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(82c)** and **(82d)** 205

6.5 Synthetic Procedures for Chapter 5 206

6.5.1 Synthesis of imines 206

Preparation of (*E*)-*N*-benzylideneaniline **(93)** 207

Preparation of (*E*)-2-(benzylideneamino)phenol **(94)** 207

Preparation of (*E*)-*N*-benzylidene-2-phenoxyaniline **(95)** 207

Preparation of (*E*)-*N*-benzylidene-P,P-diphenylphosphinic amide **(97)** 208

Preparation of (*E*)-*N*-benzylidene-2-methoxyaniline **(96)** 209

Preparation of (*E*)-*N*-(2-chlorobenzylidene)-2-methoxyaniline **(105)** 209

Preparation of (*E*)-*N*-(4-chlorobenzylidene)-2-methoxyaniline **(106)** 209

Preparation of (*E*)-2-methoxy-*N*-(2-methoxybenzylidene)aniline **(107)** 209

Preparation of (*E*)-2-methoxy-*N*-(4-methoxybenzylidene)aniline **(108)** 210

6.5.2 Products of the Reformatsky reaction with imines 210

Preparation of ethyl-2,2-difluoro-3-(2-methoxyphenylamino)-3-phenylpropanoate **(98)** 210

Preparation of ethyl-2,2-difluoro-3-(2-phenoxyphenylamino)-3-phenylpropanoate **(99)** 211

Preparation of ethyl 2,2-difluoro-3-(2-hydroxyphenylamino)-3-phenylpropanoate **(100)** 212

Preparation of ethyl-3-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methoxy-phenylamino)-2,2-difluoro-3-phenylpropanoate **(101)** 213

Preparation of ethyl-3-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-phenoxyphenyl-amino)-2,2-difluoro-3-phenylpropanoate **(102)** 213

Preparation of 3,3-difluoro-1,4-diphenylazetidin-2-one **(103)** 214

Preparation of ethyl-3-(diphenylphosphorylamino)-2,2-difluoro-3-phenyl-propanoate **(104)** 214

Preparation of ethyl-3-(2-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)-propanoate **(109)** 215

Preparation of ethyl-3-(4-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)-propanoate **(110)** 215

Preparation of ethyl-2,2-difluoro-3-(2-methoxyphenyl)-3-(2-methoxyphenylamino)-propanoate **(111)** 216

Preparation of ethyl-2,2-difluoro-3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)-propanoate **(112)** 216

General methods for asymmetric synthesis with imines 217

6.6 References 219

Appendix

A1 Determination of the amount of ethyl-2,2-difluoro-3-hydroxy-3-phenyl propanoate **(44)** and benzaldehyde by GC assay I

A2 Determination of the amount of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **(48)** and acetophenone by GC assay VII

A3 Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **(54)** XI

A4 Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate **(55)** XII

A5 Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(56)** XIII

A6 Crystal Data and Structure Refinement for ethyl 2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate **(57)** XIV

A7 Crystal Data and Structure Refinement for (*Z*)-2-(2-bromo-2,2-difluoro-1-hydroxyethylidene)-2,3-dihydro-1H-inden-1-one **(63)** XV

A8 Crystal Data and Structure Refinement for (*R*)-2,2-difluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(65b)** XVI

A9 Crystal Data and Structure Refinement for (*R*)-2,2-difluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide **(66b)** XVII

A10 Crystal Data and Structure Refinement for 2,2-difluoro-2-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)acetamide **(67a)** XVIII

A11 Crystal Data and Structure Refinement for (2*S*,3*S*)/(2*R*,3*R*)-ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate **(81)** XIX

A12 Crystal Data and Structure Refinement for (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(82b)** XX

A13 Crystal Data and Structure Refinement for (2*S*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(82c)** XXI

A14	Crystal Data and Structure Refinement for 3-(4-chlorophenyl)-2-fluoro-3-hydroxybutanoate **(85)**	XXII
A15	Crystal Data and Structure Refinement for ethyl 2-fluoro-3-hydroxy-3-phenylpentanoate **(86)**	XXIII
A16	Crystal Data and Structure Refinement for ethyl 2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(88)**	XXIV
A17	Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-(2-methoxyphenylamino)-3-phenylpropanoate **(98)**	XXV
A18	Crystal Data and Structure Refinement for 3,3-difluoro-1,4-diphenylazetidin-2-one **(103)**	XXVI
A19	Crystal Data and Structure Refinement for ethyl 3-(diphenylphosphorylamino)-2,2-difluoro-3-phenylpropanoate **(104)**	XXVII
A20	Crystal Data and Structure Refinement for ethyl 3-(2-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)propanoate **(109)**	XXVIII
A21	Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)propanoate **(112)**	XXIX
A22	Lecture Courses Attended	XXX
A23	Conferences Attended	XXX
A24	Presentations	XXX

List of Abbreviations

Ac	Acetyl
Atm	Atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl group
Boc	*tert*-butyloxycarbonyl
Bu	Butyl group
Bz	Benzoyl group
c	Cyclo
Calc.	Calculated
Cbz	Carbobenzyloxy group
Conv.	Conversion
Cp	Cyclopentyl
Cy	Cyclohexyl
d	Doublet
DAIB	(-)-N,N-Dimethylaminoisoborneol
DAST	Diethylaminosulfur trifluoride
DCM	Dichloromethane
De	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DME	Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	Dimethyl sulfoxide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
Ee	Enantiomeric excess
EI	Electron Impact
Equiv.	Equivalent
Et	Ethyl
FAB	Fast atom bombardment
GC	Gas chromatography
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
Hz	Hertz

HMDS	Hexamethyldisiloxane
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
IPA	propan-2-ol
i-Pr	*iso*-propyl
J	Coupling constant
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
MIB	Nugent's morpholine derivative
MS	Mass spectroscopy
n.d.	Not determined
NFSI	*N*-Fluorobenzenesulfonimide
No.	Number
min	minute
M.p.	Melting point
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMP	*p*-Methoxyphenyl group
ppm	Parts per million
Pr	Propyl
Psi	Pound per square inch
q	quartet
R	General alkyl or aryl fragment
r.t.	Room temperature
s	Singlet
T	Temperature
t	Triplet
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
t-Bu	*tert*-Butyl
TBAT	Tetrabutylammonium triphenylsilyldifluorosilicate
TEA	Triethylamine
TF	Triflate
TG	Triglyme

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
Ts	tosyl group
Z*	Activated zinc dust

Chapter One

Introduction

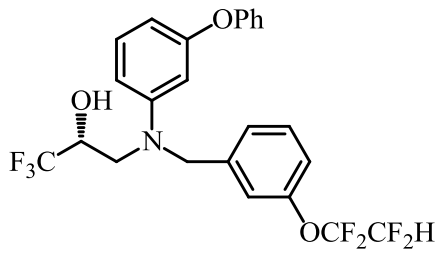
University *of*
Leicester

1.1 Introduction to organofluorine chemistry

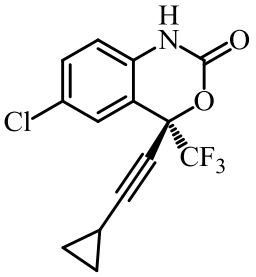
Fluorinated organic molecules play extremely important roles in the pharmaceutical and agrochemical industries since the introduction of fluorine in a specific position in a molecule can profoundly influence the biological activity.[1] Based on the van der Waals' radii (H 1.20 Å, F 1.47 Å, O 1.52 Å), fluorine is well recognised as an isopolar and isosteric replacement for a hydroxyl group. It is also possible to substitute hydrogen with fluorine without distorting the geometry of the molecule, however, the introduction of the trifluoromethyl group causes much more impact because its van der Waals volume is estimated to be close to that of an ethyl group, although of significantly different shape. Fluorine is the most electronegative element (4.0 in Pauling scale) and as a result of its high electron-withdrawing effect, the inclusion of fluorine can have a dramatic effect on the acidity or basicity of nearby ionisable groups. The small size of fluorine, which ensures good overlap of atomic orbitals, combined with its high electronegativity, causes it to form such short and strong bonds. In fact, the C-F bond is the strongest single bond known in organic chemistry and a common reason for the incorporation of fluorine into drugs is to reduce the rate of oxidative metabolism of a constituent aromatic ring. Finally, the lipophilicity of drug molecules can be modulated by the introduction of fluorine. Fluorination of saturated alkyl groups normally decreases the lipophilicity, whilst aromatic fluorination and fluorination adjacent to most atoms or groups with π electrons usually increases the lipophilicity.[2-4]

New protocols for the delivery of fluorine into drug candidates have enabled the syntheses of a new generation of potent medicines. Figure 1.1 only gives a few well-known examples of the applications of fluorine in medicinal chemistry. The cholesterol ester transfer protein inhibitor is used in coronary heart disease and the out-of-plane conformation of the OCF_2CF_2H group is responsible for more efficient binding to the target protein compared to using the non-fluorinated ethoxy group.[5] In Efavirenz, which is used in the treatment of patients with HIV, a trifluoromethyl moiety is located at a chiral center and decreases the pK_a of the cyclic carbamate, making hydrogen bonding to the protein possible.[6] The ability of a carbon-fluorine bond to participate in weak hydrogen bonding is exemplified in the two structural isomers of fluoronorepinephrine. 2-Fluoronorepinephrine (2F-NE) is a β-adrenergic agonist whilst 6-fluoronorepinephrine (6F-NE) is an α-adrenergic agonist and their different modes of action have been explained by the two different structures.

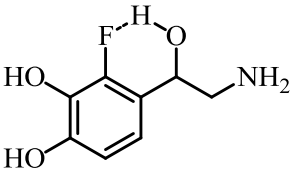
Figure 1.1 Examples of fluorinated medicines.



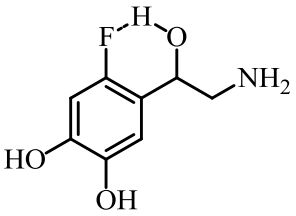
Cholesterol ester transfer protein inhibitor



Efavirenz



2-Fluoronorepinephrine (2F-NE)



6-Fluoronorepinephrine (6F-NE)

Recent work on the employment of difluoromethylene groups in pharmaceutical chemistry has shown that it is an area of organofluorine chemistry that is worth examining and exploring further (Figure 1.2). 10,10-Difluorothromboxane is an A_2 agonist where the electron withdrawing effect of the CF_2 group stabilises the glycosidic and acetal linkages by changing the electron deposition and consequently, slowing down the rate of hydrolysis by 10^8 times.[7,8] Improved stability against inactivation by enzymatic deamination in gemcitabine was achieved by replacing two hydrogens with two fluorine atoms. The increased stability of the thrombin inhibitor (Figure 1.2) was explained by a similar mechanism to this in other peptides containing difluorostatine or difluorostatone residues which have been shown to be potent inhibitors of the aspartyl protease renin. Here, the CF_2 moiety increases the electrophilicity of the ketone resulting in the formation of stable hydrates (Figure 1.3).[9] A best selling pharmaceutical in its class, Pantoprazole contains a difluorinated methoxy group and is currently one of the most potent drugs used in the treatment of heartburn, peptic ulcers and oesophageal inflammation (Figure 1.2).[10]

Figure 1.2 Medicines containing a difluoromethyl group.

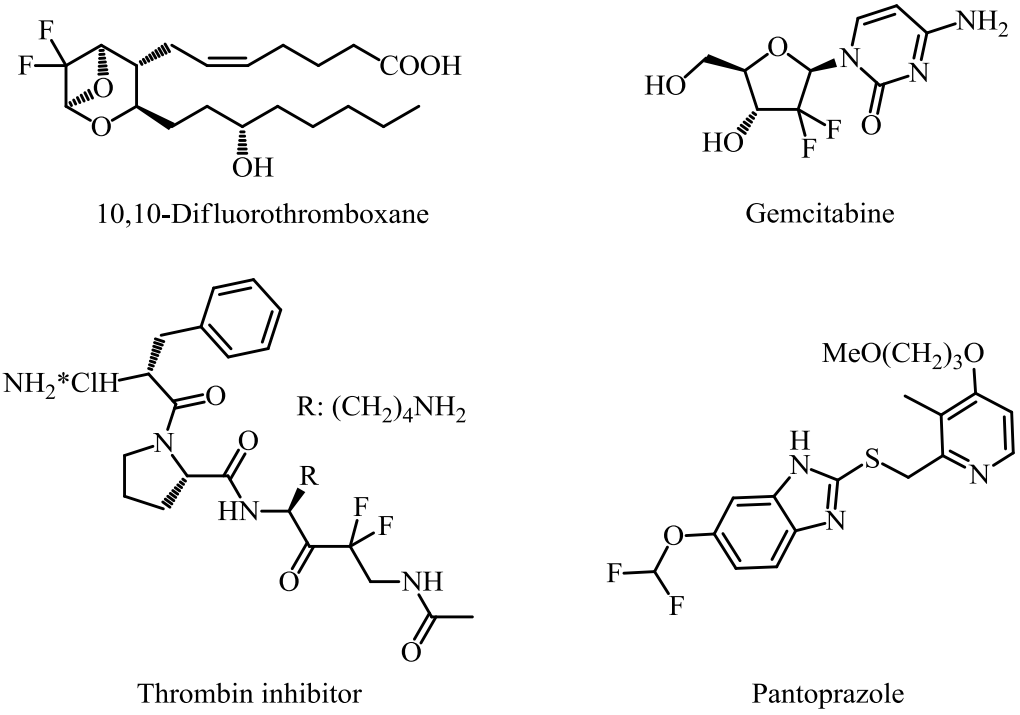
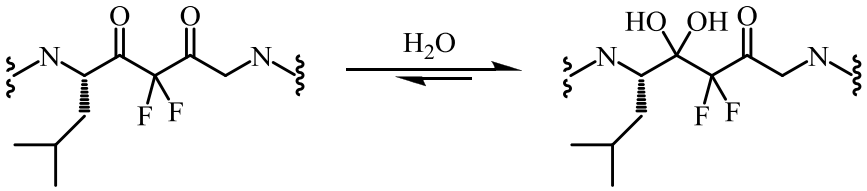


Figure 1.3 Hydration of a difluorinated ketone.



1.2 Direct methods for the introduction of a *gem*-difluoromethyl group

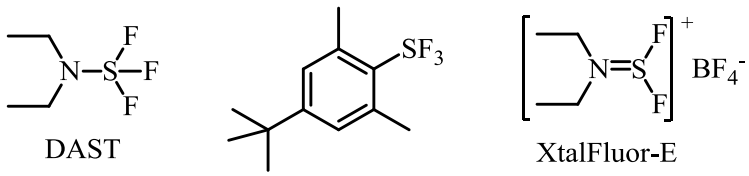
Since only a handful of naturally occurring molecules contain fluorine, new protocols for the introduction of this extremely reactive element have been developed. The methods for introducing the CF_2 moiety to a molecule can be divided into two main categories. In direct methods the nucleophilic or electrophilic fluorinating reagent is applied to introduce fluorine at specific positions in the molecule. The alternative is to use a fluorinated building block that contains a difluoromethylene group.

1.2.1 Nucleophilic fluorinating reagents

The most simple nucleophilic fluorinating reagent is HF. Hydrogen fluoride is widely used in industry; however, due to its corrosive and toxic nature in combination with it's relatively low reactivity resulting from the strong hydrogen-fluorine bond, HF is not a popular reagent in laboratory scale synthesis. For these reasons more convenient

nucleophilic fluorinating reagents have been developed over the years. The first one able to transform a carbonyl group into a difluoromethyl group was sulphur tetrafluoride.[11,12] Since it was difficult to handle the toxic gas it required special equipment and often harsh reaction conditions. The later discovery of dialkylaminosulfur trifluorides opened a new chapter in the applications of nucleophilic fluorinating reagents (Figure 1.4). The advantage of the most popular diethylaminosulfur trifluoride (DAST) **(1)** and other derivatives over previously used reagents was that for the first time it was an easy to handle liquid. DAST **(1)** reacts in a similar way to SF_4 as it has the ability to transform a carbonyl group into a CF_2 group, but it is a more selective reagent and, in general, does not react with ester groups. Consequently, DAST **(1)** has been used extensively in the fluorination of a range of biologically active molecules.[13] In the synthesis of (*R*)-14,14-difluoro-13-hydroxy-9(*Z*), 11(*E*)-octadecadienoic acid the key step was the reaction of DAST **(1)** with the enantiomerically pure ketone **(4)** (Scheme 1.1).[14] Dialkylaminosulfur trifluorides also react with dithioacetals resulting in *gem*-difluoromethylation[15,16] and thioesters[17] react with DAST **(1)** to yield *gem*-difluoro ethers.

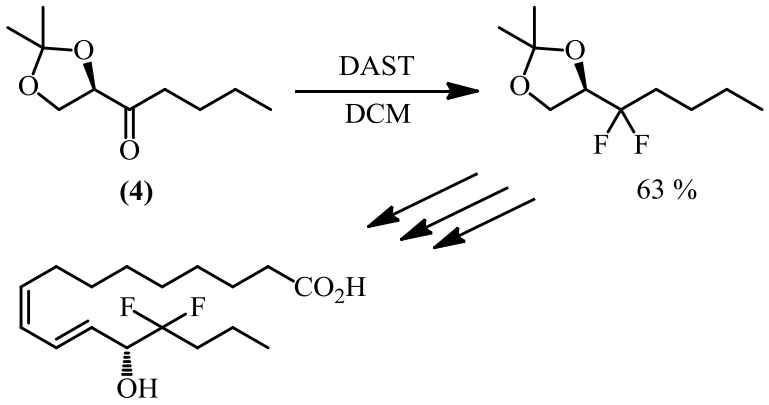
Figure 1.4 Nucleophilic fluorinating reagents.



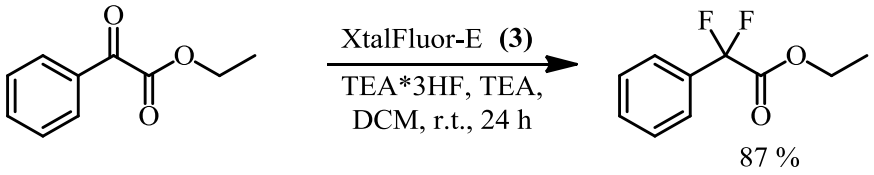
DAST **(1)** **(2)** XtalFluor-E **(3)**

In order to further improve nucleophilic fluorination, more thermally stable, less explosive and easier to handle reagents have been developed. 4-Tert-butyl-2,6-dimethylphenylsulphur trifluoride **(2)** reported by Umemoto has improved stability as a result of the presence of the C-S bond which is much stronger than the C-N bond present in DAST.[18] The use of dialkylaminodifluorosulfinium salt, XtalFluor-E **(3)**, as a fluorinating reagent was studied by Couturier *et al.*[19] This easy to use solid is able to react with a range of substrates under mild conditions with good selectivity and only a limited amount of the products resulting from elimination were formed (Figure 1.4, Scheme 1.2). It is also compatible with standard laboratory glassware as it does not release free HF.

Scheme 1.1 Synthesis of (*R*)-14,14-difluoro-13-hydroxy-9(*Z*), 11(*E*)-octadecadienoic acid.

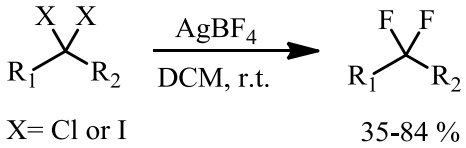


Scheme 1.2 *gem*-Difluorination of an α-keto ester.



The substitution of a halogen with fluorine using nucleophilic fluorinating reagents is a common method for the incorporation of a single fluorine atom into a molecule. The substitution of two halogen atoms present on the same carbon with fluorines turned out to be achievable, but difficult due to the formation of co-products or products of monofluorination. Silver tetrafluoroborate was used by Praly to replace *gem*-dichloro and *gem*-diiodo groups with CF_2 (Scheme 1.3).[20] The successful application of this technique has been reported as a step in the synthesis of a *gem*-difluorinated glycosyl. Here, silver fluoride was used to replace one bromine and one chlorine atom present on the same carbon with two fluorine atoms.[21]

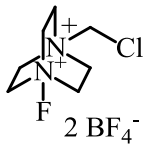
Scheme 1.3 Substitution of halogens with fluoride.



1.2.2 Electrophilic fluorinating reagents

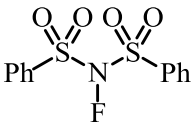
With the development of the first electrophilic reagents, most attention was focused on monofluorination and difluorinated products were perceived as unwanted side-products. Although there were some attempts at *gem*-difluorination in the literature,[22-25] these early methods were limited by too low or too high reactivity, lack of selectivity or the toxic nature of the reagents. A breakthrough in electrophilic fluorination came with the discovery of N-F reagents, which turned out to be mild, easy to use and selective sources of electrophilic fluorine. Many of them, like Selectfluor (F-TEDA-BF_4) **(5)** and NFSI (N-Fluorobenzenesulfonimide) **(6)** soon became commercially available (Figure 1.5).

Figure 1.5 Electrophilic fluorinating reagents.



Selectfluor

(5)



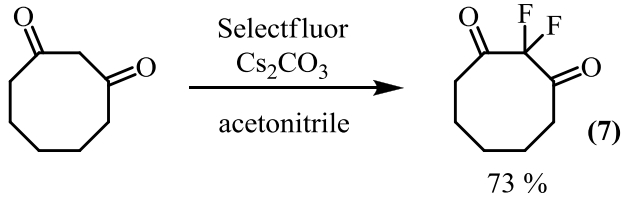
NFSI

(6)

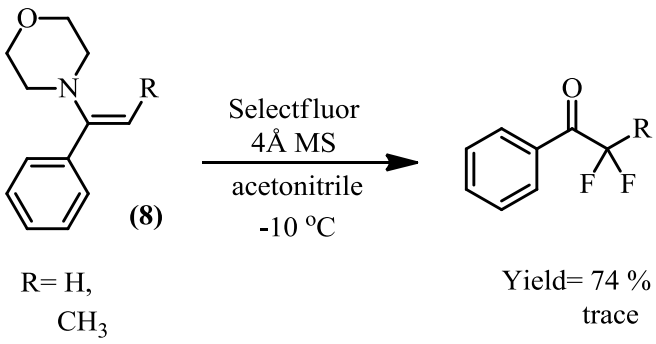
Bertozzi obtained 2,2-difluoro-1,3-cyclooctanedione **(7)** in the reaction of the corresponding 1,3-diketone with Selectfluor **(5)** in the presence of Cs_2CO_3 in 73 % yield (Scheme 1.4).[26] The direct difluorination of easily enolisable β-keto esters and amides with Selectfluor under neutral conditions was reported by Banks[27] and it was found that the reaction time could be reduced by running the reaction stepwise. In this approach the monofluorination with Selectfluor **(5)** was followed by transformation of the monofluorinated product into an enolate using sodium hydride and a consecutive reaction with a second equivalent of the fluorinating reagent. A stepwise approach was essential for the difluorination of less reactive substrates. The starting material was converted into an enol or enol ether before each fluorination. This method was used to introduce a difluoromethylene group in the α-position to ketones but, low yields (27-64 % yield) and low selectivities were obtained.[28] De Kimpe reported *gem*-difluorination of 2-aryl-5-(bromomethyl)-1-pyrrolines with **(5)** but, the typical yields were low and polyfluorinated co-products were formed in the reaction.[29] A better method for *gem*-difluorination of ketones was reported by Shreeve.[30] Here, a ketone with only one enolisable side was condensed with morpholine to the corresponding enamine **(8)** which

was used in the reaction with Selectfluor **(5)** in dry acetonitrile in the presence of molecular sieves. The reaction was successful with acetophenone (74 % yield); however, the additional methyl group in propiophenone decreased the acidity of the neighbouring hydrogen and the majority of the product was monofluorinated with only a trace amount of the desired *gem*-difluorinated product (Scheme 1.5).

Scheme 1.4 Synthesis of 2,2-difluoro-1,3-cyclooctanedione.



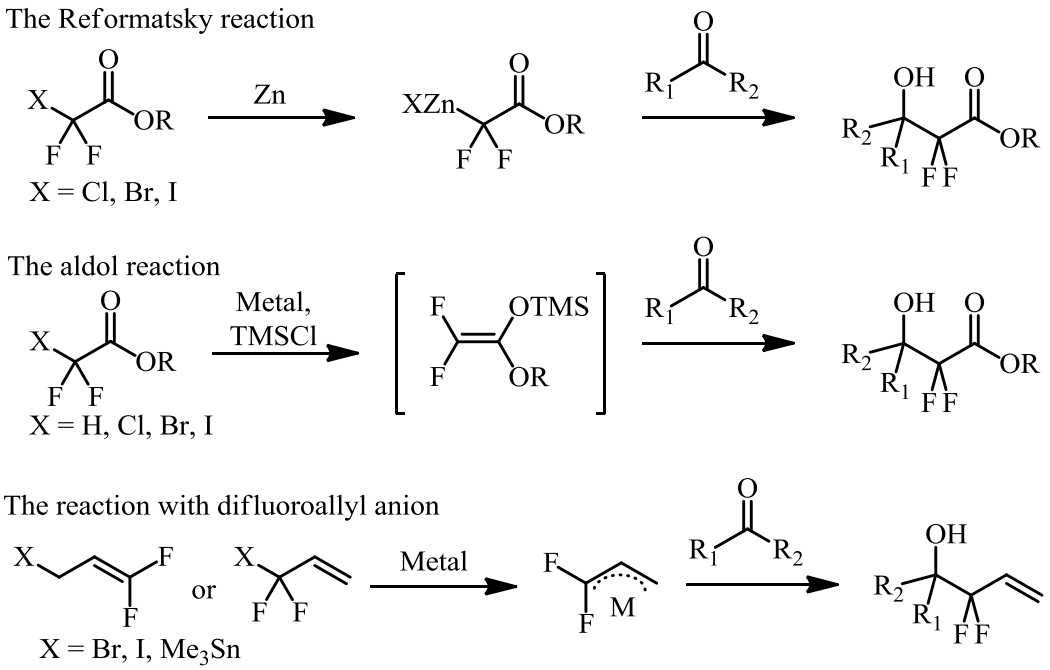
Scheme 1.5 Synthesis of α,α-difluoroketones.



1.3 Fluorinated building blocks containing the difluoromethylene group

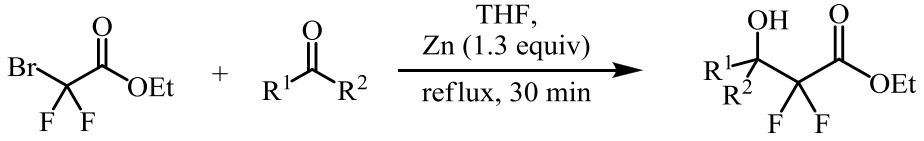
The reactions with *gem*-difluorinated building blocks (FBB) became a method of choice for the introduction of the CF_2 group into a molecule. These reactions are highly selective and can be performed under mild conditions at different stages of the synthesis. Other benefits of using a fluorinated building block approach are the formation of a new carbon-carbon bond and the introduction of functional groups that are amenable to further synthesis. In this section, a difluorinated synthon approach to *α,α*-difluoro-*β*-hydroxy esters and related products will be discussed. The most popular methods for *gem*-difluorination are the Reformatsky reaction and the aldol reaction and these will be discussed in more detail (Scheme 1.6). Other methods like the reaction with trimethylsilyl-*α,α*-difluoroacetate ester and difluoroallyl anions with carbonyl substrates and alternative routes will also be discussed.

Scheme 1.6 The general equations for the Reformatsky reaction, aldol reaction and the reaction of difluoroallyl anion with carbonyl substrates.



1.3.1 Reformatsky reaction of *gem*-difluorinated halogenated esters

Table 1.1 Results for Fried's one step procedure for the Reformatsky reaction.[31]



(9) **(10)**

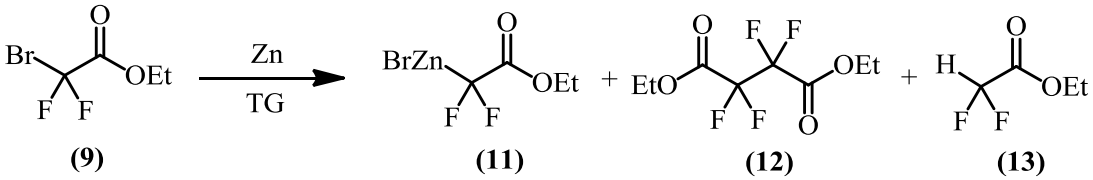
Entry	Substrate	Conditions	Yield [%][a]
1	PhCHO	THF, reflux, 30 min	57
2	$C_5H_{11}CHO$	THF, reflux, 30 min	35
3	cyclohexanone	THF, reflux, 30 min	72

[a] Isolated yield.

Despite the Reformatsky reaction being known for more than 120 years, the first difluorinated version was discovered by Fried in 1984 and is a convenient method for obtaining *α,α*-difluoro-*β*-hydroxy esters **(10)**.[31] The classical one step protocol involved the addition of a mixture of ethyl bromodifluoroacetate **(9)** and the carbonyl substrate dissolved in THF to a suspension of freshly activated zinc dust refluxing in

THF to yield the product **(10)** in moderate to good yields (Table 1.1). In the two step procedure activated zinc dust was refluxed with **(9)** in THF to make the Reformatsky reagent and after two minutes the carbonyl substrate was added dropwise. The two step procedure was more useful because it gave slightly higher yields (72 % in the reaction with benzaldehyde).

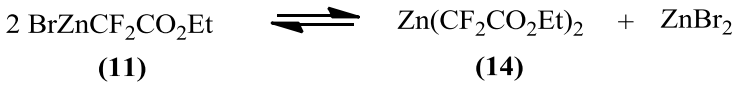
Scheme 1.7 The synthesis of the Reformatsky reagent.



(9) **(11)** **(12)** **(13)**

The structure and the stability of the Reformatsky reagent synthesised from ethyl bromodifluoroacetate was studied by Burton.[32] Initially, the fluorinated Reformatsky reagent **(11)** was generated in triethylene glycol dimethyl ether, $(CH_3O)(CH_2CH_2O)_3CH_3$ (TG), in 77 % yield (determined by ^{19}F NMR spectroscopy) although small amounts of tetrafluorosuccinate **(12)** and difluoroacetate **(13)** were also observed (Scheme 1.7). The ^{19}F NMR spectrum of the fluorinated Reformatsky reagent showed two peaks, at -115.2 ppm and -115.3 ppm which could be assigned to the mono (**11**) and bis species (**14**) according to the equilibrium shown in Scheme 1.8.

Scheme 1.8 Equilibrium between mono and bis species of the Reformatsky reagent.



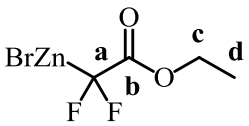
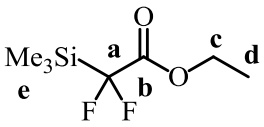
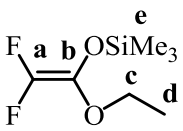
(11) **(14)**

The singlet fluorine signals provided evidence that the molecule is carbon-metallated, otherwise for each vinylic fluorine an AB pattern would be observed, as in the case of difluoroketene silyl acetal (Table 1.2). The ^{13}C NMR spectra confirmed the assignment of a carbon-metallated structure for the fluorinated Reformatsky reagent and the data was compared to that for 2,2-difluoro-2-(trimethylsilyl)acetate and the presence of the carbonyl carbon was observed in both compounds (Table 1.2, bold values).

^{19}F NMR Spectroscopy was also used to determine the level of decomposition of the zinc reagent in different solvents. In triethylene glycol dimethyl ether there was

8.5 % decomposition after 20 h and 23 % after 45 h, whilst the fluorinated Reformatsky reagent fully decomposed in THF after 20 hours at room temperature. Another group reported the decomposition of the zinc reagent derived from methyl iododifluoroacetate. In acetonitrile, 80 % of the reactive zinc reagent decomposed after 2 hours at room temperature and it completely decomposed within a few minutes at 80 ^{o}C.[33]

Table 1.2 ^{13}C NMR data for difluorinated compounds.[32]

Structure	Chemical shift [ppm] (in order for a,b,c,d and e)	Coupling constant [Hz] (in order for a and b)
	135.18 (t), **170.46** (t), 60.11 (s), 14.43 (s)	291.4, 20.9
	121.6 (t), **166.0** (t), 62.2 (s), 14.2 (s), -5.1 (s)	268.0, 25.6
	147.9 (t), 125.1 (t), 64.3 (s), 12.9 (s), -2.3 (s)	270.7, 37.7

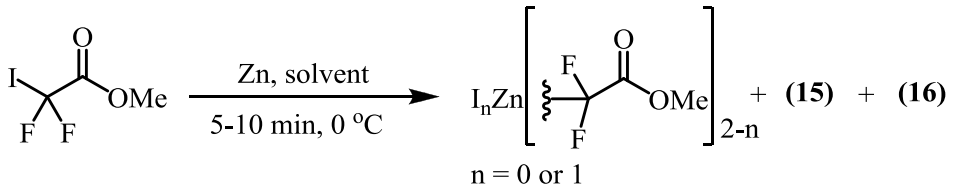
Chlorodifluoroacetic acid derivatives can also be used as starting materials for the fluorinated Reformatsky reaction.[34] When ethyl chlorodifluoroacetate and benzaldehyde were heated in dry DMF in the presence of freshly activated zinc for 20 h at 70 ^{o}C the corresponding product, *α*,*α*-difluoro-*β*-hydroxy-*β*-phenylpropionate, was isolated in 68 % yield (Table 1.3). Only low yields were obtained with aliphatic aldehydes, but this can be improved significantly by the use of ultrasonic irradiation. This method was interesting as the chlorinated derivative is cheaper than the brominated one.

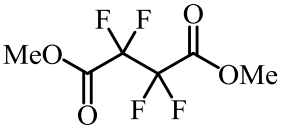
Table 1.3 Reformatsky reaction with ethyl chlorodifluoroacetate.[34]

Run	Substrate	Conditions	Yield [%][a]
1	PhCHO	DMF, 20 h, 70 ^{o}C	68
2	$(CH_3)_3CCHO$	DMF, 32 h, 70 ^{o}C	49

[a] Isolated yield.

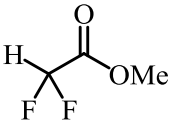
Table 1.4 Reaction of methyl iododifluoroacetate with zinc dust in different solvents.[33]





dimethyl 2,2,3,3-tetrafluorosuccinate

(15)



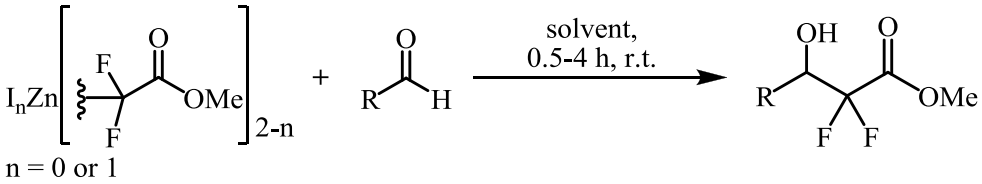
methyl 2,2-difluoroacetate

(16)

Run	Solvent	Reformatsky reagent[a]	(15) [a]	(16) [a]
1	CH_3CN	75-85	10	5-7
2	THF	50-55	20	Trace
3	Et_2O	0	40	-
4	1,4-dioxane	25	25	-
5	DMF	55	-	-
6	DME	21	17	18

[a] Determined by ^{19}F NMR spectroscopy.

Table 1.5 Reaction of the fluorinated Reformatsky reagent with aldehydes.[33]



Run	Substrate	Conditions	Yield [%][a]
1	PhCHO	THF, 4 h	90
2	$PhCH_2CH_2CHO$	THF, 2 h	68
3	$PhCH_2CH_2CHO$	CH_3CN, 2 h	79
4	*E*-PhCH=CHCHO	CH_3CN, 30 min	68

[a] Isolated yield.

Methyl iododifluoroacetate was also used to generate a fluorinated Reformatsky reagent and since the iodide is a more reactive starting material, it reacts with zinc dust in acetonitrile in 5 to 10 minutes at 0 °C.[33] Small amounts of by-products, **(15)** and **(16)** (Table 1.4), were also generated under these reaction conditions. Acetonitrile was found

to be the best solvent for the reaction of the Reformatsky reagent with aldehydes and aromatic aldehydes gave higher yields than aliphatic aldehydes (Table 1.5).

Shen reported that in the Reformatsky reaction no catalyst is needed in the reaction with aldehydes and aromatic ketones (Table 1.6, runs 1-4).[35] However, in the absence of catalyst aliphatic ketones gave lower yields (Table 1.6, runs 5-7) and the substoichiometric addition of 2 mol% of $CeCl_3$ or $CeCl_3 . 7\ H_2O$ was necessary.

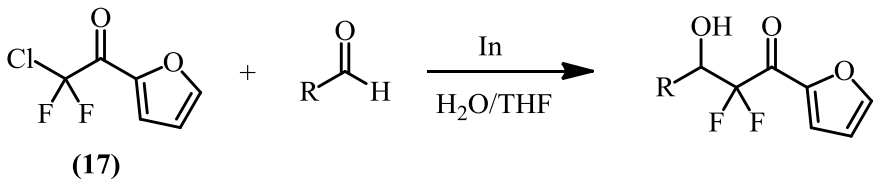
Table 1.6 Preparation of *α,α*-difluoro-*β*-hydroxyesters from aldehydes and ketones without and in the presence of catalyst.[35]

Run	Substrate	Yield [%][a] without catalyst	Yield [%][a] $CeCl_3$[b]	Yield [%][a] $CeCl_3 . 7\ H_2O$[b]
1	PhCHO	94	92	-
2	$CH_3(CH_2)_3CHO$	90	91	-
3	$PhCOCH_3$	90	92	-
4	PhCOPh	86	90	-
5	cyclohexanone	32	90	89
6	cycloheptanone	32	90	90
7	$CH_3(CH_2)_2COCH_3$	30	92	90

[a] Isolated yields, [b] 2 mol%.

Other molecules like *α*-halogenated ketones can be used in Reformatsky like reactions with carbonyl substrates. In 2001 Welsh presented an indium mediated reaction of 2,2-difluoro-2-chloro-1-furan-2-yl ethanone **(17)** with aldehydes in 20 % THF in water (Scheme 1.9).[36] The starting material was prepared from chlorodifluoroacetic acid and furan.

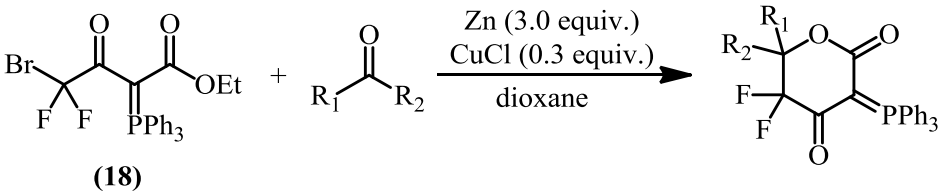
Scheme 1.9 The reaction of 2,2-difluoro-2-chloro-1-furan-2-yl ethanone with aldehydes.



(17)

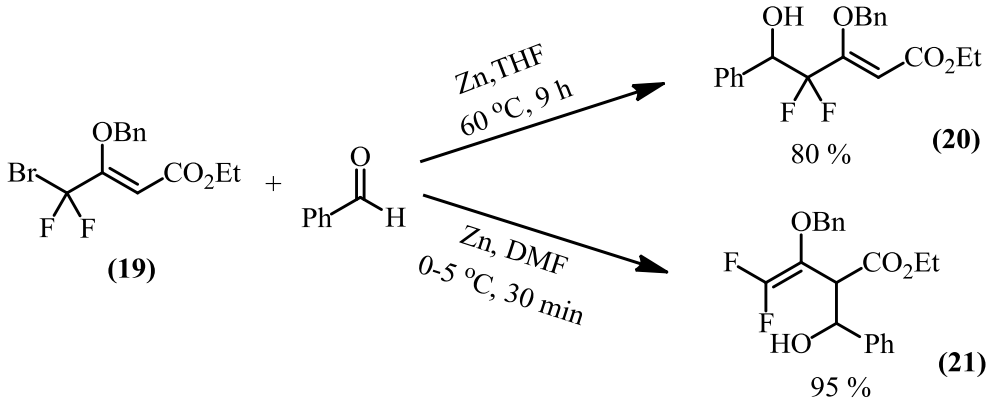
Wu *et al.* reported the synthesis of *gem*-difluorinated lactones and amines from ethyl 4-bromo-4,4-difluoro-3-oxo-2-(triphenylphosphoranylidene)butanoate **(18)** and carbonyl compounds.[37] The reaction was promoted by 3.0 equivalents of zinc dust and 0.3 equivalents of cuprous chloride (Scheme 1.10).

Scheme 1.10 Synthesis of *gem*-difluorinated lactones.



Zhu reported the result of the reaction of ethyl 3-bromodifluoromethyl-3-benzyloxy-acrylate **(19)** with aldehydes.[38] The reaction yielded a Reformatsky type product **(20)** (80 % yield) when it was run in the presence of zinc dust at 60 ^{o}C in THF. However, by changing the solvent to DMF and running the reaction at 0-5 ^{o}C for 30 min resulted in the formation of the Barbier's product **(21)** in 95 % yield (Scheme 1.11).

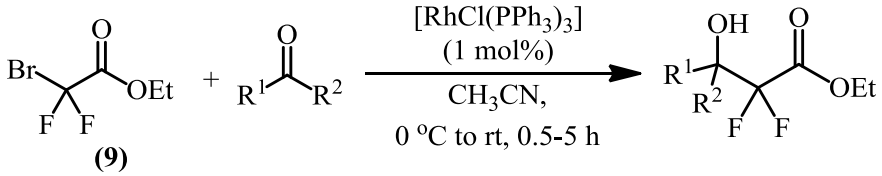
Scheme 1.11 The reaction of ethyl 3-bromodifluoromethyl-3-benzyloxy-acrylate with aldehydes.



Most methods for synthesising the fluorinated Reformatsky reagent from ethyl bromodifluoroacetate include some zinc activation protocols as well as refluxing or ultrasonic irradiation. In 2004 Kumadaki and co-workers proved, that the Reformatsky reagent can be generated in the homogeneous reaction between ethyl bromodifluoroacetate **(9)** and diethyl zinc under mild reaction conditions.[39] The carbonyl substrate, **(9)** and 1 mole% of Wilkinson's catalyst were stirred for 30

minutes in acetonitrile at 0 °C before adding diethylzinc (1.5 equivalents). The reaction time was dependent on the carbonyl compound, and was typically between 0.5 and 7 h at 0 °C. Both aliphatic and aromatic aldehydes gave good to excellent yields, and the reaction was also successful with ketones (Table 1.7).

Table 1.7 Rhodium catalysed fluorinated Reformatsky reaction with aldehydes and ketones.[39]

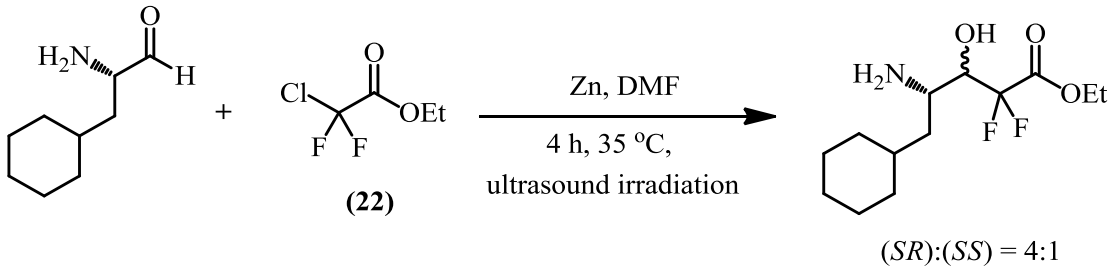


Entry	Substrate	Conditions	Yield [%][a]
1	PhCHO	0 °C, 4.5 h	86
2	*p*-$MeOC_6H_4CHO$	0 °C, 5 h	93
3	*p*-ClC_6H_4CHO	0 °C to rt, 0.5 h	94
4	$C_7H_{15}CHO$	0 °C to rt, 0,5 h	82
5	$PhCH_2CH_2CHO$	0 °C to rt, 1 h	82
6	cyclohex-2-enone	0 °C, 1 h	80
7	cyclohexanone	0 °C to rt, 1 h	78
8	PhCOPh	0 °C to rt, 0.5 h,	91[b]

[a] Isolated yields, [b] 3.0 equivalents of Et_2Zn were used.

1.3.2 Diastereoselective fluorinated Reformatsky reaction

Scheme 1.12 Diastereoselective Reformatsky reaction of (*S*)-2-amino-3-cyclohexylpropanal.



The first diastereoselective Reformatsky reaction with an aldehyde was reported in 1988 by Lang.[34] The chiral substrate was made according to Thaisrivongs

method[9] and the reaction with the Reformatsky reagent prepared from ethyl chlorodifluoroacetate **(22)** gave 63 % yield and a 4:1 diastereoselectivity of (*SR*):(*SS*) (Scheme 1.12).[33]

Scheme 1.13 Reaction of the fluorinated Reformatsky reagent starting from ethyl iododifluoroacetate.

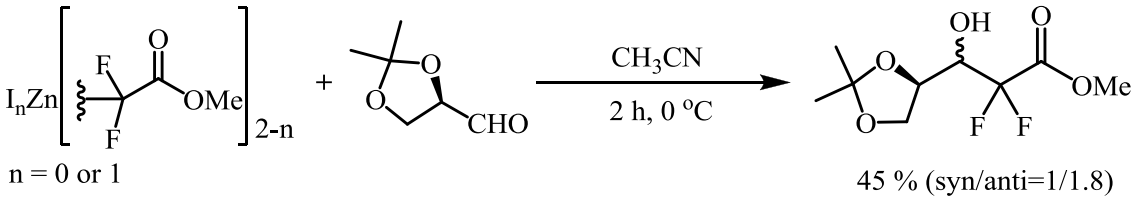
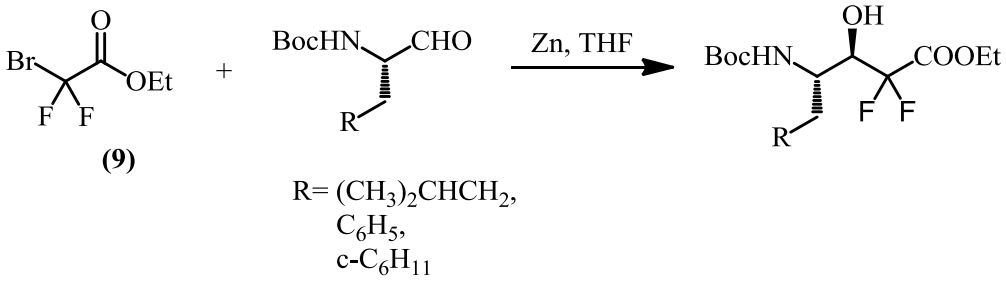
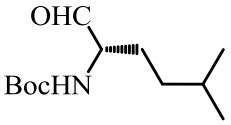
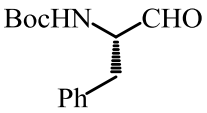
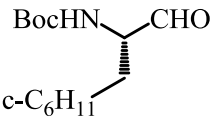


Table 1.8 Preparation of 2,2-difluoro-3-hydroxyesters from Boc-L-leucinal.[33]



Entry	Substrate	Conditions	Yields [%][a]	De [%] (3*R*,4*S*):(3*S*,4*S*)
1		Sonication	80	70:30
2		Reflux	-	100 (3*R*,4*S*)
3		Sonication and reflux	-	100 (3*R*,4*S*)
4		Sonication	87	Not reported
5		Sonication	97	Not reported

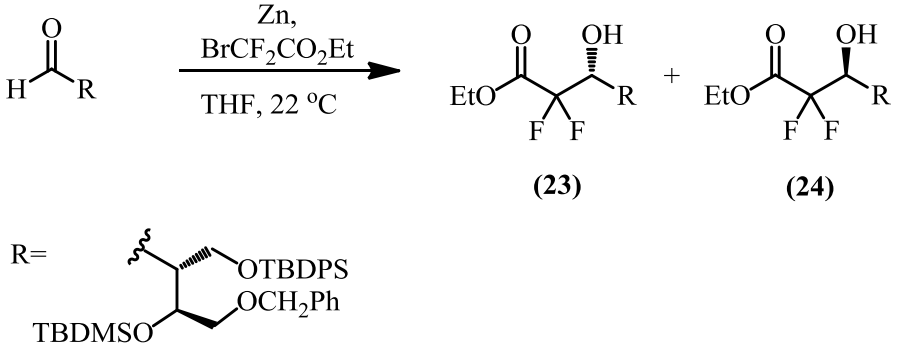
[a] Isolated yield.

Kitagawa compared the diastereoselectivity obtained in the fluorinated aldol reaction (Table 1.16) and the Reformatsky reaction with a chiral aldehyde (Scheme 1.13).[33] The diastereoselectivity obtained in the reaction with the Reformatsky reagent

was lower (syn/anti = 1/1.8) than that obtained with the difluoro silyl enol ether (syn/anti = 1/9).

The key step for introducing a CF_2 group to potent peptides containing difluorostatine and difluorostatone was the fluorinated Reformatsky reaction with Boc-L-leucinal, which was prepared by the oxidation of Boc-L-leucinol. Zinc powder was suspended in THF in a sonicating bath and (tert-butyloxycarbonyl)-L-leucinal and ethyl bromodifluoroacetate **(9)** were added dropwise. After work up, the diastereoisomers were separated by column chromatography. Under ultrasonic irradiation conditions a 70:30 % mixture of diastereomers (Table 1.8) was obtained. On refluxing the reaction, however, only one diastereoisomer (3*R*,4*S*) was obtained preferentially and when the ultrasonicated reaction was refluxed for 30 minutes the thermodynamically favoured (3*R*,4*S*) diastereoisomer was the only product.

Scheme 1.14 Fluorinated Reformatsky reaction step in synthesis of (+)-10,10-difluorothromboxane A_2.



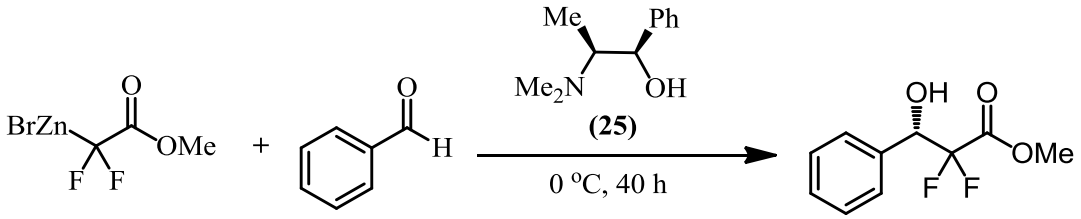
In 1992 Fried published the total synthesis of (+)-10,10-difluorothromboxane A_2 where one of the steps was a diastereoselective fluorinated Reformatsky reaction.[7] The introduction of the CF_2 group added stability to the glycosidic and acetal linkages. Ethyl bromodifluoroacetate was reacted with the aldehyde in THF in the presence of zinc at room temperature. Under these reaction conditions the reaction gave an 81 % yield, but the ratio of products **(23)**:**(24)** was only 1.38:1 (Scheme 1.14).

1.3.3 Enantioselective Reformatsky reaction with aldehydes

The first example of an enantioselective fluorinated Reformatsky reaction was reported by Braun.[40] The Reformatsky reagent, generated from methyl bromodifluoroacetate and activated zinc (1,2-dibromoethane, heating and addition of

chlorotrimethylsilane) in THF, was reacted with benzaldehyde in the presence of different chiral carbinols (62-65 % yield, 55-62 % ee), amino alkoxides (46 % yield, 5 % ee) and amino alcohols (45-93 % yield, 54-84 % ee). The best results were obtained with two equivalents of (1*R*,2*S*)-*N*-methylephedrine **(25)** and 3 equivalents of the Reformatsky reagent (Table 1.9, run 4). Braun tested the optimized conditions with a few aldehydes, but the yields and enantiomeric excesses obtained with aliphatic aldehydes were much lower than those obtained with aromatic aldehydes (Table 1.10).

Table 1.9 Enantioselective Reformatsky reaction in the presence of *N*-methylephedrine.[40]



Entry	*N*-methylephedrine[a]	Reformatsky reagent[a]	Yields [%][b]	Ee [%][c]
1	0.1	1	45	54
2	0.3	1	47	79
3	1	3	93	79
4	2	3	61	84

[a] Equivalents relative to benzaldehyde, [b] isolated yield, [c] enantiomeric excess was determined by either ^{1}H NMR spectroscopy or chiral GC.

Table 1.10 Braun's optimised reaction conditions with different aldehydes.[40]

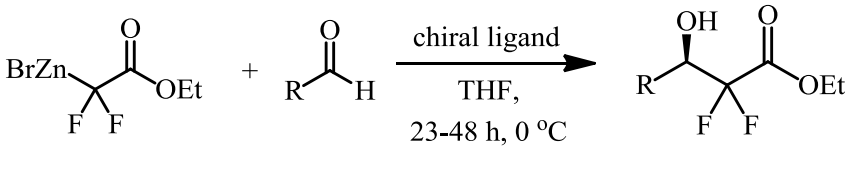
Entry	Substrate	Yields [%][a]	Ee [%]
1	4-chlorobenzaldehyde	56	67
2	2,5-dimethoxybenzaldehyde	71	71
3	isobutyraldehyde	63	46

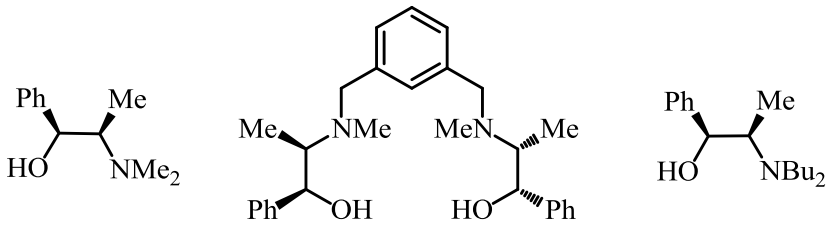
[a] Isolated yield. [c] enantiomeric excess was determined by either ^{1}H NMR spectroscopy or chiral GC.

This procedure was later improved by Pedrosa and co-workers, who investigated the effects of a series of chiral amino alcohols.[41] In the two step procedure the Reformatsky reagent was first generated by the addition of ethyl

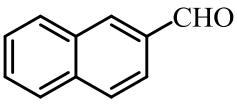
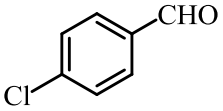
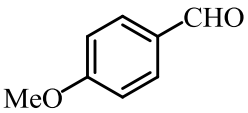
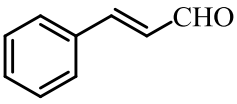
bromodifluoroacetate in THF to the mixture of activated zinc dust and chlorotrimethylsilane in THF which had been previously refluxed for 15 minutes. In the second step, the mixture of aldehyde and chiral ligand were stirred for 20 minutes at 0 ^{o}C before the Reformatsky reagent was added via syringe (Table 1.11).

Table 1.11 Enantioselective fluorinated Reformatsky reaction in the presence of chiral aminoalcohols.[41]





(26) **(27)** **(28)**

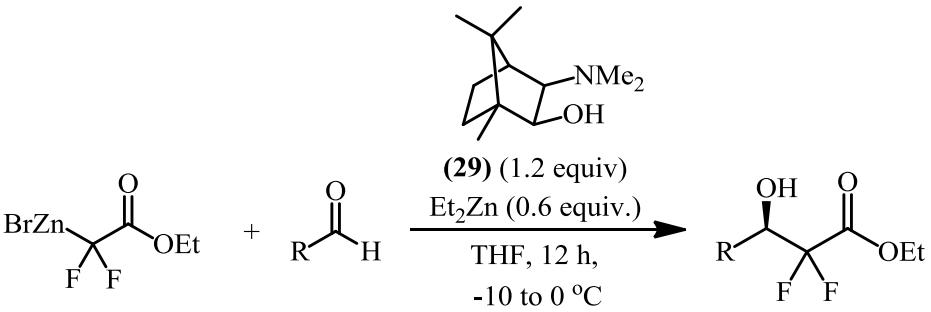
Entry	Substrate	Conditions	Yield[a]	Ee[b]
1	PhCHO	1:3:1[c], THF, 24 h, 0 ^{o}C	65	82
2		1:3:1[c], THF, 48 h, 0 ^{o}C	34	81
3		1:4:1[c], THF, 24 h, 0 ^{o}C	69	83
4		1:3:1[c], THF, 46 h, 0 ^{o}C	38	71
5		1:4:1[c], THF, 23 h, 0 ^{o}C	68	74
6		1:4:1[c], THF, 24 h, 0 ^{o}C	60	60
7		1:4:1[c], THF, 24 h, 0 ^{o}C	63	41
8	$CH_3CH_2CH_2CHO$	1:4:1[c], THF, 24 h, 0 ^{o}C	42	58

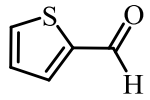
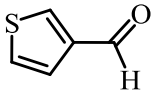
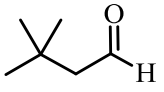
[a] Isolated yields, [b] determined by ^{1}H and ^{19}F NMR spectroscopy of Mosher derivatives, [c] molar ratio of aldehyde:Reformatsky reagent:chiral ligand.

From the chiral amino alcohols (Table 1.11) that were tested in the reaction with benzaldehyde, *N*-methylephedrine **(26)** (82 % ee, 65 % yield) and bisamino alcohol **(27)** (80 % ee, 38 % yield) gave high enantiomeric excesses, whereas

dibutylnorephedrine **(28)** gave only a moderate 68 % ee and 42 % yield. Since *N*-methylephedrine gave not only good ee but also high yields, it was chosen for further testing. The use of four equivalents of Reformatsky reagent gave better results than using three equivalents resulting in higher yields and slightly higher enantiomeric excesses (Table 1.11, entries 2 and 3, 4 and 5). The best results were obtained with aromatic aldehydes, such as benzaldehyde (entry 1) and 2-naphthaldehyde (entry 2), whereas aliphatic aldehydes gave low ee and, in the case of butyraldehyde low yields (42 %). The absolute configuration (*R*) of the product was assigned based on the assumption that the reaction followed the same mechanism as the asymmetric addition of diethylzinc to aldehydes.

Table 1.12 Fluorinated Reformatsky reaction using (-)-DAIB as chiral ligand.[42]



Entry	Substrate	Conversion [%]	Yield [%][a]	Ee [%][b]
1	PhCHO	92	82	88
2	*p*-Br-PhCHO	96	83	87
3	*p*-CN-PhCHO	91	88	84
4		66	90	90
5		69	84	87
6		91	81	80

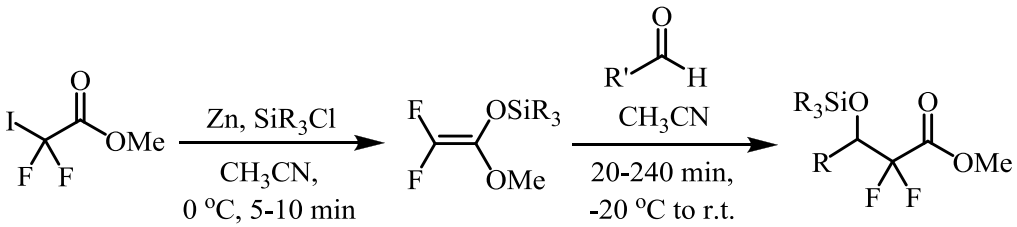
[a] Isolated yield, [b] the absolute stereochemistry (*R*) was assigned by comparison of the optical rotation with literature data.

The highest enantioselectivity was reported by Knochel and co-workers using (-)-DAIB **(29)** as the chiral amino alcohol (Table 1.12), which could be recovered at the

end of the reaction, and performing the reaction at -10 °C.[42] Good yields (81-90 %) of the isolated product and high enantioselectivities (84-90 % ee) were obtained with a range of aromatic aldehydes. The highest ee was obtained with thiophene-2-carbaldehyde (run 4), probably because the sulphur helps to stabilise the chiral complex with zinc. The lowest enantioselectivity was obtained for a sterically hindered aliphatic aldehyde (run 6). Although it was mentioned that in the non-fluorinated version of the reaction with benzaldehyde the addition of tetrahydrothiophene (1.2 equivalents) improved the ee from 86 to 88 % and the conversion from 75 % to 84 %, there is no information on whether the same additive can improve the fluorinated version of the reaction.

1.3.4 Fluorinated aldol reaction with aldehydes and ketones

Table 1.13 Reaction of aldehydes and ketones with difluoroketene silyl acetal.[33]



Entry	Substrate	R	Conditions	Yield [%][a]
1	PhCHO	Et	CH_3CN, 20 min, 0 °C	81
2	$PhCH_2CH_2CHO$	Et	CH_3CN, 20 min, 0 °C	77
3	$PhCH_2CH_2CHO$	Me	CH_3CN, 20 min, 0 °C	59[b]
4	$C_6H_{10}CHO$	Et	CH_3CN, 4 h, r.t.	28

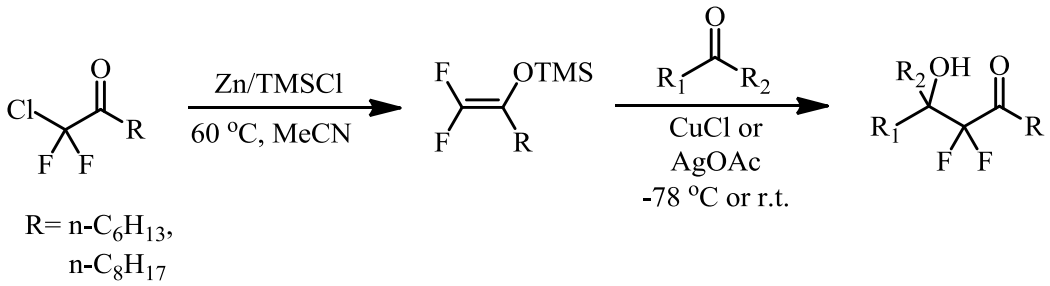
[a] Isolated yield, [b] the product was identified as the *β*-hydroxyester.

An accessible route to *α*,*α*-difluoro-*β*-hydroxy esters using the aldol reaction with aldehydes and ketones was reported by Kitagawa.[33] In the first step the Reformatsky reagent, which was synthesised in acetonitrile from methyl iododifluoroacetate and zinc dust (Table 1.13), was reacted with chlorotrialkylsilanes. The fluorinated silyl enol ethers were then reacted with aldehydes or ketones in a 2:1 ratio (Table 1.13). The stability of the difluorinated silyl enol ethers was dependent on the trialkylsilyl group. Trimethylsilyl enol ethers were less stable and decomposed within 24 h, whereas triethyl and *t*-butyldimethyl silyl enol ethers were relatively stable.

This is probably why the reaction product with these two stable derivatives, are oxygen silylated whilst the trimethylsilyl derivative yielded the *β*-hydroxy product (entry 3). Monitoring of the reaction by TLC showed that the *α,α*-difluoro-*β*-hydroxy product is formed initially and then the hydrogen is slowly replaced by the silyl group.

Ishihara reported the first synthesis of difluoroenoxysilanes from chlorodifluoromethyl ketones (Scheme 1.15).[43] 1-Chloro-1,1-difluorooctan-2-one and 1-chloro-1,1-difluorodecan-2-one formed enols in the reaction with zinc dust. These enols were trapped with trimethylsilyl chloride and after purification were used in the reaction with aldehydes and ketones in the presence of copper (I) chloride or silver acetate. The initial protocol employing titanium did not perform well with aromatic and *α,β*-unsaturated carbonyl substrates.[43-45]

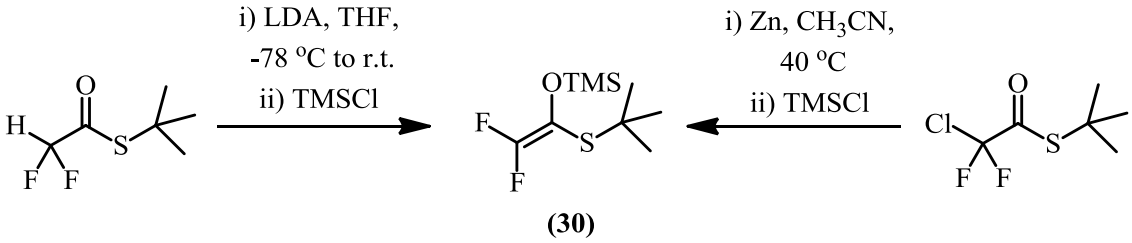
Scheme 1.15 The formation of silyl enol ether and its reaction with carbonyl substrates.



R= n-C_6H_{13}, n-C_8H_{17}

Weigel used *O,S*-acetal enols **(30)** which in contrast to lithium enolates obtained from difluoroacetate do not suffer from self-condensation.[46] Scheme 1.16 shows the synthesis of the enol **(30)** by two different methods. Compound **(30)** was generated by reacting *S-tert*-butyl 2,2-difluoroethanethioate with LDA and trapping the lithium enolate with TMSCl at -78 °C. A different synthesis of **(30)** was the Reformatsky reaction of *S-tert*-butyl 2-chloro-2,2-difluoroethanethioate with zinc dust followed by the addition of TMSCl. In the next step, shown in Scheme 1.17, the solution of **(30)** was added to an aldehyde at -78 °C and the reaction flask was slowly warmed to room temperature. The reaction gave *S-tert*-butyl *α,α*-difluoro-*β*-hydroxythioate in 42-77 % yields. In the reaction performed with a chiral aldehyde a higher yield and diastereoselectivity was obtained with **(30)** (74 % yield, 95/5, erythro/threo) than with the lithium enolate (64 % yield, 85/15, erythro/threo).

Scheme 1.16 The synthesis of ((1-(tert-butylthio)-2,2-difluorovinyl)oxy)trimethylsilane.



Scheme 1.17 The aldol reaction of *S*-tert-butyl 2,2-difluoroethanethioate with aldehydes.

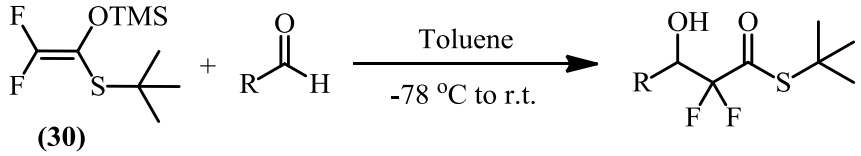
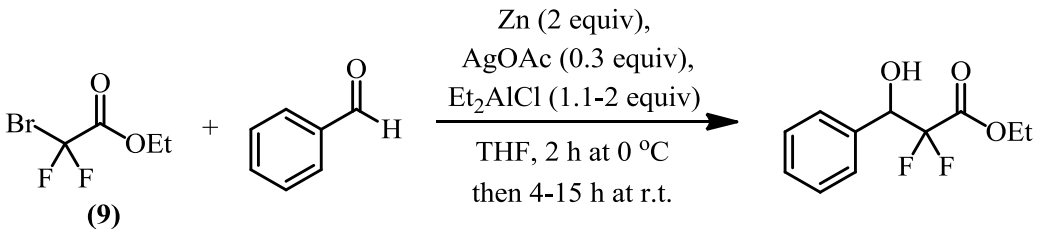


Table 1.14 Ethyl *α,α*-difluoro-*β*-hydroxyesters by the modified Reformatsky reaction.[47]



Entry	Substrate	Yield [%][a]
1	PhCHO	69
2	$PhCH_2CH_2CHO$	64
3	$PhCOCH_3$	62
4	$PhCH_2CH_2COCH_3$	51

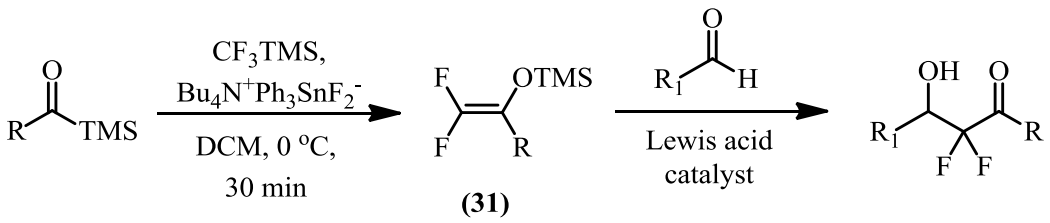
[a] Isolated yield.

In order to synthesise transition-state mimicking enzyme inhibitors, it was necessary for Curran to investigate the modified fluorinated Reformatsky reaction with *N*-protected-α-amino aldehydes.[47] The reaction was also tested with aromatic and aliphatic aldehydes and ketones. Ethyl bromodifluoroacetate was added in small portions to the mixture of aldehyde, activated zinc dust and catalyst (AgOAc) in THF at 0 °C. Et_2AlCl was then added dropwise and the mixture was stirred for 2 h at 0 °C before warming to room temperature. According to the mechanism proposed by

Yamamoto, the Reformatsky reagent is formed initially and it is attacked by dialkylaluminium to generate the difluorinated aluminium enolate.[48] *N*-Protected-*α*-amino aldehydes gave much higher yields with this new protocol than with previously reported methods. It was also mentioned that the use of Me_2AlCl instead of Et_2AlCl can improve the selectivity of the reaction. Curran's procedure was also used in the reaction with ketones[47] and acetophenone gave 62 % of the desired product whilst a 51 % yield was obtained in the reaction with 4-phenylbutan-2-one (Table 1.14).

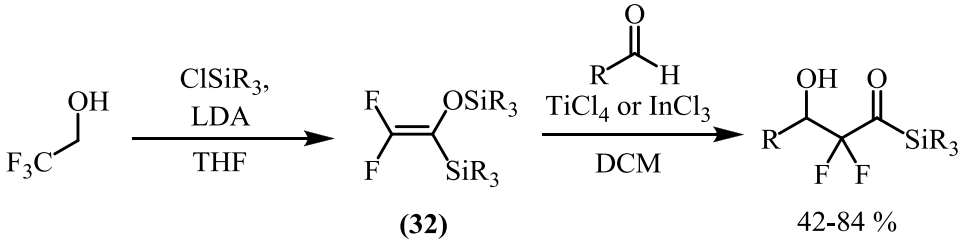
Difluoroenoxysilanes **(31)** were first synthesised by Xu in the reaction of trifluoroacetyltriphenylsilane with organolithium reagents.[49] Uneyama reported the generation of **(31)** from trifluoromethylketones in the reaction with magnesium and TMSCl in THF or DMF.[50] The same intermediate **(31)** was later generated *in situ* by Portella from trifluoromethyltrimethylsilane and trimethylsilyl ketone.[51,52] The difluorenoxysilane **(31)** reacted with ketones in the presence of $TiCl_4$ (1.5 equivalents) or $BF_3.OEt_2$ (1.2 equivalents) and typical yields were 58-78 % (Scheme 1.18). This methodology was later applied to the synthesis of the difluorinated derivatives of dihydroartemisin[53] and monoterpenes.[54]

Scheme 1.18 The reaction of difluoroenoxysilane with aldehydes.



Welch prepared difluorinated silyl enol ethers **(32)** in the reaction of 2,2,2-trifluoroethanol with LDA and chlorotrialkylsilanes and used them in a Lewis acid catalysed aldol reaction with aldehydes (Scheme 1.19).[55] Aromatic aldehydes gave slightly better yields than aliphatic aldehydes.

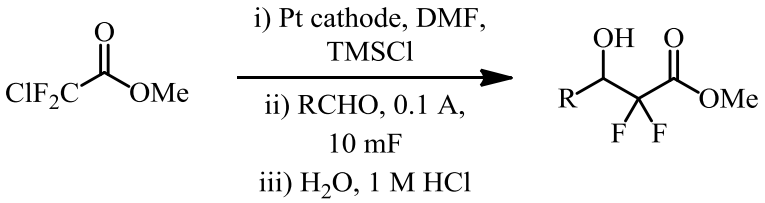
Scheme 1.19 The reaction of silyl enol ether with aldehydes.



1.3.5 Electroreductive aldol reaction with aldehydes

Shono *et al.* reported the electrochemical reactions between methyl chlorodifluoroacetate and various aldehydes (Table 1.15).[56] After the electrochemical cell was prepared, the chlorodifluoro ester and the aldehyde (5 equivalents) were mixed with chlorotrimethylsilane (3 equivalents) in DMF and an electric current was passed through the reaction vessel (0.1 A, 10 mF). Although the mechanism was not explained, Uneyama suggested that the silyl enol ethers were formed and reacted *in situ* with the aldehyde. The results in Table 1.15 show that the reactions with benzaldehyde and 2-butenal gave the product in 56 % and 38 % yields respectively, whereas the reactions with aliphatic aldehydes, which are usually less reactive, gave excellent yields of 81-91 %.

Table 1.15 Electroreductive reaction of methyl chlorodifluoroacetate with aldehydes.[56]



Run	Aldehyde	Conditions	Yield [%][a]
1	n-C_3H_7CHO	5 mmol of chlorodifluoroacetate, 25 mmol of aldehyde, 15 mmol of TMSCl, 10 mF, 0.1 A	91
2	i-C_3H_7CHO		81
3	$CH_3CH=CHCHO$		38
4	PhCHO		56

[a] Isolated yields.

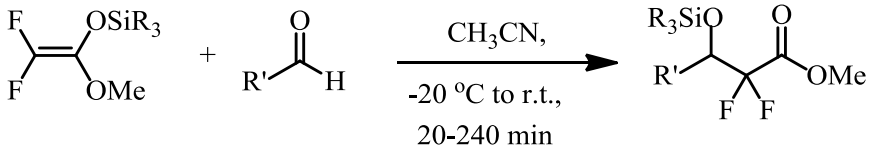
1.3.6 Diastereoselective aldol reaction with aldehydes

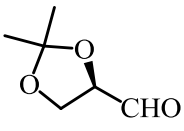
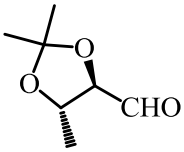
In 1988 Kitagawa *et al.* reported not only the aldol reaction with achiral aldehydes and ketones but also with chiral substrates.[33] The reactions with (*D*)-glyceraldehyde acetonide (Table 1.16, entries 1 and 2) showed a 1:9 (syn/anti) diastereoselectivity which was much higher than the same reaction with the fluorinated Reformatsky reagent (Scheme 1.13).

The aldol reaction of the difluorinated aluminium enolate reported by Curran, was also conducted with chiral substrates (Table 1.17).[47] The optimised reaction conditions enabled *N*-Boc-γ-amino-α,α-difluoro-β-hydroxy ester to be obtained (entry 1)

in 64 % yield with only a low diastereoselectivity (anti:syn=3:2). Although the aldehydes from entries 2 and 3 were used as racemic mixtures, the anti:syn diastereomeric ratio obtained for the Boc protected species was 1.4:1.

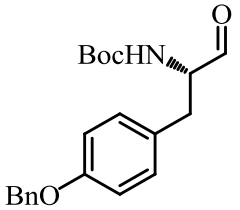
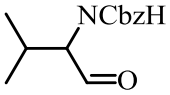
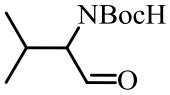
Table 1.16 Reaction of 2,2-difluoroketene silyl acetal with chiral substrates.[33]



Run	Substrate	R	Conditions	Yield [%][a]	De [%]
1		Me[b]	CH_3CN, 30 min, -20 °C	46	1:9
2		Et	CH_3CN, 20 min, 0 °C	74	1:9
3		t-BuMe_2	CH_3CN, 20 min, 0 °C	58	Not reported
4		Et	CH_3CN, 40 min, 0 °C	90	1:17

[a] Isolated yield, [b] the product was hydrolysed to alcohol.

Table 1.17 Ethyl *α,α*-difluoro-*β*-hydroxyesters prepared by the modified Reformatsky reaction.[47]

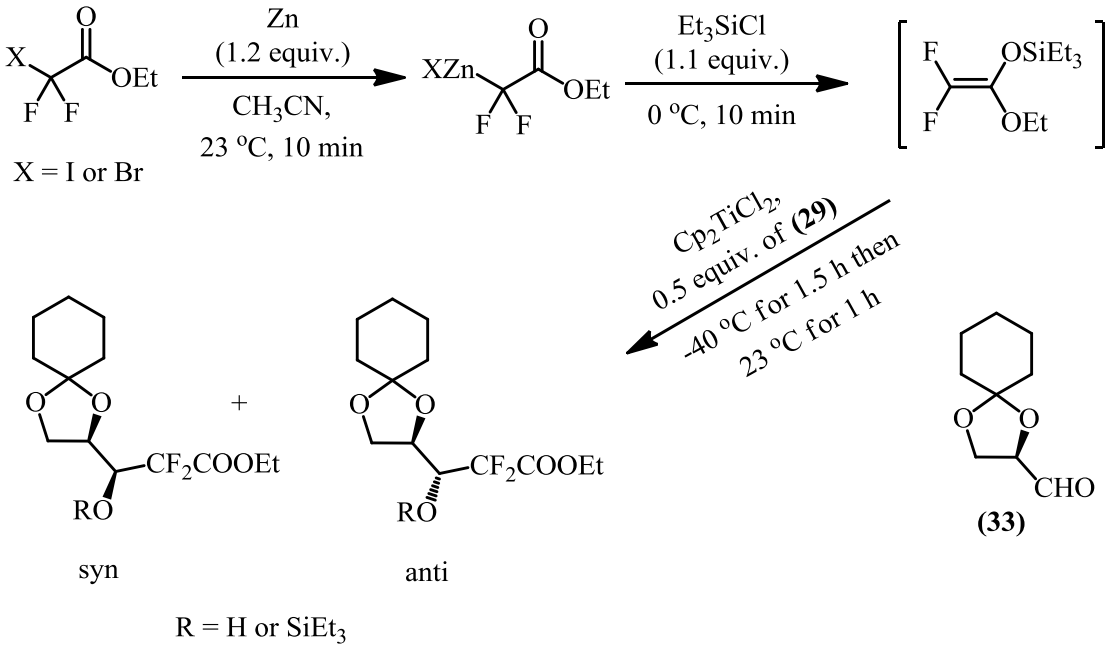
Run	Substrate	Yield [%][a]	Anti:syn
1		64	3:2
2[b]		55	1:1
3[b]		54	1.4:1

[a] Isolated yield, [b] racemic mixture.

High diastereoselectivity in the fluorinated aldol reaction between 2,2-difluoro enol silyl ether with 2,3-*O*-cyclohexylidene-*D*-glyceraldehyde **(33)**, promoted by a

titanium Lewis acid catalyst was described by Matsumura and co-workers (Scheme 1.20).[57] The Reformatsky reagent was generated in CH_3CN at room temperature by the reaction of the iodo or bromo derivative of ethyl difluoroacetate with activated zinc dust. After adding chlorotriethylsilane, a mixture of *D*-glyceraldehyde **(33)** and catalyst were added to the reaction mixture.

Scheme 1.20 Yields of *α*,*α*-difluoro-*β*,*γ*-dihydroxyesters obtained in presence of different Lewis acid catalysts.



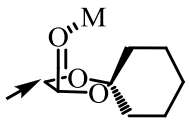
The diastereoselectivity and yield were improved by using the right choice of Lewis acid catalyst (Table 1.18, entries 7-10). Significantly, when the catalyst was used in substoichiometric amounts (0.1 equivalent), it was almost as effective as when 1.1 equivalents were used. Results obtained in the reaction with ethyl bromodifluoroacetate gave slightly higher yields and a similar level of diastereoselectivity to the results obtained with iododifluoroacetate (entries 9 and 10 versus 7 and 8). Apart from the above mentioned *D*-glyceraldehyde, two other chiral aldehydes (2,3-*O*-isopropylidene-*D*-glyceraldehyde and 2,3-*O*-dibenzyl-*D*-glyceraldehyde) were also tested but gave products with only diastereomeric excesses of up to 80 %. It was suggested by the authors that the *anti* product was obtained preferentially, as the Reformatsky reagent attacked from the less hindered (*Si*) face of the aldehyde (Figure 1.6).

Table 1.18 Yields of *α*,*α*-difluoro-*β*,*γ*-dihydroxyesters obtained in presence of different Lewis acid catalysts.[57]

Run	X [a]	Lewis acid	Conditions	R [b]	Yield[c] [%]	Anti:syn[d]
1	I	None	40 min at 0 °C	Et_3Si	60	85:15
2	I	BF_3*OEt_2	1 h at -40 °C	H	47	91:9
3	I	Me_2AlCl	20 min at -40 °C	H	80	78:22
4	I	Cp_2ZrCl_2	0.5 h at -40 °C then 1 h at 23 °C	H	41	83:17
5	I	Ti(O-*i*Pr)$_4$	1.5 h at -40 °C	H	50	78:22
6	I	$TiCl_4$	4 h at -40 °C	H	74	89:11
7	I	Cp_2TiCl_2	1 h at -40 °C then 1 h at 23 °C	Et_3Si	68	>95:5
8	I	Cp_2TiCl_2[e]	1 h at -40 °C then 1 h at 23 °C	Et_3Si	80	90:10
9	Br	Cp_2TiCl_2	1 h at -40 °C then 1 h at 23 °C	Et_3Si	84	>95:5
10	Br	Cp_2TiCl_2[e]	1 h at -40 °C then 1 h at 23 °C	Et_3Si	92	91:9

[a] Iodo or bromo derivative of ethyl difluoroacetate was used, [b] Type of product, [c] isolated yield, [d] determined by ^{19}F NMR spectroscopy, [e] 0.1 equivalent of catalyst was used.

Figure 1.6 Preferred transition state and direction of attack by the Reformatsky reagent.

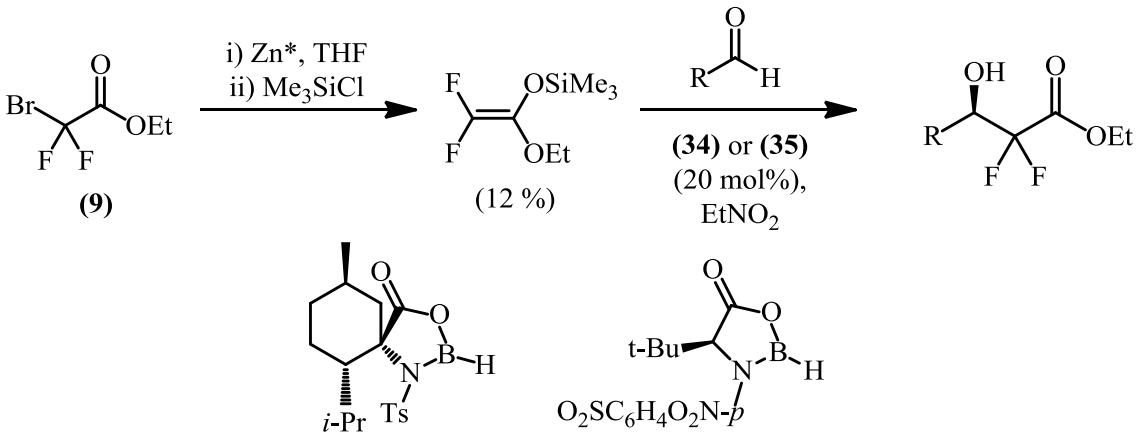


1.3.7 Enantioselective Mukayama's aldol reaction

The first, and so far only, asymmetric Mukayama-aldol reaction between difluoroketene ethyl trimethylsilyl acetal and aldehydes in the presence of a chiral catalyst (20 mol%) was reported by Iseki in 1997.[58,59] Difluoroketene ethyl trimethylsilyl acetal was generated in THF from activated zinc, ethyl bromodifluoroacetate and trapped with chlorotrimethylsilane (Table 1.19). Hence, the prepared reagent contained a zinc salt which could act as an achiral Lewis acid catalyst and affect the enantioselectivity in the reactions with aldehydes. The salt was removed by a triple cycle of dilution in *n*-pentane, filtration and concentration *in vacuo*. After

distilling the oil under vacuum, the pure difluoroketene ethyl trimethylsilyl acetal was reacted with the aldehyde in nitroethane at a range of temperatures (-20 to -78 ^{o}C) for 1-2 h in the presence of either Masamune's catalyst **(34)** or an analogue of Kiyooka's catalyst **(35)**, that was chosen from a range of catalysts reported in the non-fluorinated version of the reaction.

Table 1.19 Enantioselective Mukayama's aldol reaction with chiral boron catalysts.[59]



Entry	Aldehyde	Catalyst	Temp. [^{o}C]	Optical rotation	Yield[a] [%]	ee[b] [%]
1	PhCHO	**(30)**	-78	(-)	99	97 (*R*)
2	PhCHO	**(31)**	-20	(-)	96	65 (*R*)
3	*c*-$C_6H_{11}CHO$	**(30)**	-78	(+)	87	76
4	*c*-$C_6H_{11}CHO$	**(31)**	-45	(+)	97	94
5	$CH_3CH_2CH_2CHO$	**(30)**	-78	(+)	91	97
6	$CH_3CH_2CH_2CHO$	**(31)**	-45	(+)	90	94

[a] Isolated yields, [b] determined by HPLC.

The reaction gave excellent yields and moderate to excellent enantiomeric excesses with a range of aromatic and aliphatic aldehydes (Table 1.19). Interestingly, as indicated by the results in Table 1.20, the procedure using Masamune's catalyst **(34)** enabled both enantiomers to be obtained by changing the reaction temperature. The reaction with cyclohexanecarboxaldehyde (Table 1.20, entries 4 and 5) at -78 ^{o}C yielded 87 % of the (+)-enantiomer (76 % ee) whilst when the same reaction was run at -45 ^{o}C the (-)-enantiomer (92 % ee) was obtained in 90 % yield. One possible explanation of the reversal of the optical rotation, proposed by the authors, is that at temperatures ≤-60

^{o}C the difluorinated acetal attacks on the *si* face of the aldehydes, whereas at ≥-45 ^{o}C the preferred reaction is on the *re* face. The fluorine-free silyl acetal did not show reversal of the optical activity, only a decrease in the enantiomeric excess was obtained with an increase in the temperature. *Ab initio* molecular orbital calculations showed that the non-fluorinated acetal is planar (the silicon and methyl groups lie on the same plane as the double bond), whereas the fluorinated equivalent is not planar and this could explain their differences in behaviour.

The main disadvantage of this protocol is the inconvenient purification step of the difluoroketene ethyl trimethylsilyl acetal, which was obtained in only 12 % yield, and a low enantioselectivity was obtained if the catalyst was used in concentrations lower than 20 mol%.[59]

Table 1.20 Temperature dependence in the enantioselective Mukayama's aldol reaction with chiral boron catalyst **(34)**.[59]

Entry	Aldehyde	Temp. [^{o}C]	Yield[a] [%]	ee[b] [%]	Optical rotation
1	PhCHO	-78	99	97 (*R*)	(-)
2	PhCHO	-45	94	33 (*S*)	(+)
3	PhCHO	0	80	32 (*S*)	(+)
4	*c*-C_6H_{11}CHO	-78	87	76	(+)
5	*c*-C_6H_{11}CHO	-45	90	92	(-)

[a] Isolated yields, [b] determined by HPLC.

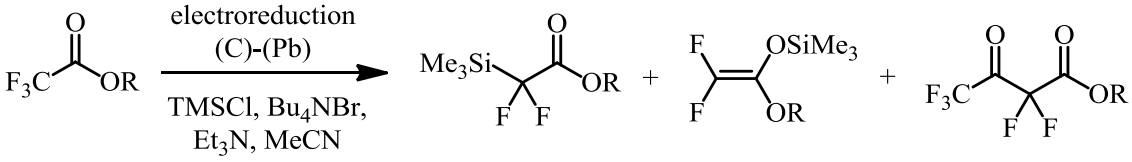
1.3.8 The reaction of trimethylsilyl-*α,α*-difluoroacetate ester with aldehydes

Since the trimethylsilyl group in ethyl-2,2-difluoro-2-(trimethylsilyl)acetate is located on the carbon atom, it is much more stable than the fluorinated Reformatsky reagent or the difluorosilyl enol ether, and can be isolated and stored for a long time. However, a catalytic amount of fluoride is required to create the CF_2-carbanion that will react with the carbonyl group.

In 1999 Stepanov conducted an electroreductive synthesis of ethyl pentafluoroacetoacetate and he also reported that ethyl 2,2-difluoro-2-(trimethylsilyl)acetate was obtained as a co-product in 10-20 % yield.[61] In the same year Uneyama described the electrosynthesis of different *α*-trimethylsilyl-*α,α*-difluoroacetates. Acetonitrile was used as the solvent in an H-divided cell equipped with

carbon and lead electrodes.[62] Chlorotrimethylsilane (4.0 equivalents) was reacted with different esters of trifluoroacetic acid (Table 1.21) in the presence of Et_3N (4 equivalents) and Bu_4NBr (2.4 equivalents) at 50 ^oC. After passing an electric current (80 mA cm^{-2}, 2 F mol^{-1}) through the cell, the silyl enol ether **(37)** was formed initially as the kinetic product and then under the reaction conditions it was transformed to the desired product **(36)**. The reaction yielded predominantly **(36)** with no indication of the silyl enol ether, and less than 1 % of the Claisen product **(38)** was obtained. The results also exhibited that the reaction is temperature dependant (entry 4) and that chlorotrimethylsilane must be used in a large excess (entry 2). The disadvantage of this protocol is that the conversion was limited by the passivation of the electrodes and that the best yield was obtained with an ester that is not commercially available. Hexyl 2,2-difluoro-2-(trimethylsilyl)acetate (entries 3 and 4) was then used in the reaction with benzaldehyde (Scheme 1.21) in THF at -78 ^oC catalysed by fluoride (tetrabutylammonium fluoride) to give hexyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate in 82 % yield.

Table 1.21 Electrochemical synthesis of α-trimethylsilyl-α,α-difluoroacetates.[62]

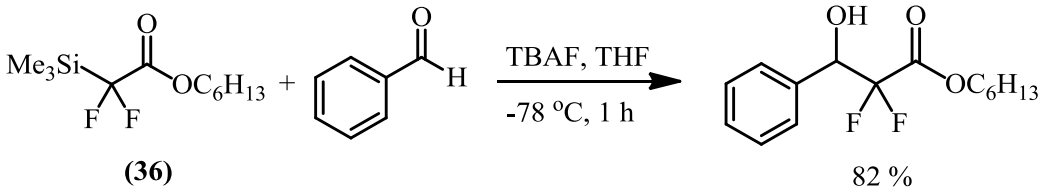


(36) **(37)** **(38)**

Entry	R	Conditions	Yield[a] of (36) [%]	Yield[a] of (37) [%]
1	Et	50 ^oC	47 (65)	0
2	Et	0 ^oC, 1 equiv. of TMSCl	<5	0
3	*n*-C_6H_{13}	50 ^oC	62 (68)	0
4	*n*-C_6H_{13}	0 ^oC	41	(18)
5	Bu^t	50 ^oC	58 (68)	0

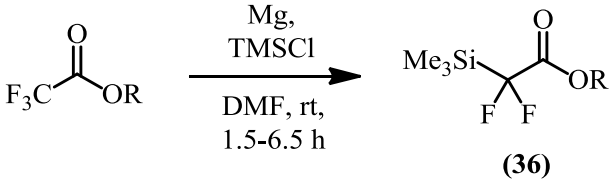
[a] Isolated product (conversion determined by ^{19}F NMR spectroscopy in parenthesis).

Scheme 1.21 Reaction of *α*-trimethylsilyl-*α*,*α*-difluoroacetate with benzaldehyde.



Later Uneyama showed that *α*-trimethylsilyl-*α*,*α*-difluoroacetate esters can be obtained by the reduction of phenyltrifluoroacetate with a mixture of magnesium and chlorotrimethylsilane in DMF.[63] The pure product was obtained in a 66 % yield after Kugelröhr distillation. The reaction was tested with different esters but unfortunately it did not work with any of the commercially available esters (Table 1.22). Another disadvantage of this protocol is that a large excess of magnesium (8 equivalents) and chlorotrimethylsilane (16 equivalents) is required.

Table 1.22 Synthesis of *α*-trimethylsilyl-*α*,*α*-difluoroacetate.[63]



(36)

Entry	R	Time	Yield [%][a]
1	C_6H_{13}	24	0[b]
2	Ph	2.5	66
3	4-$MeOC_6H_4$	6.5	64
4	4-MeC_6H_4	4.5	56
5	4-ClC_6H_4	1.5	55

[a] Isolated yield, [b] complete recovery of the starting material.

An efficient protocol for the synthesis of trimethylsilyldifluoro esters starting from commercially available ethyl chlorodifluoroacetate was described by Biran and co-workers.[64] The relatively cheap ester reacted with chlorotrimethylsilane under electroreductive conditions in THF (HMPA, DMPU were used as co-solvent) to yield ethyl trimethylsilyldifluoroacetate **(36)** in 81-85 % yield. A Claisen type product **(39)** was also generated in 10-15 % (Scheme 1.22) but was easily removed by vacuum distillation to give the pure product in 70 % yield. The ethyl *α*-trimethylsilyl-*α*,*α*-

difluoroacetate was then reacted with a number of aldehydes and ketones (Table 1.23) in DMF using a catalytic amount of KF (0.05 equivalent) for desilylation. The aromatic aldehydes gave slightly higher yields (85 %) than the aliphatic aldehydes (73-74 %) and the yields were lower with ketones. Again, aromatic ketones reacted better than aliphatic ketones. Only the products of the reaction with cyclohexanone and 5-methylhexan-3-one were isolated and for the rest of the reactions conversions were determined by ^{19}F NMR spectroscopy. There are no examples of diastereoselective or enantioselective reactions of *α*-trimethylsilyl-*α,α*-difluoroacetate.

Scheme 1.22 Electrosynthesis of ethyl *α*-trimethylsilyl-*α,α*-difluoroacetate from ethyl chlorodifluoroacetate.

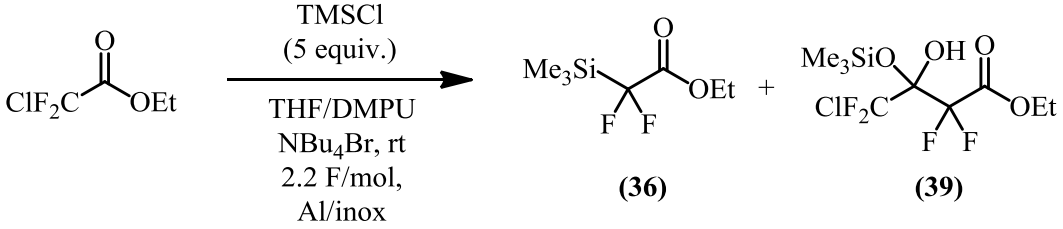
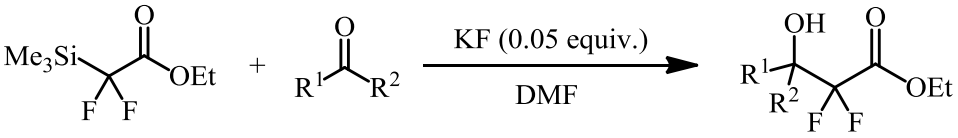
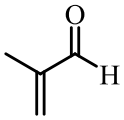


Table 1.23 Reaction of ethyl *α*-trimethylsilyl-*α,α*-difluoroacetate with aldehydes catalysed by fluoride.[64]



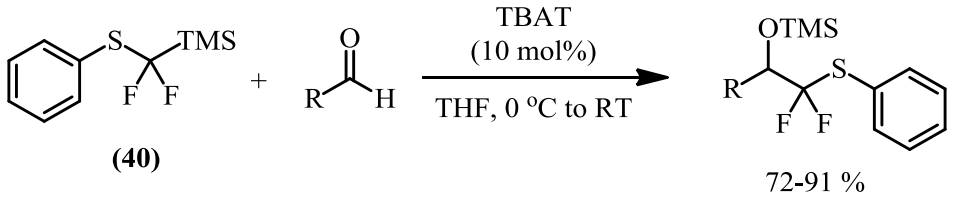
(36)

Entry	Substrate	Conversion[a] [%]
1	PhCHO	85
2	$(CH_3)_2CHCHO$	74
3		73
4	$PhCOCH_2CH_3$	60[b]
5	cyclohexanone	50
6	$(CH_3)_2CHCOCH_2CH_3$	38[b]

[a] Determined by ^{19}F NMR spectroscopy, [b] isolated yield.

Prakash reported recently that [difluoro(phenylthio)methyl]trimethylsilane (TMS-CF_2SPh) **(40)**, which was easily obtained from bromodifluoromethylphenyl sulphide and chlorotrimethylsilane in 85 % yield, was successfully used in the nucleophilic addition to a range of aldehydes. The reaction was promoted by 10 mole% of tetrabutylammonium triphenyldifluorosilicate (TBAT) and was performed in THF under mild conditions (Scheme 1.23).[65]

Scheme 1.23 The reaction of [difluoro(phenylthio)methyl]trimethylsilane (TMS-SF_2SPh) with aldehydes.



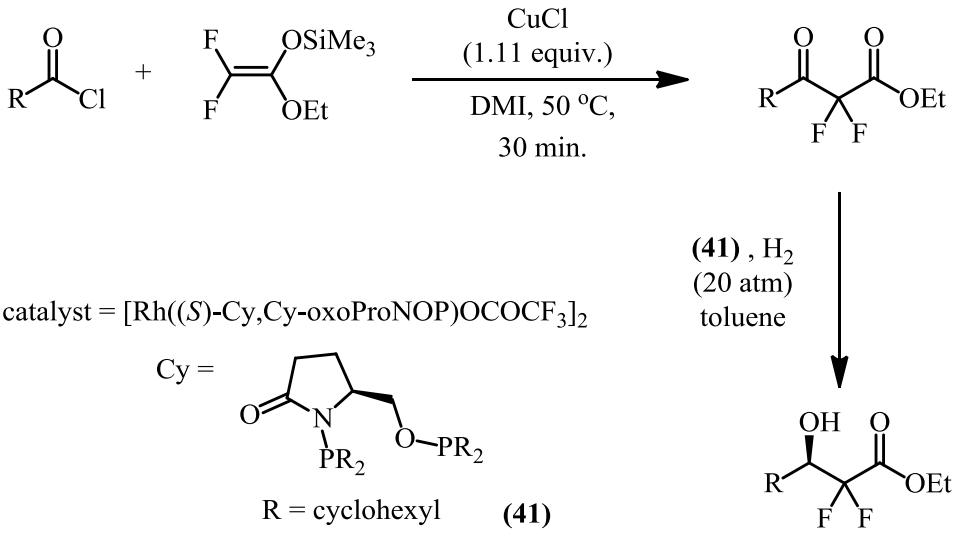
(40)

72-91 %

1.4 Enantioselective rhodium-catalysed hydrogenation of 2,2-difluoro-3-oxocarboxylates

Since the very high conversions and enantioselectivities obtained in the asymmetric Mukayama aldol reactions with aldehydes[58,59] were limited by the low yield in the difluorinated acetal purification step, and required the use of large amounts of the chiral boron catalysts, Iseki decided to try a different synthetic route.[60] 2,2-Difluoro-3-oxocarboxylates underwent hydrogenation in the presence of chiral catalysts that promote the asymmetric hydrogenation of *β*-keto esters yielding 2,2-difluoro-3-hydroxycarboxylates. A chiral catalyst [Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$ **(41)** was used with a range of aliphatic substrates (Table 1.24) yielding good to excellent yields (63-100 %) and high enantiomeric excesses (92-96 % ee) but the hydrogenation of the aromatic substrate obtained from benzoyl chloride gave 97 % conversion and only 84 % enantiomeric excess.

Table 1.24 Asymmetric hydrogenation of 2,2-difluoro-3-hydroxycarboxylates using $[Rh((S)\text{-Cy,Cy-oxoProNOP})OCOCF_3]_2$.[60]



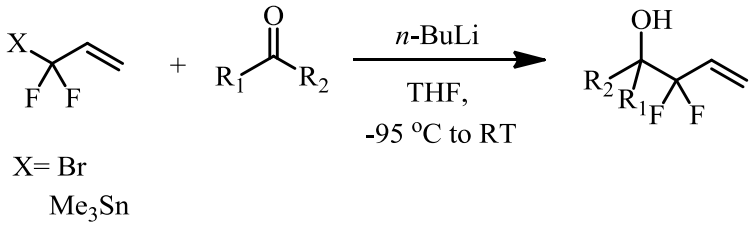
Entry	R	Conditions	Yield[a] [%]	Ee[b,c] [%]
1	CH_3	30 °C, 20 h	93	96 (*R*)
2	$(CH_3)_2CHCH_2$	70 °C, 20 h	95	92 (*R*)
3	Ph	30 °C, 20 h	97	84 (*R*)
4	$PhCH_2$	30 °C, 20 h	63	94 (*R*)
5	$PhCH_2CH_2$	30 °C, 20 h	100	96 (*R*)
6	$PhCH_2OCH_2$	30 °C, 20 h	95	95 (*R*)

[a] Isolated yields, [b] determined by HPLC, [c] the absolute configuration was determined by modified Mosher's method.

1.5 Reaction of difluoroallyl moiety with carbonyl substrates

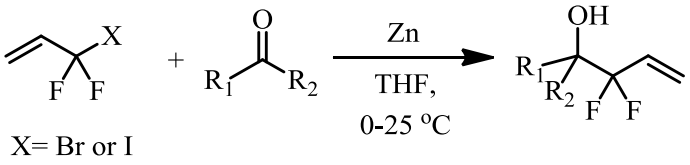
The reaction of the difluoroallyl moiety with carbonyl substrates was reported as a convenient method for the introduction of the CF_2 group and a functional group that is available for further synthesis. Seyferth and Strausz reported the reaction of *gem*-difluorinated allyllithium with aldehydes and ketones. The allyl lithiate was formed *in situ* either by the reaction of *n*-butyl lithium with either 3-bromo-3,3-difluoroprop-1-ene or difluoroallyltrimethyltin (Scheme 1.24).[66-68] The reaction gave good results (59-95 % yield) with aromatic and aliphatic aldehydes and ketones, but only moderate 20 % yield with an *α,β*-unsaturated aldehyde. In this case 51 % of the product was identified as a result of the addition of the *n*-butyl anion to the carbonyl group.

Scheme 1.24 The reaction of difluoroallyl lithiate with aldehydes and ketones.



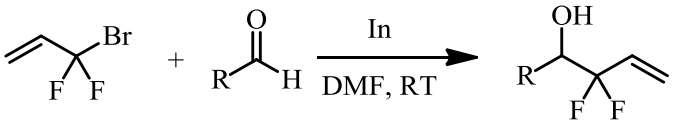
Hiyama found that *α*,*α* and γ,γ-difluoroallylsilanes obtained from 3,3,3-trifluoropropene reacted with carbonyl compounds at room temperature if activated by substoichiometric amounts of KO^{t}Bu or TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate).[69, 70] High yields were obtained with aromatic aldehydes, but only moderate yields were obtained with ketones, aliphatic aldehydes and *α*,*β*-unsaturated aldehydes. Burton found that the same product could be obtained in the reaction of carbonyl substrates with 3-bromo- or 3-iodo-3,3-difluoropropene in the presence of zinc dust (Scheme 1.25).[71,72] Other metals like tin, cadmium and manganese were also found to be capable of promoting the reaction, but the application of zinc was the most convenient protocol. The reaction was carried out in THF at 0-25 °C and gave moderate to good yields with a variety of aldehydes and ketones.

Scheme 1.25 *gem*-Difluorination of aldehydes and ketones.



Momose reported the indium-mediated reaction of 3-bromo-3,3-difluoropropene **(42)** with aldehydes (Table 1.25).[73,74] The reaction was run in either DMF or water at room temperature and high conversions were obtained with a range of aromatic and aliphatic aldehydes (runs 1-4). The only slightly lower 87 % yield was obtained in the case of a more hindered substrate (run 5). When 3-bromo-3,3-difluoropropene **(42)** was reacted with benzaldehyde in THF, only a moderate 33 % yield was obtained. In the reaction with a starting material that contained both a ketone and aldehyde group, the reaction of **(42)** occurred at the aldehyde (run 6).

Table 1.25 Indium-mediated reaction of 3-bromo-3,3-difluoropropene with aldehydes.[74]



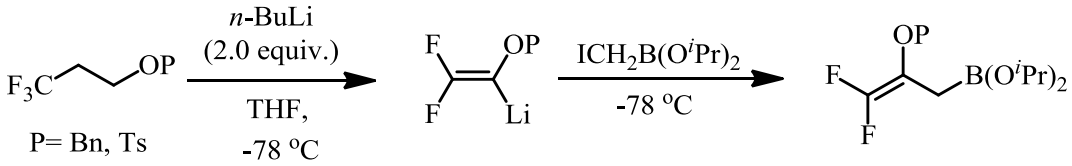
(42)

Entry	R	Yield[a] [%]
1	C_6H_5	99 (100)
2	*p*-OH-C_6H_4	97
3	*p*-Br-C_6H_4	95
4	$CH_3(CH_2)_7$	93 (100)
5	$PhCH(CH_3)$	87
6	$PhCO(CH_2)_4$	77

[a] Isolated yield (yield obtained in the reaction run in water is reported in parenthesis)

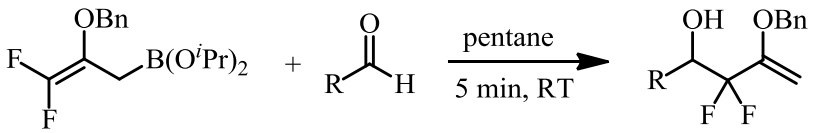
Ramachandran reported the reaction of *γ*,*γ*-difluoroallylboranes with aldehydes (Table 1.26).[75] Allylboronates **(43)** were formed in two steps from benzyl or tosyl protected 3,3,3-trifluoropropan-1-ol (Scheme 1.26). The reaction of benzaldehyde added to the unpurified **(43)** gave 45 % of the desired product. This was later improved to 82 % by using the distilled allyl boronate **(43)** (Scheme 1.27). All of the screened aldehydes gave high yields in very short reaction times. Only in the case of the sterically hindered pivalaldehyde (run 5) was the reaction time extended to 30 hours in order to obtain complete conversion.

Scheme 1.26 Preparation of *γ*,*γ*-difluoroallylboranes.



(43)

Scheme 1.27 Difluoroallylboration of aldehydes.



(43)

Table 1.26 Difluoroallylboration of aldehydes.[75]

Entry	R	Yield[a] [%]
1	C_6H_5	82
2	*p*-MeO-C_6H_4	88
3	*p*-NO_2-C_6H_4	76
4	CH_3	85
5	$(CH_3)_3C$	85
6	CF_3	75

[a] Isolated yield.

1.6 Conclusions and research objectives

The Reformatsky reaction is a convenient method for making *α*,*α*-difluoro-*β*-hydroxy esters and has been applied to the synthesis of a number of medicinally important target compounds such as gemcitabine. However, its applications are limited by inconvenient zinc activation such as refluxing or microwave irradiation.[41] Since there have been no reports of the asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with ketones, the initial aim of this project was to extend the protocol developed by Kumadaki (Table 1.7), which involves the reaction of ethyl bromodifluoroacetate with diethyl zinc in the presence of Wilkinson's catalyst, to the asymmetric reaction with aldehydes and ketones in the presence of a chiral aminoalcohol such as *N*-methylephedrine. If successful, this new method would also be extended to imines in order to develop the first enantioselective synthesis of *α*,*α*-difluoro-*β*-amino esters.

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Chapter Two

The Asymmetric Reformatsky reaction of Ethyl Bromodifluoroacetate with Benzaldehyde

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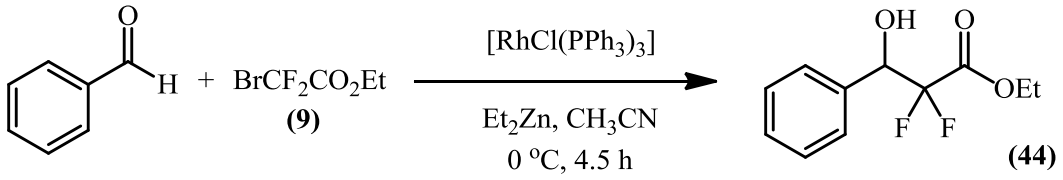
2.1 Introduction

The aim of the work in chapter two was to investigate whether Kumadaki's convenient one-pot reaction could be developed into an asymmetric Reformatsky reaction with benzaldehyde and ethyl bromodifluoroacetate by simply incorporating a chiral aminoalcohol. The chiral auxiliary, (1*S*,2*R*)-*N*-methylephedrine **(26)**, was chosen because it is relatively cheap, has been used in similar work to give good enantioselectivity (up to 84 % ee)[1,2] and can be recovered and reused. The chiral reactions in Tables 2.2, 2.3, 2.4, 2.6 (only runs with 1.0 and 0.2 equivalents of the chiral ligand) and Table 2.7 run 1 were run in duplicate).

2.2 Synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate

Kumadaki's one-pot protocol was used to synthesise and fully characterise ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)**.[3] Benzaldehyde, Wilkinson's catalyst (1 mole %) and ethyl bromodifluoroacetate **(9)** were mixed in acetonitrile at 0 ^{o}C. Diethylzinc was added in order to generate the fluorinated Reformatsky reagent *in situ* and the reaction was stopped after 4.5 h (Scheme 2.1). Under these reaction conditions, there was a 100 % conversion to ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** and the product was purified by column chromatography. This was a much more convenient method for synthesising the fluorinated Reformatsky reagent than the normal procedure, which involves refluxing ethyl bromodifluoroacetate **(9)** over activated zinc.

Scheme 2.1 Reaction of ethyl bromodifluoroacetate with benzaldehyde.



Since the role of Wilkinson's catalyst was uncertain, the reaction was repeated without the addition of the rhodium catalyst to the reaction mixture. Under these reaction conditions, there was a 91 % conversion to ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)**, demonstrating that Wilkinson's catalyst is not required to promote the formation of the fluorinated Reformatsky reagent.

The purified compound **(44)** was then used to develop methods for separating the two enantiomers in order to determine the enantiomeric excess for when the reaction was carried out in the presence of a chiral ligand. Two different analytical techniques were used. Initially, compound (**44)** was dissolved in a pre-mixed solution of an NMR shift reagent, diisopropyl l-tartrate, with chloroform and ^{19}F NMR spectroscopy was used to integrate the fluorine signals from the two enantiomers.[4] Chiral HPLC was also used to separate the two enantiomers of **(44)** and an AS column was used with 10 % isopropanol in hexane as the eluting solvent. However, the main disadvantage of the latter technique is that, unlike the ^{19}F NMR spectroscopy, only the pure product can be tested, meaning that every reaction mixture must be purified by column chromatography before the enantioselectivity can be determined.

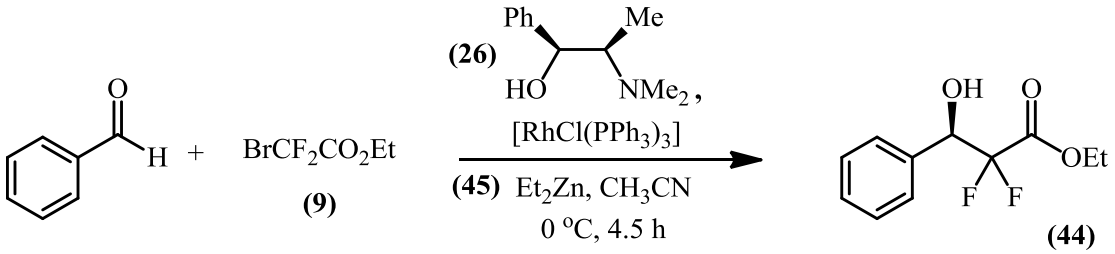
2.3 Asymmetric synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate with diethylzinc and *N*-methylephedrine

Initially, the asymmetric synthesis of ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate was investigated using the same reaction conditions as those in Kumadaki's work, except that *N*-methylephedrine was added. At first, there were difficulties in dissolving the chiral amino alcohol in acetonitrile, but this was because the *N*-methylephedrine was wet, and the problem was resolved by purifying the *N*-methylephedrine by Kugelröhr distillation. Benzaldehyde was also distilled under reduced pressure and was stored under nitrogen in a Schlenk flask. During the purification process the antioxidant added for stabilisation was removed and benzaldehyde became difficult to handle and oxidised easily to benzoic acid.

All of the reactions were conducted in a three neck round bottom flask at 0 ^{o}C. Wilkinson's catalyst was introduced as a solid which dissolved in the acetonitrile. After charging ethyl bromodifluoroacetate and benzaldehyde, the reaction mixture was stirred for 30 min at 0 ^{o}C before adding *N*-methylephedrine and diethylzinc. The reaction was run for 4.5 hours before quenching with dilute hydrochloric acid (1 M). All of the reactions which were run in the presence of *N*-methylephedrine yielded lower conversions and only low enantiomeric excesses, but the reactions yielded no by-products (Table 2.1). Although the amount of *N*-methylephedrine was varied at 0.8 (run 1), 1.0 (run 2) and 1.2 equivalents (run 4), in all cases, a similar level of enantioselectivity was obtained. In the absence of the rhodium catalyst in run 3, a lower

conversion and isolated yield was obtained compared to run 2, but the enantiomeric excess increased very slightly.

Table 2.1 Asymmetric reaction of ethyl bromodifluoroacetate with benzaldehyde in acetonitrile.



Run	$RhCl(PPh_3)_3$ [mol%]	(26)	(9)	(45)	Conversion[a]	Ee[b]
		[No. of equivalents]			[%]	[%]
1	1	0.8	1.5	2.0	78 (61)	34 (29)
2	1	1.0	1.5	2.1	79 (74)	37
3	0	1.0	1.5	2.1	67 (61)	41 (35)
4	1	1.2	1.5	2.2	66 (42)	37

[a] Determined by ^{1}H NMR spectroscopy, the isolated yield is in parenthesis; [b] ee was determined by chiral ^{19}F NMR spectroscopy, except values in parenthesis which were determined by chiral HPLC.

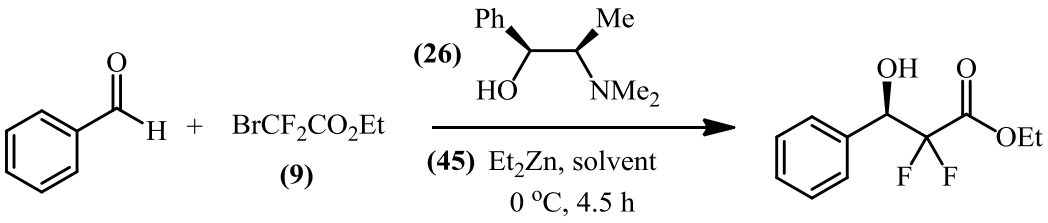
2.3.1 Screening different solvent systems

Since only low enantioselectivity was obtained in acetonitrile, a range of different solvent systems were screened for the asymmetric Reformatsky reaction with benzaldehyde (Table 2.2). All of the reactions were run for 4.5 h at 0 °C using *N*-methylephedrine (1.0 equivalent), ethyl bromodifluoroacetate (1.5 equivalents) and diethylzinc (2.1 equivalents). Since the diethylzinc was used to perform two different roles in this reaction, an excess of diethylzinc was used. Diethylzinc (1.5 equivalents) was reacted with ethyl bromodifluoroacetate (1.5 equivalents) in order to form the Reformatsky reagent *in situ* as well as being used to deprotonate the chiral aminoalcohol (0.5 equivalents of diethylzinc for each equivalent of *N*-methylephedrine). Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, was not used to promote any of these reactions.

The conversions to product were determined by either ^{1}H NMR spectroscopy or by GC using di-*p*-tolyl ether as the internal standard. Before the GC method was used, a series of samples containing a known amount of benzaldehyde, product and internal

standard were made. The samples were analysed by GC and the results were used to determine the error in this technique. The same series of samples were then eluted through a short silica gel column, in the same way that the real samples were purified during work up, to make sure that it had no impact on the final analysis (Appendix A1). Although lower conversions were often obtained by GC, it was a more accurate method than ^{1}H NMR spectroscopy. In determining the conversion by ^{1}H NMR spectroscopy, two signals, one from the aldehyde proton of the starting material and one from the product are integrated and the calculation does not take into account the amount of benzaldehyde that reacted to form other by-products like benzoic acid. In GC the calculation is more accurate because it is based on the amount of product compared directly to a known amount of the internal standard. The enantioselectivity was determined by chiral GC using a B-DM column.

Table 2.2 Screening different solvent systems.



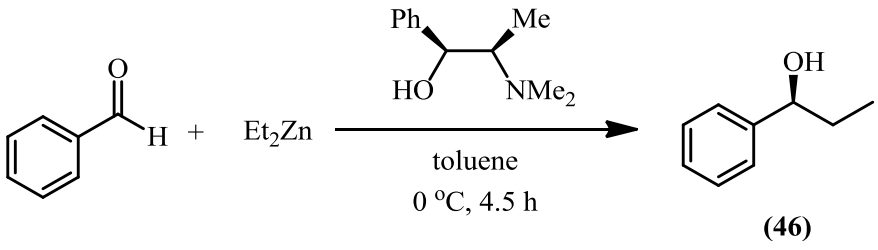
Run[a]	Solvent	Conversion[b] [%]	Ee[c] [%]
1	CH_3CN	67	35
2	THF	67 (54)	75 (69)
3[d]	THF	86 (81)	56
4[d]	Dioxane	76	60
5	THF/Dioxane	(60)	63
6	Et_2O	8 (7)	60
7	Hexane	~12[e]	65
8	DCM	46 (22)	42
9	Toluene	11	62

[a] In all reactions the ratio of **(26)**:**(9)**:**(45)** was 1.0:1.5:2.1, [b] conversion was determined by ^{1}H NMR spectroscopy or GC (in parenthesis), [c] ee was determined by chiral GC, except values in parenthesis which were determined by chiral HPLC, [d] reaction was run at room temperature, [e] affected by oxidation of benzaldehyde.

The reaction in THF (run 2) gave the highest enantioselectivity (69 % ee) and conversion (67 %). The reaction in dioxane (run 4) also proceeded well with an excellent conversion to product (76 %) though the reaction had to be conducted at room temperature due to the high melting point of dioxane (12 ^{o}C). Considering the higher reaction temperature, a good enantiomeric excess (60 %) was also obtained. When exactly the same reaction was repeated at room temperature using THF as the solvent (run 3), the conversion improved to 86 %, however, a slightly lower enantiomeric excess of 56 % was obtained. The higher enantioselectivity obtained when the reaction was performed in dioxane rather than THF at room temperature (runs 3 and 4) suggested that the use of a mixture of these two solvents at 0 ^{o}C could improve the enantiomeric excess. Unfortunately, this was not the case and the enantiomeric excess dropped to 63 % ee in run 5 with the conversion (60 %) being only slightly better than in THF (54 %).

Although reasonable enantioselectivities were obtained in diethyl ether and hexane (runs 6 and 7, 60-65 % ee), the conversions to the desired product were extremely low. A low conversion was also obtained in dichloromethane, but with even lower enantiomeric excess (42 %). In general, it was observed that better conversions were observed in polar solvents such as THF, dioxane and acetonitrile than in non-polar solvents.

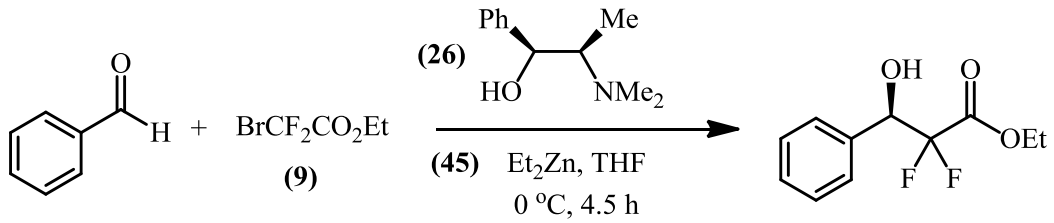
Scheme 2.2 Enantioselective addition of diethylzinc to benzaldehyde.



(46)

The reaction in toluene was extremely interesting because the major product **(46)** was formed by the nucleophilic addition of diethylzinc to benzaldehyde (Scheme 2.2) and not from the nucleophilic addition of the fluorinated Reformatsky reagent. Compound **(46)** was identified from the ^{1}H NMR spectrum of the crude reaction mixture by the characteristic signal for the single proton at 5.7 ppm (1H, dd, $^{3}J_{HH}$ 7.9 Hz, $^{3}J_{HH}$ 6.1 Hz, C(OH)*H*CH$_A$H$_B$).[5,6]

Table 2.3 The asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with and without Wilkinson's catalyst.



Run	$RhCl(PPh_3)_3$ [mol%]	(26) [No. of equivalents]	(9) [No. of equivalents]	(45) [No. of equivalents]	Conversion[a] [%]	Yield[b] [%]	Ee NMR	Ee HPLC	Ee GC
1	0	0	1.5	1.5	100	92			
2	1	0	1.5	1.5	94	57			
3	0	1.0	1.5	2.1	67 (54)	44	73	69	74
4	1	1.0	1.5	2.1	78	52	74	68	68
5	0	1.2	1.5	2.2	81	57	77	-	71
6	1	1.2	1.5	2.2	97	52	77	-	69
7	0	1.0	3.0	3.5	100	88	77	68	73

[a] Conversion was determined by either ^{1}H NMR spectroscopy or GC (in parenthesis), [b] isolated yield.

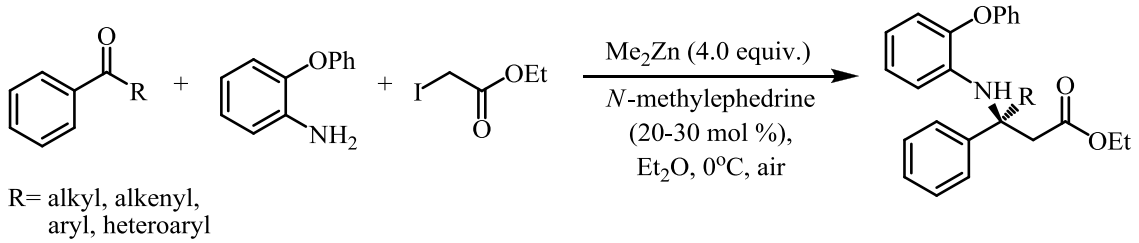
Since the reaction in THF gave the best results, the asymmetric Reformatsky reaction of ethyl bromodifluoroacetate was further investigated in THF in order to determine whether the reaction required Wilkinson's catalyst or not (Table 2.3). The initial runs (1 and 2) proved that Wilkinson's catalyst was not necessarily required for the formation of the Reformatsky reagent. Both reactions afforded excellent conversions. In runs 4 and 6, where 1.0 and 1.2 equivalents of *N*-methylephedrine were used, the presence of Wilkinson's catalyst improved the conversion suggesting it may increase the rate of formation of the Reformatsky reagent. With 1.2 equivalents of *N*-methylephedrine compared to 1.0 equivalent, the enantioselectivity was very similar but the conversion was better. Chiral GC and chiral HPLC are more reliable methods for determining the enantioselectivity than ^{19}F NMR spectroscopy. Interesting results were also obtained when the reaction was conducted without Wilkinson's catalyst with 3.0 equivalents of Reformatsky precursor yielding 100 % conversion and 88 % isolated yield, without loss of enantioselectivity. This result can be explained by the slow formation of the

Reformatsky reagent from ethyl bromodifluoroacetate and diethylzinc. Results of the reactions with (run 3) and without *N*-methylephedrine (run 1) suggest that the Reformatsky reaction is suppressed by the addition of the chiral ligand leading to ligand decelerated catalysis.

2.3.2 Screening the influence of oxygen and dimethylzinc

In 2005 Cozzi reported a highly enantioselective, one-pot, three component Reformatsky reaction with imines that were generated *in situ*. The Reformatsky reagent was formed from ethyl iodoacetate and dimethylzinc in the presence of nickel (II) salts.[7] Recently, the same author published results proving that the addition of air makes the zinc reagent more reactive, and therefore, the catalyst is no longer required to increase the rate of formation of the Reformatsky reagent (Scheme 2.3).[8] The addition of air was therefore examined for the reaction between diethylzinc and ethyl bromodifluoroacetate.

Scheme 2.3 Protocol developed by Cozzi.

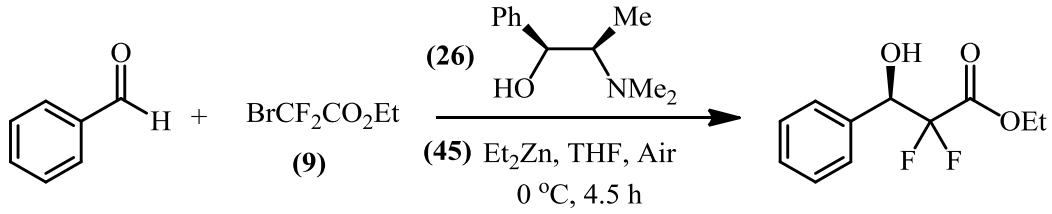


R= alkyl, alkenyl,
aryl, heteroaryl

After the addition of diethylzinc to the reaction mixture, the flow of inert gas was switched off and air was allowed to enter through a silica gel drying tube. For another 4.5 hours air replaced the nitrogen or argon in the reaction vessel. In run 1, where nitrogen was used as the inert atmosphere, a conversion of 96 % was obtained (Table 2.4). This is higher than in the reaction with Wilkinson's catalyst where only 78 % conversion was obtained (Table 2.3, run 4), however, only 38 % pure product was isolated suggesting that the reaction afforded a higher amount of co-products, making purification more difficult. In run 2 nitrogen was replaced by argon and a lower 54 % conversion and isolated yield (33%) was observed. Both values were lower than in the same reaction without air. The reaction was repeated with three equivalents of the Reformatsky reagent (Table 2.4, run 3) and 100 % conversion was confirmed, however, the reaction in an inert atmosphere was cleaner and the isolated yield was higher (Table

2.3, run 7). On comparing the enantioselectivity for all of the runs in Table 2.4 with those conducted under an inert atmosphere (Table 2.3) showed that similar levels of enantiomeric excess were obtained.

Table 2.4 Asymmetric reaction of ethyl bromodifluoroacetate with benzaldehyde with addition of air.

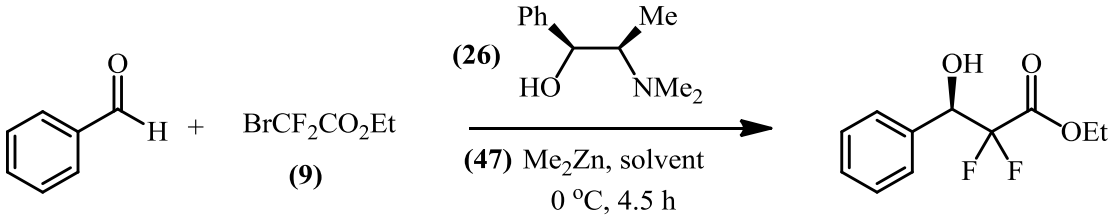


Run	Air/N_2 or Ar	(26) [No. of equivalents]	(9) [No. of equivalents]	(45) [No. of equivalents]	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	Air (N_2)	1.0	1.5	2.1	96	38	74 (75)
2	Air (Ar)	1.0	1.5	2.1	54	33	82 (70)
3	Air (Ar)	1.0	3.0	3.5	100	72	69 (67)

[a] Conversion was determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] ee was determined by chiral ^{19}F NMR spectroscopy, except values in parenthesis which were determined by chiral GC.

In all of Cozzi's work dimethylzinc was used and so the effect of using dimethylzinc instead of diethylzinc is summarised in Table 2.5. In run 1 the optimum conditions developed for diethylzinc were used with dimethylzinc but no product was visible by GC or by ^{1}H NMR spectroscopy. On using either 5 mol% of Wilkinson's catalyst or air to promote the reaction in runs 2 and 3 respectively, only traces of the desired product were observed. Finally, the reaction was attempted in toluene but none of the desired product was obtained, nor was the product resulting from the nucleophilic addition of Me_2Zn to benzaldehyde. Therefore, the use of dimethylzinc was abandoned since it was not sufficiently reactive.

Table 2.5 Asymmetric Reformatsky reaction mediated by dimethylzinc.



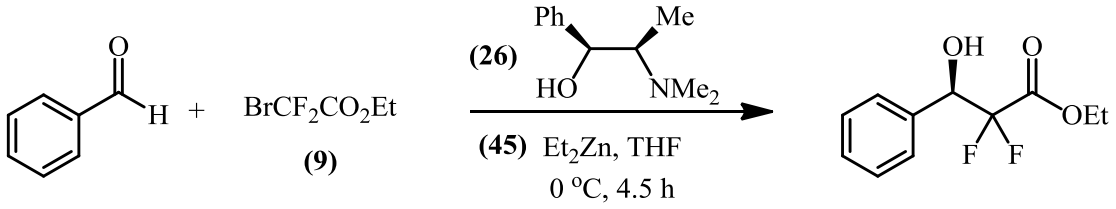
Run	Solvent	Catalyst [mol%]	(26) [No. of equivalents]	(9) [No. of equivalents]	(47) [No. of equivalents]	Conversion[a] [%]	Ee[b] [%]
1	THF	0	1.0	1.5	2.1	0	-
2	THF	Rh (5)	1.0	1.5	2.0	Trace	74
3	THF	Air	1.0	1.5	2.0	Trace	-
4	toluene	0	1.0	1.5	2.1	0	-

[a] conversion was determined by ^{1}H NMR spectroscopy and GC; [b] enantioselectivity was determined by chiral GC.

2.3.3 Investigating different ratios of the reagents

To develop the optimum ratio of reagents for the addition of the fluorinated Reformatsky reagent to benzaldehyde, a series of reactions with 0.2, 0.6, 1.0 and 1.4 equivalents of *N*-methylephedrine were conducted. Each series contained four different reactions. In the first reaction 1.5 equivalents of ethyl bromodifluoroacetate and 1.5 equivalents of diethylzinc were used. In the second set of conditions an extra amount of diethylzinc was added to deprotonate the chiral ligand as well as to form the Reformatsky reagent resulting in 1.5 equivalents of ethyl bromodifluoroacetate and (1.5 + 0.5 x *N*-methylephedrine) equivalents of diethylzinc. For example, with 1.4 equivalents of *N*-methylephedrine this resulted in 1.5 equivalents of ethyl bromodifluoroacetate and 2.2 equivalents of diethylzinc. In the third reaction the amount of Reformatsky reagent was increased to 2.1 equivalents and in the fourth run an excess of diethylzinc was used to enable deprotonation of the chiral ligand as well as formation of the Reformatsky reagent. The results for all of the reactions are summarised in Table 2.6 and Figure 2.1.

Table 2.6 Asymmetric Reformatsky reaction with benzaldehyde.



Run	(26)	(9)	(45)	Conversion[a]	Ee[b]
	[No. of equivalents]			[%]	[%]
1	0.2	1.5	1.5	50 (67)	56
2	0.2	1.5	1.6	54 (66)	57
3	0.2	2.1	2.1	94 (97)	45 (41)
4	0.2	2.1	2.2	99 (100)	45 (42)
5	0.6	1.5	1.5	51 (67)	70 (75)
6	0.6	1.5	1.8	71 (80)	67 (74)
7	0.6	2.1	2.1	94 (96)	66 (72)
8	0.6	2.1	2.4	95 (98)	60 (70)
9	1.0	1.5	1.5	37 (41)	68 (66)
10	1.0	1.5	2.1	56 (65)	69 (74)
11	1.0	2.1	2.1	82 (87)	67 (74)
12	1.0	2.1	2.6	92 (96)	65 (65)
13	1.4	1.5	1.5	0 (0)	-
14	1.4	1.5	2.2	27 (33)	68 (65)
15	1.4	2.1	2.1	25 (33)	70 (70)
16	1.4	2.1	2.8	60 (70)	64 (73)

[a] Conversion was determined by either GC or ^{1}H NMR spectroscopy (in parenthesis), [b] ee were determined by chiral HPLC, except values in parenthesis which were determined by chiral GC.

Similar to the results shown in Table 2.3, the conversion decreased as the amount of *N*-methylephedrine increased. In fact, the reactions conducted in the absence of a chiral ligand were complete after 4.5 hours, but when 0.2 equivalents of chiral ligand were added with 1.5 equivalents of the Reformatsky reagent (run 1), much lower conversions (50 %) were obtained. Such a dramatic drop in conversion was unexpected. Using the same reaction conditions with 0.6 equivalents of *N*-methylephedrine (run 5) gave very

similar conversions, however, it was found that higher amounts of *N*-methylephedrine slowed the reaction right down, and with 1.4 equivalents there were no traces of the desired product (run 13). Results with 2.1 equivalents of the Reformatsky reagent (black triangles Figure 2.1, runs 3, 7, 11 and 15 in Table 2.6) showed again that the conversion was lower when the amount of *N*-methylephedrine was increased, but the conversion increased when a larger excess of the Reformatsky reagent was used. By comparing reaction conditions 1 (blue diamond) with 2 (brown square) as well as conditions 3 (black triangle) with 4 (green circle), it can be seen that it is important to add an excess of diethylzinc in order to deprotonate the *N*-methylephedrine as well as to generate the Reformatsky reagent. Interestingly, the enantiomeric excess obtained with 0.6, 1.0 and 1.4 equivalents of *N*-methylephedrine was similar (entries 5-16). The highest enantioselectivity (69-70 %) was obtained with 1.4, 1.0 and 0.6 equivalents of chiral ligand but, the conversion depended on the amount of *N*-methylephedrine as well as the amount of the Reformatsky reagent that was used in the reaction and the ee dropped significantly when the amount of chiral aminoalcohol was reduced to 0.2 equivalents (run 1-4).

Figure 2.1 Equivalents of *N*-methylephedrine against conversion for asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with benzaldehyde.

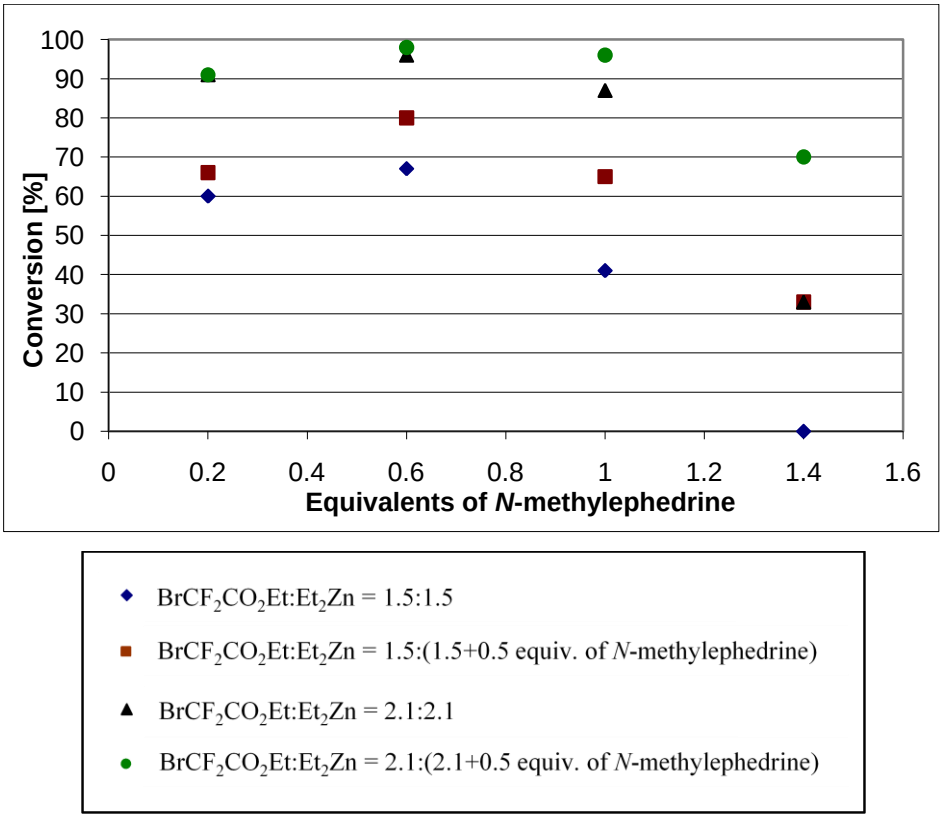
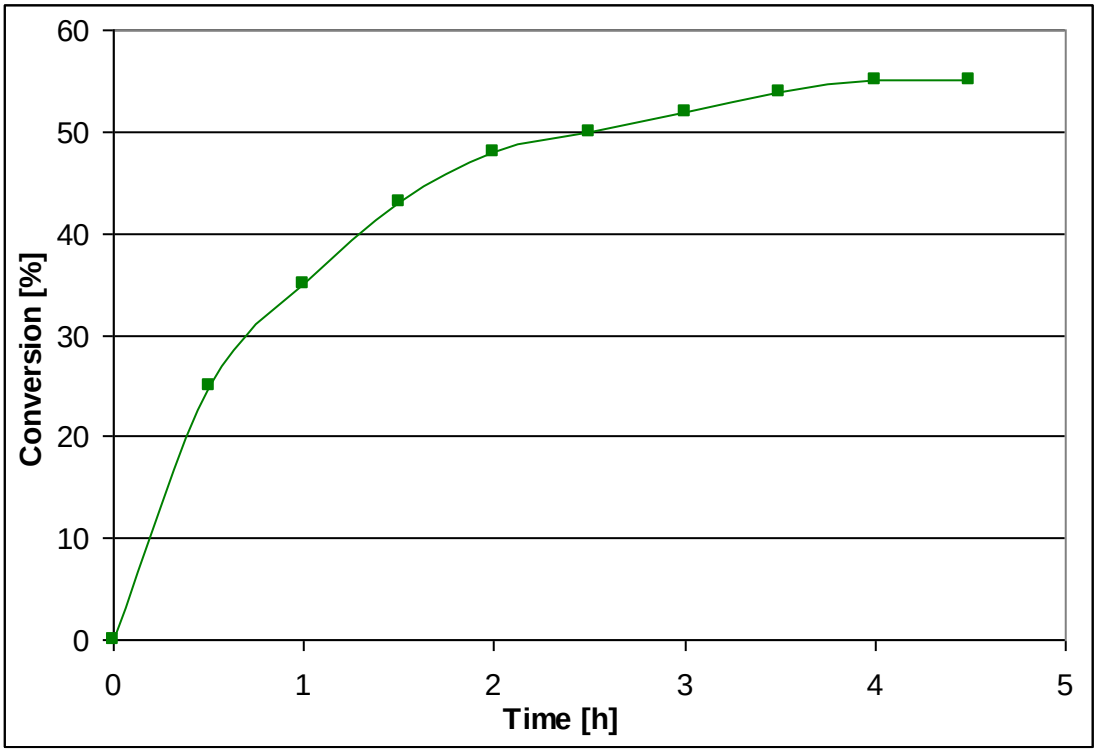


Figure 2.2 Monitoring of asymmetric Reformatsky reaction with benzaldehyde by GC.



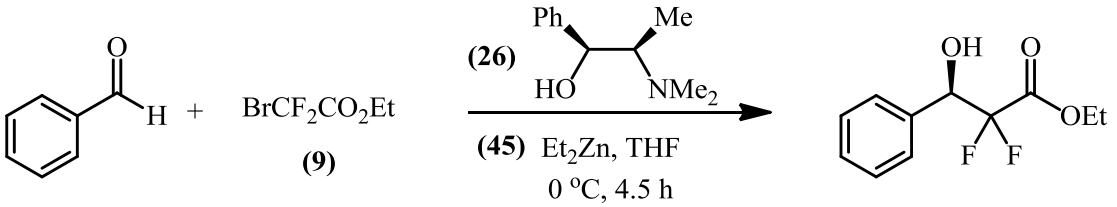
Using the standard reaction conditions of run 10 in Table 2.6, samples were taken every 30 minutes and were analysed by GC in order to monitor the yield of product over time (Figure 2.2). Although the reaction proceeded well over the first 2 hours to give a 48 % yield of desired product, the reaction then slowed down considerably to give a 55 % yield after 4 hours.

A final set of different reaction conditions were screened and the results are displayed in Table 2.7. When the reaction time was increased to 24 hours the yield of product increased slightly to 66 %. Since the reaction monitoring had shown clearly that the reaction rate was faster over the first two hours, the reaction was repeated at -10 ^{o}C in order to slow the reaction down. This resulted in a lower conversion (27 %), but a higher enantiomeric excess of 75 % (run 2). The low conversion was probably due to the slow formation of the Reformatsky reagent and only 8 % of the desired product was obtained at -20 ^{o}C (run 3), even though there was no *N*-methylephedrine present.

In a final attempt to improve the conversion, whilst maintaining the high enantioselectivity, a number of different addition protocols were investigated. In run 4 the diethylzinc was divided into two equal portions and the second portion was added after 2 hours resulting in a low 15 % conversion. *N*-Methylephedrine was mixed with diethylzinc before a solution of ethyl bromodifluoroacetate and benzaldehyde was

added slowly over 3 hours in run 5. The high enantioselectivity (70 % ee) was maintained but only a 38 % conversion was obtained. When the same protocol was repeated with a normal addition of *N*-methylephedrine and diethylzinc to a solution of ethyl bromodifluoroacetate and benzaldehyde, a similar result was obtained (run 6). Finally, using 0.6 equivalents of *N*-methylephedrine, the solution of diethylzinc was added dropwise over 1 hour. Again, the conversion dropped to 42 % but this time the enantioselectivity increased slightly to 71 % ee (compared to 67 % ee, run 6, Table 2.6). Since diethylzinc was normally used as a 1.0 M solution in hexane, run 8 investigated the effect of using a 1.0 M solution of diethylzinc in THF. The reaction yielded a similar level of enantiomeric excess (70 %) but a much lower conversion (13 %).

Table 2.7 Screening conditions for the asymmetric Reformatsky reaction with benzaldehyde.



Run	Temperature	(26)	(9)	(45)	Conversion[a]	Ee[b]
		[No. of equivalents]			[%]	[%]
1[c]	0 °C	1.0	1.5	2.1	66	68
2	-10 °C	1.0	1.5	2.1	27	75
3	-20 °C	0	1.5	1.5	8	-
4	0 °C	1.0	1.5	2.1	15	71
5	0 °C	1.0	1.5	2.1	38	70
6	0 °C	1.0	1.5	2.0	40	69
7	0 °C	0.6	1.5	1.8	42	71
8[d]	0 °C	1.0	1.5	2.1	13	70

[a] Conversion determined by GC, [b] enantiomeric excess determined by chiral HPLC, [c] 24 hours, [d] 1.0 M Et_2Zn in THF.

2.4 Conclusions

The first example of a convenient one-pot asymmetric Reformatsky reaction of ethyl bromodifluoroacetate using diethylzinc to generate the Reformatsky reagent homogenously and *N*-methylephedrine as the chiral auxiliary has been developed. The reaction did not work when diethylzinc was replaced by dimethylzinc. Under the optimum conditions using 1.5 equivalents of ethyl bromodifluoroacetate, 2.1 equivalents of diethylzinc and 1.0 equivalent of *N*-methylephedrine in THF at 0 ^{o}C for 24 h gave 66 % yield of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** with a 68 % enantiomeric excess.

Although Pedrosa reported a better enantiomeric excess (82 %) using the two-step asymmetric Reformatsky reaction with ethyl bromodifluoroacetate (3.0 equivalents), zinc dust and *N*-methylephedrine (1.0 equivalent) in THF at 0 ^{o}C,[2] a similar yield was obtained in the one-step protocol using half the amount of ethyl bromodifluoroacetate.

2.5 References

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Chapter Three

The Asymmetric Reformatsky reaction of Ethyl Iododifluoroacetate with Ketones

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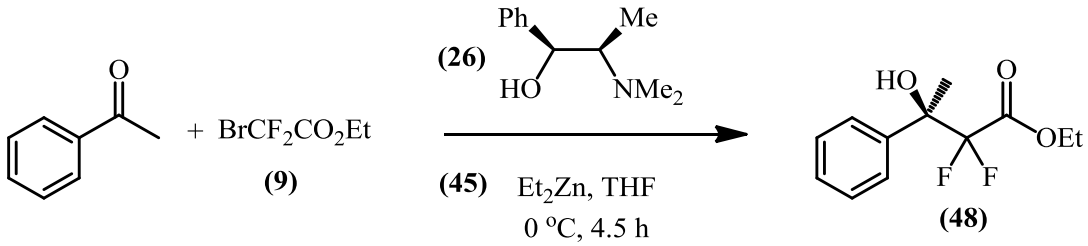
3.1 Introduction

Although the Reformatsky reaction of ethyl bromodifluoroacetate has been reported with ketones, there are no reports of carrying out this reaction enantioselectively. The aim of the work in this chapter was to develop a one-pot asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with ketones using *N*-methylephedrine as the chiral auxiliary starting from the optimised conditions that were developed in Chapter 2 from the work with benzaldehyde. All the chiral reactions reported in this chapter were carried out in duplicate, with an average of the two runs being reported. The usual difference in the conversion and the enantiomeric excess between these runs was less than 5 % and 2 % respectively.

3.2. Optimisation of the one-step procedure using diethylzinc

Acetophenone was chosen as the model ketone substrate and the optimised reaction conditions developed in chapter two for the asymmetric Reformatsky reaction with benzaldehyde were first tested with acetophenone. The results in Table 3.1 summarise the asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with acetophenone in the presence of 1.0, 0.6, 0.4 and 0.2 equivalents of *N*-methylephedrine.

Table 3.1 Asymmetric Reformatsky reaction of ethyl bromodifluoroacetate using different amounts of *N*-methylephedrine.



Run	(26)	(9)	(45)	Conversion[a]	Ee[b]
	[No. of equivalents]			[%]	[%]
1	0	1.5	1.5	100	-
2	1.0	1.5	2.0	23	68
3	0.6	1.5	1.8	49	59
4	0.4	1.5	1.7	49	57
5	0.2	1.5	1.6	51	40

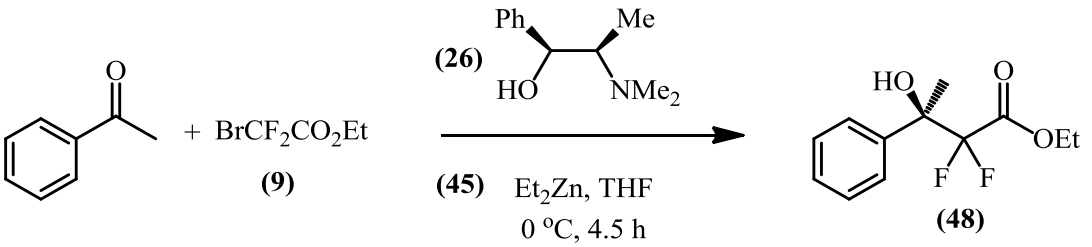
[a] Conversion was determined by GC, [b] ee was determined by chiral HPLC.

No chiral aminoalcohol was used in run 1 and this initial reaction with 1.5 equivalents of ethyl bromodifluoroacetate and 1.5 equivalents of diethylzinc confirmed that it was not necessary to use Wilkinson's catalyst to form the fluorinated Reformatsky reagent (Table 3.1, run 1). Acetophenone was then reacted with 1.5 equivalents of ethyl bromodifluoroacetate and 2.0 equivalents of diethylzinc in the presence of 1.0 equivalent of *N*-methylephedrine at 0 ^{o}C in THF (run 2). After 4.5 hours the reaction gave a lower 23 % conversion than the identical reaction with benzaldehyde (56 %), but a good enantiomeric excess of 68 % was determined by chiral HPLC. Surprisingly, the results obtained with 0.6 equivalents of *N*-methylephedrine (49 % conversion, 59 % ee) were very similar to the results obtained with 0.4 equivalents (49 % conversion, 57 % ee), but the enantioselectivity dropped significantly to 40 % ee without an improvement in the conversion (51 %) with 0.2 equivalents of *N*-methylephedrine (run 5). Since the reaction run without the chiral ligand gave 100 % conversion, it was a surprise to observe the dramatic drop in conversion in the presence of 0.2 equivalents of the chiral aminoalcohol.

Initially, it was decided to optimise the asymmetric Reformatsky reaction with acetophenone using 1.0 equivalent of *N*-methylephedrine (Table 3.2). Consequently, the reaction with 1.5 equivalents of $BrCF_2CO_2Et$ and 2.0 equivalents of Et_2Zn was monitored by GC every 30 minutes (run 2). The reaction profile shown in Figure 3.1 was similar to the one obtained with benzaldehyde (Figure 2.2). The rate of the reaction was much faster over the first 1.5 hours, but then slowed down to obtain the maximum conversion after 4 hours (Figure 3.1).

The same reaction conditions were repeated, but Wilkinson's catalyst was added in order to improve the conversion (run 3). The results showed clearly that the addition of the catalyst improved the conversion to 60 %, but the enantiomeric excess decreased to 50 %. In run 4 there was no delay in the addition of *N*-methylephedrine which was added 30 minutes before the addition of diethylzinc. The conversion (21 %) was similar to run 1 where *N*-methylephedrine was added 5 minutes before the addition of diethylzinc and there was only a small drop in the enantiomeric excess (64 %).

Table 3.2 Asymmetric Reformatsky reaction of ethyl bromodifluoroacetate (1.5 equivalents) with acetophenone in the presence of 1.0 equivalent of *N*-methylephedrine.



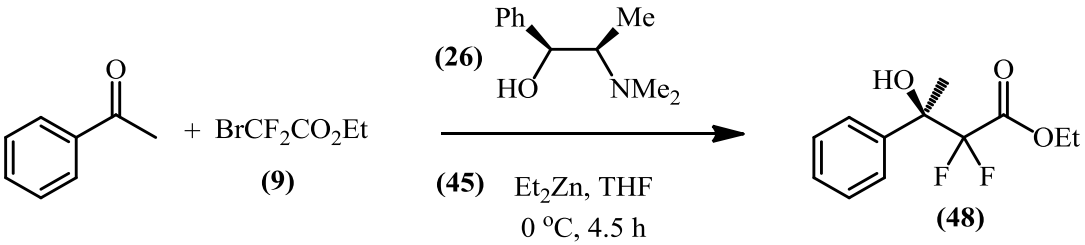
Run	Equivalents of (9)			Equivalents of (45)			Conversion[a]	Ee[b]
	t1	t2	t3	t1	t2	t3	[%]	[%]
1	1.5			2.0			23	68
2[c]	1.5			2.0			31	-
3[d]	1.5			2.0			60	50
4[e]	1.5			2.0			21	64
5	1.5			2.0	0.5 (2 h)		23	-
6	1.5			2.0	0.5 (2 h)	0.5 (4 h)	22	-
7	1.5	0.5 (2 h)		2.0			40	61
8	1.5	0.5 (2 h)		2.0	0.5 (2 h)		53	61
9	1.5	0.5 (2 h)	0.5 (4 h)	2.0	0.5 (2 h)	0.5 (4 h)	72	57
10	1.5	0.5 (2 h)[f]		2.0	0.5 (3 h)[f]		43	64
11	1.5	0.5 (2 h)[f]	0.5 (4 h)[f]	2.0	0.5 (3 h)[f]	0.5 (5 h)[f]	53	63

[a] Conversion was determined by GC, [b] ee was determined by chiral HPLC, [c] monitoring of the reaction by GC, [d] 1 mole% of Wilkinson's catalyst, [e] *N*-methylephedrine was added straight after acetophenone and 30 minutes before diethylzinc was added, [f] added dropwise over 5 min.

In the next two runs (runs 5 and 6) the addition of further aliquots of diethylzinc were investigated in order to try to improve the conversion. Unfortunately, there was no difference in the conversion compared to runs 1 and 4 and so, the enantiomeric excess was not determined. Interestingly, when an extra 0.5 equivalent of ethyl bromodifluoroacetate was added after 2 hours in run 7, the conversion improved to 40 % and the enantiomeric excess decreased slightly to 61 %. In run 8 the addition of 0.5 equivalents of both ethyl bromodifluoroacetate and diethylzinc after 2 hours led to a further improvement in the conversion (53 %) without loss in enantioselectivity (61 %

ee). Although the conversion improved to 72 % when further aliquots were added after 2 and 4 hours (run 9), the enantiomeric excess decreased to 57 %. In order to slow the reaction down the initial charge of diethylzinc and further aliquots of ethyl bromodifluoroacetate (after 2 hours) and diethylzinc (after 3 hours) were added dropwise over 5 min (run 10). Compared to the normal addition (run 8) the conversion was lower (43 %) but good enantioselectivity (64 % ee) was obtained. The reaction with dropwise additions was repeated in run 11, but this time further aliquots of ethyl bromodifluoroacetate were added dropwise after 2 and 4 hours whilst aliquots of diethylzinc were added dropwise after 3 and 5 hours. The conversion increased slightly to 53 % whilst maintaining a high enantiomeric excess (63 % ee). The same 53 % conversion was obtained in run 8 with a similar enantiomeric excess (61 %) but a smaller amount of reagent was used.

Figure 3.1 Monitoring of the asymmetric Reformatsky reaction with acetophenone by GC.



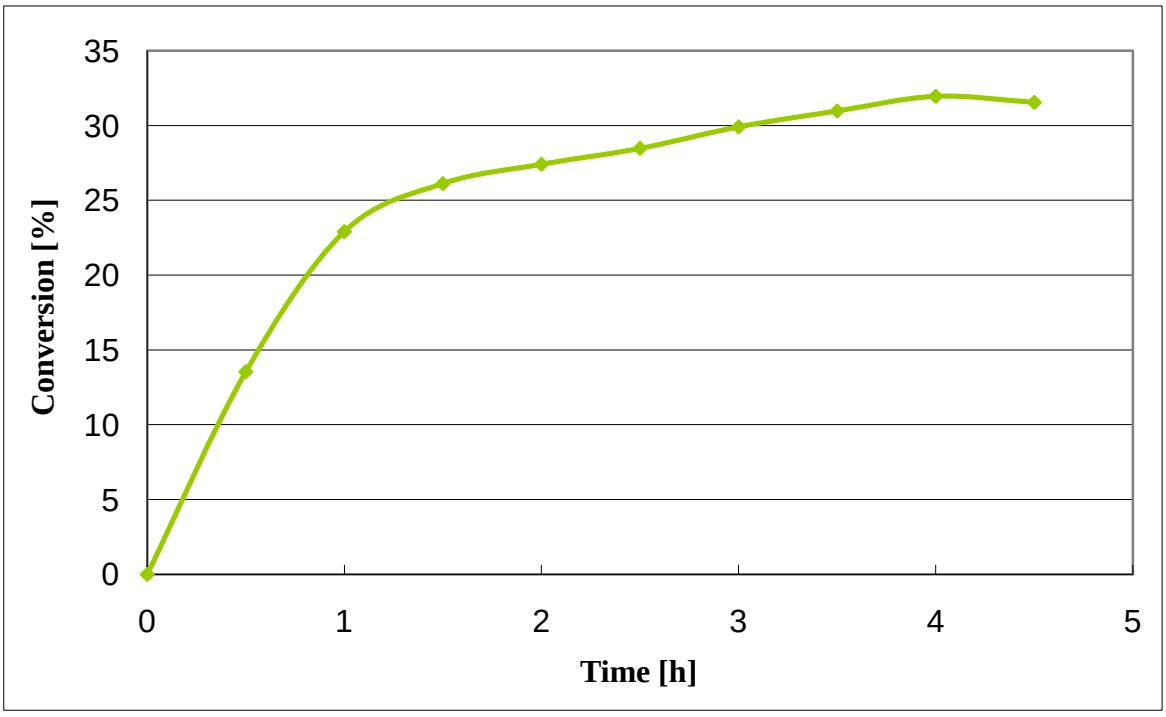
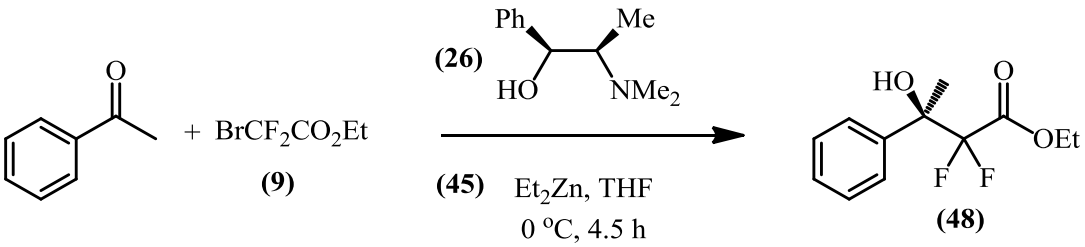


Table 3.3 Asymmetric Reformatsky reaction of ethyl bromodifluoroacetate (2.0 equivalents) with acetophenone in the presence of 1.0 equivalent of *N*-methylephedrine.



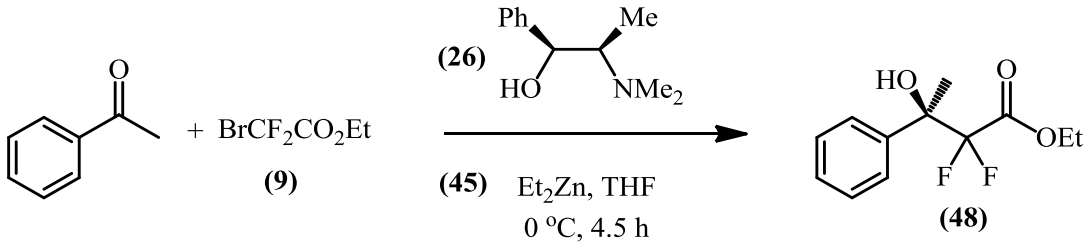
Run	Equivalents of (9)			Equivalents of (45)			Conv.[a]	Ee[b]
	t1	t2	t3	t1	t2	t3	[%]	[%]
1	2.0			2.0			20	65
2	2.0			2.0	0.5 (2 h)		36	65
3	2.0			2.5			33	59
4	2.0	0.5 (2 h)		2.0	0.5 (2 h)		39	65
5	2.0	0.5 (2 h)	0.5 (4 h)	2.0	0.5 (2 h)	0.5 (4 h)	78	57
6	3.0			3.5			84	52

[a] Conversion was determined by GC, [b] ee was determined by chiral HPLC.

The reaction of 2.0 equivalents of ethyl bromodifluoroacetate with acetophenone in the presence of 2.0 equivalents of diethylzinc and 1.0 equivalent of *N*-methylephedrine (Table 3.3, run 1) gave a similar conversion (20 %) and enantioselectivity (65 % ee) as the same reaction run with 1.5 equivalent of ethyl bromodifluoroacetate (Table 3.2, run 1 - 23 % conversion, 68 % ee). However, unlike when 1.5 equivalents of ethyl bromodifluoroacetate (Table 3.2, run 5) were used, the addition of a further aliquot of diethylzinc after 2 hours (Table 3.3, run 2) almost doubled the conversion (36 %) and maintained a good enantiomeric excess (65 % ee). This result also substantiates the claim that 0.5 equivalents of diethylzinc are necessary for deprotonating 1.0 equivalent of the chiral ligand. In the next reaction the same total amount of diethylzinc was injected at the beginning of the reaction. Although the same level of conversion (33 %) was obtained, a lower enantioselectivity (59 % ee) was observed (run 3). The result insinuated that the reaction was faster, which would explain the decreased enantiomeric excess, and that the maximum conversion in the reaction was obtained quicker than in the reaction where aliquots were added. For this reason the low conversion could not be improved without increasing the amount of ethyl

bromodifluoroacetate. Surprisingly, the addition of aliquots of both ethyl bromodifluoroacetate and diethylzinc after two hours only gave a very small increase in the conversion to 39 % whilst maintaining the high 65 % ee. When two aliquots were added, after two and four hours, the conversion improved to 78 % but the enantiomeric excess dropped to 57 %. This result was very similar to run 9 in Table 3.2 (72 % conversion and 57 % ee) where only 1.5 equivalents of ethyl bromodifluoroacetate was used at the beginning of the reaction. The best conversion (84 %) was obtained when 3.0 equivalents of ethyl bromodifluoroacetate and 3.5 equivalents of diethylzinc were used, but there was a further decrease in the enantiomeric excess (52 %). There was always a fine balance between the conversion in the reaction and the enantiomeric excess. Unfortunately, a high enantiomeric excess could only be obtained by sacrificing the conversion.

Table 3.4 Asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with acetophenone in the presence of 0.4 equivalents of *N*-methylephedrine.



Run	(26)	(9)	(45)	Conversion[a]	Ee[b]
	[No. of equivalents]			[%]	[%]
1	0.4	1.0	1.2	20	62
2[c]	0.4	1.0 + 0.5	1.2 + 0.5	35	59
3	0.4	1.5	1.7	49	57

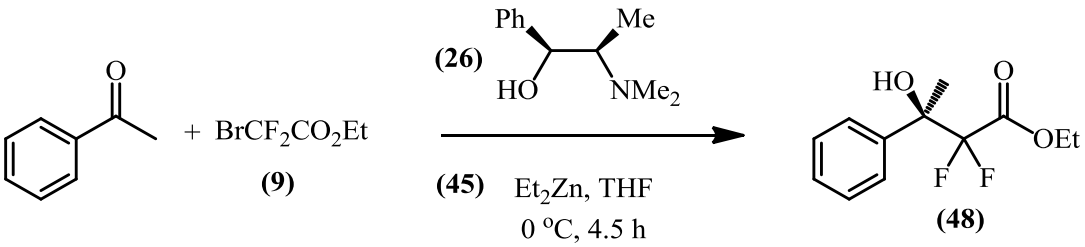
[a] Conversion was determined by GC, [b] ee was determined by chiral HPLC, [c] aliquots of $BrCF_2CO_2Et$ and diethylzinc were added after 2 h.

To confirm that high levels of enantioselectivity can be obtained with substoichiometric amounts of chiral ligand, the reaction was performed using 0.4 equivalents of *N*-methylephedrine (Table 3.4). Initially, in order to slow down the asymmetric Reformatsky reaction only 1.0 equivalent of ethyl bromodifluoroacetate and 1.2 equivalents of diethylzinc were used to give a 20 % conversion with a good

enantiomeric excess (62 % ee). When the same reaction was repeated, but 0.5 equivalents of ethyl bromodifluoroacetate and diethylzinc were added after 2 hours, the conversion improved to 35 % but the enantiomeric excess decreased to 59 % ee (run 2). When the same total amount of ethyl bromodifluoroacetate and diethylzinc were added in one portion at the beginning of the reaction (run 3), the conversion improved further to 49 %, however, there was a small drop in the enantiomeric excess. The results from Table 3.4 showed clearly that having less of compounds **(9)** and **(45)** to begin with and adding aliquots of ethyl bromodifluoroacetate and diethylzinc gives a slower reaction which consequently gave a lower conversion accompanied by a higher enantioselectivity.

In order to determine the optimum conditions for the enantioselective Reformatsky reaction, the order of the addition of the reagents was investigated (Table 3.5). Run 1 shows the result for the reaction with the normal order of addition, where acetophenone and ethyl bromodifluoroacetate were mixed before *N*-methylephedrine and diethylzinc were added. In all of the other runs (runs 2-7) ethyl bromodifluoroacetate and diethylzinc were mixed together to form the Reformatsky reagent followed by the addition of *N*-methylephedrine and a solution of acetophenone in dry THF. In run 2 ethyl bromodifluoroacetate was allowed to react with diethylzinc for 1 hour before *N*-methylephedrine and acetophenone were added. The reaction yielded a 54 % conversion with a moderate 49 % enantiomeric excess. When *N*-methylephedrine and acetophenone were added after 30 minutes in run 3, a lower conversion (44 %) with a higher enantioselectivity (54 % ee) was obtained. In run 4 *N*-methylephedrine was added without a delay and the acetophenone was added after an hour. Here, the conversion increased to 51 % and the good enantioselectivity (54 % ee) was maintained. In runs 5 and 6 acetophenone was added straight away, but was added dropwise over 30 and 60 minutes respectively. Although the conversion decreased to 38 % in run 6, the enantiomeric excess improved to 61 %. In the penultimate approach, (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (Figure 3.2) was used as the chiral aminoalcohol instead of *N*-methylephedrine. In comparison to run 4, where *N*-methylephedrine was used, the reaction yielded only a low conversion (30 %), but a much higher enantiomeric excess (67 %) (run 7). Finally, the conversion was improved dramatically to 94 % when ethyl iododifluoroacetate was used in run 8 instead of ethyl bromodifluoroacetate (run 1).

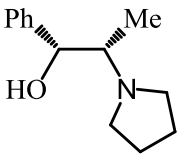
Table 3.5 Different order of reagent addition in the asymmetric Reformatsky reaction with 0.4 equivalents of *N*-methylephedrine.[a]



Run	(9) (1.5 equiv.)	(45) (1.7 equiv.)	(26) (0.4 equiv.)	Acetophenone (1 equiv.)	Conv.[b] [%]	Ee[c] [%]
1	0	35 min	30 min	0	49	57
2	0	0	55 min	60 min	54	49
3	0	0	25 min	30 min	44	54
4	0	0	0	60 min	51	54
5[d]	0	0	0	0 (over 30 min)	49	55
6[d]	0	0	0	0 (over 60 min)	38	61
7[e]	0	0	0	60 min	30	67[f]
8[g]	0	35 min	30 min	0	94	50

[a] The times in Table 3.5 show the delay between reagent additions, with 0 being the initial addition. The time in parenthesis indicates dropwise addition. [b] Conversion was determined by GC, [c] ee was determined by chiral HPLC, [d] dropwise addition of acetophenone, [e] (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol **(49)** was used as the chiral aminoalcohol, [f] the major enantiomer had the opposite configuration (*S*) (by chiral HPLC), [g] the reaction with ICF_2CO_2Et.

Figure 3.2 (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol.

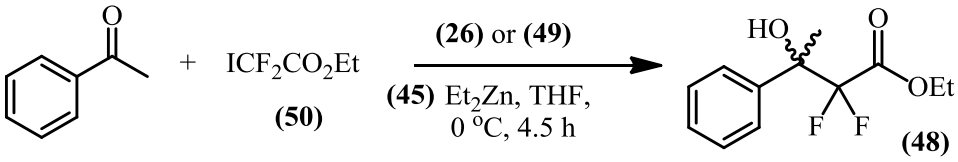


(49)

Since the conversion was increased dramatically by using ethyl iododifluoroacetate and a higher enantiomeric excess was obtained when (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol was used (Table 3.5), in the next approach these reagents were tested in the reaction with 1.0 equivalent of the chiral ligand and the

normal order of addition. The results are summarised in Table 3.6. A good 72 % conversion combined with 63 % enantiomeric excess (run 1), which is a lot better than the result obtained with ethyl bromodifluoroacetate run under exactly the same conditions (23 % conversion, 68 % ee (Table 3.2, run 1)). In the next approach, when aliquots of both ethyl iododifluoroacetate and diethylzinc were added after 2 hours, the conversion reached 97 % whilst the enantiomeric excess decreased slightly to 58 %. In run 3 the chiral ligand was changed to (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol and the normal order of addition was used. Compared to the reaction with *N*-methylephedrine (run 1), although the conversion (61 %) was slightly lower, the enantiomeric excess (76 %) was significantly better. The addition of further aliquots of ethyl iododifluoroacetate and diethylzinc after 2 h in run 4 improved the conversion to 94 % with only a small loss in the enantioselectivity (74 % ee). Finally, run 5 demonstrated clearly that although the conversion increased to 99 % when the reagents were added in one portion at the beginning of the reaction, the enantiomeric excess was lowered slightly (71 % ee).

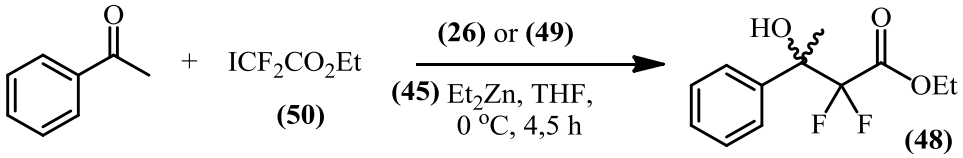
Table 3.6 Asymmetric Reformatsky reaction of ethyl iododifluoroacetate with acetophenone in the presence of 1.0 equivalent of chiral aminoalcohol.



Run	(50) [No. of equiv.]	(45) [No. of equiv.]	Ligand	Conversion[a] [%]	Ee[b] [%]
1	1.5	2.0	**(26)**	72	63
2	1.5 + 0.5	2.0 + 0.5	**(26)**	97	58
3	1.5	2.0	**(49)**	61	76
4	1.5 + 0.5	2.0 + 0.5	**(49)**	94 (66)	74
5	2.0	2.5	**(49)**	99 (92)	71

[a] Conversion was determined by GC (isolated yield in parenthesis), [b] ee was determined by chiral HPLC.

Table 3.7 Different order of addition in the asymmetric Reformatsky reaction with acetophenone in the presence of 1.0 equivalent of aminoalcohol.



Run	Aminoalcohol	(45) (equiv.)	(50) (equiv.)	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	**(26)**	0.5 + 1.5	1.5	60	52	65
2	**(49)**	0.5 + 1.5	1.5	26		~66
3	**(49)**	0.5 + 2.0	2.0	69		63

[a] Conversion was determined by GC, [b] isolated yield, [c] ee was determined by chiral HPLC.

In order to ensure that the chiral ligand was fully deprotonated before the Reformatsky reagent was generated, a new order of addition was investigated. The chiral aminoalcohol was allowed to react with diethylzinc for 10 minutes before ethyl iododifluoroacetate was added to form the Reformatsky reagent and start the reaction. When the new protocol was tested with *N*-methylephedrine, a good conversion (60 %) and enantiomeric excess (65 % ee) was achieved (run 1). However, when the same reaction conditions were used with (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol **(49)**, the reaction was slower and only gave a 26 % conversion accompanied by a 66 % enantiomeric excess (run 2). In order to improve the conversion with **(49)** in run 3, a larger excess of both ethyl iododifluoroacetate and diethylzinc were used. The reaction yielded an improved conversion (69 %) but the enantiomeric excess decreased to 63 % and was lower than the results obtained with *N*-methylephedrine. Although the results showed that the new protocol can slightly improve the reaction with *N*-methylephedrine, the normal addition of reagents gave better results with (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol **(49)**.

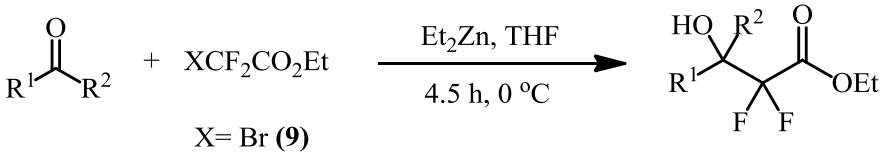
3.3 The Reformatsky reaction with a series of ketones

The aim of this section was to isolate and characterise the products formed in the Reformatsky reaction with a series of ketones that would also be used as substrates for

screening the scope and limitations of the asymmetric Reformatsky reaction. In addition, methods for separating the enantiomers by chiral HPLC would also be developed. The results are summarised in Table 3.8 which shows the range of ketones that were reacted with either ethyl bromodifluoroacetate or ethyl iododifluoroacetate. In runs 1, 2, 4, 7 and 8 the products were synthesised following Kumadaki's procedure.[2] The rest of the results were obtained by reacting the ketones with either ethyl bromodifluoroacetate or ethyl iododifluoroacetate in the presence of diethylzinc without Wilkinson's catalyst. All of the reactions with Wilkinson's catalyst proceeded well giving > 55 % conversion to the desired product. In the reaction with ethyl bromodifluoroacetate, 2-methoxyacetophenone gave only a trace of the desired product whilst the aliphatic ketones gave about 30 % isolated yield of the desired products. In order to improve the conversions, the same reactions were performed using the more reactive ethyl iododifluoroacetate. The conversion in the reaction with 2-methoxyacetophenone was 100 % whilst 5-methylhexa-2-one gave an 89 % isolated yield of the desired product. Unfortunately, the reaction of ethyl bromodifluoroacetate with (*E*)-4-phenylbut-3-en-2-one in THF gave a mixture of products and none of the deired product was detected but by using ethyl iododifluoroacetate in acetonitrile the desired product was obtained in 78 % isolated yield. The reaction did not work with either 4-nitroacetophenone or 4-nitrobenzophenone, but it is known that the Reformatsky reaction does not work with substrates that contain the nitro group

Ethyl-2,2-difluoro-3-hydroxy-3-phenylpentanoate **(54)** was synthesised previously by Biran[1] but the reaction mixture was only analysed by ^{19}F NMR spectroscopy and the pure product was not isolated or fully characterised. Ethyl 2,2-difluoro-3-hydroxy-3-(2-methoxyphenyl)butanoate **(53)**, ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate **(55)**, ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(56)**, ethyl-3-(2,3-dihydro-1H-inden-1-yl)-2,2-difluoro-3-hydroxybutanoate **(57)**, ethyl 2,2-difluoro-3-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)butanoate **(58)**, ethyl 2,2-difluoro-3-hydroxy-3,6-dimethylheptanoate **(61)** and ethyl 2,2-difluoro-3-hydroxy-3,4,4-trimethylpentanoate **(62)** are new compounds that have not previously been synthesised. Crystals of **(54)**, **(55)**, **(56)** and **(57)** suitable for X-ray crystallography were grown by slow evaporation from hexane or 10 % EtOAc in hexane and the solid-state structures are shown in Figure 3.3. In all cases there is intermolecular hydrogen bonding from O3-H3 to O2.

Table 3.8 Reformatsky reaction with aromatic, aliphatic and *α,β*-unsaturated ketones.

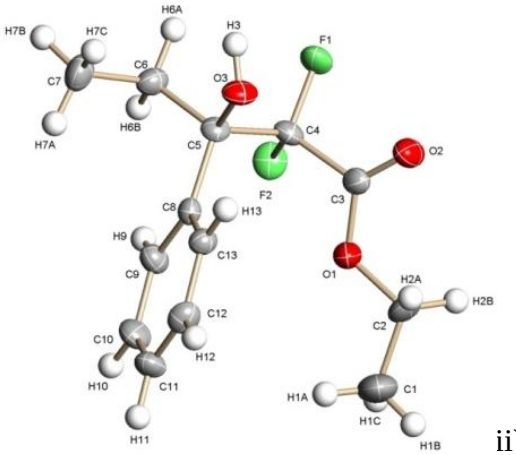


X= Br **(9)**
I **(50)**

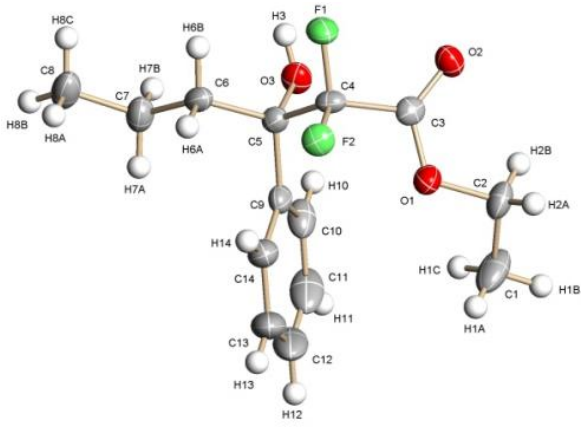
Run	Ketone	XCF_2CO_2Et	Product No.	Conversion[a] [%]	Yield[b] [%]
1	*p*-chloroacetophenone	Br[c]	**(51)**	55	52
2	*p*-methoxyacetophenone	Br[c]	**(52)**	83	43
3	*o*-methoxyacetophenone	Br	**(53)**	Trace	-
		I	**(53)**	100	83
4	propiophenone	Br[c]	**(54)**	81	26
5	1-phenylbutan-1-one	Br	**(55)**	87	35
6	3-methyl-1-phenylbutan-1- one	Br	**(56)**	78	17
7	indanone	Br[c]	**(57)**	89	64
8	tetralone	Br[c]	**(58)**	98	39
9	(*E*)-4-phenylbut-3-en-2-one	Br	[d]	-	-
		I[f]	**(59)**	[e]	78
10	pentan-2-one	Br	**(60)**	[e]	30
11	5-methylhexan-2-one	Br	**(61)**	[e]	31
		I	**(61)**	[e]	89
12	3,3-dimethylbutan-2-one	Br	**(62)**	[e]	31

[a] Conversion was determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] Wilkinson's catalyst was used, [d] no desired product, [e] not calculated, [f] the reaction in acetonitrile.

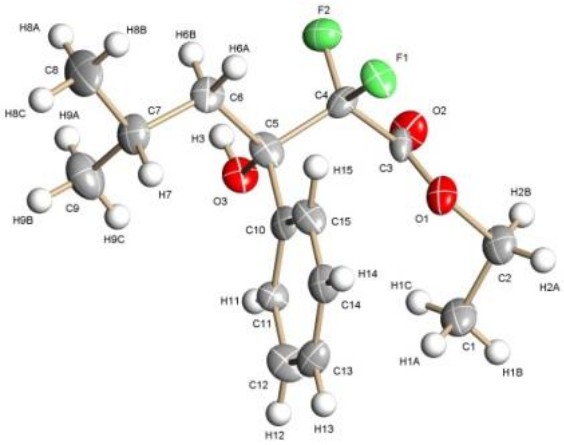
Figure 3.3 The crystal structures of: i) ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **(54)**, ii) ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate **(55)**, iii) ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(56)**, iv) ethyl 2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate **(57)**. Figures show 50 % displacement ellipsoids and hydrogen atoms in calculated positions.



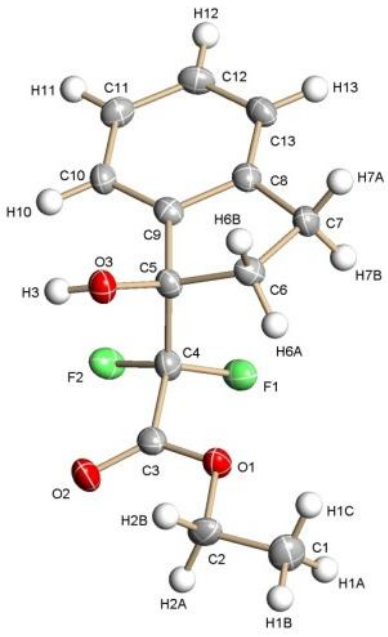
i)



ii)



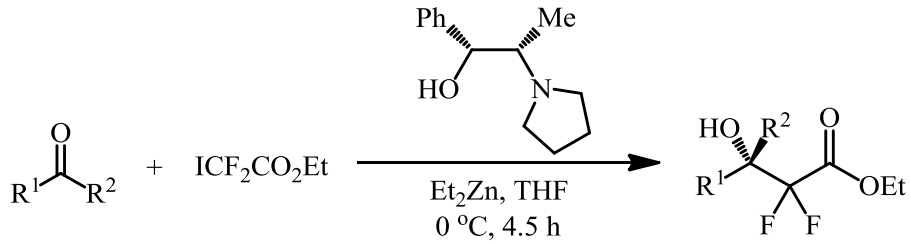
iii)



iv)

3.4 The asymmetric Reformatsky reaction with a series of ketones

Table 3.9 Asymmetric Reformatsky reaction of ethyl iododifluoroacetate with ketones in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol.[a]



Run	Ketone	Conversion[b] [%]	Yield[c] [%]	Ee[d] [%]
1	Acetophenone	61 (27)[e,f]	-	76
2		100	93	73
3	*p*-Methoxyacetophenone	88[f]	77	79
4		100	95	78
5	*o*-Methoxyacetophenone	100	81	75
6	*p*-Chloroacetophenone	100	87	70
7	Propiophenone	100	93	66
8	1-Phenylbutan-1-one	100	91	64
9	3-Methyl-1-phenylbutan-1-one	98	98	58
10	Benzaldehyde	80[f]	53	60
11		100	87	60
12	Indanone	57	42	64
13	Tetralone	87	73	78
14	(*E*)-4-Phenylbut-3-en-2-one	19	4	20
15		100[g]	94	8
16	5-Methyl-hexa-2-one	100	89	5[h]
17	2-Pentanone	100	90	4[h]
18	Pinacolone	100	36	-

[a] Optimise conditions (Table 3.6 run 4), [b] conversion was determined by ^{1}H NMR spectroscopy, [c] isolated yield, [d] enantiomeric excess was determined by chiral HPLC, [e] conversion was determined by GC (unreacted acetophenone in parenthesis), [f] no aliquots were used in the reaction, [g] reaction in acetonitrile, [h] enantiomeric excess was determined by chiral GC.

After extensive optimisation studies, the best result in terms of conversion to product and enantiomeric excess was obtained with 1.5 equivalents of ethyl iododifluoroacetate and 2.0 equivalents of diethylzinc (Table 3.9). The extra 0.5 equivalent of diethylzinc was used to deprotonate the chiral aminoalcohol (run 1). The reaction was further improved by the addition of 0.5 equivalents of both ethyl iododifluoroacetate and diethylzinc after two hours. The conversion improved significantly with only a small decrease in the enantiomeric excess (run 2). Surprisingly, the reaction with 4-methoxyacetophenone yielded 88 % conversion (77 % isolated yield) and a high 79 % enantiomeric excess (run 3). When extra aliquots were added in run 4, the reaction went to completion with only a 1 % decrease in the enantiomeric excess. The presence of a methoxy group, which is strongly electron donating, did not decrease the reactivity of the carbonyl group. In run 5, 2-methoxyacetophenone was used and it was hoped that the methoxy group in the *ortho*-position would form a chelate and hence, improve the enantiomeric excess in the reaction. Unfortunately, this did not appear to happen and a similar result was obtained compared to the reaction with 4-methoxyacetophenone. The reaction with an electron withdrawing group on the ring (4-chloroacetophenone, run 6) went to completion but gave a slightly lower enantiomeric excess (70 % ee).

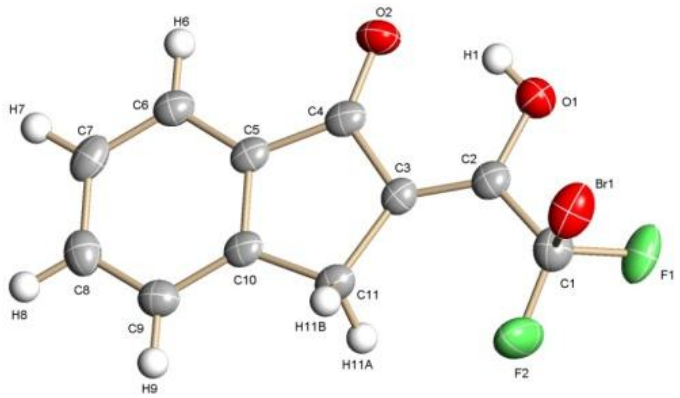
The reactivity of propiophenone was also very good but, presumably because the ethyl group was more bulky than the methyl group in acetophenone, the enantiomeric excess decreased and reached only 66 % ee (run 7). Extending the aliphatic side of the ketone resulted in a further decrease in the enantiomeric excess to 64 % ee in the case of 1-phenylbutan-1-one (run 8) and 58 % ee in the reaction with 3-methyl-1-phenylbutan-1-one (run 9).

The reaction of 1.5 equivalents of ethyl iododifluoroacetate with benzaldehyde gave 80 % conversion with only 60% enantiomeric excess (run 10). The addition of a further aliquot of ethyl iododifluoroacetate and diethylzinc after 2 hours improved the conversion to 100 % and the enantiomeric excess was still 60 % (run 11). The result was very similar to that obtained in the reaction with ethyl bromodifluoroacetate in the presence of one equivalent of *N*-methylephedrine which gave 94 % conversion and 60 % enantiomeric excess.

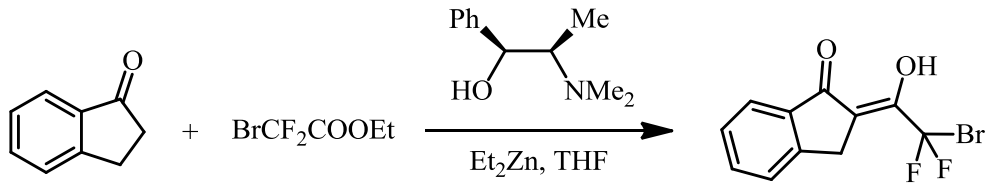
A similar level of enantiomeric control was obtained in the reaction with the cyclic ketone indanone, however, the conversion was much lower (57 %, run 12).

Interestingly, the Reformatsky reaction of ethyl bromodifluoroacetate with indanone in the presence of *N*-methylephedrine had resulted in the formation of (*Z*)-2-(2-bromo-2,2-difluoro-1-hydroxyethylidene)-2,3-dihydro-1H-inden-1-one **(63)** with a 68 % yield (Scheme 3.1) and not the desired product ester **(57)**. The molecular structure of **(63)** (Figure 3.4) showed that it is the enol because of intramolecular hydrogen bonding between O2 and H1 forming a six membered ring. The asymmetric Reformatsky reaction of ethyl iododifluoroacetate was better with tetralone (run 13) which gave a better conversion (87 %) and a higher enantiomeric excess (78 %). In the reaction with an α,β-unsaturated ketone in THF only a 19 % conversion and a very low 20 % enantiomeric excess was obtained (run 14). However, ^{1}H NMR spectroscopy did not show the product of the addition of the Reformatsky reagent to the double bond reported by Kumadaki.[2] The reaction was repeated in acetonitrile and although complete conversion to **(59)** was achieved, the enantiomeric excess decreased to 8 % ee (run 15). Unfortunately, the developed protocol did not work well with aliphatic ketones. The reactions with 5-methyl-hexa-2-one and 2-pentanone gave good conversions and isolated yields, however, the reaction with pinacolone gave only 36 % isolated yield. The enantiomeric excesses were determined for the first two aliphatic ketones to be 5 % and 4 % ee respectively. Unfortunately, determination of the enantiomeric excess of the product obtained in the reaction with pinacolone was not achieved either by chiral GC or chiral HPLC.

Figure 3.4 The crystal structure of (*Z*)-2-(2-bromo-2,2-difluoro-1-hydroxyethylidene)-2,3-dihydro-1H-inden-1-one **(63)**. Figures show 50 % displacement ellipsoids and hydrogen atoms in calculated positions.



Scheme 3.1 The reaction of indanone with ethyl bromodifluoroacetate in the presence of diethylzinc and *N*-methylephedrine.



68 % yield

(63)

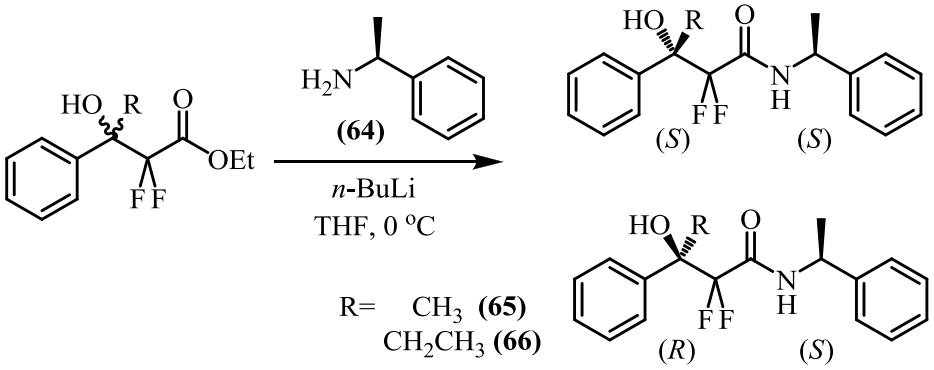
3.5 Determination of the absolute configuration and proposed mechanism

The enantiomerically pure crystal of ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **(54)** was obtained and was confirmed by chiral HPLC; however, the X-ray crystallography was not conclusive in the determination of the absolute configuration. The molecule **(54)** contains only light atoms and the Flack parameter, which is based on the anomalous dispersion effect, cannot be used. For this reason, the absolute configuration of the major enantiomers obtained in the asymmetric Reformatsky reaction with acetophenone, propiophenone and tetralone were confirmed by using the method reported by Braun (Table 3.10).[3] Since the reaction with (*S*)-1-phenylethanamine introduced a chiral centre with known configuration, it was used as a reference in the assignment of the absolute configuration of the unknown chiral centre in the molecule.

To determine the absolute configuration of the major enantiomer obtained in the asymmetric Reformatsky reaction with acetophenone, a sample of the ester **(48)** (72 % ee) was reacted with (*S*)-1-phenylethanamine **(64)**. The reaction gave 100 % conversion and the diastereomeric ratio, determined by ^{1}H NMR spectroscopy by integrating the signals for the methyl groups of the two diastereomers, was 68 % de. The diastereomeric excess in the crude product could not be confirmed by ^{19}F NMR spectroscopy because the signals for the two diastereoisomers were overlapping. The diastereoisomers were separated by flash chromatography and fully characterised. The minor diastereoisomer turned out to be a solid and a good quality crystal was grown by slow evaporation from a solution in 20 % EtOAc in hexane and used for X-ray crystallography. The solid-state structure of α,α-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(65)** showed that the unknown chiral centre in the minor

diastereoisomer had an (*R*)-configuration (Figure 3.5) and so, the (*S*)-configuration was assigned to the major diastereoisomer.

Table 3.10 Determination of the absolute configuration of the products obtained in the asymmetric reaction with acetophenone and propiophenone.



R	Diastereoisomer	Conversion[a] [%]	Yield[b] [%]	De[c] [%]	Compound No.
CH_3	(*S*,*S*)	85	62	70	**(65a)**
	(*R*,*S*)	15	5		**(65b)**
CH_2CH_3	(*S*,*S*)	88	79	76	**(66a)**
	(*R*,*S*)	12	- [d]		**(66b)**

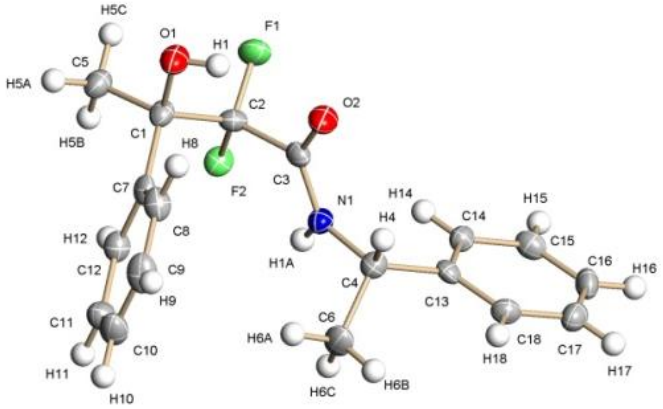
[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by ^{1}H NMR spectroscopy, [d] obtained in the reaction with the racemic ester.

The same experiment was repeated with product **(54)** from the Reformatsky reaction with propiophenone. The enantiomeric excess determined for the starting material **(54)** was 78 % ee. Once again, the enantiomeric excess of the starting material and the diastereomeric excess in the crude product were consistent. Unfortunately, because of the small scale of the reaction and the high enantiomeric excess of the starting material, only the major diastereoisomer was isolated and fully characterised. For this reason the reaction was repeated with a racemic sample of **(54)**. This time both diastereoisomers were obtained in a significant quantity, allowing full characterisation of both products. After recrystallisation, a solid-state structure of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide **(66)** (the minor product from original chiral sample**)** was obtained (Figure 3.5). Hence, the configuration of the major

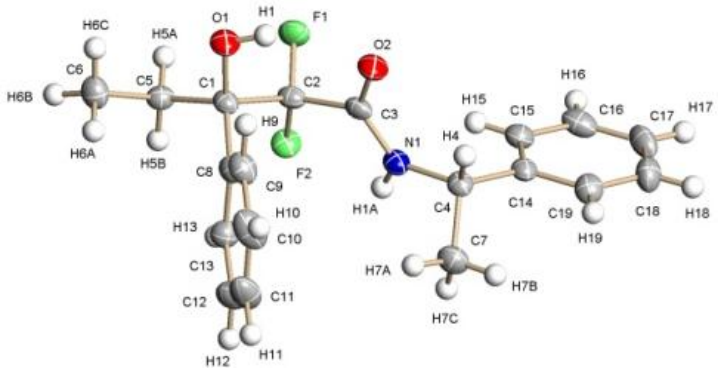
enantiomer of the product formed in the asymmetric Reformatsky reaction with acetophenone and propiophenone was (*S*) in both cases.

Figure 3.5 The molecular structures used in the determination of the absolute configuration of the unknown chiral centre: i) 2,2-difluoro-3-hydroxy-3(*R*)-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(65b)**, ii) 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide **(66b)**, iii) 2,2-difluoro-2-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)acetamide **(67a)**. Figures show 50 % displacement ellipsoids and hydrogen atoms in calculated positions.

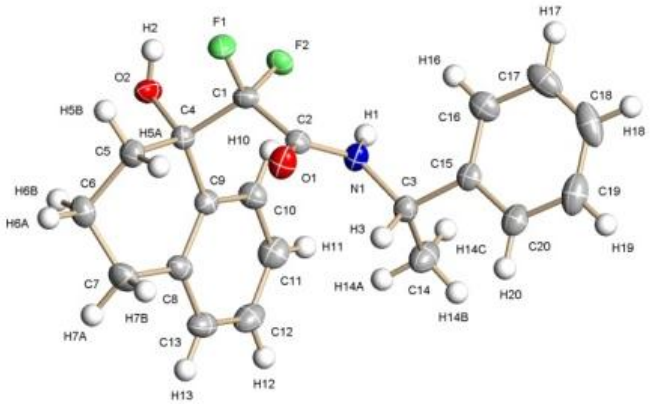
i)



ii)

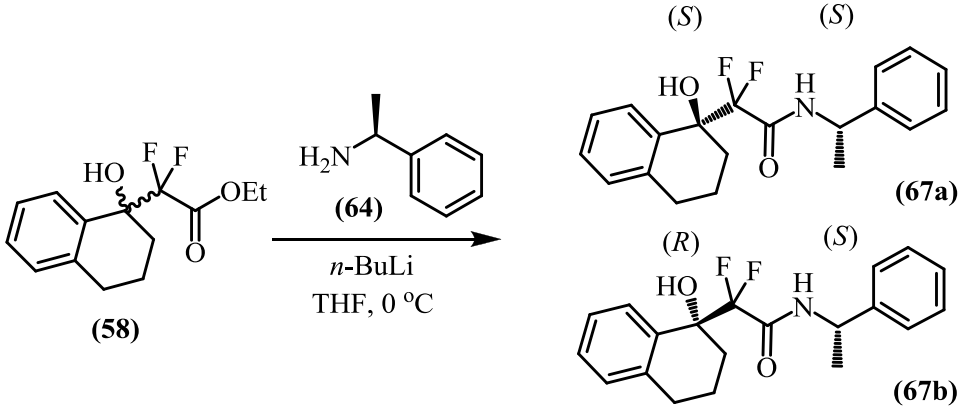


iii)



To determine the absolute configuration of the major enantiomer obtained in the Reformatsky reaction with tetralone, the racemic sample of ester **(58)** was reacted with (*S*)-1-phenylethanamine and the two diastereoisomers were separated by flash chromatography. 2,2-Difluoro-2-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)acetamide **(67)** gave a crystal suitable for X-ray crystallography and the molecular structure is shown in Figure 3.5. In the next step the reaction with (*S*)-1-phenylethanamine was repeated on a much smaller scale using the ester obtained in the chiral Reformatsky reaction. There was consistency between the enantiomeric excess of the starting material (88 % ee) determined by chiral HPLC and the diastereomeric excess obtained by ^{19}F NMR spectroscopy (82 % ee) of the two diastereoisomeric products. A direct comparison of the crude ^{1}H and ^{19}F NMR spectra with those obtained for **(67)** proved that the crystal structure shown in Figure 3.5 (iii) belongs to the major enantiomer obtained in the asymmetric Reformatsky reaction with tetralone.

Scheme 3.2 Determination of the absolute configuration of the products obtained in the asymmetric reaction with tetralone.



The most likely mechanism for the asymmetric addition of the Reformatsky reagent to aldehydes and ketones in the presence of a chiral aminoalcohol is the same as the one reported for the asymmetric addition of diethylzinc **(45)** to benzaldehyde. The reaction of diethylzinc with aldehydes in the presence of (-)-3-exo-(dimethylamino)isoborneol (DAIB) **(29)** was studied by Noyori (Scheme 3.3).[4] In his reaction the ligand which had the same absolute configuration as (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol gave the (*R*)-enantiomer of the alcohol **(46)**. On the other hand, the α,α-difluoro-β-hydroxyesters obtained in the asymmetric Reformatsky reaction had an (*S*)-configuration because of the different order in priority of the

substituents on the chiral centre. This result shows that in both reactions the same side of the carbonyl molecule was exposed to the nucleophilic attack. The postulated mechanism for the asymmetric addition of the Reformatsky reagent to the carbonyl compound is presented in Figure 3.6. In the first step, the molecule of Reformatsky reagent is coordinated to the (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol and the CF_2CO_2Et group is coordinated to the zinc atom as far away as possible from the phenyl group and the methyl group of the chiral aminoalcohol. In the next step the ketone coordinates to the zinc with the larger phenyl group away from the bridging CF_2CO_2Et group. The structure is stabilised by the second zinc atom. Due to the steric hindrance of the pyrrolidine group only the *si*-face of acetophenone was exposed to the transfer of the Reformatsky reagent.

Scheme 3.3 Enantioselective addition of diethylzinc to benzaldehyde.

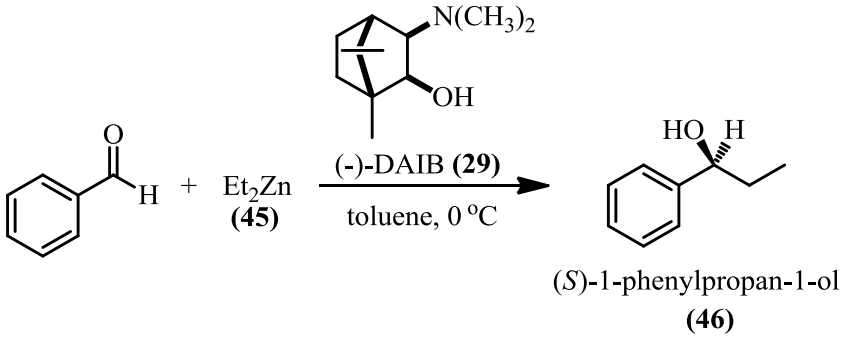
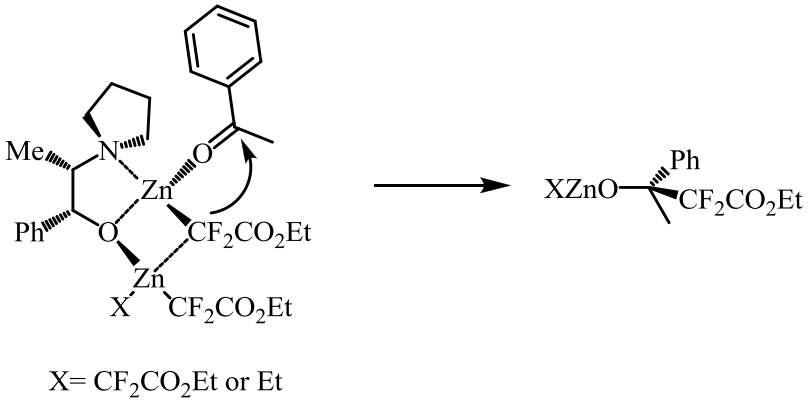


Figure 3.6 The proposed mechanism of the asymmetric addition of Reformatsky reagent to acetophenone in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol.

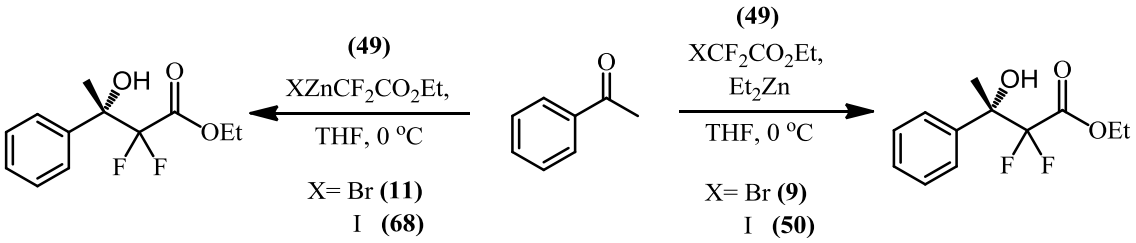


X= CF_2CO_2Et or Et

3.6 The asymmetric Reformatsky reaction using two-step protocol with zinc dust

In the classical Reformatsky reaction the Reformatsky reagent is normally generated by the reaction between the α-halogenated ester and activated zinc dust. The reaction can be performed in one step with the Reformatsky reagent generated *in situ*, [5,6] but normally a two step protocol is used with the pre-made reagent added to the aldehyde or ketone.[3,7,8] In fact, the asymmetric Reformatsky reaction of the difluorinated reagent with aldehydes has only been reported as a two step protocol.

Table 3.11 Two step protocol of the Reformatsky reaction with acetophenone in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol.



Run	Conditions	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	Zn*, $BrCF_2CO_2Et$	81	70	73
2	Zn*, ICF_2CO_2Et	91	75	84
3	Et_2Zn, $BrCF_2CO_2Et$	71	42	70
4	Et_2Zn, ICF_2CO_2Et	100	94	68

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

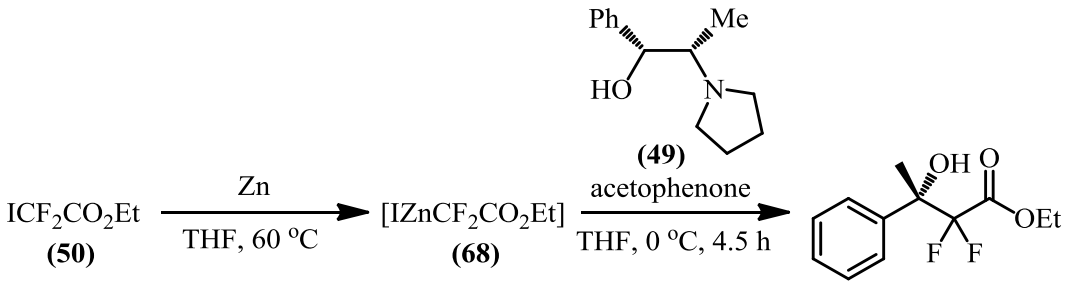
The results of the addition of the premade Reformatsky reagent with acetophenone in the presence of 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)** are presented in Table 3.11. The Reformatsky reagent was generated by using the protocol described by Knochel and a large excess (2.5 equivalents) was used in order to deprotonate the chiral aminoalcohol as well as to react with acetophenone.[8] In order to activate the zinc dust, it was washed with 17 % HCl for approximately one minute before it was washed with water, acetone, alcohol and finally diethyl ether before drying under vacuum at 120 °C for 4 h. To generate the fluorinated Reformatsky reagents **(11)** and **(68)**, ethyl bromodifluoroacetate (run 1) or ethyl iododifluoroacetate (run 2) were added to the suspension of activated zinc dust in dry

THF at 60 ^{o}C over 2-3 minutes. The heating was then turned off and the Reformatsky reagent was ready to use within a few minutes, indicated by the disappearance of the zinc dust. The reaction of ethyl iododifluoroacetate was visibly faster. The concentration of the Reformatsky reagent was not confirmed by any analytical method and calculations were based on the complete conversion of starting material. ^{19}F NMR spectroscopy was used to characterise the Reformatsky reagents and the results of these experiments will be discussed in section 3.7.2. Acetophenone was premixed with the chiral ligand in a small amount of THF at 0 ^{o}C. The Reformatsky regent was then added to that mixture within 10 minutes of its generation. The reaction was quenched after 4.5 hours of stirring at 0 ^{o}C. Conversions in both reactions were fairly similar (81 % and 91 % respectively), however, the difference in enantiomeric excess was really interesting. The Reformatsky reagent generated from the bromo derivative gave a good 73 % ee but the enantiomeric excess in the reaction with ethyl iododifluoroacetate, regardless of its better conversion, gave an excellent 84 % ee. Such a big difference in enantiomeric control between these two reagents was unexpected. Surprisingly, the two step protocol gave better results than the optimised one-pot synthesis with diethylzinc.

For comparison, the same conditions were repeated but diethylzinc was used instead of zinc dust to form the Reformatsky reagent. Interestingly, the enantiomeric excesses obtained in the reactions with diethylzinc were very similar but the reaction with ethyl bromodifluoroacetate gave only 71 % conversion compared to the excellent 100 % conversion obtained with ethyl iododifluoroacetate.

In order to optimise the reaction conditions for the two step protocol, the Reformatsky reagent obtained from ethyl iododifluoroacetate and zinc dust was used in a series of reactions with different amounts of the chiral aminoalcohol (Table 3.12). In the absence of chiral aminoalcohol the conversion of acetophenone was surprisingly low (17 %) (run 1). Addition of only 0.4 equivalents of the chiral ligand improved the conversion to 62 % along with 76 % enantiomeric excess (run 2). The conversion in the reaction appears to be dependant on the amount of chiral ligand used; as the amount of chiral ligand decreases so does the conversion. The reactions run in the presence of 0.6, 0.8, 1.0 and 1.4 equivalents of the chiral ligand **(49)** gave the same enantiomeric excesses (runs 4 to 7). The drop in the enantiomeric excess to 76 % ee with 0.4 equivalents of **(49)** (run 2) can be increased to 81 % ee by using a lower ratio of the Reformatsky reagent to chiral aminoalcohol (run 3).

Table 3.12 The two step asymmetric Reformatsky reaction of acetophenone using different amounts of the chiral aminoalcohol **(49)**.



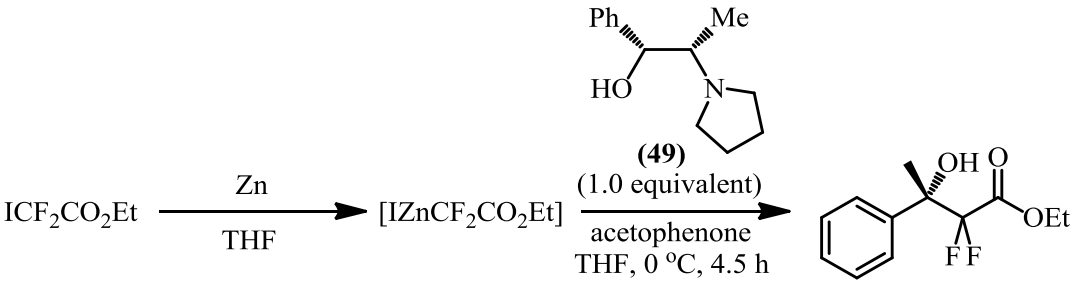
Run	(68) [No. of equiv.]	(49) [No. of equiv.]	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	1.5	-	17	-	-
2	1.9	0.4	62	51	76
3	1.4	0.4[d]	53	46	81
4	2.1	0.6	70	61	83
5	2.3	0.8	78	63	83
6	2.5	1.0	91	75	84
7	2.9	1.4	92	87	82

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC, [d] 1.0 equivalent of the Reformatsky reagent.

Table 3.13 summarises the results from further optimisation of the two step enantioselective Reformatsky reaction using 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol and 2.5 equivalents of ethyl iododifluoroacetate. In run 2 the Reformatsky reagent was formed at 0 °C and added dropwise over 35 minutes resulting in a low 42 % conversion and an unimproved enantiomeric excess (82 %). When the Reformatsky reagent was formed at 60 °C and then cooled to room temperature and added over 45 minutes, the conversion improved to 78 % but the enantiomeric excess remained at 84 %. To reduce costs, diethylzinc was used to deprotonate the chiral aminoalcohol. In the first approach 0.5 equivalent of diethylzinc and 1.5 equivalents of ethyl iododifluoroacetate gave a 76 % conversion and an 83 % ee (run 4). The conversion did not improve when 1.0 equivalent of diethylzinc was used in run 5. Finally, a lower reaction temperature was investigated in run 6 but there was a

significant drop in the conversion to 20 % and there was no improvement in the enantiomeric excess.

Table 3.13 Optimisation of the two step enantioselective Reformatsky reaction with acetophenone.

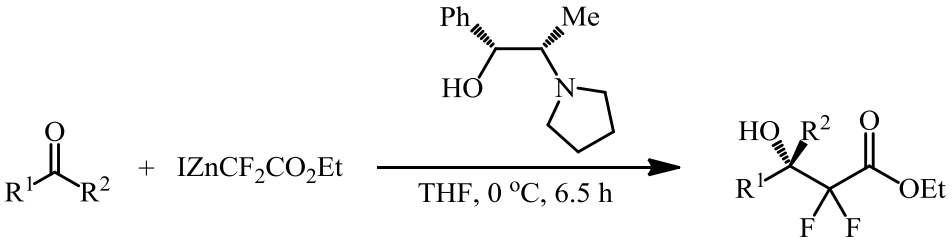


Run	Conditions	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	0 °C	91	75	84
2	0 °C (35 min)	42	23	82
3	60 °C (45 min)	78	72	84
4	Et_2Zn (0.5 equiv.)	76	62	83
5	Et_2Zn (1.0 equiv.)	77	-	-
6	at -10 °C	26	22	84

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

Finally, a series of ketones were tested under the optimised reaction conditions and the results are presented in Table 3.14. The addition of 2.5 equivalents of the Reformatsky reagent to the reaction mixture enabled the deprotonation of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol as well as the reaction with the ketones. The reaction with acetophenone was repeated and a 98 % conversion, a high isolated yield (94 %) and high enantiomeric excess (80 %) was obtained. The reaction with *p*-methoxyacetophenone that contained an electron donating group (run 2) gave an excellent conversion (95 %) and enantiomeric excess (84 %). However, the reaction with 2-methoxyacetophenone (run 3) gave a lower conversion probably due to steric hindrance, but the enantiomeric excess remained high at (82 %). The electron withdrawing effect of chlorine in 4-chloroacetophenone (run 4) did not improve the conversion (88 %) or the enantiomeric excess (80 %).

Table 3.14 The asymmetric Reformatsky reaction of ICF_2CO_2Et and Zn dust with ketones.



Run	Ketone	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	Acetophenone	98	94	80 (*S*)
2	4-Methoxyacetophenone	95	94	84
3	2-Methoxyacetophenone	76	63	82
4	4-Chloroacetophenone	88	81	80
5	Propiophenone	46	40	79 (*S*)
6	1-Phenylbutan-1-one	96	69	80
7	3-Methyl-1-phenylbutan-1-one	46	29	75
8	Benzaldehyde	100	71	78
9	Indanone	100	99	82
10	Tetralone	100	70	82 (*S*)
11	(*E*)-PhCH=CHCOCH$_3$	100	97	13

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

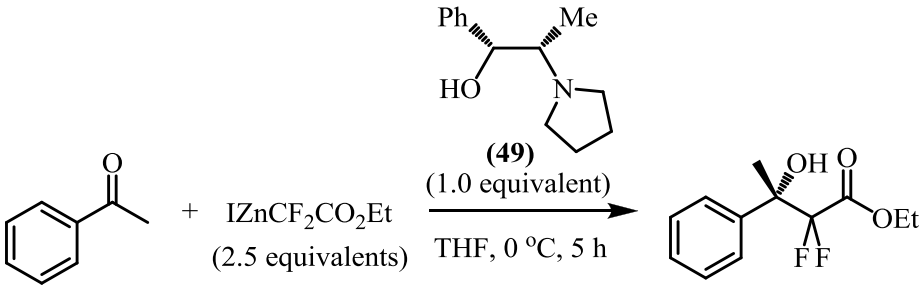
The two step enantioselective Reformatsky reaction has a much wider scope of substrates in comparison to the one-pot method using diethylzinc. In contrast to the results with diethylzinc, a high enantioselectivity was maintained with the two step protocol when the methyl group was substituted by an ethyl group (79 % ee), propyl group (80 % ee), hydrogen atom (78 %) and there was only a small drop in enantiomeric excess to 75 % ee with the bulky *iso*-butyl group. Additionally, both cyclic ketones, indanone (run 9) and tetralone (run 10) gave 100 % conversion and a high 82 % enantiomeric excess. The reaction with *α,β*-unsaturated ketone gave excellent 100 % conversion but the enantiomeric excess was only 13 % ee.

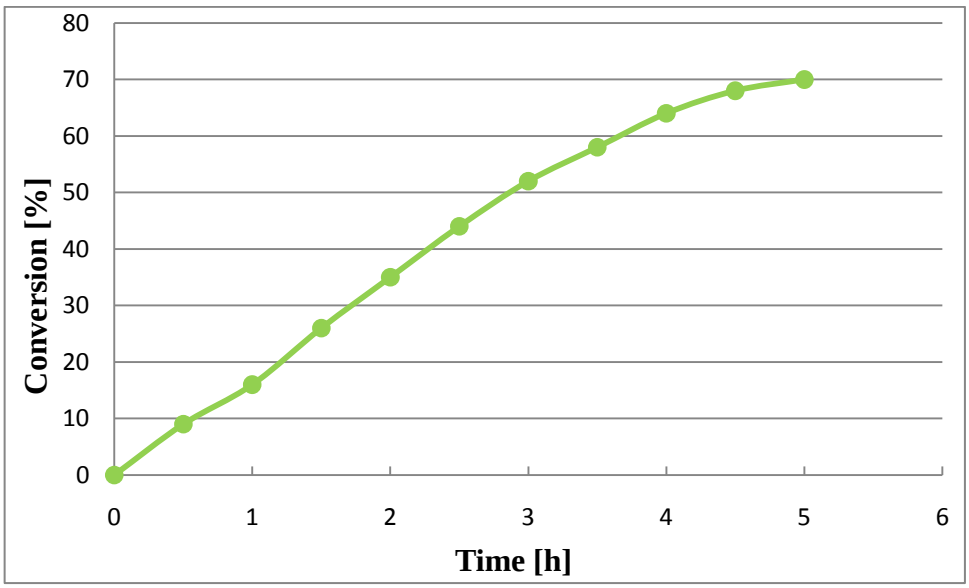
3.7 Comparison between the one-step and two-step protocols

3.7.1 Monitoring of the Reformatsky reactions

Since the two step protocol using the preformed Reformatsky reagent generated from ethyl iododifluoroacetate and zinc dust gave better enantiomeric excess with a series of ketones than the one step protocol, which generated the Reformatsky reagent *in situ* from ethyl iododifluoroacetate and diethylzinc, both of these reactions were monitored by GC.

Figure 3.7 Monitoring of the two step Reformatsky reaction of ethyl iododifluoroacetate and zinc dust with acetophenone.

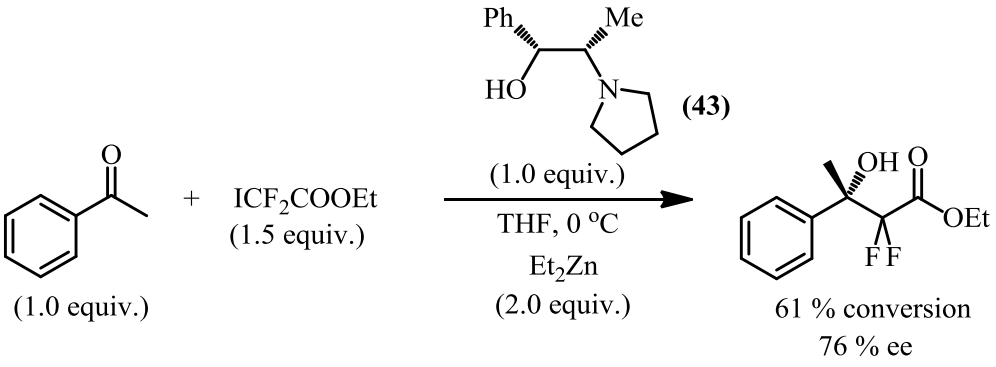


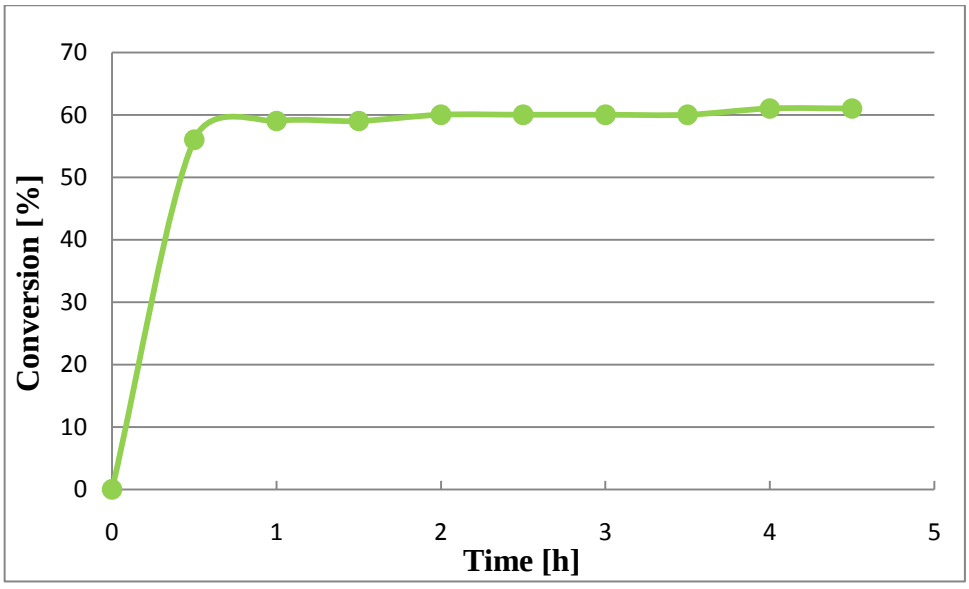


The reaction run in the presence of 1.0 equivalent of the chiral ligand **(49)** and 2.5 equivalents of the Reformatsky reagent prepared from ethyl iododifluoroacetate and zinc dust was monitored first. The samples were collected every 30 minutes over 5 hours. From the graph shown in Figure 3.7, it became apparent that the profile of the

reaction is very different to those obtained for the reaction of acetophenone with ethyl bromodifluoroacetate in the presence of diethylzinc (Figure 3.1). In the first 60 minutes both reactions reached a similar conversion (23 % vs. 17 %). However, after that time the reaction with diethylzinc rapidly slowed down. The reaction with zinc dust progressed with a constant rate up to approximately the fourth hour when the reaction started to slow down.

Figure 3.8 Monitoring of the Reformatsky reaction of ethyl iododifluoroacetate and diethylzinc with acetophenone.





The optimised protocol used in the reaction with ketones in section 3.4 was not practical for monitoring the reaction because it included the addition of aliquots of ethyl iododifluoroacetate and diethylzinc after 2 hours (Table 3.9, run 2). Therefore, the reaction with 1.5 equivalents of ethyl iododifluoroacetate **(50)**, 1.0 equivalent of the chiral ligand **(49)** and 2.0 equivalents of diethylzinc **(45)** at 0 °C was monitored (Table

3.9, run 1). The reaction was extremely fast and the first sample which was collected after 30 minutes showed the maximum conversion which could be obtained under these conditions (Figure 3.8). Because of the difference in the temperature between the reaction vessel (0 ^{o}C) and the syringe used to collect the samples for monitoring (~22 ^{o}C), this could have been a false result. To confirm the result, two reactions were run under the same conditions and were quenched 10 minutes after the addition of diethylzinc. A 78 % conversion and 75 % enantiomeric excess were obtained in both reactions (Table 3.15).

Table 3.15 The Reformatsky reaction of acetophenone with ethyl iododifluoroacetate and diethylzinc at 0 ^{o}C quenched after 10 minutes.

Run	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	78	56	75
2	77	57	75

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

The one-step protocol of the reaction of ethyl iododifluoroacetate and diethylzinc with acetophenone was a much faster reaction than the two step protocol, and consistent with this, gave lower enantiomeric excesses. The results of the reaction monitoring insinuated that the active zinc intermediate generated in the one-step protocol is different to the one generated from ethyl iododifluoroacetate and zinc dust and this may also give rise to different enantiomeric excess. Consequently, the active species of the Reformatsky reagent formed from the one-step and two step protocols were investigated by ^{19}F NMR spectroscopy.

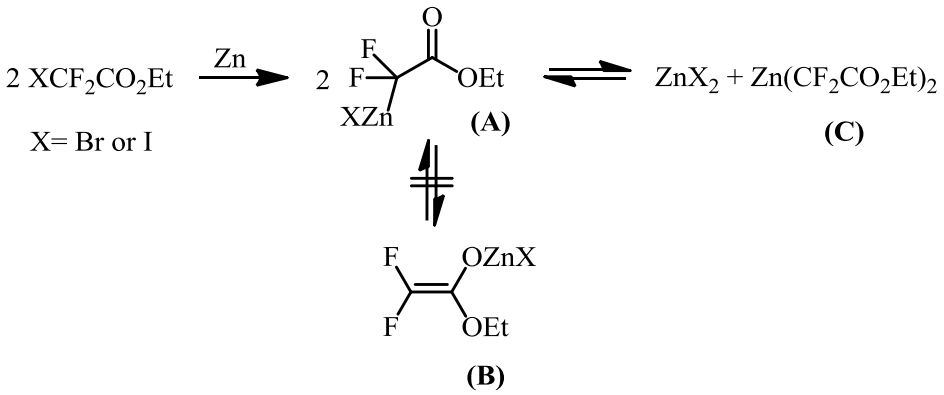
3.7.2 Investigation into the active species of the Reformatsky reagent in one-step protocol using diethylzinc and traditional two step protocol with zinc dust

The results obtained have shown that the rate of the reaction, conversion and the enantiomeric excess obtained in the Reformatsky reaction with ketones depended strongly on whether ethyl iododifluoroacetate or ethyl bromodifluoroacetate was used and whether the reaction was performed with zinc dust or diethylzinc. ^{19}F NMR

spectroscopy was used to observe the active intermediates formed in the reactions between the difluorinated ester and either diethylzinc or zinc dust by the same procedures as those used in the reactions with ketones. Samples were kept under argon in a Young's NMR tube containing a lock tube filled with C_6D_6. Since diethylzinc was used as a 1.0 M solution in hexane, it was impossible to obtain ^{1}H or ^{13}C NMR spectra of the fluorinated species as they would be completely dominated by the signals from the aliphatic solvent. The ^{13}C and ^{19}F NMR spectra of $BrZnCF_2CO_2Et$ were previously reported,[3,9] however, there was no information about the chemical shifts for $IZnCF_2CO_2Et$ in the literature. Also, NMR spectroscopy studies of the reaction between either ICF_2CO_2Et or $BrCF_2CO_2Et$ and Et_2Zn have not been reported before.

Scheme 3.4 shows that the reaction between the difluorinated ester and zinc dust could lead to either the carbon-metallated form **(A)** or the oxygen metallated form **(B)**. The ^{19}F NMR spectrum of **(A)** would be expected to show a singlet, whereas the enolate form **(B)** would have two inequivalent fluorine atoms which should appear as an AB pattern similar to the one reported for ((1-ethoxy-2,2-difluorovinyl)oxy)trimethylsilane.[10] In addition, Scheme 3.4 shows that the reaction is further complicated by a Schlenk equilibrium between the mono-species **(A)** and the bis-species **(C)**.

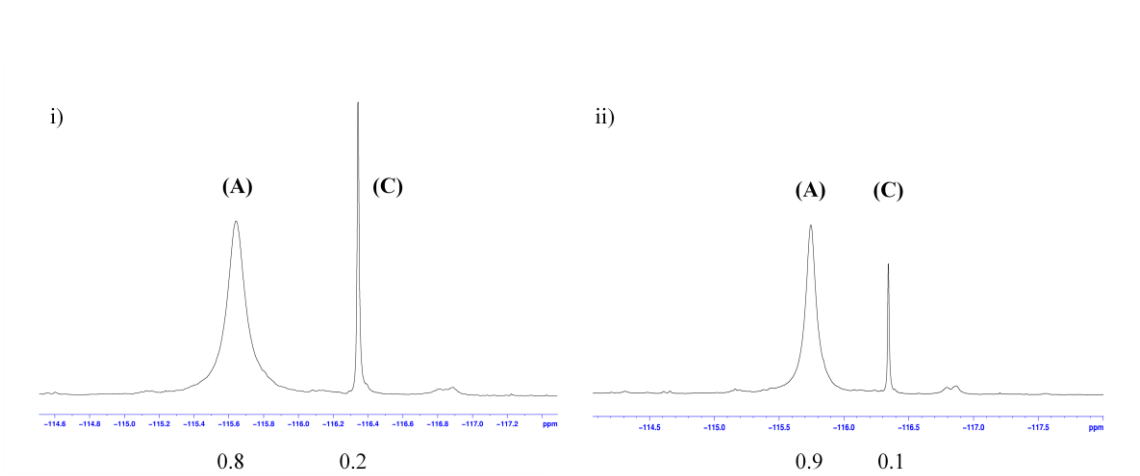
Scheme 3.4 The Schlenk equilibrium in the Reformatsky reagents obtained from either $BrCF_2CO_2Et$ or ICF_2CO_2Et and Zn dust.



In the first experiment the Reformatsky reagent was prepared from the reaction of ethyl bromodifluoroacetate with Zn dust in THF. The two main signals observed were singlets at -115.8 ppm and -116.4 ppm and so, they were assigned to the mono- and bis-carbon-metallated species (Figure 3.9). Similar chemical shifts for the presence

of the Schlenk equilibrium in the Reformatsky reagent formed from ethyl bromodifluoroacetate and zinc dust in triglyme were first reported by Burton.[9] There were also sharp singlets at -120.7 ppm and -128.0 ppm of much lower intensity and these were assigned as ethyl tetrafluorosuccinate and ethyl-2,2-difluoroacetate ($^2J_{HF}$ 52.9 Hz).[11]

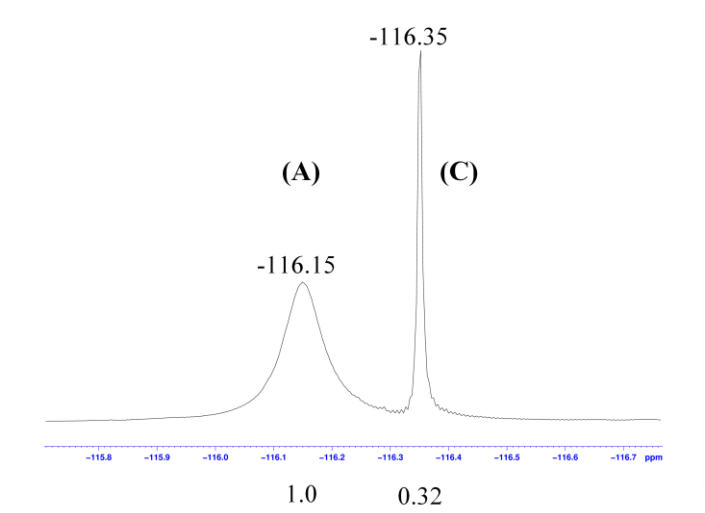
Figure 3.9 The ^{19}F NMR spectra of i) the Reformatsky reagent obtained from ethyl bromodifluoroacetate and zinc dust; ii) the Reformatsky reagent added to anhydrous $ZnBr_2$.



The Schlenk equilibrium was used to assign the mono- **(A)** and the bis-species **(C)**. A sample of the Reformatsky reagent was added to a Young's NMR tube containing anhydrous zinc (II) bromide which shifted the Schlenk equilibrium from 0.8:0.2 to 0.9:0.1 in favour of the mono-species which was assigned as the broad singlet at -115.8 ppm (Figure 3.9 (ii)).

A similar ^{19}F NMR spectrum of the Reformatsky reagent was obtained from the reaction between ethyl iododifluoroacetate and zinc dust. As expected, there were two signals, which could be assigned to the mono- **(A)** and the bis-species **(C)** which were respectively a broad singlet at -116.2 ppm with an integration of 1.0 and a sharp singlet at -116.4 ppm with an integration of 0.32 (Figure 3.10). There were also sharp singlets at -120.7 ppm and -128.0 ppm, assigned to ethyl tetrafluorosuccinate **(12)** and ethyl 2,2-difluoroacetate **(13)**.[12]

Figure 3.10 The ^{19}F NMR spectrum of the Reformatsky reagent obtained from ethyl iododifluoroacetate and zinc dust.



Scheme 3.5 shows the Schlenk equilibrium for the Reformatsky reagent generated from either ethyl iododifluoroacetate or ethyl bromodifluoroacetate with diethylzinc. The ^{19}F NMR spectrum obtained for the reaction of ethyl iododifluoroacetate with diethylzinc showed two singlets at -116.5 ppm and -117.8 ppm. The mono- and the bis-carbon metallated species were assigned by the assumption that the bis-species would always have the same chemical shift regardless of whether the Reformatsky reagent was generated from either zinc dust or diethylzinc. Initially the proportion of the bis-species (δ_F = 116.5 ppm) to the mono-species (δ_F = 117.9 ppm) was 1.0:1.6 (Figure 3.11). The first ^{19}F NMR spectrum was obtained approximately seven minutes after the addition of diethylzinc. The same sample was examined repeatedly by ^{19}F NMR spectroscopy and after 13 minutes the ratio changed to 1.0:1.0, and after 19 minutes it was 1.0:0.9. Within this initial time, soon after the addition of diethylzinc to the ethyl iododifluoroacetate, there was a trace of an AB pattern visible on the ^{19}F NMR spectra. The signals at -123.2 ppm and -124.8 ppm with a coupling constant of 94 Hz were assigned as the oxygen metallated enolate form of the Reformatsky reagent. These signals were no longer present after one hour from the addition of diethylzinc to the ester.

Scheme 3.5 The expected Schlenk equilibrium in the Reformatsky reagents obtained from either $BrCF_2CO_2Et$ or ICF_2CO_2Et and Et_2Zn.

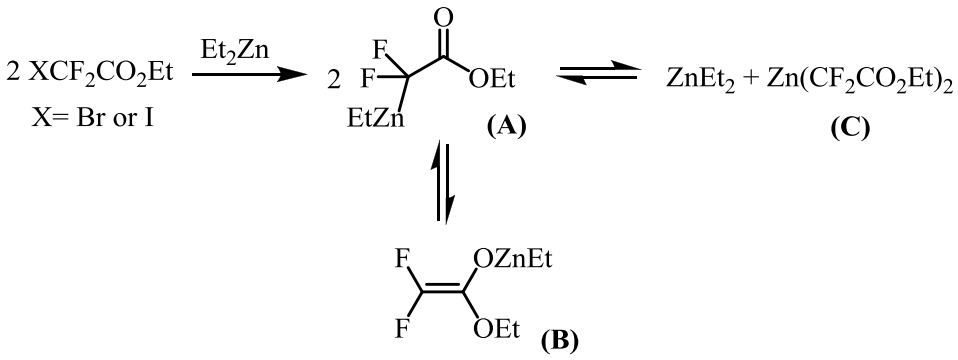
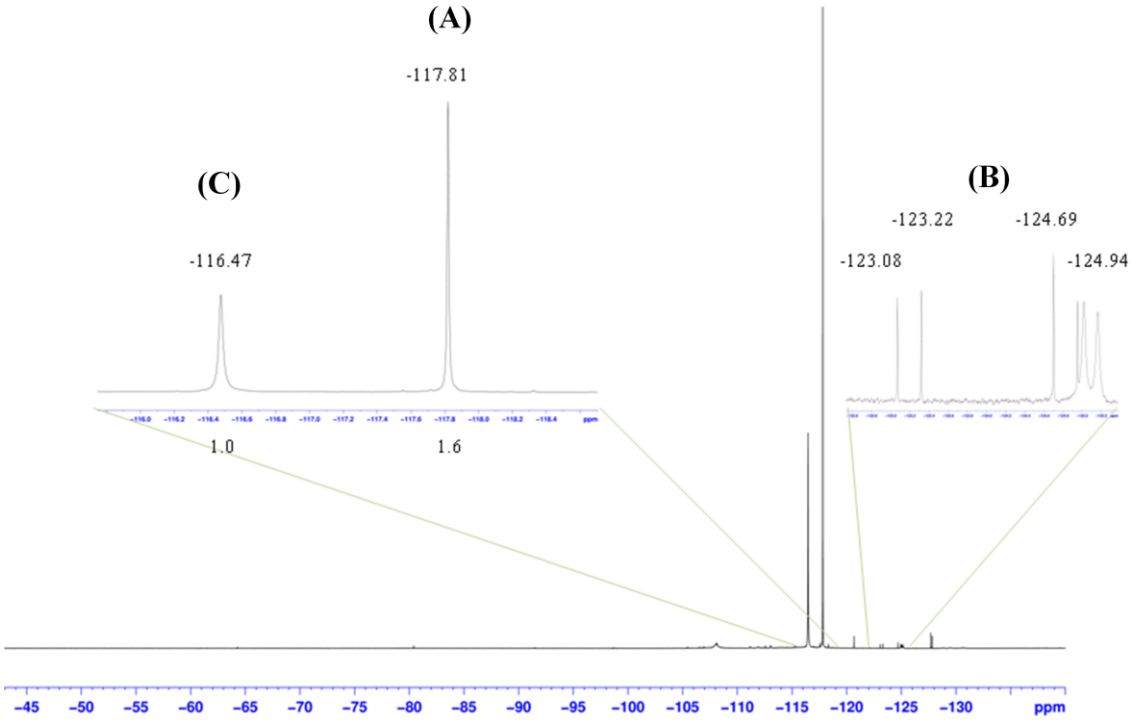


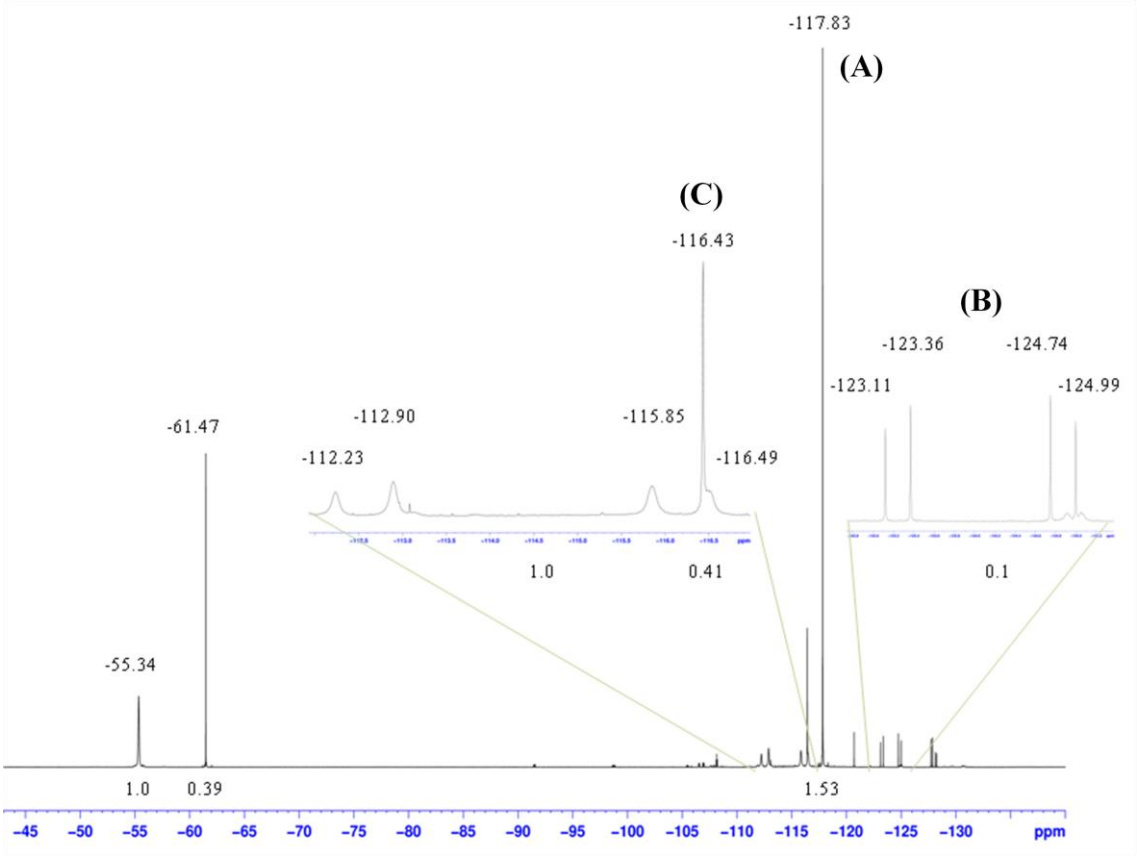
Figure 3.11 The initial ^{19}F NMR spectrum of the Reformatsky reagent obtained from ethyl iododifluoroacetate and diethylzinc.



The ^{19}F NMR spectrum of the Reformatsky reagent obtained from ethyl bromodifluoroacetate and diethylzinc was much more complicated (Figure 3.12). As predicted, there was a singlet for the bis-species and the mono-species of the Reformatsky reagent at -116.4 ppm and -117.8 ppm respectively which was identical to those observed previously in the reagent obtained from ethyl iododifluoroacetate and diethylzinc. There was also a signal for the starting material at -61.5 ppm which was not visible after 80 minutes from the addition of diethylzinc. This provided the evidence

that diethylzinc reacted with ethyl bromodifluoroacetate slower than with ethyl iododifluoroacetate. The AB pattern of signals at -123.3 ppm and -124.9 ppm suggested that the presence of the oxygen metallated enolate form was stronger than the one observed on the spectra obtained for the Reformatsky reagent obtained from ethyl iododifluoroacetate. There were also additional signals in the ^{19}F NMR spectrum which had never been observed in any of the spectra of the Reformatsky reagents obtained previously; a broad singlet at -55.3 ppm and an AB pattern at -112.6 ppm and -116.2 ppm with a coupling constant of 250.2 Hz, which is characteristic for an aliphatic CF_2 group situated next to a chiral centre. The integrations of these two signals were very close to being equal. These signals were more stable than the singlets for the mono- and bis-carbon metallated species of the Reformatsky reagent.

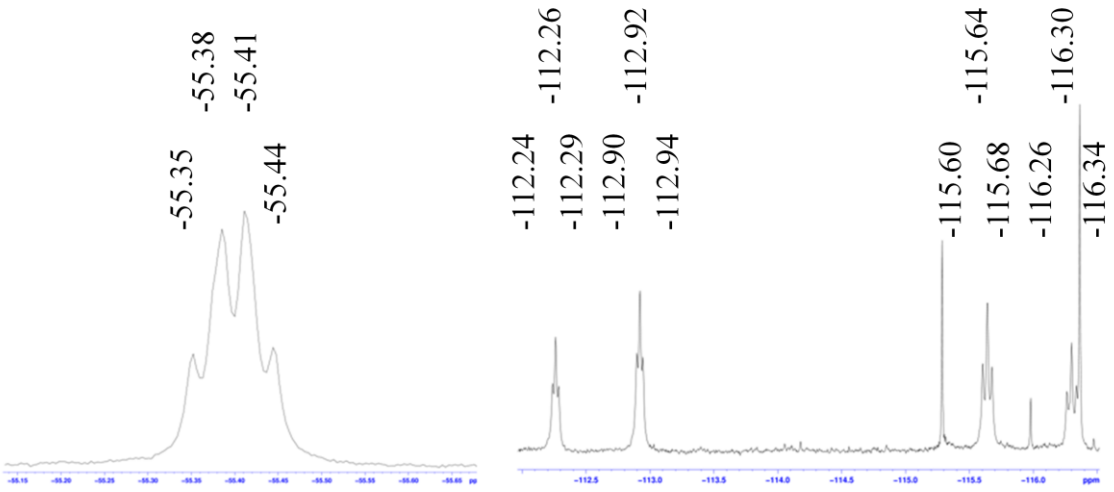
Figure 3.12 The initial ^{19}F NMR spectrum of the Reformatsky reagent obtained from ethyl bromodifluoroacetate and diethylzinc.



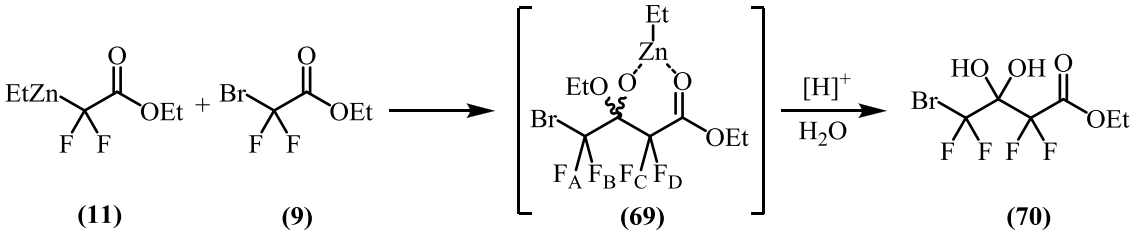
The ^{19}F NMR spectrum obtained in the experiment performed with 0.5 equivalent of diethylzinc showed that these unidentified signals in fact had more complicated structure. As shown in Figure 3.13 the signal at -112.59 ppm is a doublet of

triplets with coupling constants of $^{2}J_{FF}$ = 250 Hz and $^{4}J_{FF}$ = 8.5 Hz, and the signal at -115.97 ppm is a doublet of triplets with coupling constants of $^{2}J_{FF}$ = 250 Hz and $^{4}J_{FF}$ = 13.5 Hz. What in Figure 3.12 was a broad singlet at -55.34 ppm is in fact an AB multiplet at -55.4 ppm (Figure 3.13). These signals were assigned to the intermediate **(69)** (Scheme 3.6). The CF_CF_D group is located next to the chiral centre and has a $^{2}J_{FF}$ coupling constant of 250 Hz, similar to those in *α,α*-difluoro-*β*-hydroxyesters. The intermediate **(69)** was formed as a result of the addition of the mono-species of the Reformatsky reagent to ethyl bromodifluoroacetate. Quenching the reaction with 1 M HCl resulted in the formation of ethyl 4-bromo-2,2,4,4-tetrafluoro-3,3-dihydroxybutanoate **(70)** which was isolated as a co-product in the Reformatsky reaction with 3,3-dimethylbutan-2-one (Table 3.8, run 12) and identified by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. The characteristic ^{19}F NMR spectroscopy signals for compound **(70)** are two triplets at -59.69 ppm and -117.62 ppm with a $^{4}J_{FF}$ coupling constant of 13.8 Hz. These signals were present on the ^{19}F NMR spectra of the crude product obtained in the reaction with acetophenone; however, the Reformatsky reaction with aromatic ketones seems to be much faster than with 3,3-dimethylbutan-2-one and for this reason much less of the co-product **(70)** was formed. Wilkinson's catalyst was used by Kumadaki[2] to increase the rate of formation of the Reformatsky reagent and consequently, there was less unreacted ethyl bromodifluoroacetate to form **(70)** and hence, higher yields were obtained with carbonyl substrates.[13,14]

Figure 3.13 The fluorinated intermediate **(69)** observed in the ^{19}F NMR spectrum of the Reformatsky reagent obtained from ethyl bromodifluoroacetate and diethylzinc.

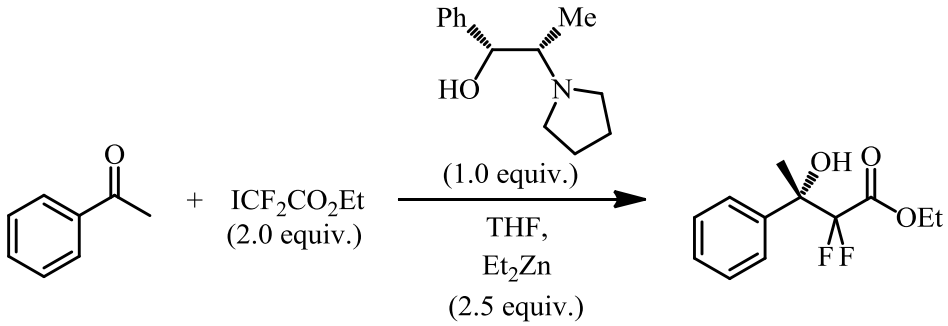


Scheme 3.6 The formation of ethyl 4-bromo-2,2,4,4-tetrafluoro-3-oxobutanoate.



3.8 Final optimisation studies of the one-step protocol

Table 3.16 The Reformatsky reaction of ethyl iododifluoroacetate with acetophenone at temperatures lower than 0 ^{o}C.



Run	Conditions	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]
1	0 ^{o}C	99	92	71
2	-10 ^{o}C	100	90	80
3	-20 ^{o}C	98	95	80
4	-40 ^{o}C	98	86	87
5	-40 ^{o}C	88[d]	79	70
6	-40 ^{o}C	41[e]	-	-
7	-50 ^{o}C	56	46	91

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC, [d] 0.2 equivalents of the chiral ligand, [e] without chiral ligand.

Since the monitoring of the one-step Reformatsky reaction of ethyl iododifluoroacetate with diethylzinc had shown that this reaction is extremely fast at 0 ^{o}C, the reaction was repeated at subzero temperatures (Table 3.16). The protocol was simplified by mixing 2.0 equivalents of ethyl iododifluoroacetate and 1.0 equivalent of

chiral ligand 30 minutes before the addition of 2.5 equivalents of diethylzinc with no addition of further aliquots. The temperature was monitored by the internal thermometer and the reaction mixture was stirred for 4.5 hours. The reaction at -10 ^{o}C gave 100 % conversion and an improved 80 % enantiomeric excess (run 2) compared to the reaction performed at 0 ^{o}C (run 1). The reaction at -20 ^{o}C gave 98 % conversion and an unimproved 80 % enantiomeric excess (run 3) but at -40 ^{o}C the reaction reached the same 98 % conversion and the enantiomeric excess improved to an excellent 87 % ee (run 4). The same conditions were repeated with 0.2 equivalents of the chiral ligand and gave a very good 88 % conversion showing that the reaction can be performed with a catalytic amount of the chiral ligand, but the enantiomeric excess decreased to 70 % ee (run 5). This was most likely caused by the achiral background reaction as the reaction performed at -40 ^{o}C without the chiral ligand gave 41 % conversion (run 6). Finally, the reaction performed in the presence of 1.0 equivalent of the ligand at -50 ^{o}C resulted in decreased conversion (56 %) with only a slight improvement in the enantiomeric excess to 91 % ee (run 7).

Table 3.17 The Reformatsky reaction of ethyl iododifluoroacetate and diethylzinc with acetophenone in the presence of 1.0 equivalent of the chiral ligand at -78 ^{o}C.

Run	**Conditions**	**Conversion**[a] **[%]**	**Yield**[b] **[%]**	**Ee**[c] **[%]**
1	-78 ^{o}C	50	46	91
2	-78 ^{o}C to -10 ^{o}C	99	94	84
3	-78 ^{o}C, preformed reagent	72	62	88
4	-78 ^{o}C, 0.2 equiv. of ligand	21	16	88
5	-78 ^{o}C, No ligand	0	-	-

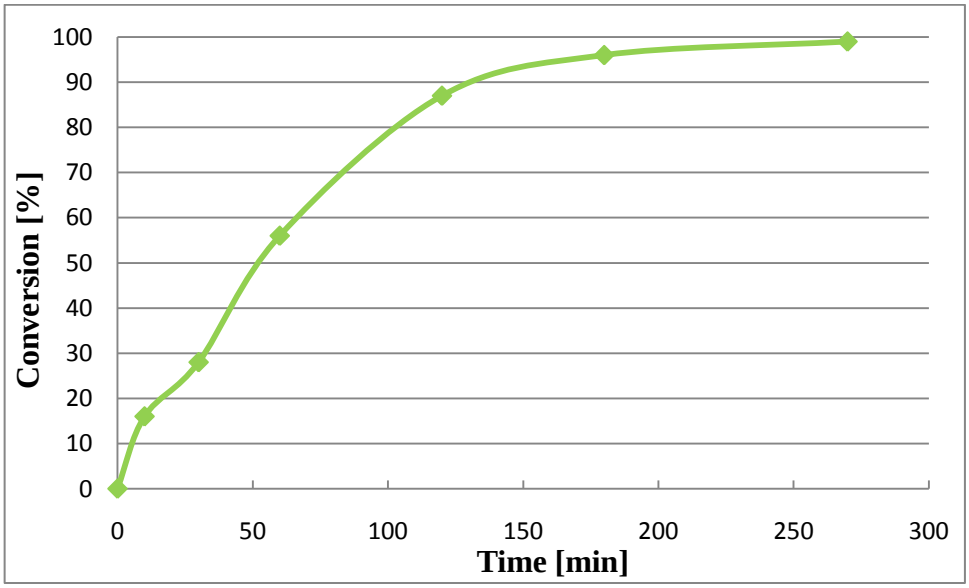
[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

The final step of the optimisation studies are shown in Table 3.17. The reaction with 2.0 equivalents of ethyl iododifluoroacetate in the presence of 1.0 equivalent of the ligand run at -78 ^{o}C yielded a 50 % conversion and an excellent 91 % enantiomeric excess (run 1). In the next approach diethylzinc was added at -78 ^{o}C but after 10 minutes the temperature was allowed to gradually increase to -10 ^{o}C over a period of 45 minutes (run 2). As expected, the conversion improved (99 %), but the enantiomeric

excess dropped to 84 % (run 2). In the next approach a solution of 2.0 equivalents of the Reformatsky reagent was formed at 0 ^{o}C by reacting ethyl iododifluoroacetate and diethyl zinc before cooling this mixture to -78 ^{o}C and adding it to the solution of 1.0 equivalent of acetophenone and 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol (run 3). After 4.5 hours of stirring the reaction mixture at -78 ^{o}C, the desired product was obtained in 72 % conversion with only a small drop in the enantiomeric excess (88 % ee). This result shows that the lower conversion obtained at -78 ^{o}C was not only caused by the slower addition of the Reformatsky reagent to the ketone but also by a slower rate of formation of the Reformatsky reagent. The reaction at -78 ^{o}C performed with 0.2 equivalents of the chiral amino alcohol gave an excellent 88 % enantiomeric excess but only 21 % conversion (run 4). This very small decrease in the enantiomeric excess compared to the reaction performed with 1.0 equivalent of the chiral ligand shows that at -78 ^{o}C there was no background reaction which was later confirmed in run 5. These results indicate that the presence of the minor enantiomer may not only be the consequence of the achiral reaction between the Reformatsky reagent and acetophenone, but a small quantity of this unwanted product could be formed within the chiral bimetallic intermediate proposed in Figure 3.6.

In the Reformatsky reaction of ethyl iododifluoroacetate and acetophenone the best balance between conversion and enantiomeric excess was obtained at -40 ^{o}C (Table 3.16, run 4). Therefore, the reaction of 2.0 equivalents of ethyl iododifluoroacetate in the presence of 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol and 2.5 equivalents of diethylzinc was monitored. It soon turned out to be impossible to collect the samples with a syringe as the difference in the temperature between the syringe and the flask increased the conversion in the sample giving false results. To overcome this problem a series of reactions were run under the optimised conditions and each of them was quenched after a certain period of time. The obtained conversions were used to prepare a graph of the conversion against time for the reaction (Figure 3.14). The reaction was significantly slower compared to the one run at 0 ^{o}C. This method allowed an excellent 86 % enantiomeric excess to be determined in the sample which was quenched 30 minutes after the addition of diethylzinc. This proved that the excellent enantiomeric excess was maintained throughout the reaction and there was no significant improvement in the last few hours when the reaction was slowing down.

Figure 3.14 Monitoring of the Reformatsky reaction of ethyl iododifluoroacetate with diethylzinc and acetophenone in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)** at -40 °C.



Finally, the convenient one-step protocol was screened with a range of aromatic ketones under the optimised conditions (Scheme 3.7, Table 3.18). When the aromatic ring was substituted with electron-donating and electron-withdrawing groups, the excellent enantiomeric excess was maintained at 85-91 % ee and the excellent conversion was only lowered when a methoxy group was in the *ortho*-position. The reaction worked well with a range of aromatic ketones and the aliphatic group can be a methyl (86 % ee), ethyl (81 % ee), propyl (81 % ee) or iso-butyl (84 % ee) group. The enantiomeric excess did, however, decrease to 76 % when a hydrogen atom replaced the methyl group in benzaldehyde. Excellent conversions and enantiomeric excesses (84-90 % ee) were also obtained with the two cyclic ketones, indanone and tetralone.

Scheme 3.7 Screening of a series of ketones under the optimised conditions.

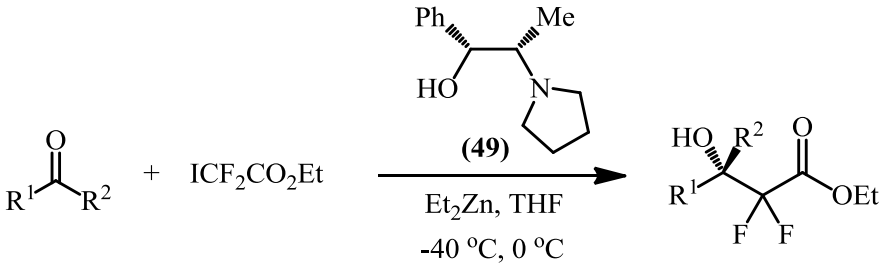


Table 3.18 Screening of a series of ketones under the optimised conditions.

Run	Ketones	Conversion[a] [%]	Yield[b] [%]	Ee[c] [%]	Optical rotation [°]	Product No.
1	Acetophenone	97	90	86*(S)*	10.723	**(48)**
2	*p*-Methoxyacetophenone	93	78	89	17.988	**(52)**
3	*o*-Methoxyacetophenone	66	57	91	-15.257	**(53)**
4	*p*-Chloroacetophenone	99	79	85	14.655	**(51)**
5	Propiophenone	72	59	81*(S)*	5.529	**(54)**
6	1-Phenylbutan-1-one	85	62	81	15.493	**(55)**
7	3-Methyl-1-phenylbutan-1- one	79	62	84	3.837	**(56)**
8	Indanone	88	85	84	-7.678	**(57)**
9	Tetralone	80	69	90*(S)*	1.264	**(58)**
10	Benzaldehyde	100	88	76	12.979	**(44)**

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

3.9 Conclusions

Two different approaches have been developed for the asymmetric reaction of ethyl iododifluoroacetate with aromatic ketones for the first time. In the traditional two-step Reformatsky reaction with ethyl iododifluoroacetate and zinc dust at 0 °C, good isolated yields (63-99 %) and high enantiomeric excesses (75-84 %) were obtained. The more convenient one-pot asymmetric Reformatsky reaction with ethyl iododifluoroacetate and diethylzinc at -40 °C also gave good isolated yields (62-90 %) combined with even better enantiomeric excesses (81-91 %). The absolute configuration of the chiral centre in the product obtained from both approaches in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol was determined to be (*S*).

3.10 References

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Chapter Four

The Asymmetric Reformatsky reaction of Ethyl Iodofluoroacetate with Ketones

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Leicester

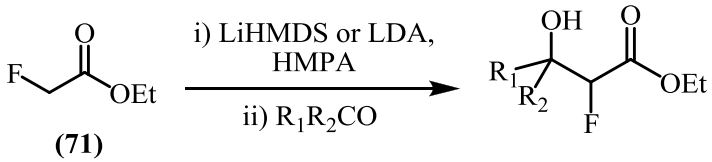
4.1 Introduction

The development of new methods for introducing fluorine into molecules has always been highly desirable to the pharmaceutical and the agrochemical industries due to fluorine's ability to enhance the biological activity of the molecules. The insertion of a single fluorine atom is often more tolerated by the biological systems than larger polyfluorinated groups. Asymmetric fluorination is particularly challenging. Several methods using electrophilic fluorinating reagents, including reactions with enantioselective fluorinating reagents, asymmetric catalysis with transition metal catalysts and organocatalysts have been used to make new fluorinated chiral centres. A different approach to the problem is asymmetric synthesis using a fluorinated building block. In this chapter, the development of an asymmetric synthesis of α-fluoro-*β*-hydroxy esters by the Reformatsky reaction of ethyl iodofluoroacetate with ketones in the presence of a chiral aminoalcohol will be discussed.

4.1.1 The aldol reaction

The first successful synthesis of *α*-fluoro-*β*-hydroxy esters from aldehydes and ketones by the aldol reaction with ethyl fluoroacetate **(71)** was reported by Welch *et al*. in 1984 (Scheme 4.1).[1] A high conversion of **(71)** to the lithium enolate was achieved with either lithium bis(trimethylsilyl)amide (LiHMDS) or lithium diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) between -105 ^{o}C and -85 ^{o}C. The reaction was very fast and was completed 10 minutes after the addition of the carbonyl molecule to give yields of 55-96 %. Nonetheless, the reaction suffered from a lack of diastereomeric control and the fact that ethyl fluoroacetate **(71)** is extremely toxic.

Scheme 4.1 The aldol reaction of ethyl fluoroacetate with aldehydes and ketones.

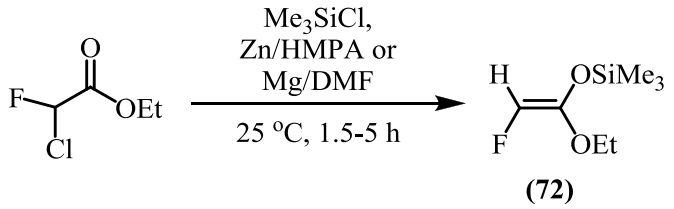


(71)

Chen *et al*. prepared (1-ethoxy-2-fluorovinyloxy)trimethylsilane **(72)** from ethyl chlorofluoroacetate. The reaction of activated zinc dust and trimethylsilylchloride in HMPA or DMF gave a high conversion to the enol (Scheme 4.2).[2] After purification,

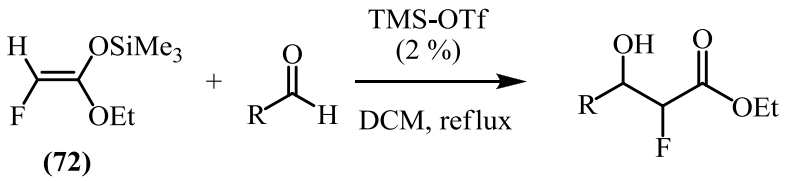
which included an aqueous work-up, extraction with diethyl ether and distillation under reduced pressure, a very good isolated yield (80 %) was obtained. In contrast to the difluorinated silyl enol ether,[3] which reacted with benzaldehyde at -78 ^{o}C in the absence of catalyst, **(72)** was inert even in the presence of a range of Lewis acid catalysts at 25-50 ^{o}C. The reaction of **(72)** with aldehydes performed in DCM in the presence of 2 % Me_3Si-OTf under reflux gave good results with deactivated and activated aromatic aldehydes (Table 4.1, runs 1-5). However, the conversions obtained in the reactions with the highly activated aromatic aldehyde (run 6) and aliphatic aldehydes (run 7) were only 70 % and 60 % respectively and purification was not attempted.

Scheme 4.2 Synthesis of α-fluoro silyl enol ethers.



(72)

Table 4.1 Me_3Si-OTf promoted aldol reaction of **(72)** with aldehydes.[2]



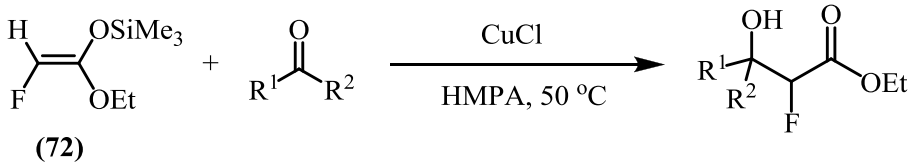
(72)

Run	R	Conv.[a] [%]	Yield[b] [%]	*Syn*/*anti*[c]
1	Ph	100	81	53:47
2	*p*-$CF_3C_6H_4$	100	85	54:46
3	*m*-$CF_3C_6H_4$	100	80	50:50
4	*p*-$NO_2C_6H_4$	100	87	56:44
5	*p*-$CH_3C_6H_4$	100	60	44:56
6	*p*-$CH_3OC_6H_4$	70	-	-
7	$CH_3CH_2CH_2$	60	-	-

[a] Determined by ^{19}F NMR spectroscopy, [b] isolated yield, [c] determined by ^{19}F NMR spectroscopy.

The reaction with *p*-methylbenzaldehyde was repeated in HMPA at 50 °C (Table 4.2) and a 100 % conversion with a 55 % isolated yield was obtained (run 1). In the next attempt, the reaction was promoted by 1.1 equivalents of CuCl and even though the conversion was the same, a higher isolated yield (84 %) was observed (run 2). The reaction also gave good results with *p*-methoxybenzaldehyde (run 3) and an aromatic (runs 4) and aliphatic ketone (run 5). Only very low diastereomeric ratios were obtained in each case (runs 2-4).

Table 4.2 CuCl promoted aldol reaction of **(72)** with aldehydes and ketones.[2]

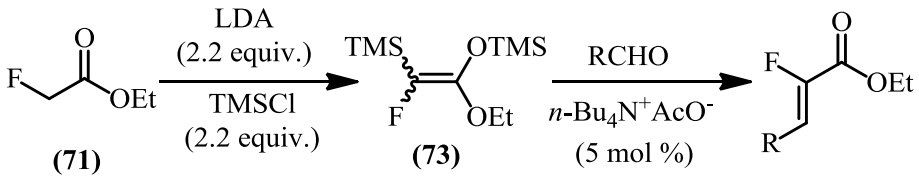


(72)

Run	R^1	R^2	Yield[a] [%]	*Syn*/*anti*[b] [%]
1	*p*-$CH_3C_6H_4$	H	55[c]	-
2	*p*-$CH_3C_6H_4$	H	84	53:47
3	*p*-$CH_3OC_6H_4$	H	82	62:38
4	C_6H_5	CH_3	76	44:56
5	cyclohexanone		72	-

[a] Isolated yield, [b] determined by ^{19}F NMR spectroscopy, [c] the reaction without CuCl.

Scheme 4.3 Synthesis of *α*-fluoro-α-unsaturated esters.[4]



(71) **(73)**

Z:E = 1:1

There are also examples of the monofluorinated aldol reaction with aldehydes and ketones, which yielded *α*-fluoro-α-unsaturated esters, known as *α*-fluoroacrylates. The reaction of fluoro(trimethylsilyl)ketene ethyl trimethylsilyl acetal **(73)** with aldehydes resulted in the formation of *α*-fluoroacrylates in high yields (Scheme 4.3). The (*Z*) diastereomer was obtained as almost an exclusive product in all reactions apart from

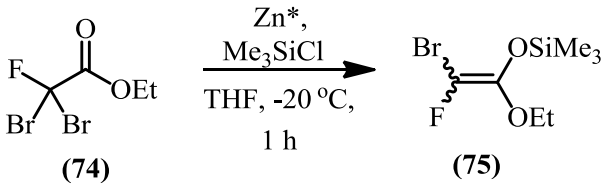
one run with an *α*,*β*-unsaturated aldehyde. In this case the diastereomeric ratio was (*Z*):(*E*) = 83:17.[4]

4.1.2 The asymmetric Mukaiyama aldol reaction of ethyl dibromofluoroacetate

An asymmetric aldol reaction of bromofluoroketene silyl acetal **(75)** with aldehydes was reported by Iseki.[3,5] Initially, compound **(75)** was synthesised by the reaction of ethyl dibromofluoroacetate **(74)** with zinc dust and trimethylsilylchloride in THF (Scheme 4.4). Compound **(75)** had to be extremely pure in order to get a high enantiomeric excess in the subsequent reactions with aldehydes and a long purification that consisted of three cycles of filtration/distillation was used. Compound **(75)** was then used in the aldol reaction with a range of aldehydes which was promoted by Masamune's catalyst. In general, very good yields (90-96 %) were obtained with most aldehydes (Table 4.3). Only the reactions with hindered carbonyls (runs 4 and 7) gave lower yields (70-74 %). The enantiomeric excesses for these reactions were very high (89-99 % ee) except for the *α*,*β*-unsaturated aldehyde (run 2), which gave a lower 83 % ee.

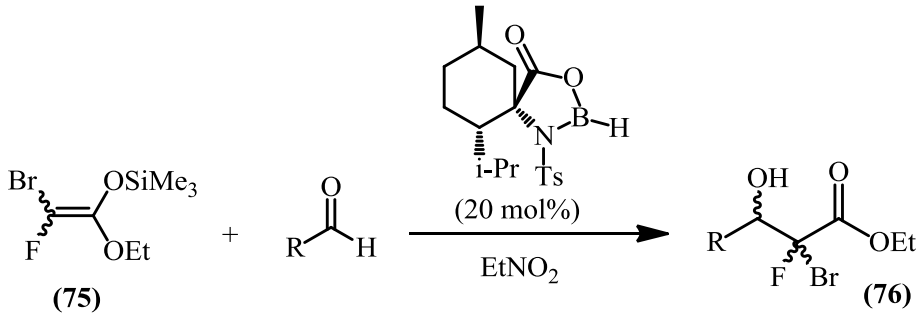
The absolute configuration of ethyl *α*-bromo-*α*-fluoro-*β*-hydroxy-*β*-phenylpropanoate **(76)** obtained in the reaction with benzaldehyde (run 1) was determined as (2*S*,3*R*) for the major and (2*R*,3*R*) for the minor diastereoisomer. This was achieved by X-ray crystallography of the product from the reaction of **(76)** with enantiomerically pure (1*S*)-(-)-camphanic chloride. Finally, compound **(76)** was reduced with $Bu_3SnH/Et_3Al/Et_3B$ to the corresponding ethyl *α*-fluoro-*β*-hydroxy-*β*-phenylpropanoate **(77)** (Scheme 4.5). Not only was the yield very high (95 %) and a high enantiomeric excess (98 % ee) was maintained but, more significantly, the diastereomeric excess improved from 69:31 to 91:9. It was not mentioned if the enantiomeric excess was determined for both diastereoisomers or only the major diastereoisomer. The main drawback of this reaction is the unavoidable long purification of the starting material **(75)**.

Scheme 4.4 Synthesis of bromofluoroketene silyl acetal **(75)**.



(74) **(75)**

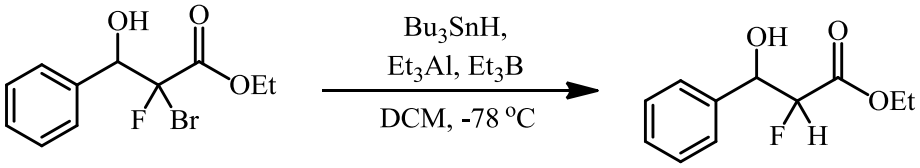
Table 4.3 Enantioselective aldol reaction of **(75)** with aldehydes.[5]



Run	Carbonyl compound	*Syn*/*anti*[a] [%]	Ee[b] [%]	Yield[c] [%]
1	benzaldehyde	69:31	98 (2*S*,3*R*), 90(2*R*,3*R*)[d]	90
2	(*E*)-C_6H_5CH=$CHCHO$	57:43	83, 83	96
3	$C_6H_5CH_2CH_2CHO$	46:54	98, 98	89
4	c-$C_6H_{11}CHO$	52:48	94, 89	74
5	$CH_3CH_2CH_2CHO$	46:54	97, 98	90
6	$(CH_3)_2CHCH_2CHO$	48:52	98, 98	96
7	$(C_2H_5)_2CHCHO$	54:46	99, 98	70

[a] Determined for isolated yields, [b] determined by chiral HPLC, [c] isolated yields, [d] determined by X-ray crystallography after reaction with (1*S*)-(-)-Camphanic chloride.

Scheme 4.5 Reduction of ethyl *α*-bromo-*α*-fluoro-*β*-hydroxy-*β*-phenylpropanoate **(77)**.[8]



(76)
Syn / *Anti*
69 % : 31%
ee= 98 %, 90 %

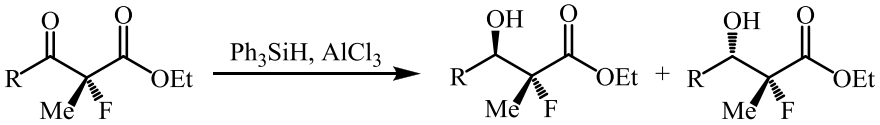
(77)
Syn / *Anti*
91 % : 9%
ee= 98 %

Ishihara *et al.* have also reported the reduction of racemic ethyl *α*-bromo-*α*-fluoro-*β*-hydroxy esters obtained in the Reformatsky reaction of ethyl dibromofluoroacetate with aldehydes to ethyl *α*-fluoro-*β*-hydroxy esters.[6,7] The reduction with trimethylaluminium and tributyltin hydride in the presence of triethylborane in toluene at -78 °C gave good results and diastereomeric excesses similar to the one reported by Iseki.[8]

4.1.3 A highly diastereoselective reduction of *α*-fluoro-*α*-methyl-*β*-keto esters

Kitazume reported that the reduction of enantiomerically pure *α*-fluoro-*α*-methyl-*β*-keto esters with hydrosilanes gave *α*-fluoro-*α*-methyl-*β*-hydroxy esters with the retention of a high enantiomeric excess (Table 4.4).[9] The enantiomerically pure starting materials were obtained by enzymatic methods,[10-12] which allowed higher enantiomeric excesses to be obtained than by asymmetric synthesis.[13,14] Table 4.4 summarises the results of the reduction of *α*-fluoro-*β*-keto esters with the combination of Ph_3SiH and $AlCl_3$. Good yields and excellent diastereomeric excesses were obtained. Unfortunately, the presence of the methyl group next to the fluorine was essential as the difference in size between the methyl and the fluorine in the *α*-fluoro-*α*-methyl-*β*-keto ester was responsible for the high diastereomeric excess obtained during the reduction with hydrosilanes.

Table 4.4 Diastereoselective reduction of the enantiomerically pure *α*-fluoro-*α*-methyl-*β*-keto esters.[9]



anti (erythro) *syn* (threo)

Run	R	Conditions	*Anti*/*syn* [%]	Yield[a] [%]
1	Me	0 °C, 2 h	97:3	57
2	Et	rt, 2 h	98:2	64
3	*n*-Pr	rt, 4 h	99:1	77
4	*n*-Bu	rt, 3 h	98:2	63
5	Ph	rt, 5 h	99:1	68

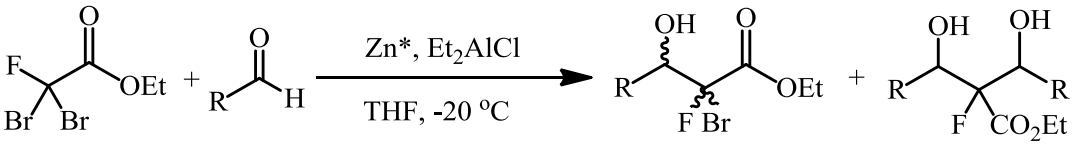
[a] Isolated yield.

4.1.4 The Reformatsky reaction of ethyl dibromofluoroacetate with diethylzinc

Ishihara reported the Reformatsky reaction of ethyl dibromofluoroacetate **(74)** with a small excess of an aldehyde or ketone in the presence of zinc and diethylaluminium chloride.[15] The reaction yielded mainly ethyl *α*-bromo-*α*-fluoro-*β*-hydroxy esters; however, other co-products were present (Table 4.5). The optimised temperature was -20 °C; even though the low temperature led to low conversion, it

reduced the formation of the co-product which was abundant in reactions performed at higher temperatures. Under the optimised conditions only 2-19 % of dihydroxyester was isolated. Good yields (66-77 %) were obtained in the reactions with aldehydes (runs 1-8) in comparison to only 49 % yield with an aliphatic ketone (run 9). In the reaction with 3-pentanone, the co-product was isolated in 15 % yield and identified as *α*-fluoro-*α*,*β*-unsaturated ester (run 9). The reaction of aldehydes with an excess of **(74)** gave 70-79 % yield of dihydroxyester and 10-20 % yield of *α*-fluoro-*α*,*β*-unsaturated ester.

Table 4.5 Zinc-diethylaluminium chloride promoted Reformatsky reaction of ethyl dibromofluoroacetate **(74)** with aldehydes.[15]



(74)

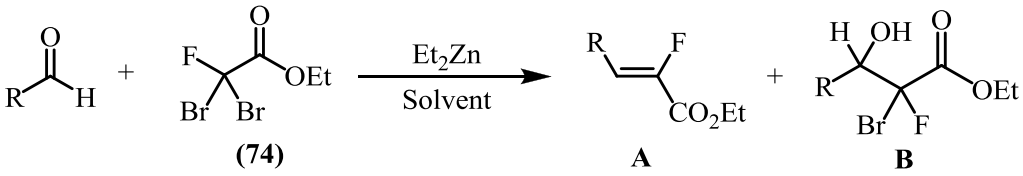
Run	R	Yield[a] [%]	De (erythro/threo)[b] [%]	Yield[c] [%]
1	$CH_3CH_2CH_2$-	69	67:33	13
2	$(CH_3)_2CHCH_2$-	70	67:33	2
3	*c*-C_6H_{11}-	67	63:37	14
4	CH_3CH=CH-	68	55:45	19
5	C_6H_5-	71	59:41	8
6	*p*-$CH_3C_6H_4$-	77	51:49	3
7	*p*-$CH_3OC_6H_4$-	74	52:48	2
8	*p*-ClC_6H_4-	66	63:37	15
9	3-pentanone	49	-	15[d]

[a] Isolated product, [b] determined by ^{19}F NMR spectroscopy, [c] isolated yield of *β*,*β*-dihydroxy ester, [d] the co-product was identified as *α*-fluoro-*α*,*β*-unsaturated ester.

Jubault *et al*. studied the Reformatsky reaction of ethyl dibromofluoroacetate **(74)** with aldehydes and ketones promoted by diethylzinc.[16] The initial reaction with aldehydes yielded a mixture of two products: *α*-bromo-*α*-fluoro-*β*-hydroxy esters and *α*-fluoro-*α*-unsaturated ester (Table 4.6). The conditions were optimised with the substrate *p*-methoxybenzaldehyde, and the reaction in THF at room temperature with two equivalents of diethylzinc gave ethyl *α*-bromo-*α*-fluoro-*β*-hydroxy-*β*-(*o*-

methoxyphenyl)propanoate as the exclusive product, although with poor diastereoselectivity (run 1). In the next approach, the amount of diethylzinc was increased to 4.0 equivalents which resulted in a mixture of 51 % *α*-fluoroacrylate and 49 % *α*-bromo-*α*-fluoro-*β*-hydroxy-*β*-(*o*-methoxyphenyl)propanoate (run 2) and a small improvement in the diastereomeric excess. In run 3 the solvent was changed to DCM and the ratio of the product changed to 63:37 in favour of *α*-fluoro-*α*-unsaturated ester. The obtained *β*-hydroxyester was almost a single diastereoisomer (*syn*). A range of aldehydes were then screened (runs 4-10) and in all cases the mixture of the two products were obtained. All isolated *α*-fluoroacrylates contained (*Z*)-alkenes and the *α*-fluoro-*β*-hydroxy esters were in most cases the pure *syn* diastereoisomers. The product of the reactions with *o*-formylbenzonitrile (run 7) gave a lower diastereomeric excess of 80 % de. There was no diastereomeric control in the reaction with an aliphatic aldehyde (run 9).

Table 4.6 The Reformatsky reaction of ethyl dibromofluoroacetate with aldehydes.[16]



(74) **A** **B**

Run[a]	**R**	**Yield**[b] **[%]**	**Ratio of the products (A:B)**[c]	***anti*/*syn***[c] **[%]**
1[d]	*p*-MeO-C_6H_4	96	0:100	45:55
2[e]	*p*-MeO-C_6H_4	51	51:49	24:76
3	*p*-MeO-C_6H_4	84	63:37	<1:99
4	C_6H_5	80	35:75[f]	<1:99
5	*p*-CH_3-C_6H_4	84	63:37	<1:99
6	*p*-F-C_6H_4	90	59:41	<1:99
7	*p*-CN-C_6H_4	62	56:44	10:90
8	$C_6H_5(CH_2)_2$	67	58:42	<1:99
9	$CH_3(CH_2)_4$	85	63:37	45:55

[a] The reaction with 4 equiv. of Et_2Zn in DCM for 3 hours at r.t., [b] isolated yield, [c] determined by ^{19}F NMR spectroscopy or GC-MS on the crude product, [d] the reaction with 2 equivalents of Et_2Zn in THF for 2 h, [e] the reaction in THF with 4 equiv. of Et_2Zn for 3 days, [f] as reported.

Using the optimised conditions for aldehydes, the reaction was repeated with acetophenone and resulted in 52 % of (*E*)-*α*-fluoroacrylate and 20 % of ethyl *α*-bromo-*α*-fluoro-*β*-hydroxy-*β*-phenylbutanoate being isolated (Scheme 4.6). In contrast to the previous reaction, the *anti*-*β*-hydroxyester was formed preferentially (95 %). When the reaction was repeated under reflux conditions and was stopped when *β*-hydroxyester was no longer detectable by ^{19}F NMR spectroscopy, ethyl *α*-fluoro-*β*-phenylbut-*α*-enoate was obtained as the exclusive product.

Scheme 4.6 The Reformatsky reaction of ethyl dibromofluoroacetate with acetophenone.[16]

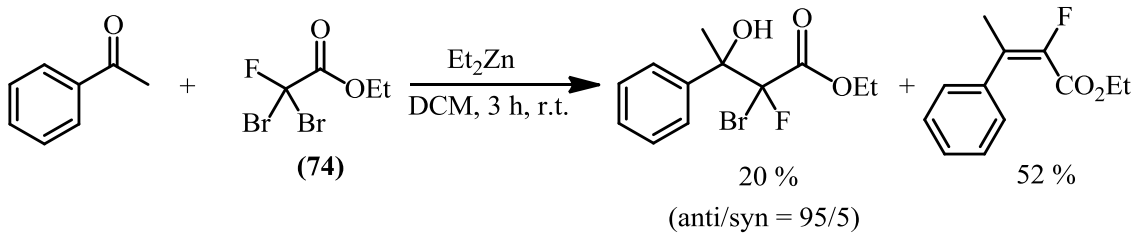
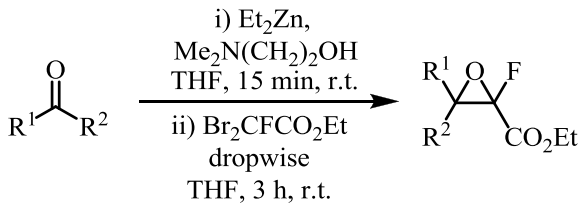


Table 4.7 The Reformatsky reaction of ethyl dibromofluoroacetate in presence of *N*,*N*-dimethylaminoethanol.[17]



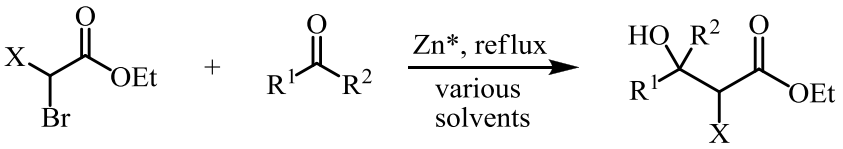
Run	R^1	R^2	Yield[a] [%]	*cis*:*trans*[a] [%]
1	Ph	Me	83	47:53
2	Ph	Et	>95	44:56
3	Ph	*i*Pr	98[b]	9:91
4	Ph	*t*Bu	98[b]	7:93
5	Ph	Ph	>95	-
6	*i*Pr	Me	>95	52:48

[a] Determined on crude mixture (based on the recovered mass) by ^{19}F NMR and ^{1}H NMR spectroscopy, [b] purified by silica gel column chromatography.

Recently, Jubault reported that the addition of dimethylaminoethanol to diethylzinc and the ketone followed by dropwise addition of ethyl dibromofluoroacetate **(74)** resulted in the formation of monofluorinated epoxides (Table 4.7).[17] Good stereocontrol was obtained only in the reaction with ketones that contained one bulky side (runs 3 and 4) and unfortunately, the rest of the ketones screened did not give any diastereomeric excess. A *trans* configuration was confirmed as the major diastereoisomer.

4.1.5 The Reformatsky reaction of ethyl bromoacetate and ethyl bromofluoroacetate

Table 4.8 The Reformatsky reaction of ethyl bromoacetate and ethyl bromofluoroacetate with aldehydes and ketones.[18]



X= H **(78)**
F **(79)**

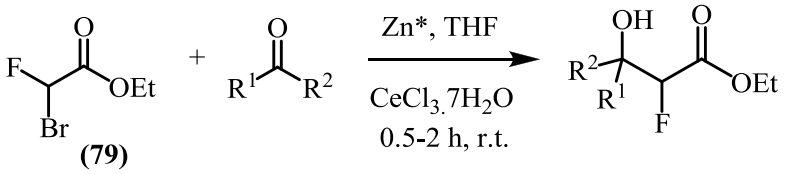
Run	Carbonyl compound	$BrCFHCO_2Et$ Yield[a] [%]	$BrCH_2CO_2Et$ Yield[a] [%]
1	C_6H_5CHO	68	67
2	$CH_3(CH_2)_5CHO$	50	54
3	$(CH_3)_3CCHO$	39	46
4	$CH_3HC{=}CHCHO$	58	61
5	$C_6H_5HC{=}CHCHO$	27	53
6	$C_4H_9COC_2H_5$	56	54
7	acetophenone	29	98
8	$C_6H_5COC_6H_5$	14	95
9	$C_6H_5HC{=}CHCOC_6H_5$	12	98
10	$(CH_3)_2C{=}CHCOH_3$	44	55

[a] Isolated yield.

The first example of the Reformatsky reaction of ethyl bromoacetate **(78)** was reported by McBee (Table 4.8).[18] A solution of **(78)** and a solution of the carbonyl

compound were added simultaneously to a suspension of activated zinc dust under reflux. High to moderate yields were obtained with all the substrates tested, including aliphatic and aromatic aldehydes (runs 1-3), aliphatic and aromatic ketones (runs 6-8) as well as aliphatic and aromatic *α,β*-unsaturated aldehydes and ketones (runs 4-5 and 9-10). The same reaction using ethyl bromofluoroacetate **(79)** as reagent gave comparable yields for the aldehydes (runs 1-3), aliphatic ketones (run 6) and aliphatic *α,β*-unsaturated aldehyde (run 4) but a greatly reduced yield for the aromatic ketone (run 8) and aromatic *α,β*-unsaturated aldehydes and ketones (run 5 and run 9). Here, the yields obtained with **(79)** were much lower compared to those obtained with ethyl bromoacetate **(78)**. The slow reaction of ethyl bromofluoroacetate was explained by the shortening and strengthening of the C-Br bond due to the incorporation of the strongly electronegative fluorine; however, there was no explanation as to why it would influence only some starting materials but not the others.

Table 4.9 The Reformatsky reaction in the presence of cerium catalyst.[19]



Run	Carbonyl compound	Yield[a] [%]	Erythro/threo[b] [%]
1	butyraldehyde	83	48:52
2	pentanal	90	48:52
3	benzaldehyde	92	50:50
4	acetone	89	-
5	cyclohexanone	94	-
6	3,3-dimethylbutan-2-one	61	59:41
7	acetophenone	90	42:58[c]
8	1,2-diphenylethanone	92	42:58[c]

[a] Isolated yield, [b] determined by ^{19}F NMR spectroscopy, [c] The diastereomers were separated (95 % pure) by crystallization or flash column chromatography.

An improved version of the monofluorinated Reformatsky reaction was presented by Dolbier in 2002.[19] Ethyl bromofluoroacetate **(79)** was reacted with a range

of aldehydes and ketones in the presence of 4 mole% of $CeCl_3.7H_2O$. The reactants were mixed and vigorously stirred at room temperature to give between 61-92 % yield (Table 4.9). The addition of the cerium catalyst resulted in good yields even with aromatic ketones (run 7). The ratios of the *erythro* to *threo* isomers were determined by ^{19}F NMR spectroscopy, but no substantial diastereomeric excess was observed. In some cases the separation of the diastereomers was possible either by flash column chromatography or by recrystallisation. In the ^{19}F NMR spectra of the product obtained in the reaction with aldehydes, the *erythro* isomer was always downfield and its $^2J_{FH}$ coupling was 16-20 Hz smaller in comparison to the *threo* isomer. Unfortunately, there was no correlation like this in the case of the products obtained in the reactions with ketones. These esters were also hydrolysed to the *α*-fluoro-*β*-hydroxy carboxylic acids in very high yields (>90 %) with 0.2 M solution of NaOH in ethanol.

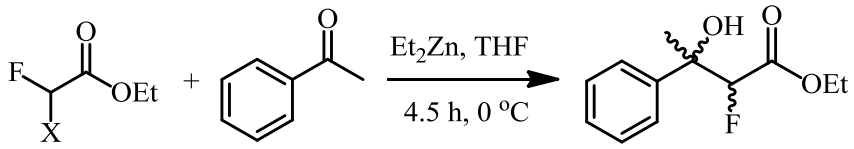
4.2 Results and discussion

4.2.1 The Reformatsky reaction of ethyl bromofluoroacetate and ethyl iodofluoroacetate with benzaldehyde and acetophenone

Initially, the Reformatsky reaction with acetophenone was run with 1.5 equivalents of ethyl bromofluoroacetate **(79)** or ethyl iodofluoroacetate **(80)** and 1.5 equivalents of diethylzinc in THF at 0 ^oC. The reaction with ethyl bromofluoroacetate was sluggish and the conversion only reached 29 % after 4.5 hours (Table 4.10). The 61:39 diastereomeric ratio was determined by ^{19}F NMR spectroscopy on the crude product (run 1) by comparing the integrations for the signals of the major (-194.54 ppm) and the minor (-192.00 ppm) diastereoisomer and was found to be almost identical to the diastereomeric excess (58:42) reported by Dolbier.[19] As expected, the reaction with the more reactive ethyl iodofluoroacetate **(80)** was successful and 100 % conversion was observed after 4.5 hours (run 2) with the ratio of diastereoisomers being practically the same as the reaction with ethyl bromofluoroacetate. Purification of the product by column chromatography was very efficient (98 %). After a short period of time crystals of the major diastereoisomer formed and slow recrystallisation from hexane gave a good quality crystal suitable for X-ray crystallography. The solid-state structure (Figure 4.1) showed that the major diastereoisomer of ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate **(81)** is a mixture of the (2*R*,3*R*) and (2*S*,3*S*) enantiomers which is in agreement with the results reported by Dolbier.[19] A pure sample of the minor

(2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer was obtained after purification on the chromatotron with 5 % Et_2O in hexane and it is a liquid.

Table 4.10 The Reformatsky reaction with acetophenone.



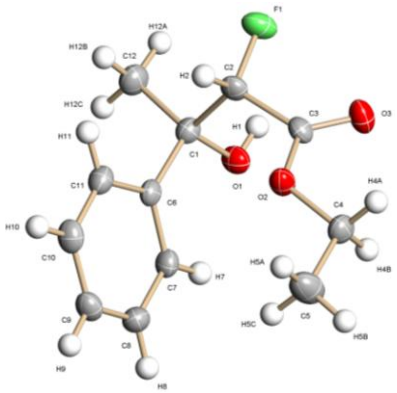
X= Br **(79)**
I **(80)**

(81)

Run	Reagent (1.5 equiv.)	Conversion[a] [%]	Yield[b] [%]	Ratio[c] (*S*,*S*)(*R*,*R*)/(*S*,*R*)(*R*,*S*)
1	$BrCFHCO_2Et$	29	-	61:39
2	$ICFHCO_2Et$	100	98	63:37

[a] Determined by ^1H NMR spectroscopy, [b] isolated yield, [c] determined by ^{19}F NMR spectroscopy for crude product.

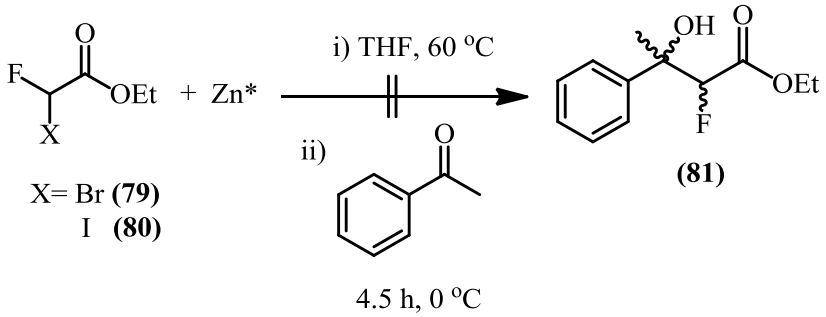
Figure 4.1 Molecular structure of (2*S*,3*S*)/(2*R*,3*R*)-ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate **(81)**. Figures show 50 % displacement ellipsoids and hydrogen atoms in calculated positions.



The conditions for the chiral HPLC were developed in order to separate the enantiomers for each diastereoisomer so that the enantiomeric excess could be determined for chiral reactions in future work. Due to the fact that the reaction with acetophenone had been chosen for further optimisation, it was essential to find conditions that would allow the determination of the enantiomeric excess for both diastereoisomers in a single run. The sample containing a mixture of diastereoisomers

was eluted with 1 % IPA in hexane on the OD-H column with a flow rate of 1 mL/min at 25 ^{o}C. The retention times of the enantiomers for the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer were R_t= 9.52 min and R_t= 11.08 min whilst the enantiomers of the minor (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer had retention times of R_t= 12.25 min and R_t= 14.36 min.

Table 4.11 The attempt at the two step Reformatsky reaction with acetophenone.



Run	Reagent (1.5 equiv.)	Conversion[a] [%]
1	$BrCFHCO_2Et$	0
2	$ICFHCO_2Et$	0

[a] Determined by ^{1}H NMR spectroscopy.

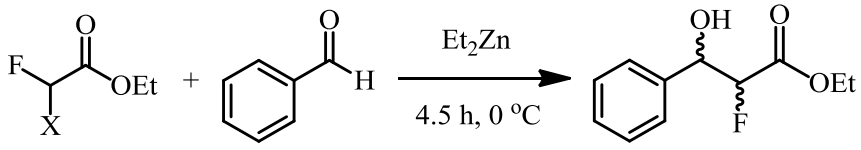
In the next step ethyl bromofluoroacetate **(79)** and ethyl iodofluoroacetate **(80)** were used to attempt a classic two-step Reformatsky reaction with acetophenone. A solution of the ester was added dropwise to a suspension of activated zinc dust at 60 ^{o}C in THF. The gray suspension had a slightly green colour towards the end of the addition. An accurate amount of the mixture was transferred by syringe to a flask containing a solution of acetophenone at 0 ^{o}C. After the reactions with acetophenone were worked up, it became obvious that neither the reaction with **(79)** nor with **(80)** resulted in the desired product and there were no new aromatic signals on any of the obtained spectra. In both reactions the ^{1}H NMR spectra showed unreacted acetophenone, a trace of a doublet for ethyl 2-fluoroacetate **(71)** at 4.8 ppm and two broad signals integrating 2:3 (integration of acetophenone was 2.2) in the regions where the CH_2 (4.2-4.4 ppm) and CH_3 (1.2-1.35 ppm) groups of the ester are expected. On the ^{19}F NMR spectra there were multiple signals present but none of them could be identified except for **(71)**.

The excess Reformatsky reagent from both **(79)** and **(80)** was syringed into a Young's NMR tube containing a small capillary lock tube with C_6D_6 in it. In both cases there were no signals corresponding either to ethyl bromofluoroacetate **(79)** or ethyl iodofluoroacetate **(80)** in the ^{19}F NMR spectra and, unfortunately, there were no other signals that could be assigned as the Reformatsky reagent either. The only signal strong enough to be considered was a very weak triplet at -231.15 ppm which was recognised as ethyl 2-fluoroacetate **(71)**.[20]

For comparison, a solution of diethylzinc was added to a THF solution of **(80)** and a known amount of hexafluorobenzene was used as the internal standard. A small sample of the mixture was closed immediately in a Young's NMR tube with a C_6D_6 lock tube and ^{19}F NMR spectra were recorded over time. There was no signal for the starting material and only a trace of ethyl 2-fluoroacetate **(71)** was present. There was a small broad signal at -159.70 ppm, which decreased over time, and several other similar signals between -186 ppm and -202 ppm, which were present in the mixture even after several hours. On the ^{19}F NMR spectrum obtained in the experiment with ethyl bromofluoroacetate **(79),** the integration of the signals for starting material (-150.60 ppm) and the internal standard (-163.64 ppm) showed that half of the ester **(79)**, after approximately 5 minutes, was still unreacted. The signal for **(79)** was slowly decreasing and after 2.5 hours less than 10 % was still unreacted. There were small, broad signals appearing similar to those described above in the reaction of diethylzinc with **(80)**. The solutions obtained in the reaction of **(79)** or **(80)** and diethylzinc were not tested in the two-step Reformatsky reaction with carbonyl molecules.

All of the above reactions were repeated with benzaldehyde (Table 4.12). The reaction with ethyl bromofluoroacetate **(79)** and diethylzinc gave 34 % conversion to ethyl *α*-fluoro-*β*-hydroxyphenylpropanoate **(77)**, which was only 5 % higher than the same reaction with acetophenone. The reaction with ethyl iodofluoroacetate **(80)**, once again, gave a 100 % conversion. The diastereoisomers were assigned by the ^{19}F NMR spectroscopy chemical shift for the (*S*,*S*)/(*R*,*R*)-diastereoisomer at -197.59 ppm and the (*S*,*R*)/(*R*,*S*)-diastereoisomer at -202.62 ppm as reported by Mima.[7] The two-step Reformatsky reaction between benzaldehyde and either ethyl iododifluoroacetate or ethyl bromofluoroacetate resulted in unreacted benzaldehyde and the same mixture of unidentified products as observed in the reaction with acetophenone (Scheme 4.7).

Table 4.12 The Reformatsky reaction with benzaldehyde.



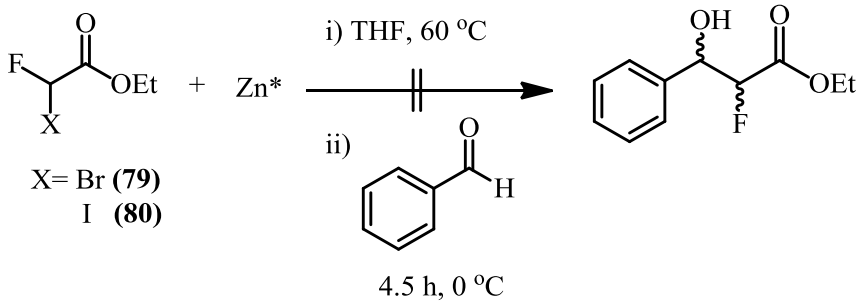
X= Br **(79)**
I **(80)**

(77)

Run	Conditions (1.5 equiv.)	Conversion[a] [%]	Yield[b] [%]	(*S*,*S*)(*R*,*R*)/(*S*,*R*)(*R*,*S*)[c] [%]
1	$BrCFHCO_2Et$	34	-	58:42
2	$ICFHCO_2Et$	100	61	63:37

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by ^{19}F NMR spectroscopy for crude product.

Scheme 4.7 The two-step Reformatsky reaction with benzaldehyde.

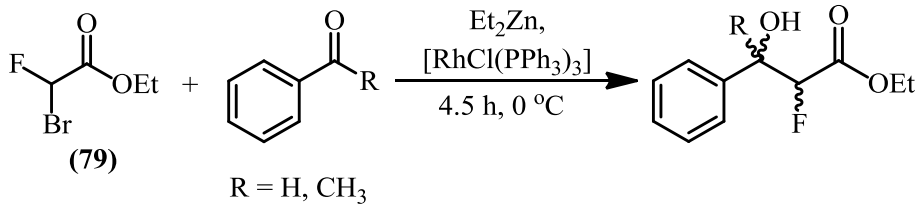


X= Br **(79)**
I **(80)**

4.2.2 The Reformatsky reaction promoted by Wilkinson's catalyst

Wilkinson's catalyst was incorporated in order to improve the low conversion obtained in the reaction with ethyl bromofluoroacetate **(79)** and diethylzinc (Table 4.13). A comparison of the non-catalysed reactions (run 1 and run 4) and the reactions where 1 mol% of the catalyst was used (run 2 and run 5) shows that there was a significant improvement in the conversion. In the reaction with benzaldehyde the conversion increased from 34% to 70 % (run 2) and with acetophenone the conversion improved from 29 % to 76 %. When the catalyst loading was increased to 5 mol% in the reaction with benzaldehyde a further improvement was observed (95 % conversion). However, no further improvement was observed in the reaction with acetophenone (run 6).

Table 4.13 The reaction of ethyl bromofluoroacetate in the presence of Wilkinson's catalyst.



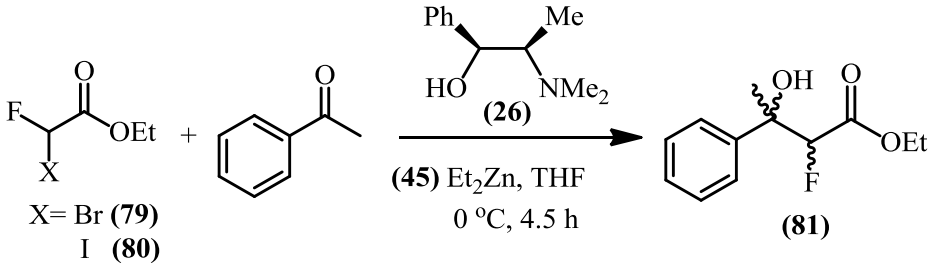
Run	Carbonyl compound[a]	Wilkinson's catalyst	Conversion[b] [%]	(*S*,*S*)(*R*,*R*)/(*S*,*R*)(*R*,*S*)[c] [%]
1	benzaldehyde	-	34	58:42
2		1 mol%	70	50:50
3		5 mol%	95	52:48
4	acetophenone	-	29	61:39
5		1 mol%	76	60:40
6		5 mol%	70	60:40

[a] The reactions were run in THF at 0 °C with 1.5 equivalents of $BrCFHCO_2Et$ and 1.5 equivalents of diethylzinc, [b] determined by ^1H NMR spectroscopy, [c] determined by ^{19}F NMR spectroscopy for crude product.

4.2.3 The Reformatsky reaction in the presence of (1*S*,2*R*)-*N*-methylephedrine

All chiral reactions were carried out in duplicate. The first chiral reactions were run with 2.0 equivalents of either ethyl bromofluoroacetate **(79)** or ethyl iodofluoroacetate **(80)** in the presence of 1.0 equivalent of (1*S*,2*R*)-*N*-methylephedrine **(26)** at 0 °C (Table 4.14). In order to deprotonate the chiral aminoalcohol, 0.5 extra equivalents of diethylzinc **(45)** were used for each equivalent of the chiral ligand. Consequently, in all of the reactions using 1.0 equivalent of *N*-methylephedrine, 2.5 equivalents of diethylzinc were used instead of the 2.0 equivalents necessary for the reaction with either **(79)** or **(80)**.

Table 4.14 The reactions with acetophenone in presence of (1*S*,2*R*)-*N*-methylephedrine.



Run	(26)	(80)	(45)	Conv.[a]	(*S*,*S*)(*R*,*R*)/(*S*,*R*)(*R*,S)[b]	Yield[c]	Ee[d]
	[No. of equivalents]			[%]	[%]	[%]	[%]
1	1.0	2.0[e]	2.5	42	84:16	-	-
2	1.0	2.0	2.5	100	76:24	72	67, 58
3	1.0[f]	2.0	2.5	100	70:30	94	55[g], 36[g]
4	1.0	1.5	2.5	95	76:24	87	64, 38
5	0	1.5	2.5	100	63:37	98	-

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy for crude product, [c] isolated yield, [d] determined by chiral HPLC and reported for major (2*S*,3*S*)/(2*R*,3*R*)-diastereomer, minor (2*S*,3*R*)/(2*R*,3*S*)-diastereomer, [e] the reaction with **(79)**, [f] (1*R*,2*S*)-*N*-methylephedrine was used, [g] the major enantiomers had opposite configuration (chiral HPLC).

As expected, the reaction with **(79)** gave a low conversion (Table 4.14, run 1) and was not investigated further. Complete conversion was observed in the reaction with **(80)** and the diastereomeric ratio of the products improved from 63:37 to 76:24 (run 2). At this stage it was unclear if the difference was caused by the higher excess of the Reformatsky reagent or by the addition of the chiral ligand. The enantiomeric excess was 58 % ee for the minor and 67 % for the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer. The reaction with (1*R*,2*S*)-*N*-methylephedrine, which is the opposite enantiomer to that used in the rest of the optimisation work (run 3), was expected to give a similar enantiomeric excess but with a bias towards the opposite enantiomers in each distereoisomer. The conversion and the isolated yield were similar to those obtained in run 2, but the diastereomeric excess and the enantiomeric excesses within the pairs of diastereoisomers were significantly lower (run 3). In the next run the amount of ethyl iodofluoroacetate was reduced to 1.5 equivalents but the amount of diethylzinc was still 2.5 equivalents as in run 2 (run 4). The conversion dropped to 95 % but the

diastereomeric excess was the same. Interestingly, the enantiomeric excess determined for the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer was almost identical in both reactions; however, the enantiomeric excess determined for the minor diastereoisomer was significantly lower (runs 2 and 4).

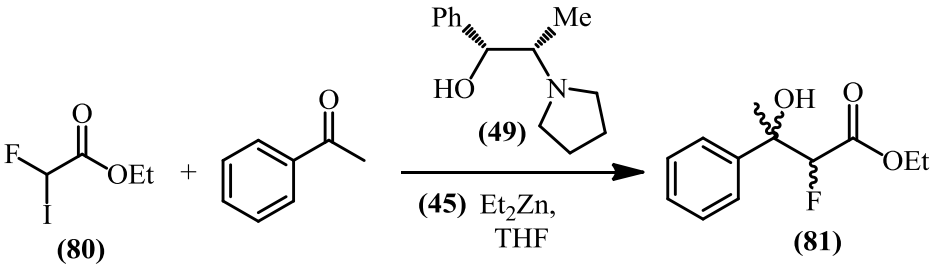
Finally, the conditions described in run 4 were repeated without *N*-methylephedrine (run 5). The diastereomeric excess in the reaction was lower, which proved that the presence of the chiral aminoalcohol was responsible for the improved diastereomeric ratio.

4.2.4 Optimisation of the asymmetric Reformatsky reaction with ethyl iodofluoroacetate

In the next step (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)**, which proved to be a better chiral ligand for the difluorinated Reformatsky reaction with ketones (Chapter 3), was used as the chiral ligand (Table 4.15). In the reaction run at 0 ^{o}C, a 100 % conversion and a diastereomeric excess similar to that obtained in the reaction with *N*-methylephedrine (Table 4.14, run 2) was obtained, but the enantiomeric excess of the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer was higher (run 1). In run 2 the amount of ethyl iodofluoroacetate **(80)** was reduced to 1.5 equivalents but the amount of diethylzinc was maintained at 2.5 equivalents. Although the conversion in the reaction dropped to 84 %, the enantiomeric excess of the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer increased to 80 % ee. The enantiomeric excess of the minor diastereoisomer in the reaction with 1.5 equivalents of **(80)** (run 2) was lower compared to that obtained in the reaction with 2.0 equivalents of the Reformatsky reagent (run 1). In the next approach 2.0 equivalents of **(80)** were reacted with acetophenone at -20 ^{o}C (run 3). A drop in the conversion (84 %) and a lower diastereomeric excess were determined, but the enantiomeric excesses improved to 87 % ee and 60 % ee for the major and minor diastereoisomers respectively. Because it was not certain if the reaction was left to react for long enough, in the next reaction the reaction time was extended by 2 hours (run 4), but the conversion was identical to that obtained after 4.5 hours of stirring (run 3). In run 5 the amount of the chiral ligand was increased to 1.5 equivalents resulting in a decrease in the conversion but no improvement in the enantiomeric excess. In fact, the enantiomeric excess obtained for the minor diastereoisomer dropped to 23 % ee comparing to 60 % ee obtained in the reaction with only 1.0 equivalent of the ligand

(run 3). Once again, the decrease in the enantiomeric excess of the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer was less affected.

Table 4.15 The Reformatsky reaction of ethyl iodofluoroacetate in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)**.



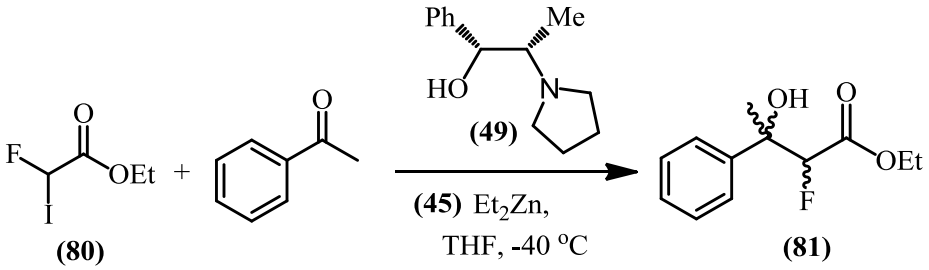
Run	(49)	(80)	(45)	Conv.[a]	(*S*,*S*)(*R*,*R*)/(*R*,*S*)(*S*,*R*)[b]	Yield[c]	Ee[d]
	[No. of equivalents]			[%]	[%]	[%]	[%]
1	1.0	2.0	2.5	100[e]	82:18 (77:23)	58	73, 51
2	1.0	1.5	2.5	84[e]	79:21 (75:25)	74	80, 46
3	1.0	2.0	2.5	84[f]	75:25 (80:20)	76	87, 60
4	1.0	2.0	2.5	82[f,g]	76:24 (75:25)	79	85, 63
5	1.5	2.0	2.75	63[f]	69:31 (66:34)	61	83, 23

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy for crude product (for pure product in parenthesis), [c] isolated yield, [d] determined by chiral HPLC and reported for major, minor diastereoisomer respectively, [e] 0 °C, [f] -20 °C, [g] for 6.5 h.

Finally, the temperature was lowered to -40 °C which resulted in a moderate conversion (66 %) and an improvement in the enantiomeric excess to 90 % ee for the major and 72 % ee for the minor diastereoisomers respectively (run 1, Table 4.16). The exact conditions were repeated without the chiral ligand and a surprisingly high conversion (59 %) was obtained (run 4). The diastereomeric excess dropped which proved that the chiral ligand was responsible for the improved diastereomeric ratio. In an attempt to enhance the conversion in the reaction with 1.0 equivalent of the chiral ligand, 3.5 equivalents of diethylzinc were used in run 2. These conditions resulted in an almost complete conversion but, more importantly, the enantiomeric excess for the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer was still very high (87 % ee) and even improved to 80 % for the minor diastereomer. In run 3 the reaction was repeated with higher

equivalents of ethyl iodofluoroacetate and diethylzinc, which had no effect on the diastereomeric excess, although the reaction suffered from small decreases in the enantiomeric excess.

Table 4.16 The asymmetric Reformatsky reaction of ethyl iodofluoroacetate at -40 °C.



(80) (81)

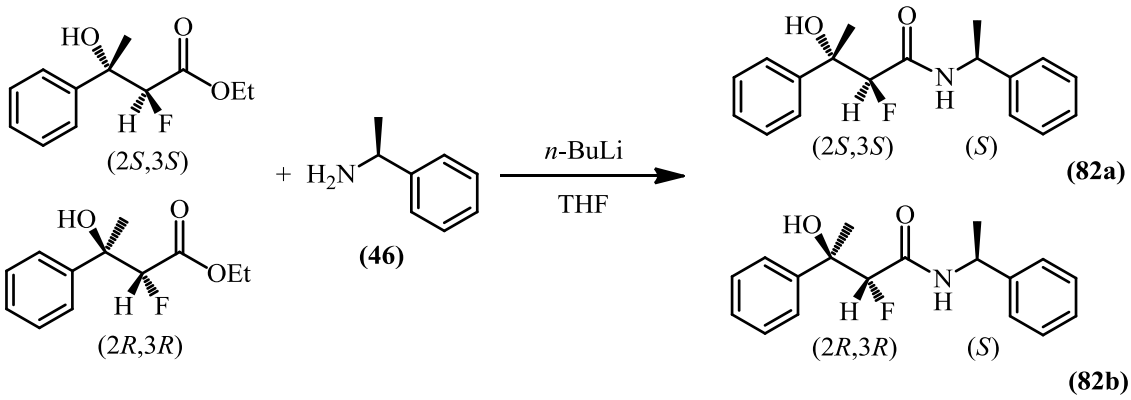
Run	(49)	(80)	(45)	Conv.[a]	(*S*,*S*)(*R*,*R*)/(*S*,*R*)(*R*,*S*)[b]	Yield[c]	Ee[d]
	[No. of equivalents]			[%]	[%]	[%]	[%]
1	1.0	2.0	2.5	66	75:25 (73:27)	66	90, 72
2	1.0	2.0	3.5	99	74:26	97	87, 80
3	1.0	3.0	3.5	100	75:25	94	84, 77
4	0	2.0	2.0	59	56:44	-	-
5	0	2.0	3.5	100	60:40	-	-

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy for crude product (for pure product in parenthesis), [c] isolated yield, [d] determined by chiral HPLC and reported for major, minor diastereomer respectively.

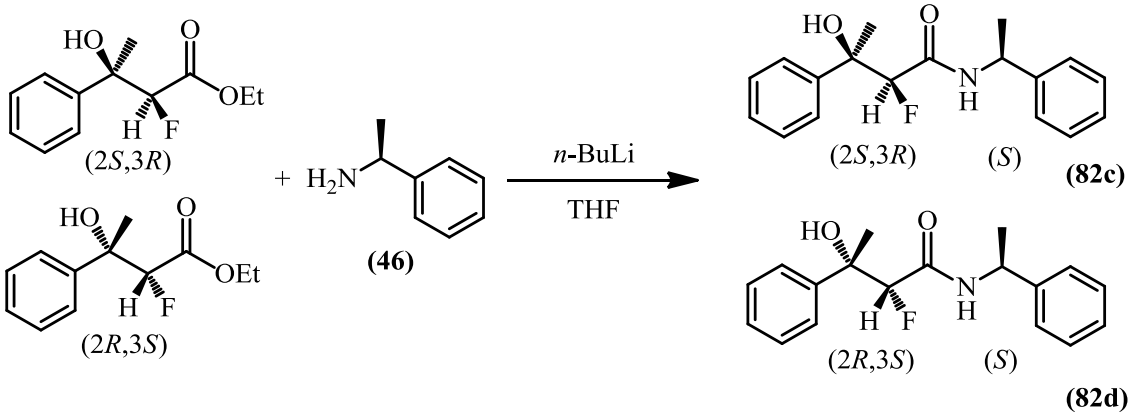
4.2.5 Determination of the absolute configuration

In order to determine the absolute configuration of the new chiral centre the diastereomers of **(81)** were separated by column chromatography (Et_2O:hexane = 1:5). Each diastereoisomer, (*S*,*S*/*R*,*R*) (Scheme 4.8) and (*R*,*S*/*S*,*R*) (Scheme 4.9), was derivatised in the reaction with (*S*)-1-phenylethanamine **(46)** into 2-fluoro-3-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)butanamide **(82)** according to the method reported by Braun.[21] After the reaction was quenched almost complete conversion to the products was determined by ^{19}F NMR spectroscopy. Transformation of the enantiomers to diastereoisomers by the addition of a new chiral centre allowed them to be separated by silica gel column chromatography.

Scheme 4.8 The reaction of the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer of **(81)** with (*S*)-1-phenylethanamine **(46)**.



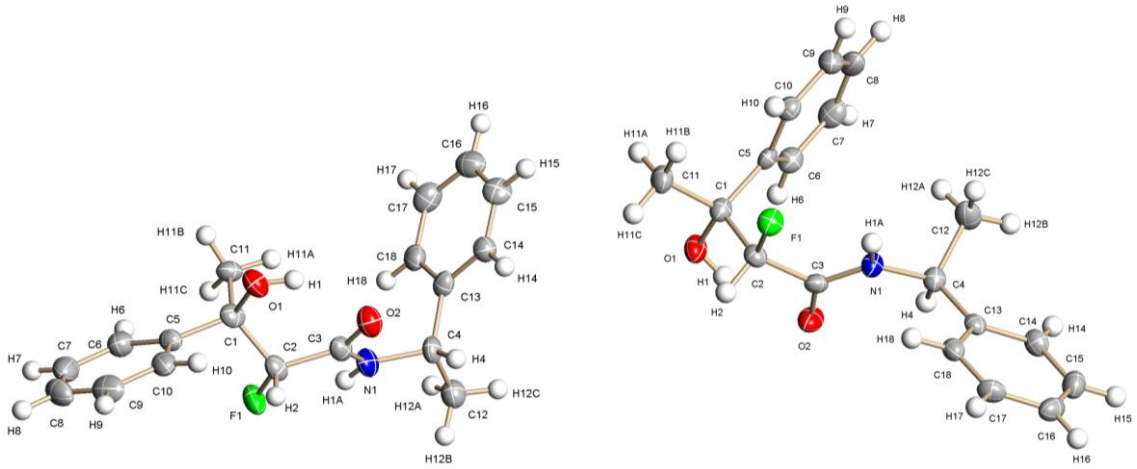
Scheme 4.9 The reaction of the minor (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer of **(81)** with (*S*)-1-phenylethanamine **(46)**.



The amides **(82a)** and **(82b)** obtained in the reaction with the major (*S*,*S*)/(*R*,*R*)-diastereoisomer were separated by column chromatography using 5 % ethyl acetate in hexane. A sample of (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-butanamide solidified **(82b)** (Scheme 4.8) and was fully characterised. After recrystallisation a crystal of (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl) **(82b)** suitable for X-ray diffraction was obtained (Figure 4.2). There was an intramolecular hydrogen bond (O1H1-O2), forming a six membered ring, as well as an intermolecular hydrogen bond (N1H1A-O2). The products obtained from the minor (*S*,*R*)/(*R*,*S*)-diastereoisomer (Scheme 4.9) were separated by column chromatography using a 40:60 mixture of diethyl ether in hexane. Only one out of the two amides was isolated and fully characterised whilst the other diastereoisomer still contained 14 % of the first diastereoisomer. Fortunately, the isolated (2*S*,3*R*)-2-fluoro-3-hydroxy-3-

phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(82c)** turned out to be a solid and after slow recrystallisation from hexane a good quality crystal was obtained (Figure 4.2). Once again, there was an intermolecular hydrogen bond and an intramolecular hydrogen bond (O1H1-O2) similar to those described for the previously discussed molecule.

Figure 4.2 The crystal structures of i) (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)butanamide **(82b)** and ii) (2*S*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)butanamide **(82c)**. Figures show 50 % displacement ellipsoids and hydrogen atoms in calculated positions.



i) ii)

The diastereoisomers of **(81)** obtained in the chiral reactions in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)** were separated and reacted with (*S*)-1-phenylethanamine **(46)**. The amount of the chiral amine **(46)** and *n*-BuLi in these reactions were increased considerably in order to ensure complete conversion. The comparison of the ^{19}F NMR spectroscopy signals obtained for the crude product obtained in the reaction with the major (*S*,*S*)/(*R*,*R*)-diastereoisomer with the ^{19}F NMR spectrum for (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide revealed that the major enantiomer obtained in the asymmetric Reformatsky reaction of ethyl iodofluoroacetate **(80)** run in the presence of **(49)** had a (2*S*,3*S*)-configuration. The ^{19}F NMR spectrum obtained for the crude product from the reaction of the minor diastereoisomer (Scheme 4.9) was compared with the ^{19}F NMR spectrum obtained for (2*S*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide. The major enantiomer formed in the Reformatsky reaction appeared to have a (2*R*,3*S*)-

configuration, which meant that the new chiral centre at the 3-position for the major enantiomer for both diastereoisomers of **(81)** had the same (3*S*)-configuration.

In the reactions performed without chiral ligand there was very little diastereomeric control (Table 4.10). The fact that there was no difference in the diastereomeric excess obtained in the reactions performed with ethyl bromodifluoroacetate and ethyl iododifluoroacetate (Table 4.10) can be rationalised by the same mechanism as that proposed for the Reformatsky reaction of ethyl iododifluoroacetate in Chapter 3, where the reactive species were identical regardless of which ester was used in the reaction. The Reformatsky reagent was obtained from racemic ethyl iodofluoroacetate and, as a consequence, its reaction with diethylzinc gave two enantiomers of the Reformatsky reagent. A small diastereomeric excess obtained in the achiral reactions shows that the energy barrier is lower for the Reformatsky reagent where the fluorine atom is located on the same side as the sp^2 carbon of the aromatic ring and the hydrogen atom is on the same side as sp^3 carbon of the aliphatic group. A probable mechanism is shown in Figure 4.3. The carbonyl can only be approached in the *p*-plane at the Bürgi-Dunitz angle (approximately 109 ^{o}) on each side of the ketone. For simplicity, only attack on the *si*-side of the ketone was illustrated in Figure 4.3. Because there was a preference towards one of the enantiomers of the Reformatsky reagent on each side of the ketone the diastereoisomer containing enantiomers (2*S*,3*S*) and (2*R*,3*R*) was obtained in a small excess.

On the other hand, the reactions performed in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol gave high enantiomeric excess and improved diastereomeric excess. Most likely, the mechanism for the addition of the Reformatsky reagent formed from ethyl iodofluoroacetate was the same as the one discussed in Section 3.5 for the asymmetric Reformatsky reaction of ethyl iododifluoroacetate with acetophenone. According to this mechanism, in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol, only the *si*-face of the ketone was exposed to attack and hence, the configuration of the new chiral centre was (*S*) (Figure 4.4). The possible explanation for much better diastereomeric control can be the right configuration of the Reformatsky reagent and the ketone coordinated to the zinc and (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol and as a consequence, the difference in the reaction rate between the preferred and non-preferred enantiomers of the Reformatsky reagent was greater than in the reaction performed without ligand.

Figure 4.3 The diastereoselectivity in the achiral Reformatsky reaction with ketone.

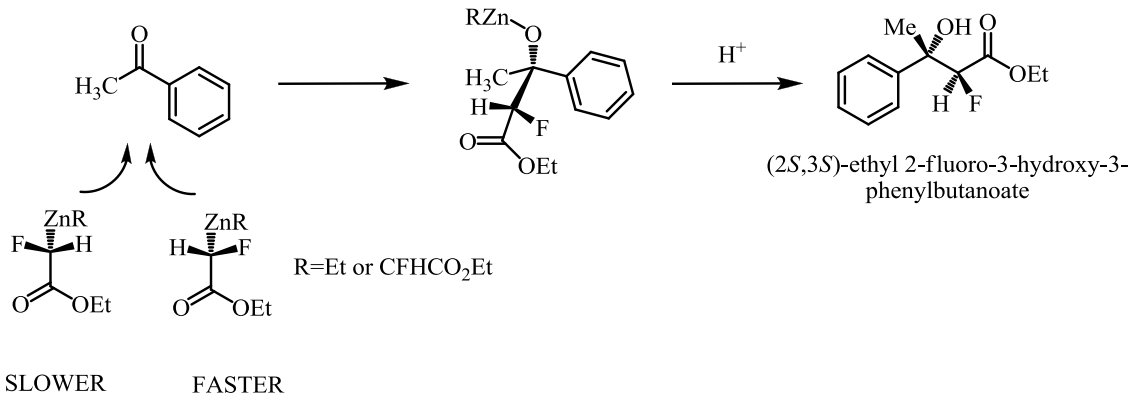
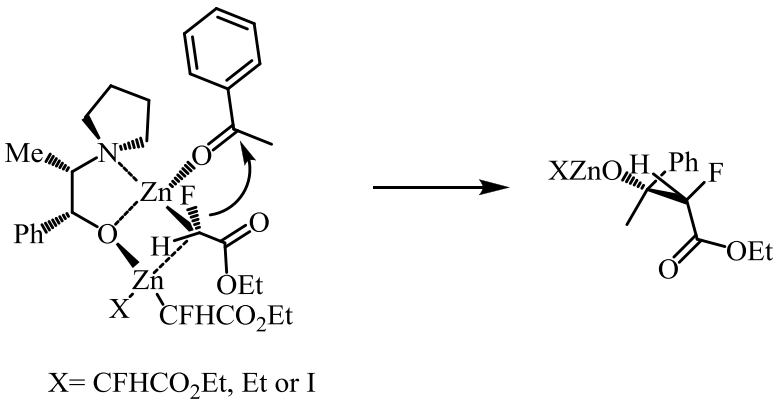


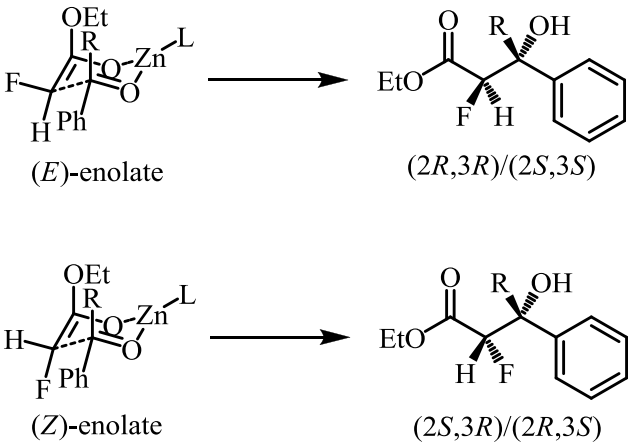
Figure 4.4 The possible mechanism for the asymmetric addition of the Reformatsky reagent to the ketone in the presence of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol.



The alternative mechanism for the reaction with an oxygen methylated enolate was considered. Here, an aldehyde or ketone and the reactive species form the six-membered transition state, similar to the one proposed by Zimmerman and Traxler (Figure 4.5).[2] The diastereomeric excess is a result of the reaction of the carbonyl molecule with (*E*)-enolate, which leads to the formation of (2*R*,3*R*)/(2*S*,3*S*)-diastereoisomers. Optionally, the reaction with (*Z*)-enolate results in the preparation of (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomers. Similar diastereomeric excess obtained in the reactions with benzaldehyde (Table 4.12) and acetophenone (Table 4.10) may suggest that the position of the phenyl ring in both reactions is the same.

The more probable mechanism is the one presented in Figures 4.3 and 4.4 since pure (*E*)-silyl enol ether **(72)** was inert and required a catalyst and refluxing to react with aldehydes giving a mixture of diastereoisomers (Table 4.1).

Figure 4.5 The Zimmerman-Traxler transition state for the aldol reaction with aldehyde.



4.2.6 The achiral Reformatsky reaction with a series of ketones

A range of ketones were reacted with 1.5 equivalents of ethyl iodofluoroacetate and diethylzinc at 0 ^{o}C for 4.5 hours (Table 4.17). All of the reactions went to completion, with the exception of 3-methyl-1-phenylbutan-1-one **(88)** which gave a 97 % conversion (run 7). The diastereomeric ratios in these reactions were low. The products were isolated and fully characterised before being used to determine the conditions for separating the enantiomers by chiral HPLC. In some cases, the conditions for the separation of both pairs of enantiomers were developed on one sample containing both diastereoisomers. In these cases, the enantiomers were assigned to the major or the minor diastereoisomer according to the integrations of the signals. The diastereomeric excess determined by HPLC was also compared with that obtained by ^{19}F NMR spectroscopy and always gave a good correlation.

The reaction with *p*-methyoxyacetophenone gave 98 % of the pure ethyl 2-fluoro-3-hydroxy-3-(4-methoxyphenyl)butanoate **(83)** containing 61:39 ratio of diastereoisomers (run 2). In order to fully characterise the diastereoisomers, they were separated by a chromatotron with 5 % diethyl ether in hexane. The minor (*S*,*R*)/(*R*,*S*)-diastereoisomer was obtained in 25 % yield and the major (*S*,*S*)/(*R*,*R*)-diastereoisomer in a 60 % yield. Due to the presence of fluorine the maximum absorbance of UV light by the aromatic ring in the molecules shifted, and as a consequence, observation of these compounds under a standard 254 nm UV lamp was difficult. For this reason the

UV light detector on the chiral HPLC analyses was set to 212 nm where the absorbance of these molecules was stronger. Chiral HPLC was the method of choice for determining the enantiomeric excess for each diastereoisomer separately. The enantiomers of ethyl 2-fluoro-3-hydroxy-3-(4-methoxyphenyl)butanoate **(83)** were separated with 0.5 % IPA in hexane eluted on an OD-H column (run 2). The retention times of the enantiomers from the minor (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer were R_t= 32.32 min and 37.30 min, and from the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer were R_t= 46.93 min and 67.96 min.

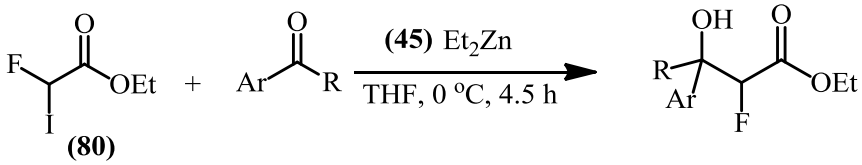
The diastereoisomers of ethyl 2-fluoro-3-hydroxy-3-(2-methoxyphenyl)-butanoate **(84)** obtained in run 3 were separated by column chromatography; however, the minor diastereoisomer was not sufficiently pure and further purification by chromatotron with 5 % diethyl ether in hexane was necessary. All four enantiomers were separated by chiral HPLC by eluting the samples with 1.0 % IPA in hexane on the OD-H column. The retention times were 12.57 min and 15.33 min, and 21.08 min and 33.94 min for the major and minor diastereoisomers respectively.

Purification of ethyl 3-(4-chlorophenyl)-2-fluoro-3-hydroxybutanoate **(85)** by column chromatography using 10 % ethyl acetate in hexane gave 5 % of the major and 20 % of the minor diastereoisomer as well as 45 % of the mixture of both diastereoisomers. The major diastereoisomer solidified and the (*S*,*S*)/(*R*,*R*) configuration was confirmed by X-ray crystallography (Figure 4.6). The enantiomers of the major diastereoisomer were separated by chiral HPLC on an AS column with 10 % IPA in hexane (R_t = 6.66 min and 13.71 min) and the enantiomers from the minor diastereoisomer were separated on an AD column with 2 % IPA in hexane (R_t = 12.86 min and 15.53 min).

The diastereoisomers of ethyl 2-fluoro-3-hydroxy-3-phenylpentanoate **(86)** obtained from propiophenone were separated by silica gel column chromatography (run 5). The major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer contained a few percent of the minor one and was further purified by chromatotron. Crystals of **(86)**, suitable for X-ray diffraction, were grown by slow evaporation from hexane and the solid state structure (Figure 4.6) determined the (*S*,*S*)/(*R*,*R*) configuration. Table 4.18 summarises selected bond lengths and angles, and compares them with the crystal structure of ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **(54)**. The key bond lengths and angles in both molecules are very similar; however, the dihedral angles indicate that there is a difference in the conformational state. Regardless of the differences in the

conformational states along the C1-C2 bond, the distance between the hydrogen bond donor (O1) and acceptor (O3) were practically the same in both molecules. The enantiomers of **(86)** were separated by chiral HPLC on an OD-H column eluted with 0.5 % of IPA in hexane. The retention times were 9.77 min and 10.86 min for the minor diastereoisomer along with 20.60 min and 23.18 min for the major (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer.

Table 4.17 Achiral Reformatsky reactions of ethyl iodofluoroacetate with ketones.



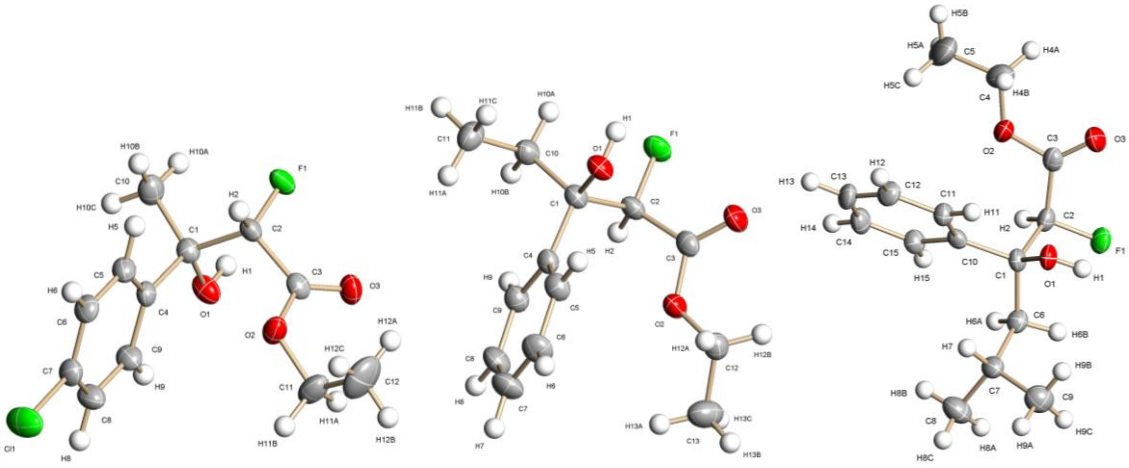
Run	Ketones	Conversion[a] [%]	Dr[b] [%]	Yield[c] [%]	Product No.
1	acetophenone	100	63[d]:37	98	**(81)**
2	*p*-methoxyacetophenone	100	61:39	98 (60:25)	**(83)**
3	*o*-methoxyacetophenone	100	63:37	42:20[e]	**(84)**
4	*p*-chloroacetophenone	100	56[d]:44	5:(45):20	**(85)**
5	propiophenone	100	55[d]:45	40[e]:40	**(86)**
6	1-phenylbutan-1-one	100	59:41	12[f]:21[e]	**(87)**
7	3-methyl-1-phenylbutan-one	97	59[d]:41	46:22	**(88)**
8	indanone	100	54:46	84	**(89)**
9	1-tetralone	100	60:40	96	**(90)**

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy, [c] isolated yield (after chromatotron in parenthesis), [d] confirmed as (*S*,*S*)/(*R*,*R*) by X-ray crystallography, [e] second purification on chromatotron, [f] recrystallisation from hexane.

The diastereoisomers of ethyl 2-fluoro-3-hydroxy-3-phenylhexanoate **(87)** obtained in run 6 were separated by column chromatography, but further purification was needed in order to obtain the pure diastereoisomers. The major (2*S*,3*S*)/(2*R*,3*R*)-diastereomer was recrystallised from hexane and the minor diastereoisomer was purified by chromatotron with 5 % diethyl ether in hexane. The enantiomers were separated by chiral HPLC on an OD-H column eluted with 0.5 % IPA in hexane. The retention times of the enantiomers were 9.25 min and 10.58 min for the minor and 17.52

min and 21.90 min for the major diastereomer respectively. The reaction with 3-methyl-1-phenylbutan-1-one (run 7) gave 97 % conversion to **(88)** and the diastereoisomers were separated by column chromatography. The major diastereoisomer solidified and a single crystal suitable for X-ray crystallography was isolated (Figure 4.6). Once again the configuration of the major diastereoisomer proved to be (*S*,*S*)/(*R*,*R*). Table 4.20 and 4.21 contain selected bond lengths and bond angles of ethyl 2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(88)** and ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(56)**. The bond lengths and angles do not differ considerably between them. However, there is a difference in the dihedral angles that is clearly visible on examination of the ethoxy group (Table 4.21).

Figure 4.6 The crystal structures of i) ethyl 3-(4-chlorophenyl)-2-fluoro-3-hydroxybutanoate **(85)**, ii) ethyl 2-fluoro-3-hydroxy-3-phenylpentanoate **(86)** and iii) ethyl 2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate **(88)**. Figures show 50 % displacement ellipsoids and hydrogen atoms in calculated positions.



(2*S*,3*S*)/(2*R*,3*R*) (2*S*,3*S*)/(2*R*,3*R*) (2*S*,3*S*)/(2*R*,3*R*)

i) ii) iii)

The reaction with indanone (run 8) yielded 84 % of ethyl 2-fluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate **(89)**. Both pairs of enantiomers were separated by chiral HPLC from the sample containing both diastereomers on an OD-H column eluted with 1.0 % IPA in hexane. The enantiomers of the major diastereoisomer had retention times of 17.56 min and 24.70 min, and the enantiomers of the minor diastereoisomer had retention times of 19.09 min and 22.14 min. Ethyl 2-fluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate **(90)** was obtained in 96 % yield from tetralone (run

9). The enantiomers were separated on an OD-H column with 0.5 % IPA in hexane. The retention times for the minor diastereomer (35.82 min and 44.38 min) were considerably different to the major diastereoisomer (68.02 min and 78.87 min).

Table 4.18 Selected bond lengths (Å) and bond angles (^{o}) with estimated standard deviations in parenthesis for **(86)** and **(54)**.

Bond Length [Å]	**(86)**	**(54)**	**Bond Angles [^{o}]**	**(86)**	**(54)**
C2-F1	1.3920(18)	1.360(3)	C3-C2-C1	112.4(14)	114.6(2)
C3-O2	1.3261(19)	1.320(3)	O2-C3-C2	110.11(14)	110.5(2)
C3-O3	1.208(2)	1.201(3)	C4-C1-C2	108.14(13)	109.4(2)
C2-C3	1.517(2)	1.540(4)	O1-C1-C2	108.48(13)	105.8(2)
C1-C2	1.551(2)	1.547(4)	O1-C1-C10	108.83(14)	109.2(2)
C1-C4	1.523(2)	1.522(4)	O3-C2-C2	124.27(16)	122.9(2)
C1-O1	1.417(2)	1.417(3)	C10-C1-C2	108.83(14)	109.2(2)

Table 4.19 Selected dihedral angles with estimated standard deviation in parenthesis for **(86)** and **(54)**.

Dihedral Angles [^{o}]	**(86)**	**(54)**
C4-C1-C2-C3	-64.99(17)	-54.1(3)
O3-C3-C2-C1	-100.10(19)	-94.0(3)
C5-C4-C1-C2	107.62(18)	105.2(3)
C2-C1-C10-C11	-177.81(15)	-177.6(2)
C3-O2-C12-C13	-163.37(16)	172.5(4)
C2-C3-O2-C12	11.0(2)	-174.4(4)

Table 4.20 Selected bond lengths (Å) and bond angles (^{o}) with estimated standard deviations in parenthesis for **(88)** and **(56)**.

Bond Length [Å]	**(88)**	**(56)**	**Bond Angles [^{o}]**	**(88)**	**(56)**
C2-F1	1.389(2)	1.364(7)	C6-C1-C2	112.45(18)	114.1(5)
C3-O2	1.330(3)	1.304(7)	O2-C3-C2	110.16(19)	110.9(5)
C3-O3	1.206(3)	1.205(6)	C10-C1-C2	109.07(17)	111.8(5)
C2-C3	1.499(3)	1.522(7)	O1-C1-C2	108.64(17)	103.8(4)
C1-C2	1.555(3)	1.555(7)	O1-C1-C6	111.32(7)	111.9(5)
C1-C10	1.525(3)	1.512(8)	C3-C2-C1	112.45(18)	114.1(5)
C1-O1	1.416(2)	1.432(6)	O3-C3-C2	126.0(2)	123.7(6)

Table 4.21 Selected dihedral angles with estimated standard deviation in parenthesis for **(88)** and **(56)**.

Dihedral Angles [^{o}]	**(88)**	**(56)**
C10-C1-C2-C3	62.8(2)	65.2(6)
O3-C3-C2-C1	97.6(3)	101.9(7)
C11-C10-C1-C2	-109.5(2)	-114.3(6)
C2-C1-C6-C7	177.59(18)	-171.8(5)
C3-O2-C4-C5	177.1(2)	-87.4(6)

Table 4.22 summarises selected bond lengths and bond angles in the monofluorinated esters **(81)**, **(85)**, **(86)** and **(88)**. In general, there was no indication of the electron withdrawing chlorine in the *para*-position or an aliphatic chain having any effect on the bond length or bond angles around the two chiral centres. The conformation between the two chiral centres represented by the dihedral angle was slightly different in the esters with methyl groups (**(81)** and **(85)**) and those with longer aliphatic groups (**(86)** and **(88)**).

Table 4.22 Selected bond lengths, bond angles and dihedral angles with estimated standard deviations in parenthesis for **(81)**, **(85)**, **(86)** and **(88)**.

		(81)	**(85)**	**(86)**	**(88)**
Bond Length	C1-O1	1.417(3)	1.424(4)	1.417(2)	1.416(2)
[Å]	C1-C2	1.556(3)	1.539(4)	1.551(2)	1.555(3)
	C2-F1	1.386(2)	1.393(3)	1.3920(18)	1.389(2)
Bond Angles	O1-C1-C2	108.4(2)	108.5(2)	108.48(13)	108.64(17)
[^{o}]	F1-C2-C1	108.70(19)	108.5(2)	108.41(13)	107.54(16)
Dihedral Angle	O1-C1-C2-F1	71.9(2)	72.6(3)	-65.29(16)	64.1(2)
[^{o}]	F1-C2-C3-O2	165.89(18)	172.9(2)	-161.94(13)	161.63(17)

Table 4.23 summarises selected chemical shifts and coupling constants for the α-fluoro-β-hydroxy esters synthesised in this chapter. The (2*S*,3*S*)/(2*R*,3*R*) diastereomers of compounds **(81)**, **(85)**, **(86)** and **(88)** had their configuration determined by X-ray crystallography (Figures 4.1 and 4.5). From Table 4.23 it can be seen that the (2*S*,3*S*)/(2*R*,3*R*) diastereomers of each of these compounds had a one bond carbon-fluorine coupling constant close to 194 Hz whilst the one bond carbon-fluorine coupling constant for the (2*S*,3*R*)/(2*R*,3*S*)-diastereomers were closer to 200 Hz. This data was used to assign the diastereomers of compounds **(83)**, **(87)** and **(90)**. In addition, the fluorine chemical shift of the (2*S*,3*S*)/(2*R*,3*R*)-diastereomer is always at lower field compared to that exhibited by the (2*S*,3*R*)/(2*R*,3*S*)-diastereomer and this data was used to assign the diastereomers of compounds **(84)** and **(89)**.

Table 4.23 Selected NMR data for *α*-fluoro-*β*-hydroxy esters.

Molecule No.	(2*S*,3*S*)/(2*R*,3*R*)	(2*S*,3*R*)/(2*R*,3*S*)
(81)	δ_H 4.84 (d, $^2J_{HF}$ 47.7 Hz) δ_F -194.5 δ_C 92.9 (d, $^1J_{CF}$ **194.2 Hz**)	δ_H 4.93 (d, $^2J_{HF}$ 47.7 Hz) δ_F -192.0 δ_C 93.5 (d, $^1J_{CF}$ **199.2 Hz**)
(83)	δ_H 4.89 (d, $^2J_{HF}$ 47.7 Hz) δ_F -193.9 δ_C 92.9 (d, $^1J_{CF}$ **194.2 Hz**)	δ_H 4.98 (d, $^2J_{HF}$ 48.1 Hz) δ_F -191.9 δ_C 92.5 (d, $^1J_{CF}$ **198.1 Hz**)
(84)	δ_H 5.43 (d, $^2J_{HF}$ 48.5) δ_F -197.0 δ_C 91.2 (d, $^1J_{CF}$ **188.1 Hz**)	δ_H 5.40 (d, $^2J_{HF}$ 48.5 Hz) δ_F -195.1 δ_C 92.5 (d, $^1J_{CF}$ **189.2 Hz**)
(85)	δ_H 4.79 (d, $^2J_{HF}$ 47.3 Hz) δ_F -194.5 δ_C 91.6 (d, $^1J_{CF}$ **194.2 Hz**)	δ_H 4.89 (d, $^2J_{HF}$ 47.7 Hz) δ_F -191.9 δ_C 93.1 (d, $^1J_{CF}$ **199.2 Hz**)
(86)	δ_H 4.88 (d, $^2J_{HF}$ 47.7 Hz) δ_F -196.4 δ_C 93.0 (d, $^1J_{CF}$ **193.2 Hz**)	δ_H 4.97 (d, $^2J_{HF}$ 47.7 Hz) δ_F -193.4 δ_C 92.3 (d, $^1J_{CF}$ **201.2 Hz**)
(87)	δ_H 4.87 (d, $^2J_{HF}$ 48.1 Hz) δ_F -196.2 δ_C 93.0 (d, $^1J_{CF}$ **193.3 Hz**)	δ_H 4.96 (d, $^2J_{HF}$ 47.7 Hz) δ_F -193.1 δ_C 92.5 (d, $^1J_{CF}$ **201.2 Hz**)
(88)	δ_H 4.80 (d, $^2J_{HF}$ 48.1 Hz) δ_F -195.4 δ_C 93.4 (d, $^1J_{CF}$ **193.2 Hz**)	δ_H 4.92 (d, $^2J_{HF}$ 47.7 Hz) δ_F -192.1 δ_C 92.8 (d, $^1J_{CF}$ **198.1 Hz**)
(89)	δ_H 4.95 (d, $^2J_{HF}$ 47.7 Hz) δ_F -196.39 δ_C 92.3 (d, $^1J_{CF}$ **192.2 Hz**)	δ_H 5.00 (d, $^2J_{HF}$ 47.7 Hz) δ_F -193.48 δ_C 90.7 (d, $^1J_{CF}$ **193.2 Hz**)
(90)	δ_H 5.09 (d, $^2J_{HF}$ 48.1 Hz) δ_F -198.00 δ_C 93.6 (d, $^1J_{CF}$ **191.2 Hz**)	δ_H 5.07 (d, $^2J_{HF}$ 47.3 Hz) δ_F -191.36 δ_C 91.8 (d, $^1J_{CF}$ **196.2 Hz**)

4.2.7 The enantioselective Reformatsky reaction with ketones

In the reaction optimisation studies (Section 4.2.4), the best balance between conversion, diastereomeric excess and enantiomeric excess is the reaction of 2.0

equivalents of ethyl iodofluoroacetate and 3.5 equivalents of diethylzinc with acetophenone at -40 ^{o}C in the presence of 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol (Table 4.16, run 2). The reaction was repeated using the same conditions with a range of ketones to determine the scope and limitations of the method (Table 4.24).

The reaction with propiophenone gave 100 % conversion and the diastereomeric ratio (87:13) was higher than that determined in the reaction with acetophenone (74:26). Extending the aliphatic side of the ketone by another CH_2 resulted in a good separation of both diastereoisomers by silica gel column chromatography. The minor diastereoisomer was isolated in 13% yield with a moderate enantiomeric excess (57 % ee). Much more exciting were the results obtained for the major distereoisomer, which was isolated in 71 % yield with a very high enantiomeric excess of 95 % ee. Hoping that the results could be further improved by extending the aliphatic chain, the reaction was repeated with 1-phenylbutan-1-one (run 3). The enantiomeric excess obtained for the minor diastereoisomer (65 % ee) was better than that obtained with propiophenone (57 % ee). However, it was still much lower compared to that obtained with acetophenone (80 % ee). Fortunately, the diastereomeric excess 86:14 was very good and the enantiomeric excess of the major distereoisomer was 94 % ee. Unfortunately, complete separation of the diastereoisomers by silica gel column chromatography was not possible. Very similar results to those with 1-phenylbutan-1-one (run 3) were obtained with the more bulky 3-methyl-1-phenylbutan-one (run 4). A high conversion (96 %) and an improved diastereomeric excess (91:9) was obtained. An excellent enantiomeric excess of 94 % was obtained for the major diastereomer.

Interesting results were obtained in the reaction with 2-methoxyacetophenone (run 5). The electron donating effect of the methoxy group did not affect the conversion. Although there was only a very small amount of diastereomeric control (42:58), a very high level of enantiomeric excess was obtained for both diastereoisomers (85 % ee). The diastereoisomers were separated easily by silica gel column chromatography. On the other hand, when the methoxy group was in the 4-position (run 6) the diastereomeric ratio increased to 80:20. The purification of the crude product by column chromatography did not allow the separation of the diastereoisomers. The enantiomeric excess determined for the minor diastereoisomer (81 % ee) was on the same level as in the case of acetophenone (80 % ee), but the ee determined for the major diastereoisomer was higher and reached 93 %. Replacing the methoxy group with the electron-

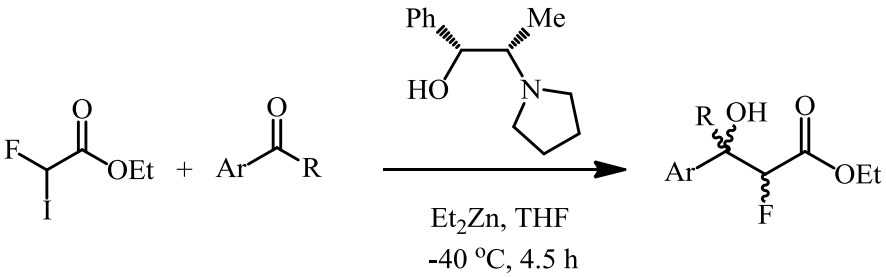
withdrawing chlorine in the *para* position (run 7) caused a small decrease in the diastereomeric excess (71:29) and the enantiomeric excesses of both diastereoisomers (88 % ee and 79 % ee) respectively. As previously mentioned, the diastereoisomers of the chlorinated product had to be separated prior to chiral HPLC. Initially, the mixture of both diastereoisomers was purified by silica gel column chromatography and a diastereomeric excess of the product was determined by ^{19}F NMR spectroscopy. In the second step the diastereoisomers were separated on the chromatotron and the enantiomeric excess was determined separately for each diastereoisomer.

The reaction with cyclic ketones also gave good results (runs 8 and 9). Although the reaction with tetralone gave a lower diastereomeric ratio (60:40), excellent enantiomeric excesses were obtained for both the major and minor diastereomers (94 and 88 % ee respectively). The reaction with indanone also gave a lower diastereomeric excess (63:37) and again, the enantiomeric excesses were very good for both diastereomers (85 % and 79 %).

Unlike in the achiral reaction, here extending the aliphatic side of the ketone significantly improved the diastereomeric excess (Table 4.24). The longer and more bulky was the aliphatic side of the ketone, the better the diastereomeric excess in the reaction but the improvement between acetophenone (74:26 de, run 1) and propiophenone (87:13 de, run 2) was much bigger than between propiophenone and 1-phenylbutan-1-one (89:11 de, run 3) or 3-methyl-1-phenylbutan-one (92:8 de, run 4). The effect of the substituents in the *para*-position on the phenyl ring was not as spectacular, but there was an indication that a slightly better diastereomeric excess can be obtained with the methoxy group (81:19 de, run 6) rather than with the chlorine atom (71:29 de, run 7). This phenomenon can be rationalised by the electron donating effect of the methoxy group causing the reaction to slow down and hence, there is a bigger chance for this enantiomer of the Reformatsky reagent to react by the lower energy pathway. On the other hand, the electron withdrawing effect of chlorine increased the rate of the reaction. The improvement in the diastereomeric excess in the reaction with indanone (run 9) was very little and there was none in the reaction with 1-tetralone (run 8). *o*-Methoxyacetophenone was the only ketone in the control group whose diastereomeric excess was lower in the reaction performed in the presence of chiral aminoalcohol than in the achiral reaction. The presence of the (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol attached to the zinc was also responsible for the fact, that

the *si*-face of the coordinated ketone was preferentially exposed to the addition of the Reformatsky reagent and a high enantiomeric excess in the reaction could be obtained.

Table 4.24 Screening of the ketones in the asymmetric Reformatsky reaction with ethyl iodofluoroacetate.



Run	Ketones	Conv.[a] [%]	Yields[b] [%]	Dr[c] (*S*,*S*)(*R*,*R*): (*S*,*R*)(*R*,*S*)	Ee[d] [%]	Product No.
1	acetophenone	99	97	74:26 (78:22)	87(*S*), 80(*S*)	**(81)**
2	propiophenone	100	71:13	87:13	95, 57	**(86)**
3	1-phenylbutan-1-one	100	95	89:11 (86:14)	94, 65	**(87)**
4	3-methyl-1-phenylbutan-one	96	94	92:8 (91:9)	94, 61	**(88)**
5	*o*-methoxyacetophenone	100	51:34	58:42	85, 85	**(84)**
6	*p*-methoxyacetophenone	100	99	81:19 (80:20)	93, 81	**(83)**
7	*p*-chloroacetophenone	100	96[e]	71:29 (71:29)	88, 79	**(85)**
8	1-tetralone	100	84	60:40 (62:38)	94, 88	**(90)**
9	indanone	98	97	64:36 (63:37)	85, 79	**(89)**

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yields, [c] determined by ^{19}F NMR spectroscopy (after column in parenthesis), [d] determined by chiral HPLC and reported for major diastereoisomer, minor diastereoisomer respectively, [e] the diastereoisomers were separated on a chromatotron (5 % diethyl ether in hexane) in order to determine enantiomeric excess.

4.3 Conclusions

The Reformatsky reaction of ethyl iodofluoroacetate **(80)** promoted by diethylzinc is a convenient method for the synthesis of α-fluoro-β-hydroxyesters from aromatic ketones. The reaction of **(80)** did not require a catalyst and the use of

diethylzinc allowed the process to be performed homogeneously under mild reaction conditions with short reaction times.

A convenient one-pot enantioselective Reformatsky reaction of **(80)** with ketones was developed. Excellent enantiomeric excesses were obtained with a range of ketones with electron-withdrawing and electron-donating groups, as well as with cyclic ketones. Extending the aliphatic side of the ketone improved the diastereomeric excess and the enantiomeric excess for the major diastereoisomer. All of the molecules discussed in section 4.2.6 have not been previously reported. The major configuration of the new chiral centre in the β-position of the β-hydroxyesters appeared to be identical for both diastereoisomers obtained in the reaction and the major enantiomer obtained in the analogous Reformatsky reaction of ethyl iododifluoroacetate (Chapter 3).

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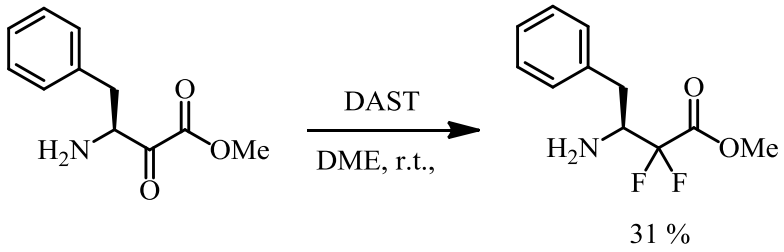
Chapter Five

The Asymmetric Reformatsky reaction of Ethyl Iododifluoroacetate with Imines

5.1 Introduction

Difluorinated *β*-amino acids and their derivatives have recently received much attention due to their applications in the synthesis of fluorinated peptides, peptidomimetics, *β*-lactam antibiotics and other biologically-active molecules. Two different approaches have been reported for the incorporation of the difluoromethylene group in *α,α*-difluoro-*β*-amino esters and *gem*-difluorinated lactams. In the first approach the fluorinating reagent (DAST) was used to transform the carbonyl group of ketoesters[1] in order to obtain the corresponding *α,α*-difluoro-*β*-amino ester[2] but the yield in the reaction was only 31 % (Scheme 5.1). In the second, more common approach, the fluorinated building blocks were employed in a 1,2-addition to the imine or imine equivalent. These molecules were only obtained with a high enantiomeric excess in the diastereomeric reaction with imines containing a chiral auxiliary or by using an enantiomerically pure fluorinated building block. The aim of this chapter is to develop a one-pot asymmetric Reformatsky reaction of ethyl iododifluoroacetate with imines in the presence of a chiral aminoalcohol.

Scheme 5.1 Fluorination of the chiral ketoester with DAST.

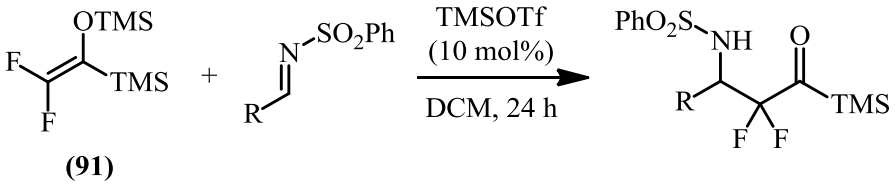


31 %

5.1.1 Synthesis of *α,α*-difluoro-*β*-amino esters

In 2005 Welch *et al.* reported the synthesis of *α,α*-difluorinated-*β*-amino esters from (2,2-difluoro-1-(trimethylsilyl)vinyloxy)trimethylsilane **(91)** and imines in the presence of a catalytic amount of a Lewis acid catalyst.[3] Compound **(91)** was prepared in THF by the reaction of 2,2,2-trifluoroethanol with LDA and trimethylsilyl chloride in 62 % yield.[4] Compound **(91)** was less reactive than difluorinated silyl enol ethers **(37)** and the reaction with benzyl imines was impossible. However, the reaction with imines activated by the presence of a sulfonyl protected group with aliphatic (at -78 ^{o}C) and aromatic character (at r.t.) was carried out in DCM. The reaction was sluggish and after 24 hours only moderate yields were obtained (Table 5.1).

Table 5.1 The reaction of **(91)** with imines.[3]

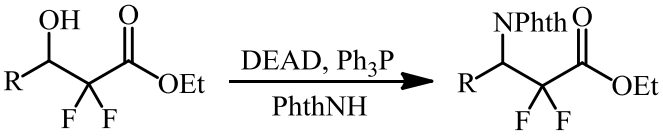


R	Yields [%][a]	R	Yield [%][a]
p-ClC_6H_4	72	cyclohexyl	63
p-$CH_3C_6H_4$	71	isopropyl	49
p-$NO_2C_6H_4$	51	isobutyl	51
p-$CH_3OC_6H_4$	56	butyl	54

[a] Isolated yield.

Fokina reported that *α,α*-difluoro-*β*-amino esters can be obtained from *α,α*-difluoro-*β*-hydroxy esters by Mitsunobu amination (Table 5.2).[5] The reaction of hydroxyl esters with diethylazodicarboxylate (DEAD), triphenylphosphine and phthalimide (PhthNH) gave very good results with esters with straight aliphatic chains but the yields were significantly lower with substrates that contain a branched aliphatic chain or an aromatic ring. These latter reactions resulted in large amounts of co-products.

Table 5.2 Mitsunobu amination of *α,α*-difluoro-*β*-amino esters.[5]



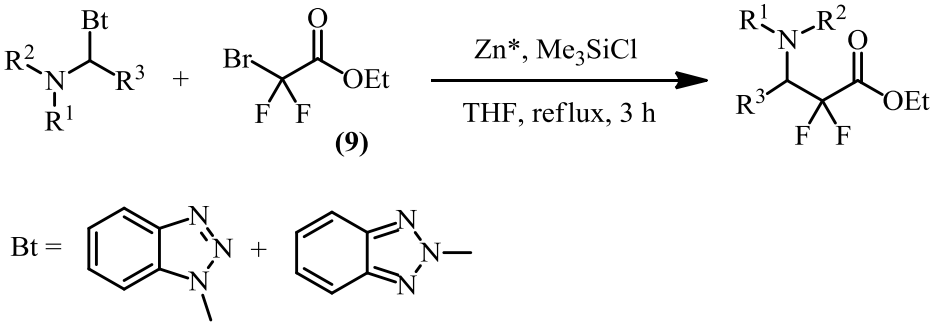
R	Yield [%][a]	R	Yield [%][a]
n-C_5H_{11}	95	*p*-ClC_6H_4	32
n-C_4H_9	90	*p*-FC_6H_4	53
i-C_3H_7	44		

[a] Isolated yield.

Katritzky *et al.* synthesised *α,α*-difluoro-*β*-amino esters from *N*-(α-aminoalkyl)benzotriazoles. These iminium salt precursors reacted with the Reformatsky reagent as the chemical equivalents of imines (Table 5.3).[6] To begin with, the starting material was prepared from aldehyde, amine and benzotriazole. There was no need to purify the obtained *N*-(α-aminoalkyl)benzotriazoles and in the next step the

Reformatsky reagent was generated from zinc dust and used *in situ* in THF. The reaction was refluxed for 3 hours and high yields were obtained. The benzyl (Bn) protecting groups present in the product obtained in run 5 were removed by hydrogenolysis ($Pd(OH)_2/C$, H_2 (45 psi), EtOH, rt, 2 days, run 6) giving the product in 80 % yields.

Table 5.3 The Reformatsky reaction with *N*-(α-aminoalkyl)benzotriazoles.[6]

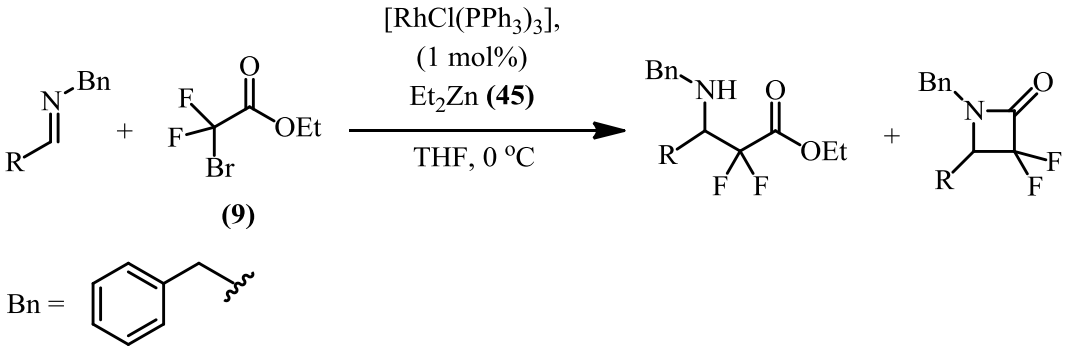


Run	R^1	R^2	R^3	Yield[a] [%]
1	Ph	Me	H	90
2	Ph	Ph	H	87
3	Ph	H	H	92
4	Ph	Me	*i*-Pr	89
5	Bn	Bn	$PhCH_2CH_2$	80[b]

[a] Isolated yield, [b] yield of deprotected product (R^1=R^2=H).

Kumadaki *et al.* extended the protocol of the rhodium catalysed Reformatsky reaction of ethyl bromodifluoroacetate promoted with diethylzinc to imines (Table 5.4).[7] After an extensive examination THF proved to be the best solvent and a high conversion to the product along with a high isolated yield (60-93 %) were obtained with aromatic imines (runs 1-6). In addition, the reaction at 0 ^oC was fast and was finished within 1-6 h. Under anhydrous conditions the *α,α*-difluorinated lactam was the exclusive product (runs 1, 3 and 5). Moisture had a significant influence on the result of the reaction and the addition of water or $MgSO_4.7H_2O$ led to the formation of α,α-difluoro-β-amino esters. In contrast, the reaction with an aliphatic imine gave a lower yield and a mixture of the two products (run 7).

Table 5.4 The rhodium catalysed Reformatsky reaction with imines.[7]



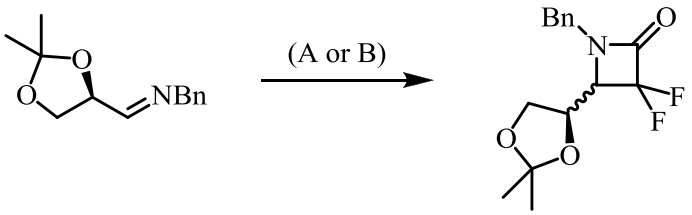
Run	R	Yield[a] [%] (ester)	Yield[a] [%] (lactam)
1	Ph	1	83
2	Ph[b]	65	trace
3	4-$MeOC_6H_4$	6	93
4	4-$MeOC_6H_4$[b]	59	trace
5	4-ClC_6H_4	1	82
6	4-ClC_6H_4[b]	60	trace
7	C_6H_{11}	18	35

[a] Isolated yield, [b] the reaction with equimolar amount of $MgSO_4.7H_2O$.

5.1.2 Diastereomerically controlled synthesis of *α,α*-difluoro-*β*-amino esters using chiral imines

Kobayashi *et al.* reported the Reformatsky reaction and Mukayama's aldol reaction of methyl iododifluoroacetate and ethyl bromodifluoroacetate with imines.[8] Two different methods were studied for the Reformatsky reaction. In the first method, methyl iododifluoroacetate was added to a suspension of zinc dust in THF at 0 °C and the mixture was stirred for twenty minutes before the imine was added (Method A). The reaction was quenched after 20 hours of stirring at the same temperature. In the second protocol, ethyl bromodifluoroacetate and the imine were gradually added to the boiling suspension of zinc dust in THF (Method B) but the length of the reflux was not reported. The isolated yields of the fluorinated lactams were almost identical in both reactions. However, a slightly better diastereomeric excess was obtained in the reaction with ethyl bromodifluoroacetate (Scheme 5.2).

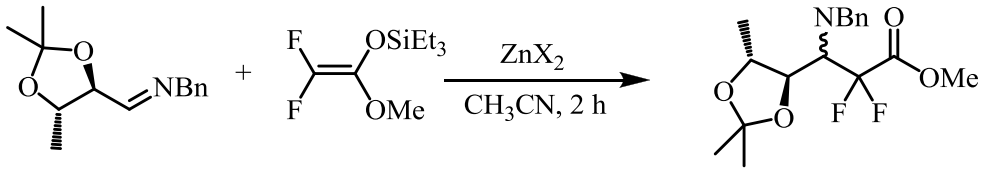
Scheme 5.2 The Reformatsky reaction of methyl iododifluoroacetate and ethyl bromodifluoroacetate.



Method A: 65 %; syn/anti= 3.1/1
Method B: 67 %; syn/anti= 4.7/1

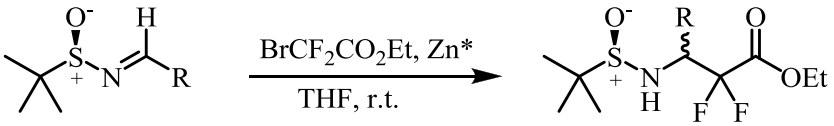
Kobayashi also studied Mukayama's aldol reaction of (2,2-difluoro-1-methoxyvinyl)triethylsilane with a chiral imine. The reaction was performed at 0 ^{o}C for 2 hours and gave a good isolated yield of 70 % (Scheme 5.3). The diastereomeric excess based on the quantities of the isolated diastereoisomers of methyl *α*,*α*-difluoro-*β*-hydroxyester was 3.7/1 (*syn*/*anti*).[8]

Scheme 5.3 Mukayama's aldol reaction with chiral imine.



70 %; syn/anti= 3.7/1

Table 5.5 The Reformatsky reaction with *N*-*tert*-butylsulfinimines.[9]



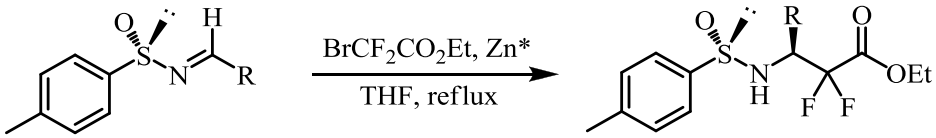
Run	R	Yield[a] [%]	De[b] [%]
1	*i*-C_4H_9	51	81:19
2	*n*-C_3H_7	55	80:20
3	Ph	82	90:10
4	*c*-C_6H_{11}	81	87:13
5	2-thiazolyl	58	95:5

[a] Isolated yield, [b] determined by HPLC.

Staas first used enantiomerically pure sulfinimines in the Reformatsky reaction of ethyl bromodifluoroacetate.[9] The reaction was performed with 3.0 equivalents of the Reformatsky reagent for 18 h at room temperature. The presence of *N-tert*-butylsulfinamide group resulted in a 51-82 % yield and a 60-90 % distereomeric excess.

Soloshonok investigated the Reformatsky reaction with *N-p*-toluenesulfinyl imines (Table 5.6).[10] The solutions of the imine and ethyl bromodifluoroacetate were added gradually to the refluxing suspension of zinc dust. Two equivalents of the Reformatsky reagent were needed in order to obtain high yields. The diastereomeric excess was better when electron-donating groups were substituted on the aromatic ring (runs 2 and 3), whilst the electron-withdrawing CF_3 group caused a decrease in the diastereomeric excess (run 4). The reactions with aliphatic imines gave a lower yield and a lower diastereomeric excess (runs 5 and 6).

Table 5.6 The Reformatsky reaction with *N-p*-toluenesulfinyl imines.[10]



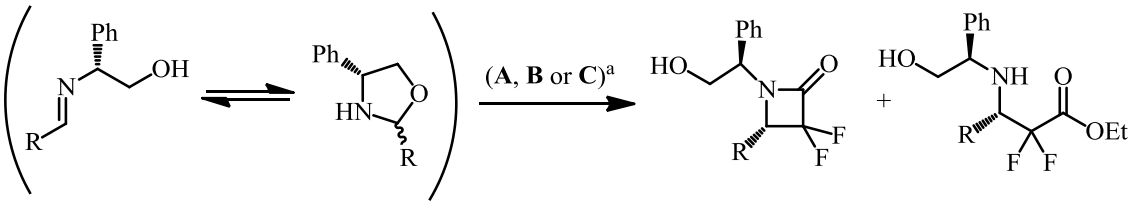
Run	R	Yield[a] [%]	De[b] [%]
1	C_6H_5	82	92
2	*p*-$MeOC_6H_4$	82	>98
3	*p*-FC_6H_4	83	94
4	*p*-$CF_3C_6H_4$	85	80
5	*n*-C_5H_{11}	65	72
6	*t*-Bu	60	76

[a] Isolated yield, [b] determined by ^1H and ^{19}F NMR spectroscopy.

Recently, Quirion has studied the Reformatsky reaction of ethyl bromodifluoroacetate with chiral imines in great detail.[11,12] Three protocols for the Reformatsky reaction were tested with imines containing an (*R*)-phenylglycinol group (Table 5.7). In Method A the suspension of activated zinc dust in THF was stirred with a catalytic amount of chlorotrimethylsilane and 1,2-dibromoethane at 50 ^oC. The solution of ethyl bromodifluoroacetate was added gradually. After 10 minutes of stirring, the imine was added and the reaction mixture was refluxed for 2 hours. In

Method B the Reformatsky reagent was formed from ethyl bromodifluoroacetate and zinc dust in the presence of a catalytic amount of Cp_2TiCl_2. The temperature was maintained at 50 ^oC during the addition of the chiral imine and the reaction was then stirred for 1 hour at room temperature. The Reformatsky reagent in Method C was generated in acetonitrile from ethyl bromodifluoroacetate and diethylzinc in the presence of Wilkinson's catalyst. The solution of imine in acetonitrile was added after 30 minutes of additional stirring. Depending on which starting material was used, the Reformatsky reaction resulted in lactam (runs 1-4) or ester (runs 5 and 7). The diastereomeric excess was high and in most examples it was greater than 98 %. Only in run 4, where the imine was obtained from 2-furylaldehyde, was a lower 85 % de obtained. The Reformatsky reaction with diethylzinc and Wilkinson's catalyst did not work in the presence of 4-pyridyl (run 6) and 3-pyridyl groups (run 8).

Table 5.7 The Reformatsky reaction with chiral imines.[12]



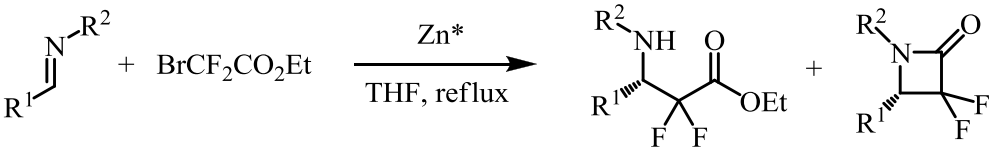
Run	R	Procedure[a]	Yield[b] [%]	Lactam/ ester	De[c] [%]
1	Ph	**A**	56	100/0	>98
2	Ph	**C**	62	100/0	>98
3	3-Thienyl	**A**	71	100/0	>98
4	2-Furyl	**A**	62	100/0	85
5	4-pyridyl	**A**	67	0/100	>98
6	4-pyridyl	**C**	-	-	-
7	4-pyridyl	**B**	47	0/100	>98
8	3-pyridyl	**C**	-	-	-

[a] **A**: Zn*, Me_3SiCl, THF, reflux, 2 h; **B**: Zn*, Cp_2TiCl (5 mol%), THF, r.t., 1 h; **C**: Et_2Zn, Wilkinson's catalyst (2 mol%), CH_3CN, r.t., 5 h, [b] isolated yield; [c] determined by ^{19}F NMR spectroscopy.

The results in Table 5.8 from screening the reaction with two other chiral auxiliaries showed that the best diastereomeric excess was obtained with (*R*)-

phenylglycinol (runs 1 and 4) and (*R*)-1-phenyl-2-methoxyethyl group (run 2). The reaction in the presence of *α*-(*R*)-methylbenzylamine with no ability to chelate (run 3) gave good yields but a low diastereomeric excess. Additionally, the reaction with (*R*)-phenylglycinol gave only one product whilst the other two auxiliaries gave a mixture of lactam and ester. According to Quirion, a strong chelating effect of (*R*)-phenylglycinol group with zinc was responsible for the high diastereomeric excess as the Reformatsky reagent could attack from only one side of the complex (Figure 5.1). A slightly lower diastereomeric excess was obtained in the reaction with (*R*)-1-phenyl-2-methoxyethyl group. Otaka proposed that the tautomeric equilibrium between imine and enamine was responsible for the formation of *E* and *Z* isomers of the imine resulting in the formation of two diastereoisomers.[13] More probable was the explanation given by Quirion who suggested that since the strongly chelating (*R*)-phenylglycinol group had been replaced by a weaker coordinating methylated group, there may be some uncoordinated imine in solution.[12] Here, once again, the complex could be attacked from only one side, but the free imine could be attacked on both sides yielding a small amount of the undesired diastereoisomer. As the *α*-(*R*)-methyl benzylamine group had no ability to coordinate to zinc, the diastereomeric excess in the Reformatsky reaction depended only on the conformation of the imine and the difference in the steric hindrance between the methyl and phenyl groups (run 3).

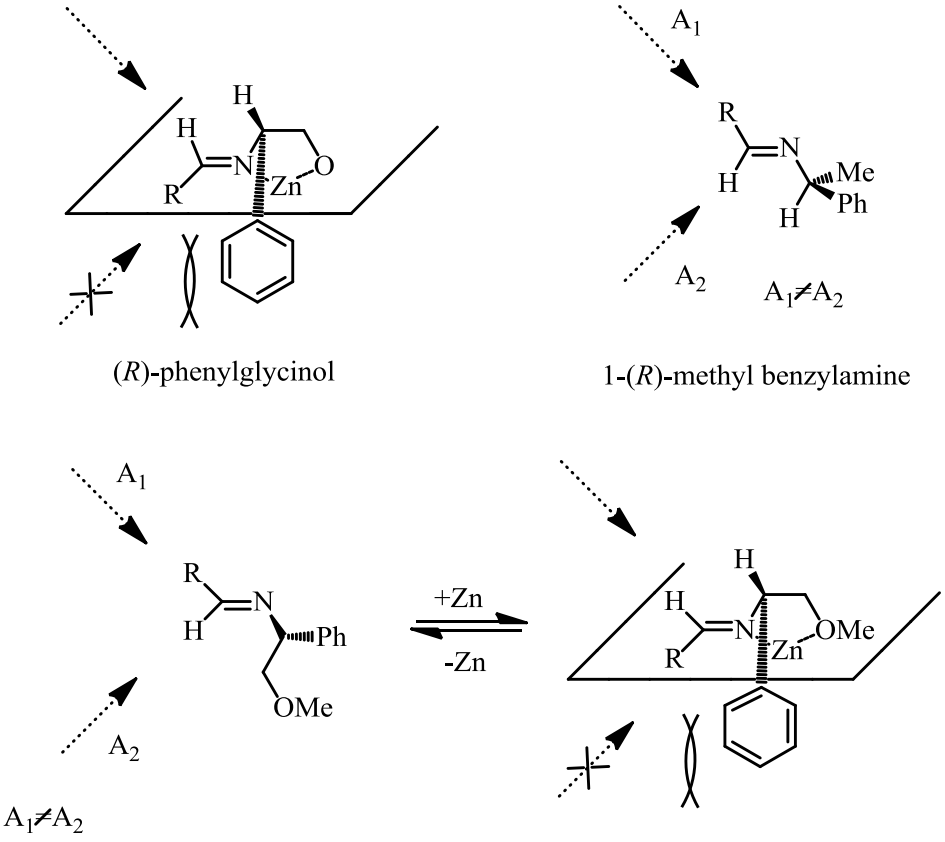
Table 5.8 The diastereoselective Reformatsky reaction with imines.



Run	R^1	R^2	Yield[a] [%]	Lactam /ester	De[b] [%]
1	Ph	(*R*)-phenylglycinol	56	100/0	>98
2	Ph	(*R*)-1-phenyl-2-methoxyethyl	53	93/7	97/94
3	Ph	*α*-(*R*)-methyl benzylamine	61	83/17	23/30
4	4-pyridyl	(*R*)-phenylglycinol	67	0/100	>98

[a] Isolated yield, [b] determined by ^{19}F NMR spectroscopy (lactam/ester).

Figure 5.1 The influence of the chiral auxiliary on diastereomeric excess.



Several imines containing the (*R*)-1-phenyl-2-methoxyethyl group were tested in the reaction with the Reformatsky reagent formed from activated zinc dust.[12] The two hour reaction took place under reflux (Scheme 5.4, Table 5.9). The diastereomeric excess and the ratio of lactam to ester in the product depended on the R group that was used. The isolated product contained mostly lactam with a very high diastereomeric excess. Particularly surprising was the excellent diastereomeric excess obtained in the reaction with imines containing aliphatic groups (runs 5 and 6).

Scheme 5.4 The diastereoselective Reformatsky reaction with imines.

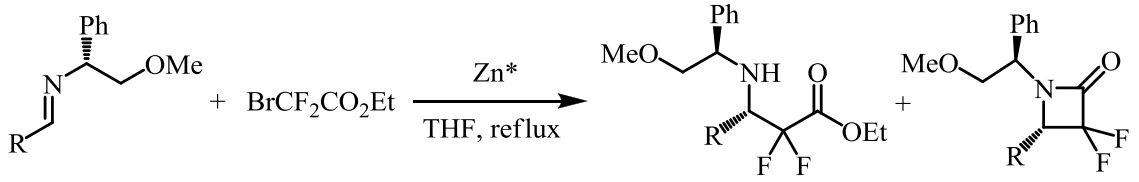


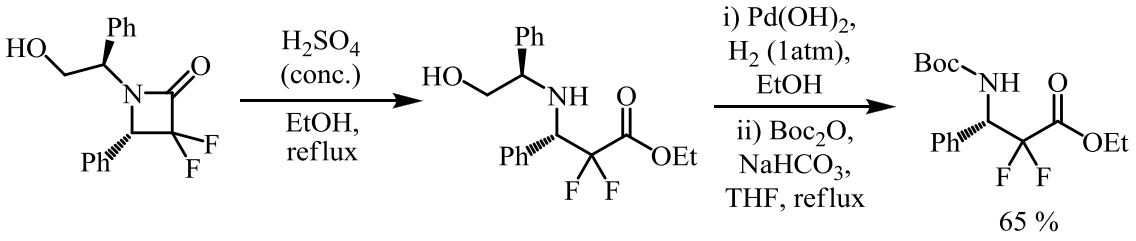
Table 5.9 The diastereoselective Reformatsky reaction (Scheme 5.4) with imines.[12]

Run	R	Yield[a] [%]	Lactam/ester	De[b] [%]
1	Ph	53	91/9	97/94
2	*p*-$NO_2C_6H_4$	45	93/7	86/n.d.
3	*o*-$NO_2C_6H_4$	58	77/23	84/n.d.
4	*p*-$CF_3C_6H_4$	48	100/0	89
5	$CH_3(CH_2)_4$	52	100/0	>98
6	$(CH_3)_3C$	33	78/22	>98

[a] Isolated yield, [b] determined by ^{19}F NMR spectroscopy (lactam/ester)

Ando has also studied the Reformatsky reaction of ethyl bromodifluoroacetate, diethylzinc and Wilkinson's catalyst with imines obtained from (*R*)-phenylglycinol and aldehydes, and obtained comparable results to those reported by Quirion (Table 5.9).[14] Ando reported that the ring of the difluorinated lactam was opened by refluxing with concentrated H_2SO_4 in ethanol and, in the next step, the chiral auxiliary was removed by hydrogenolysis. The overall yield for two steps was 65 % (Scheme 5.5).

Scheme 5.5 The ring opening and the removal of the chiral auxiliary.



5.1.3 Diastereomerically controlled synthesis of *α,α*-difluoro-*β*-amino esters using a chiral bromodifluoro ester

The pure enantiomer of (-)-menthol was used in the transesterification of ethyl bromodifluoroacetate in order to form (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromo-2,2-difluoroacetate **(92)** (Scheme 5.6).[15] The Reformatsky reaction of **(92)** with the imine was performed with diethyl zinc in the presence of Wilkinson's catalyst and difluoro-*β*-lactams were formed (Table 5.10). The difluorinated menthyl ester was isolated as a co-product (11 %) from the reaction performed without the catalyst (run 2). Aromatic imines gave moderate to good yields and a high enantiomeric excess (runs 1-

4). Unfortunately, the reaction with the aliphatic cyclohexyl imine (run 5) gave a low yield and a lower diastereomeric excess and the isopropyl imine gave only a 14 % yield without any diastereomeric excess.

Scheme 5.6 Transesterification of ethyl bromodifluoroacetate.

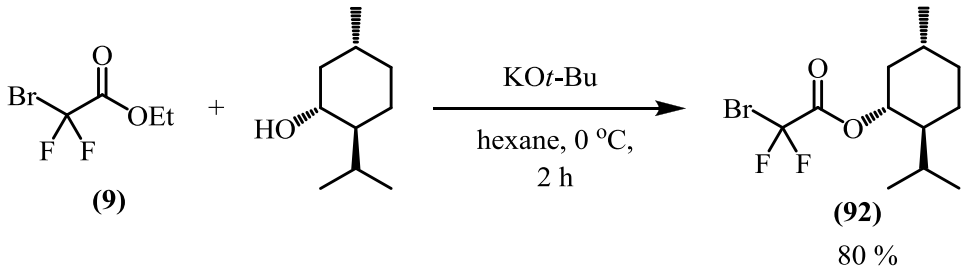
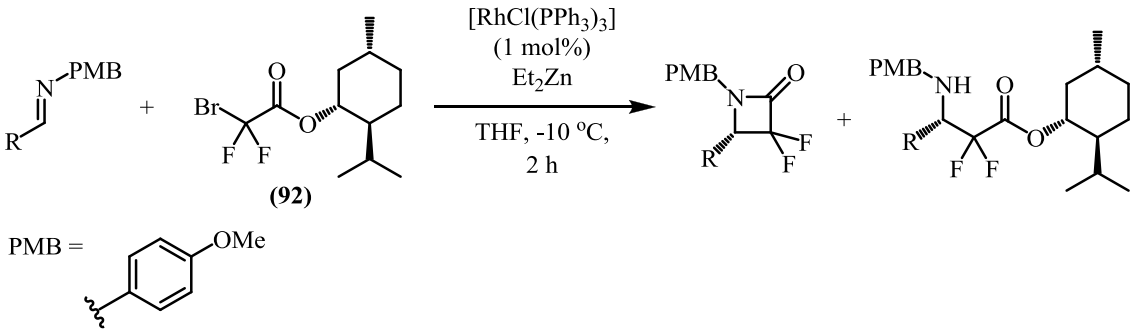


Table 5.10 The diastereoselective Reformatsky reaction with imines.



Run	R	Yield[a] [%]	De[b] [%]
1	C_6H_5	71	92
2	C_6H_5[c]	58 (11)	91
3	*p*-$MeOC_6H_4$	46	94
4	*p*-ClC_6H_4	57	87
5	*c*-C_6H_{11}	41	80
6	$CH(CH_3)_2$[d]	14	0

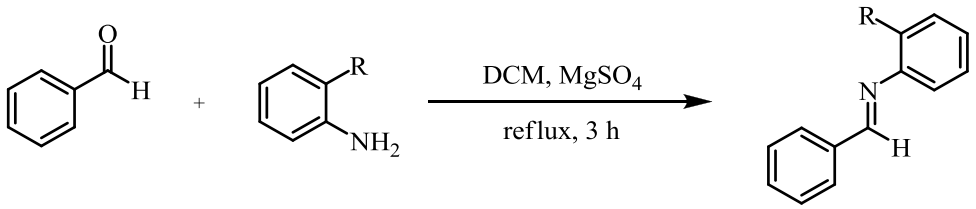
[a] Isolated yield of lactam (ester in parenthesis), [b] diastereomeric excess determined by chiral HPLC, [c] the reaction for 18 h without Wilkinson's catalyst, [d] the imine was *para*-methoxyphenyl (PMP) protected.

5.2 Results and discussion

5.2.1 Synthesis of imines

The first step to the work with an asymmetric Reformatsky reaction was the preparation of a small series of imines. The selected imines contained a hydroxy, a methoxy and a phenoxy group in the *ortho* position to the nitrogen. The presence of the two coordinating groups, the oxygen and the nitrogen, should allow a chelate ring to be formed with zinc and, as a consequence, a good enantiomeric excess in the chiral reaction was expected. The (*E*)-*N*-benzylideneaniline **(93)**, which contained a hydrogen in the *ortho* position to the nitrogen and had the ability to coordinate only by nitrogen was selected for a direct comparison.

Table 5.11 Synthesis of the imines.



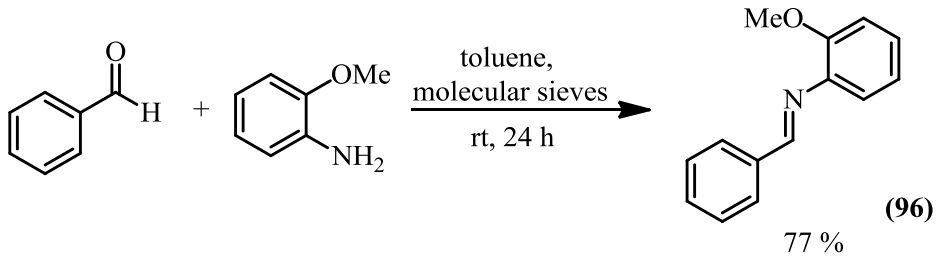
Run	R	Yield[a] [%]	Product No.
1	H	58	**(93)**
2	OH	36	**(94)**
3	OPh	65	**(95)**
4	OMe	0	**(96)**

[a] Isolated yields.

Three of the imines, **(93)** (run 1), (*E*)-2-(benzylideneamino)phenol **(94)** (run 2) and (*E*)-*N*-benzylidene-2-phenoxyaniline **(95)** (run 3) were synthesised using a modification of Quirion's methodology (Table 5.11).[16] The reaction of benzaldehyde with the appropriate aniline was performed in DCM for 3 hours under reflux. Magnesium sulphate was used in the reaction to remove any water formed and pull the equilibrium over to the imine. The crude products were purified by Kugelröhr distillation and the isolated imines were fully characterised. Unfortunately, the reaction of *o*-methoxyaniline with benzaldehyde did not go to completion and when the crude

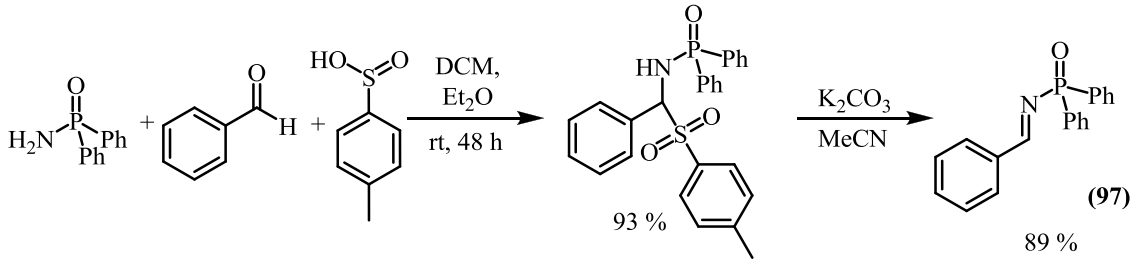
product was recrystallised from hexane equal amounts of the (*E*)-*N*-benzylidene-2-methoxyaniline **(96)** and *o*-anisidine co-crystallised together. Consequently, pure **(96)** was obtained using de Bartsch's methodology (Scheme 5.7).[17] The benzaldehyde and *o*-anisidine were added to a flask containing toluene and molecular sieves. The reaction mixture was stirred at room temperature overnight. The crude product was purified by Kugelröhr distillation giving a 77 % isolated yield. Unfortunately, since **(96)** is relatively unstable and can by hydrolysed easily, it is important to use dry $CDCl_3$ in order to obtain the ^{1}H and ^{13}C NMR spectra of the pure imine without any decomposition to the aldehyde and aniline.

Scheme 5.7 Synthesis of (*E*)-*N*-benzylidene-2-methoxyaniline **(96)**.



With the intention of finding an imine that would give a high isolated yield and enantiomeric excess, (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide **(97)** was also synthesised (Scheme 5.8). It was hoped that the electron withdrawing effect of the phosphinyl group would increase the reactivity of the imine so that the Reformatsky reaction could be performed at low temperatures and that the presence of the oxygen would enable the formation of a chelate ring with zinc in order to get a high level of enantiomeric excess. Imine **(97)** was prepared in two steps from benzaldehyde and diphenylphosphineamine with an overall of yield 83 %.[18]

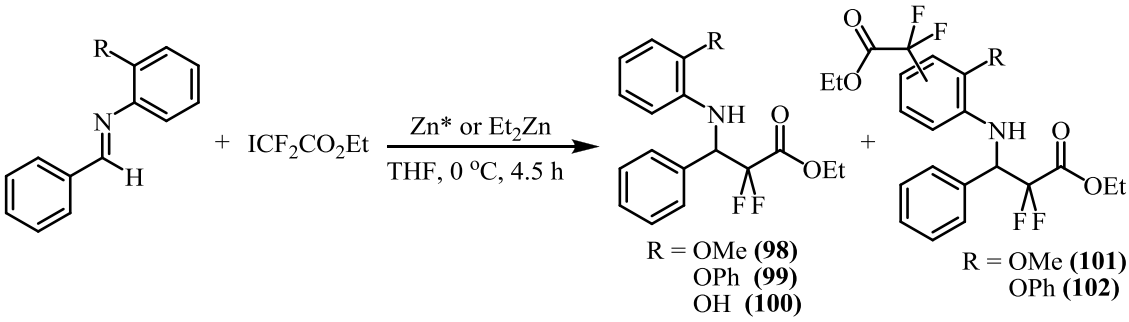
Scheme 5.8 The synthesis of (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide



5.2.2 The Reformatsky reaction with imines

The preliminary reaction of **(96)** was run with 1.5 equivalents of ethyl iododifluoroacetate and diethylzinc at 0 ^{o}C for 4.5 h (Table 5.12). At the end of the reaction there was no sign of any benzaldehyde in the ^{1}H NMR spectrum of the crude product which was an indication that all the imine had reacted. However, the ^{19}F NMR spectroscopy showed the presence of three fluorinated products (run 1). The main product was the desired ethyl 2,2-difluoro-3-(2-methoxyphenylamino)-3-phenylpropanoate **(98)**, which was isolated in 63 % yield. Recrystallisation of **(98)** by slow evaporation of the solvent from a solution in hexane gave a good quality crystal which was used for X-ray diffraction (Figure 5.2). A by-product **(101)** was also produced which was later identified as a result of the reaction between the imine and two equivalents of the fluorinated reagent, where the second substitution took place on the activated aromatic ring. There was also a trace of the product resulting from the addition of the Reformatsky reagent to benzaldehyde and it was identified by the chemical shifts in the ^{19}F NMR spectrum.

Table 5.12 The Reformatsky reaction with imines.

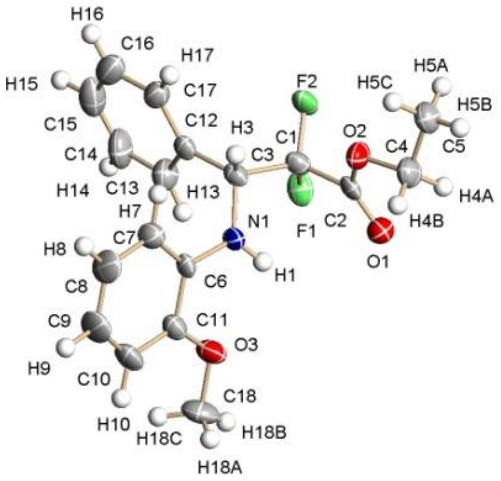


Run	R	Conditions[a]	Conversion[b] [%]	Ratio of products[c]	Yield[d] [%]	Product No.
1	OMe	Et_2Zn	100	87:13	63	**(98)**
2	OPh	Et_2Zn	99	99:1	22	**(99)**
3	OH	Zn*	79	100:0	51	**(100)**

[a] The reaction with 1.5 equivalents of the Reformatsky reagent (Zn*) or 1.5 equivalents of ICF_2CO_2Et and diethylzinc, [b] determined by ^{1}H NMR spectroscopy, [c] determined by ^{19}F NMR spectroscopy (product:disubstituted product), [d] isolated yield of desired product.

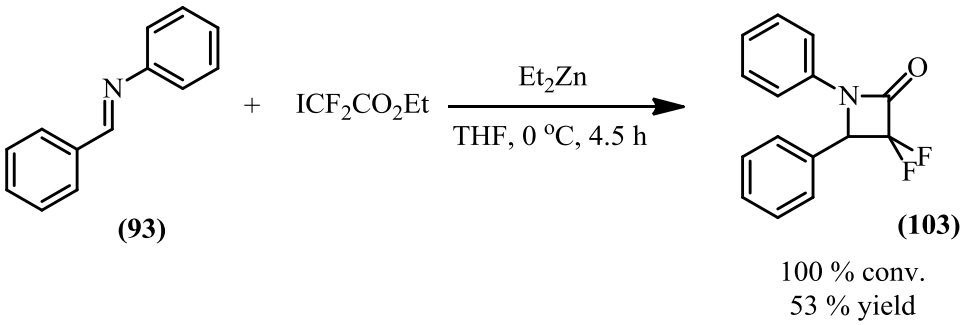
Ethyl 2,2-difluoro-3-(2-phenoxyphenylamino)-3-phenylpropanoate **(99)** along with a small amount of by-product **(102)** was obtained from (*E*)-*N*-benzylidene-2-phenoxyaniline **(95)** in 22 % yield. (*E*)-2-(Benzylideneamino)phenol **(94)** underwent the classical two-step Reformatsky reaction with 1.5 equivalents of the Reformatsky reagent prepared from ethyl iododifluoroacetate and activated zinc dust. The reaction gave a 79 % conversion to the desired product **(100)**. In the reactions where the imine did not fully react the conversion was calculated from the ^{1}H NMR spectrum of the crude product by integrating the benzaldehyde signal at 10 ppm with the signals for the single hydrogen of $CHCF_2$ for the fluorinated products at approximately 5 ppm. The ratio of these fluorinated products was later determined from the integration of the signals in the ^{19}F NMR spectrum.

Figure 5.2 The molecular structure of ethyl 2,2-difluoro-3-(2-methoxyphenylamino)-3-phenylpropanoate **(98)**. Figure shows 50 % displacement ellipsoid and hydrogen atoms in calculated positions.

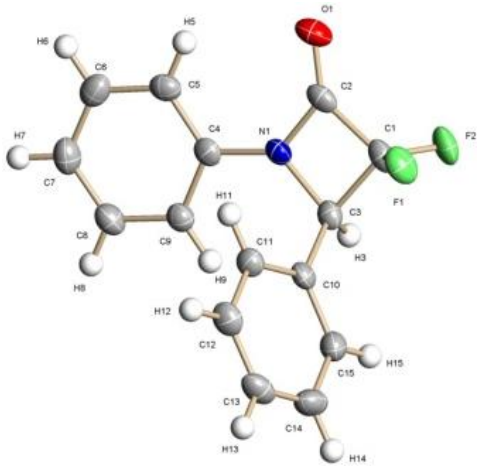


On the other hand, the reaction of **(93)** with ethyl iododifluoroacetate and diethylzinc gave 100 % conversion to the lactam instead of the ester (Scheme 5.9). The product, 3,3-difluoro-1,4-diphenylazetidin-2-one **(103),** was purified in 53 % yield by column chromatography. A good quality crystal, used for X-ray crystallography, was obtained by slow evaporation from a solution of **(103)** in hexane (Figure 5.3).

Scheme 5.9 The Reformatsky reaction with (*E*)-*N*-benzylideneaniline.



Figutre 5.3 The molecular structure of 3,3-difluoro-1,4-diphenylazetidin-2-one **(103)**. Figure shows 50 % displacement ellipsoid and hydrogen atoms in calculated positions.



The Reformatsky reaction of (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide **(97)** with 1.5 equivalents of ethyl iododifluoroacetate and diethylzinc gave 100 % conversion and 44 % isolated yield of the pure product was obtained after recrystallisation from 30 % EtOAc in hexane (Scheme 5.10). The purification resulted in a good quality crystal of ethyl 3-(diphenylphosphorylamino)-2,2-difluoro-3-phenylpropanoate **(104)** and the molecular structure is presented in Figure 5.4.

Scheme 5.10 The Reformatsky reaction with (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide.

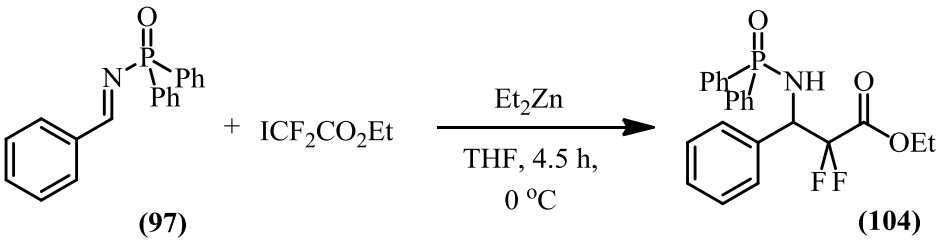


Figure 5.4 The molecular structure of ethyl 3-(diphenylphosphorylamino)-2,2-difluoro-3-phenylpropanoate **(104)**. Figure shows 50 % displacement ellipsoid and hydrogen atoms in calculated positions.

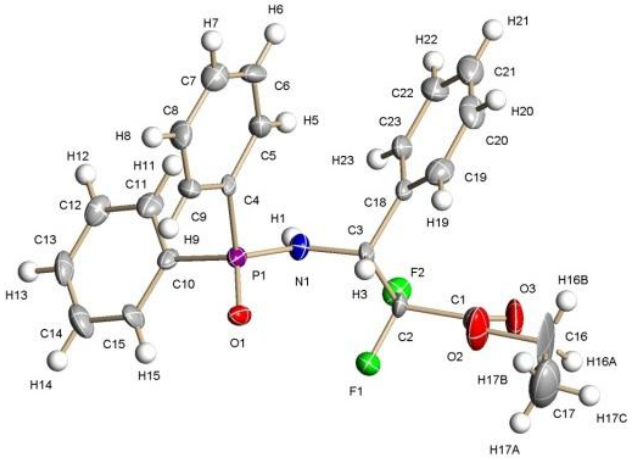


Table 5.13 Conditions for the chiral HPLC.

Product	Column	% IPA	t_1 [a]	t_2 [b]
(98)	OD-H	0.5	10.38 min	11.57 min
(99)	OD-H	2	5.29 min	5.97 min
(100)	OD-H	5	8.17 min	9.74 min
(103)	OD-H	4	5.84 min	6.84 min
(104)	AD	10	18.05 min	23.21 min

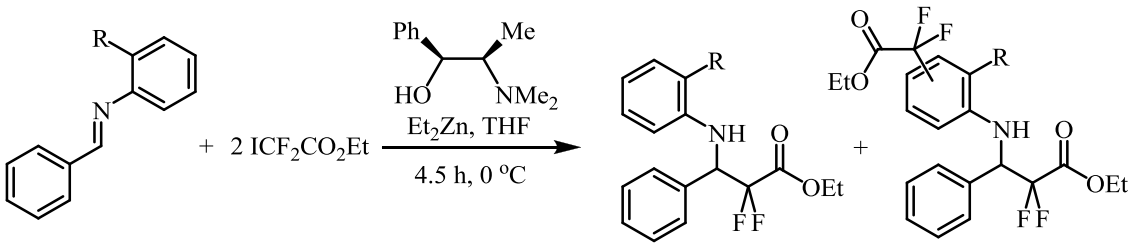
[a] The retention time of enantiomer 1, [b] the retention time of enantiomer 2.

The products obtained in the Reformatsky reaction in this section were all fully characterised and the conditions for the determination of the enantiomeric excess by chiral HPLC were developed. The enantiomers of **(98)**, **(99), (100)** and **(103)** were separated on a chiralcel OD-H column and the enantiomers of **(104)** were separated on a chiralcel AD column. The flow rate of the mobile phase was set at 1.0 mL/min. The retention times and concentrations of IPA in hexane are shown in Table 5.13. All of the solid products are stable but the liquid products and the products in solution decompose to a dark green mixture of unidentified products. It became apparent that light was accelerating the decomposition process. For that reason the purification was done without delay, the column of silica gel was protected against light and the samples were stored in a freezer.

5.2.3 The asymmetric Reformatsky reaction with ethyl iododifluoroacetate

Each of the chiral reactions with imines reported in this chapter was run in duplicate and the average of the two runs is reported. The imines listed in Table 5.13 were used for the chiral reaction with 1.0 equivalent of *N*-methylephedrine using 2.0 equivalents of ethyl iododifluoroacetate **(50)** and 2.5 equivalents of diethylzinc **(45)** at 0 ^{o}C (Table 5.14). The reaction of (*E*)-*N*-benzylidene-2-methoxyaniline **(96)** gave 93 % conversion (run 1) to a mixture of the desired product **(98)** and the disubstituted by-product **(101)** in a 67:33 ratio. The desired product **(98)** had only moderate 58 % enantiomeric excess. The by-product was isolated and characterised by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy as well as by mass spectroscopy. It seems that the second fluorinated group was substituted on the activated aromatic ring most likely in the 4-position.

Table 5.14 The asymmetric Reformatsky reaction with imines.



Run	R	Conversion[a] [%]	Ratio of products[b]	Yield[c] [%]	Ee[d] [%]	Product No.
1	OMe	93	67:33	50 (11)	58	**(98)**
2	OPh	93	86:14	62 (10)	20	**(99)**
3	OH	5	-	-	-	**(100)**
4	OH[e]	100	100:0	65	13	**(100)**
5	H	76	100:0	54[f]	0	**(103)**

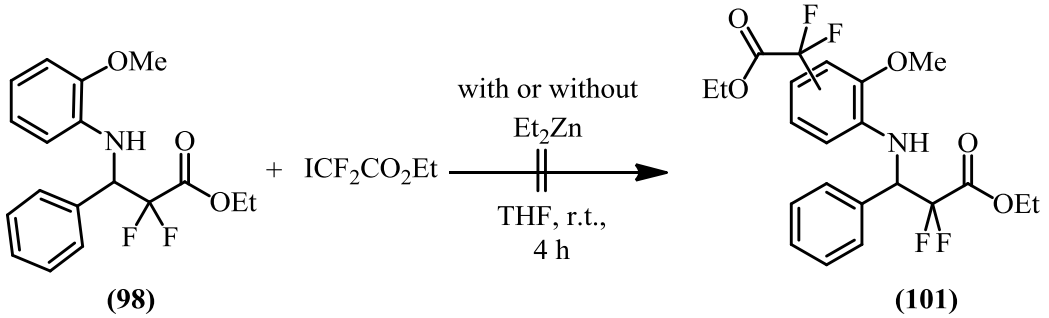
[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy (product:disubstituted by-product), [c] isolated yields (disubstituted product in parenthesis), [d] determined by chiral HPLC, [e] 3.0 equivalents of ICF_2CO_2Et and 3.5 equivalents of Et_2Zn were used, [f] conversion to the lactam.

The reaction with (*E*)-*N*-benzylidene-2-phenoxyaniline **(95)** gave 93 % conversion to the same mixture of desired product and by-product in a 86:14 ratio, and the pure product was isolated in 62 % yield (run 2). The enantiomeric excess was a

disappointingly low 20 % ee. The reaction of (*E*)-2-(benzylideneamino)phenol **(94)** gave only a 5 % conversion (run 3), presumably because either the diethylzinc or the Reformatsky reagent deprotonated the phenol group. In the next approach the reaction was repeated with 3.0 equivalents of ethyl iododifluoroacetate and 3.5 equivalents of diethylzinc (run 4) in order to overcome that problem. This time the reaction went to completion and the ester was the exclusive product. Unfortunately, however, the enantiomeric excess was very low and only reached 13 % ee. Finally, the reaction with (*E*)-*N*-benzylideneaniline **(93)** gave 100 % conversion to the racemic mixture of **(103)** (run 5). The lack of oxygen in the imine **(93)** made the formation of the chelate ring impossible. Since the enantiomeric excess obtained in the reaction with imine **(96)** was much better compared to the other results, this reaction was chosen for further optimisation work.

Two different approaches to the synthesis of the disubstituted by-product **(101)** from **(98)** have been investigated (Scheme 5.11). In the first approach 1.0 equivalent of compound **(98)** was dissolved in THF and 2.0 equivalents of ethyl iododifluoroacetate were added. The second reaction was carried out under identical conditions except that 2.0 equivalents of diethylzinc were also added. Both reactions were stirred for 4 hours at room temperature. The ^{1}H and ^{19}F NMR spectra for the first reaction contained only unreacted starting materials. There was no signal for ethyl iododifluoroacetate in the ^{1}H and ^{19}F NMR spectra obtained for the second reaction. Only unreacted **(98)** and a small amount of unidentified impurities were observed and there was no trace of the disubstituted by-product **(101)**.

Scheme 5.11 The approach to synthesis of **(97)**.

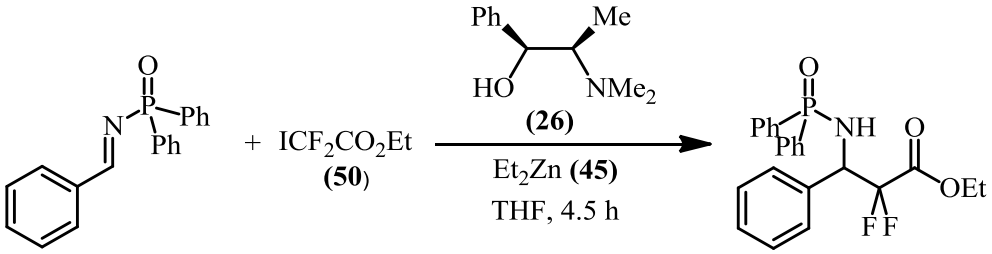


(98) **(101)**

The asymmetric Reformatsky reaction of (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide **(97)** was first investigated at -30 ^{o}C using 1.0 equivalent of

N-methylephedrine, 2.0 equivalents of ICF_2CO_2Et and 2.5 equivalents of diethylzinc (Table 5.15). There was a 100 % conversion to the product and 63 % of the pure product was isolated by column chromatography, but unfortunately the product was racemic. In the next reaction diethylzinc was added to the solution of chiral aminoalcohol and ethyl iododifluoroacetate. The reaction mixture was stirred for three minutes before cooling to -78 ^oC and then adding the solution of **(97)** (run 2). Although there was a 48 % conversion to the product, only a very low 4 % enantiomeric excess was determined.

Table 5.15 The Reformatsky reaction with (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide.



(97) **(104)**

Run	Equivalents			T	Conversion[a]	Yields[b]	Ee[c]
	(50)	(26)	(45)	[^oC]	[%]	[%]	[%]
1	2.0	1.0	2.5	-30	100	63	0
2[d]	2.0	1.0	2.5	-78	48	22	4

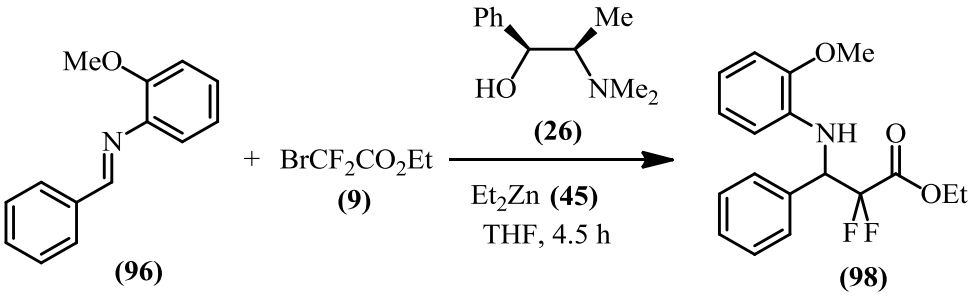
[a] Determined by ^1H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC, [d] opposite order of addition.

5.2.4 The asymmetric Reformatsky reaction with ethyl bromodifluoroacetate

The one-pot asymmetric Reformatsky reaction with ethyl bromodifluoroacetate **(9)** was also investigated with 1.0 equivalent of *N*-methylephedrine (Table 5.16). The reaction with 2.0 equivalents of ethyl bromodifluoroacetate **(9)** and 2.5 equivalents of diethylzinc **(45)** gave only a 36 % conversion but a very good 76 % enantiomeric excess (run 1). When the reaction was repeated at -20 ^oC, the conversion decreased to only 10 % and, according to ^{19}F NMR spectroscopy, most of the sample was the product from the nucleophilic addition to benzaldehyde and not to the imine. In order to improve the conversion, the reaction at 0 ^oC was repeated with 3.0 equivalents of ethyl bromodifluoroacetate and 3.5 equivalents of diethylzinc (run 3). The conversion

improved to 50 % whilst the enantiomeric excess decreased to 70 % ee. There was no disubstituted by-product formed in the reaction but the presence of the product of addition to benzaldehyde suggested partial hydrolysis of the imine.

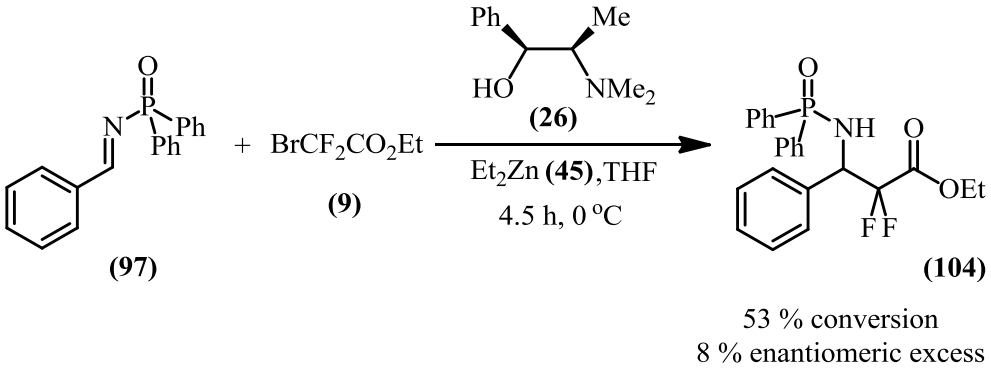
Table 5.16 The asymmetric Reformatsky reaction of ethyl bromodifluoroacetate.



Run	Equivalents		T	Conversion[a]	Ratio of	Yield[c]	Ee[d]
	(9)	(45)	[°C]	[%]	products[b]	[%]	[%]
1	2.0	2.5	0 °C	36	83:1:16	25	76
2	2.0	2.5	-20 °C	10	40:trace:60	-	-
3	3.0	3.5	0 °C	50	85:0:15	13	70

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy (product:disubstituted product:product from benzaldehyde), [c] isolated yield, [d] determined by chiral HPLC.

Scheme 5.12 The asymmetric Reformatsky reaction of ethyl bromodifluoroacetate with (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide **(97)**.



The reaction of (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide **(97)** with 2.0 equivalents of ethyl bromodifluoroacetate and 2.5 equivalents of diethylzinc at 0 °C in the presence of 1.0 equivalent of *N*-methylephedrine was unsuccessful giving only 53 % conversion, 23 % isolated yield and a low 8 % enantiomeric excess (Scheme 5.12).

5.2.5 Traditional two-step Reformatsky reaction

Since the traditional two step protocol for the Reformatsky reaction of ethyl iododifluoroacetate with ketones gave very good conversions and enantiomeric excesses in Chapter 3, the same two step protocol was also investigated in the reaction with (*E*)-N-benzylidene-2-methoxyaniline. In this chiral reaction 3.0 equivalents of the preformed Reformatsky reagent were added to a solution of **(96)** and 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)** and the reaction mixture was stirred at 0 ^{o}C (Scheme 5.13). Unfortunately, both the conversion and the enantiomeric excess were very low.

Scheme 5.13 The reaction with the Reformatsky reagent.

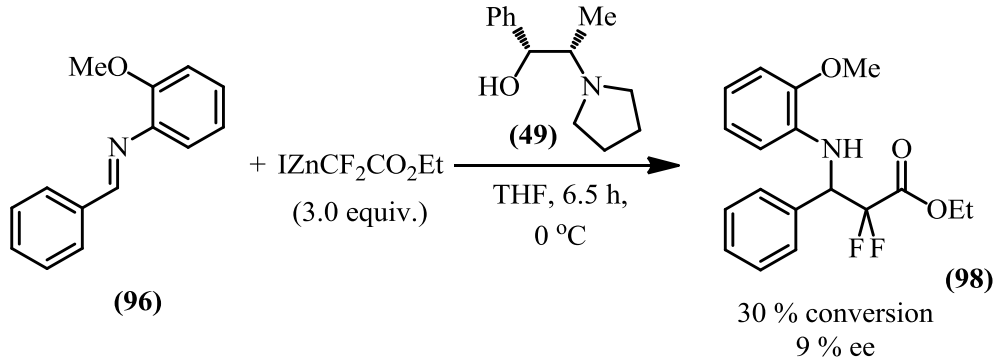
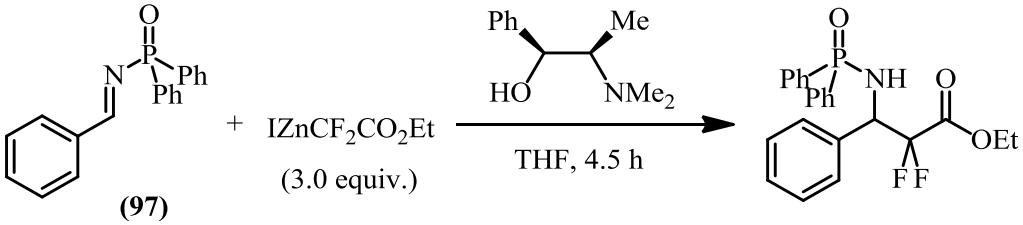


Table 5.17 The two step Reformatsky reaction with **(97)**.



Run	Temperature [^{o}C]	Conversion[a] [%]	Yields[b] [%]	Ee[c] [%]
1	0 ^{o}C	96	65	0
2	-30 ^{o}C	15	4	0

[a] Determined by ^{1}H NMR spectroscopy, [b] isolated yield, [c] determined by chiral HPLC.

Finally, imine **(97)** was subjected to a classical two-step Reformatsky reaction. The solution containing 3.0 equivalents of the Reformatsky reagent was added to the mixture of the imine and *N*-methylephedrine (1.0 equivalent) at 0 ^{o}C (run 1). A very

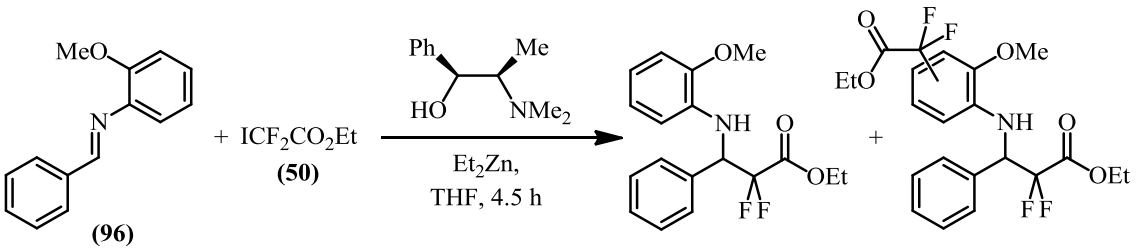
good 96 % conversion to the product was obtained, but unfortunately, the product turned out to be a racemic mixture. To slow the reaction down, the same reaction conditions were repeated at -30 ^{o}C resulting in a massive drop in the conversion, and no enantiomeric excess was detected.

5.2.6 Optimisation of the asymmetric Reformatsky reaction with ethyl iododifluoroacetate

Initially, the effect of temperature was investigated in the asymmetric Reformatsky reaction with 1.0 equivalent of *N*-methylephedrine using 2.0 equivalents of ethyl iododifluoroacetate and 2.5 equivalents of diethylzinc at -20 ^{o}C (run 2, Table 5.18). A 100 % conversion to a mixture of the product and disubstituted by-product in a 74:25 ratio was obtained. The desired product was isolated in a 63 % yield and a 59 % enantiomeric excess was obtained. When the reaction was repeated at -30 ^{o}C (run 3), although the conversion decreased to 86 %, the ratio of product to by-product increased to 87:9 and there was a significant improvement in the enantiomeric excess (68 % ee). At -40 ^{o}C there was a further decrease in the conversion to 58 % without any improvement in the enantiomeric excess (run 7).

To further enhance the reaction at -30 ^{o}C, the amount of *N*-methylephedrine was increased to 1.5 equivalents in run 4. Although the conversion decreased from 86 % to 67 %, there was only a small improvement in the enantiomeric excess (72 % ee). A dropwise addition of diethylzinc in run 5 caused a small decrease in the conversion with no effect on the enantiomeric excess. As reported in Chapter 3 (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol **(49)** gave a higher enantiomeric excess than *N*-methylephedrine in the Reformatsky reaction of ethyl iododifluoroacetate with ketones. Therefore, **(49)** was tested in the asymmetric reaction with (*E*)-*N*-benzylidene-2-methoxyaniline **(96)** (run 6). Surprisingly, the conversion was the same (87 %) but the enantiomeric excess (55 % ee) was lower than that obtained in the analogous reaction with *N*-methylephedrine (run 3). Significantly more by-product was also produced, resulting in a lower isolated yield.

Table 5.18 Optimisation of the conditions for the asymmetric Reformatsky reaction with ethyl iododifluoroacetate.



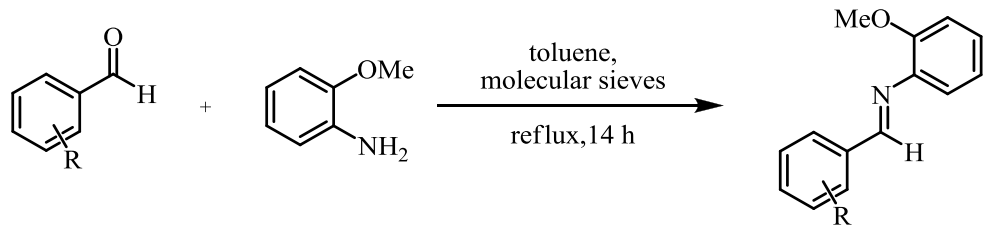
Run	Temp. [°C]	Conversion[a] [%]	Ratio of products[b]	Yield[c] [%]	Ee[d] [%]
1	0 °C	93	67:33	50 (11)	58
2	-20 °C	100	74:25:1	63	59
3	-30 °C	86	87:9:4	68	68
4[e]	-30 °C	67	80:9:11	47	72
5[f]	-30 °C	72	81:8:11	48	69
6[g]	-30 °C	87	73:23:4	46	55
7	-40 °C	58	82:9:9	28	67

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy (product:disubstituted by-product:addition to benzaldehyde), [c] isolated yield, [d] determined by chiral HPLC, [e] 1.5 equivalents of *N*-methylephedrine, [f] dropwise addition of diethylzinc over 2 minutes, [g] the reaction with 1.0 equivalent of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol.

5.2.7 Screening of imines

In order to determine the influence of substituents on the aromatic ring of the imines in the asymmetric Reformatsky reaction, a series of imines were prepared by modified Quirion's methodology and the results are summarised in Table 5.19.[16] The preparation of the imines containing chlorine on the aromatic ring was straightforward. (*E*)-*N*-(2-Chlorobenzylidene)-2-methoxyaniline **(105)** and (*E*)-*N*-(4-chlorobenzylidene)-2-methoxyaniline **(106)** were obtained in 92 % and 90 % yield respectively. (*E*)-2-Methoxy-*N*-(4-methoxybenzylidene)aniline **(107)** was also obtained in an excellent yield of 88 % (run 3) but the *ortho*-derivative **(108)** was more difficult to purify resulting in only a 45 % yield (run 4).

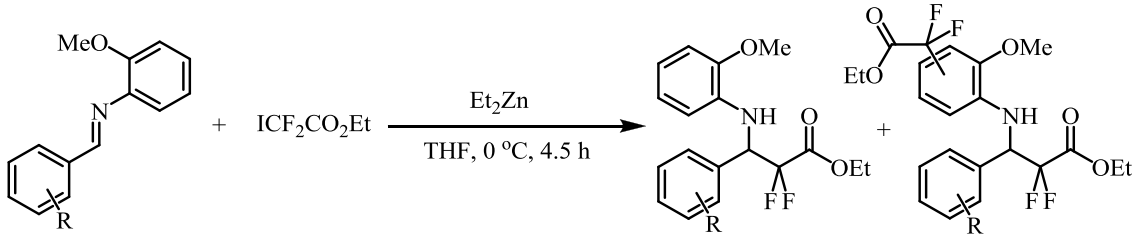
Table 5.19 Synthesis of a small series of imines.



Run	R	Yield [%]	Product No.
1	*o*-Cl	92	**(105)**
2	*p*-Cl	90	**(106)**
3	*o*-MeO	88	**(107)**
4	*p*-MeO	45	**(108)**

[a] Isolated yields.

Table 5.20 The Reformatsky reaction with a small series of derivatised imines.

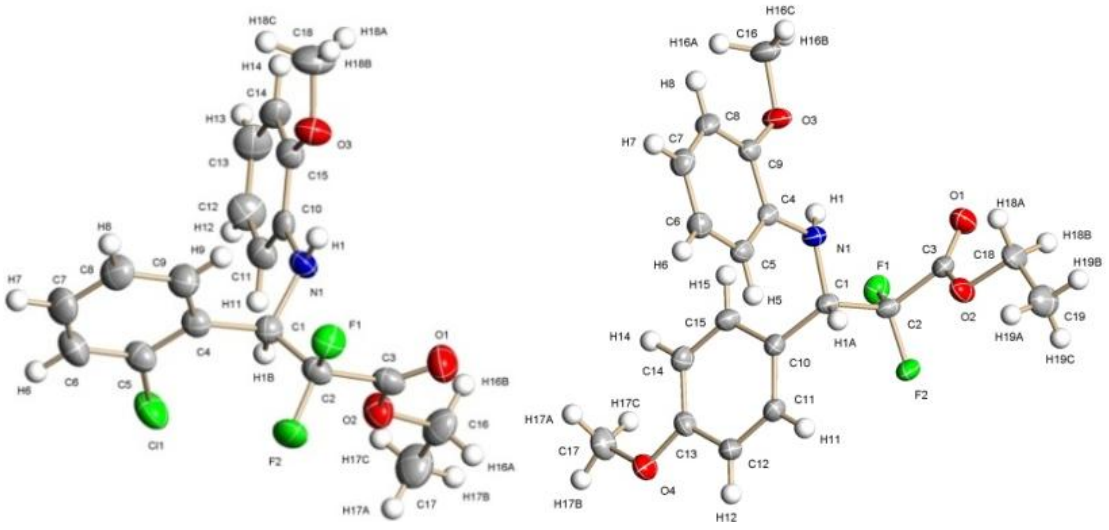


Run	R	Conversion[a] [%]	Ratio of products[b]	Yields[c] [%]	Product No.
1	H	100	87:13:trace	63	**(98)**
2	*o*-Cl	74	91:8:1	25[d]	**(109)**
3	*p*-Cl	90	93:7:trace	50	**(110)**
4	*o*-MeO	70	85:10:5	49	**(111)**
5	*p*-MeO	62	69:9:22	33[d]	**(112)**

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy (product:disubstituted by-product:addition to aldehyde), [c] isolated yield, [d] after column and recrystallisation.

Initially, each of the imines underwent an achiral Reformatsky reaction with 1.5 equivalents of ethyl iododifluoroacetate and 1.5 equivalents of diethylzinc at 0 ^{o}C in order to isolate and fully characterise each of the products, as well as to determine the conditions for separating the enantiomers by chiral HPLC (Table 5.20). In general, the conversions were lower than those obtained with the unsubstituted imine (run 1), but the amount of the disubstituted by-products was also less. Each of the products were isolated and fully characterised by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy and mass spectrometry. Crystals of ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)propanoate **(112)** and ethyl 3-(2-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)propanoate **(109)** were grown by slow evaporation of the solvent from a solution of the respective esters in 10 % EtOAc in hexane (Figure 5.5). The pure samples were also used to develop chiral HPLC procedures for the determination of the enantiomeric excess and the conditions and retention times of the enantiomers are shown in Table 5.21.

Figure 5.5 The molecular structures of i) ethyl 3-(2-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)propanoate **(109)** and ii) ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)propanoate **(112)**. Figure shows 50 % displacement ellipsoid and hydrogen atoms in calculated positions.



i) ii)

Table 5.21 Conditions for separation of the enantiomers by chiral HPLC.

Product no	Column	% IPA	t_1[a]	t_2[b]
(109)	OD-H	4.0	6.15 min	10.76 min
(110)	OD-H	4.0	9.84 min	11.76 min
(111)	OD-H	0.5	9.62 min	12.41 min
(112)	OD-H	0.5	8.81 min	10.53 min

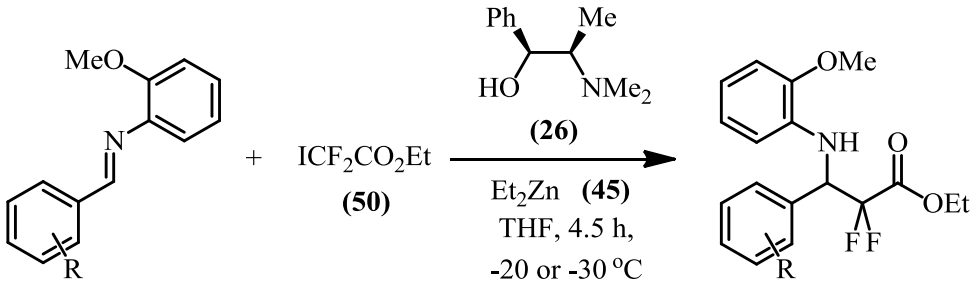
[a] Retention time of enantiomer 1, [b] retention time of enantiomer 2.

Since the optimisation of the asymmetric Reformatsky reaction with imine **(96)** showed that the best balance between yield and enantiomeric excess was obtained with 2.0 equivalents of ethyl iododifluoroacetate and 2.5 equivalents of diethylzinc at -30 ^{o}C (run 2, Table 5.22), the same conditions were used initially in the reaction with the (*E*)-N-(4-chlorobenzylidene)-2-methoxyaniline **(106)** and 54 % conversion and 67 % ee were obtained (run 5). In order to improve the conversion the reaction was repeated at -20 ^{o}C (run 4). Although the conversion was higher (72 %), there was significantly more disubstituted by-product resulting in a low isolated yield, and the enantiomeric excess dropped to 58 % ee. Interestingly, the reaction without chiral ligand showed that even at -20 ^{o}C the conversion was 58 % (run 3). The asymmetric reaction with a larger amount of diethylzinc (run 6) was repeated at -30 ^{o}C yielding a small improvement in the conversion but the enantiomeric excess dropped to 58 % again, and less of the disubstituted by-product was formed. The ^{19}F NMR signals of the product formed by nucleophilic addition to benzaldehyde were identified by comparison with literature values.[5] Finally, the reaction was repeated with 3.0 equivalents of ethyl iododifluoroacetate and 3.5 equivalents of diethylzinc (run 7) at -30 ^{o}C. Since the conversion (82 %) and the ratio of the product to by-products clearly improved, a higher isolated yield was obtained. There was also a significantly large improvement of the enantiomeric excess to 65 % ee.

When the reaction was repeated with the (*E*)-*N*-(2-chlorobenzylidene)-2-methoxyaniline **(105)** (run 9) at -30 ^{o}C an 80 % conversion along with a disappointingly low 53 % enantiomeric excess was obtained. For comparison, the reaction with 2.0 equivalents of ethyl iododifluoroacetate at -20 ^{o}C (run 8) gave a lower conversion (77 %), but a much better enantiomeric excess (66 % ee). The reactions with the (*E*)-2-methoxy-*N*-(2-methoxybenzylidene)aniline **(111)** were run with 2.0 (run 10) and 3.0 equivalents (run 11) of ethyl iododifluoroacetate at -20 ^{o}C and -30 ^{o}C respectively. The

first set of conditions yielded 68 % conversion and only 54 % ee, whilst the second reaction resulted in a better 82 % conversion but a lower 47 % enantiomeric excess. The lower enantiomeric excess obtained in the reactions of **(111)** was most likely a result of competition between coordination of the two different methoxy groups. Finally, the reaction of 3.0 equivalents of ethyl iododifluoroacetate with (*E*)-*N*-(4-chlorobenzylidene)-2-methoxyaniline **(112)** at -30 ^{o}C gave an excellent conversion (97 %) and a high 63 % enantiomeric excess.

Table 5.22 Screening imines in the asymmetric Reformatsky reaction with 1.0 equivalent of *N*-methylephedrine.



Run	R	T	Equivalents (26)	Equivalents (50)	Equivalents (45)	Conv.[a] [%]	Ratio of products[b]	Yields[c] [%]	Ee[d] [%]
1	H	-20 ^{o}C	1.0	2.0	2.5	100	74:25:1	63	59
2		-30 ^{o}C	1.0	2.0	2.5	86	87:9:4	68	68
3[e]	*p*-Cl	-20 ^{o}C	0	2.0	2.5	58	78:20:2	34	-
4[e]		-20 ^{o}C	1.0	2.0	2.5	72	75:25:trace	36	58
5		-30 ^{o}C	1.0	2.0	2.5	54	76:15:9	34	67
6[e]		-30 ^{o}C	1.0	2.0	3.5	69	87:6:7	55	58
7		-30 ^{o}C	1.0	3.0	3.5	82	90:9:1	72	65
8	*o*-Cl	-20 ^{o}C	1.0	2.0	2.5	77	81:14:5	57	66
9		-30 ^{o}C	1.0	3.0	3.5	80	92:6:2	63	53
10	*o*-MeO	-20 ^{o}C	1.0	2.0	2.5	68	70:27:3	40	54
11		-30 ^{o}C	1.0	3.0	3.5	82	77:16:7	60	47
12	*p*-MeO	-30 ^{o}C	1.0	3.0	3.5	97	84:14:2	80	63

[a] Determined by ^{1}H NMR spectroscopy, [b] determined by ^{19}F NMR spectroscopy, [c] isolated yield, [d] determined by chiral HPLC, [e] a single run.

5.3 Conclusions

A convenient one-pot asymmetric Reformatsky reaction of ethyl iododifluoroacetate with aromatic imines containing a methoxy group in the *ortho*-position has been developed. Good enantioselectivity (63-68 % ee) was obtained with a small series of imines that contained electron-withdrawing and electron-donating substituents on the aromatic aldehyde. The only exception was when a methoxy group was in the 2-position and the enantiomeric excess dropped to 54 % ee. In each reaction a disubstituted by-product was also formed but the amount was reduced significantly at lower temperatures. Unfortunately, there was not enough time to determine the absolute configuration of the new chiral centre in the major enantiomer and this requires further work before these results can be published. All of the *α,α*-difluoro-*β*-amino esters discussed in this chapter were synthesised for the first time.

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Chapter Six

Experimental Section

University *of*
Leicester

6.1 General experimental procedures

6.1.1 NMR Spectroscopy

The ^{1}H, ^{19}F and $^{13}C\{^{1}H\}$ NMR spectra were recorded on Bruker DRX 400 and Bruker AM 300 spectrometers at the ambient temperature of the probe unless otherwise stated. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced internally using the residual *protio* solvent resonance relative to $SiMe_4$ (δ = 0 ppm), whilst $^{19}F\{^{1}H\}$ NMR spectra were referenced to external $CFCl_3$ (δ = 0 ppm) and ^{31}P NMR spectra were referenced externally to 85 % H_3PO_4 (δ = 0 ppm). All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz (Hz) using the high frequency positive convention. The following spectrometer frequencies were Bruker AM 300 Spectrometer and Bruker DRX 400 Spectrometer.

Bruker AM 300 Spectrometer: ^{1}H NMR spectra, 300.03 MHz,
^{13}C NMR spectra, 75.4426 MHz,
^{19}F NMR spectra, 282.3103 MHz,
^{31}P NMR spectra, 121.99 MHz.

Bruker AM 400 Spectrometer: ^{1}H NMR spectra, 400.13 MHz,
^{13}C NMR spectra, 100.6128 MHz,
^{19}F NMR spectra, 376.4984 MHz,
^{31}P NMR spectra, 161.98 MHz.

The solvent most frequently used was deuterated chloroform ($CDCl_3$) unless otherwise stated. For some ^{19}F NMR spectra, standard solvents and a capillary insert tube with C_6D_6 were used. Spectra of air/moisture-sensitive compounds were obtained by preparing the samples under an inert atmosphere in a flush-box using dried deuterated solvents or dry THF containing a capillary insert tube (C_6D_6). The solutions were then loaded into a sealed screw-cap NMR tube.

6.1.2 Gas Chromatography

Gas chromatography was conducted on a Perkin Elmer Clarus 500 Gas Chromatograph fitted with a B-DM or PE-5 29.5 m column.

6.1.3 High Performance Liquid Chromatography

High performance liquid chromatography was carried out on a Perkin Elmer HPLC Liquid Chromatograph supported with either an OD-H (Daicel) or an AS (Daicel) column and a UV-VIS detector.

6.1.4 Mass Spectrometry

Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos concept 1 H, double focussing, forward geometry mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix for the FAB spectra. Electrospray mass spectra were obtained on a Micromass Quatro LC.

6.1.5 Elemental analysis

Elemental analyses were performed by the University of North London.

6.1.6 X-ray crystallography

X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer. Crystal data and structure refinement can be found in the appendices. X-ray crystallographic studies were performed by Mr K. Singh.

6.1.7 Specific rotation

Specific rotation data were collected on a Perkin Elmer 341 Polarimeter. The concentration of the sample was 1 g of the product in 100 mL of chloroform.

6.1.8 Starting materials

Compounds were generally used as supplied from Sigma-Aldrich, Lancaster, TCI, Acros Organics. Acetonitrile, THF, toluene, diethyl ether, hexane and dichloromethane were obtained dried from a distillation machine model Puresolve^{TM}, and were stored in sealed ampoules over 4Å molecular sieves under an atmosphere of dry nitrogen. Dry 1,4-dioxane was purchased from Lancaster.

(1*S*,2*R*)-*N*-Methylephedrine and (1*R*,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol were dried using the Kugelröhr oven at 100 ^{o}C under oil pump vacuum for 30 min. After cooling, the crystals of the chiral aminoalcohols were dissolved in dry diethyl ether and

the solvent was removed under vacuum. The second step was not a purification process, the only aim of the crystallisation from dry solvent was to obtain small crystals that were convenient to use. The dry aminoalcohols are stored in either a desiccator or a flushbox under a nitrogen atmosphere. Tolyl ether was also dried in a Kugelröhr oven at 100 ^{o}C under oil pump vacuum for 30 min.

6.1.9 Separation of enantiomers of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate (44) by ^{19}F NMR spectroscopy

Ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate (not less than 0.01 mmol) was dissolved in an NMR tube in a premixed solution (0.35 mL) of (+)-diisopropyl L-tartrate (1.25 g, 5.3 mmol) in HPLC grade chloroform (1.55 g, 13.0 mmol). A sealed capillary tube containing C_6D_6 was added and the ^{19}F NMR spectrum was recorded. The signals from the two enantiomers split into two separate AB multiplets and the enantiomeric excess was calculated by integration.

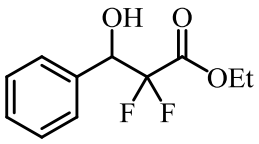
6.1.10 Determination of conversion and separation of enantiomers of ethyl-2,2-difluoro-3-hydroxy-3-phenyl propanoate (44) and ethyl-2,2-difluoro-3-hydroxy-3-phenyl butanoate (48) by chiral GC

An internal standard, tolyl ether, was added to the reaction mixture in order to calculate the conversion of benzaldehyde or acetophenone to product in their reaction with the fluorinated Reformatsky reagent. By comparing the relative amounts of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate or ethyl-2,2-difluoro-3-hydroxy-3-phenyl-butanoate to the amount of tolyl ether by GC, it was possible to determine the conversion of the starting material to product (Appendix A1). A BD-M column also enabled the enantiomers of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate to be separated and the enantiomeric excess to be determined from the areas of the respective peaks.

6.2 Synthetic procedures for Chapter two

6.2.1 Synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate (44)

Method 1.



The title compound was synthesised using Kumadaki's procedure.[1] Under a nitrogen atmosphere a dry three neck round bottom flask was charged with Wilkinson's catalyst (0.063 g, 0.07 mmol), acetonitrile (56 mL), ethyl bromodifluoroacetate (1.33 mL, 2.1 g, 10.5 mmol) and benzaldehyde (0.7 mL, 7.0 mmol) at 0 ^{o}C. After stirring the reaction mixture at 0 ^{o}C for 30 minutes, a 1.0 M solution of diethylzinc in hexane (10.5 mL, 10.5 mmol) was added and the reaction mixture was stirred for another 4.5 h at 0 ^{o}C. After quenching the reaction mixture with 1 M HCl (50 mL), it was extracted with ethyl acetate (2 x 25 mL). The organic layer was washed with 1 M HCl (50 mL), brine (50 mL) and water (50 ml) before drying over magnesium sulphate. The solvent was removed and the product was purified by silica gel column chromatography (EtOAc:hexane = 1:4) to give the desired product as a colourless oil (0.90 g, 56 %). The characterisation data was in agreement with the literature.[2] δ_H ($CDCl_3$) 1.75 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 2.44 (1H, d, $^3J_{HH}$ 5.3 Hz, OH), 4.15 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 5.02 (1H, ddd, $^3J_{HF}$ 15.3 Hz, $^3J_{HF}$ 7.9 Hz, $^3J_{HH}$ 5.3 Hz, $CHCF_2$), 7.22-7.34 (5H, m, ArH); δ_F ($CDCl_3$) -120.23 (1F, d, $^2J_{FF}$ 262.5 Hz, CF_AF_B), -113.85 (1F, d, $^2J_{FF}$ 262.5 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.8 (CH_3), 63.1 (CH_2), 73.8 (dd, $^2J_{CF}$ 27.5 Hz, $^2J_{CF}$ 23.9 Hz, CH), 113.8 (dd, $^1J_{CF}$ 259.7 Hz, $^1J_{CF}$ 254.9 Hz, CF_2), 127.7 (CH), 128.4 (CH), 129.2 (CH), 134.5 (C), 163.6 (t, $^2J_{CF}$ 31.7 Hz, CO); HRMS (FAB) 231.08325 (MH^+. $C_{11}H_{13}F_2O_3$ requires 231.08328). The enantiomers of **(38)** were separated on a Chiralpack AS column eluted with 10 % IPA in hexane. The flow rate of the mobile phase was set at 1 mL/min. R_t=6.82 min ((*S*)-ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate), 8.91 min ((*R*)-ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate).[1]

Method 2.

The title compound was synthesised using a modification of Kumadaki's protocol.[1] Under a nitrogen atmosphere a dry three neck flask was charged with ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol), benzaldehyde (0.1 mL, 0.1 g, 1.0 mmol) and acetonitrile (8 mL). After 30 minutes of stirring the reaction mixture at 0 ^{o}C,

a 1.0 M solution of diethylzinc (1.5 mL, 1.5 mmol) was added dropwise and the reaction mixture was stirred for another 4.5 h at 0 ^{o}C. After quenching the reaction with a 1.0 M solution of HCl (50 mL), it was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with 1.0 M HCl (10 mL), brine (10 mL) and water (10 mL) before being dried over magnesium sulphate. The solvent was removed on a rotary evaporator to give the crude product which was analysed by ^{1}H NMR spectroscopy (96 % conversion).

6.2.2 General methods for asymmetric syntheses of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate (44)

General method for Table 2.1

Wilkinson's catalyst (9 mg, 0.01 mmol), ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol) and benzaldehyde (0.1 mL, 0.1 g, 1.0 mmol) were added to dry acetonitrile (8 mL). After stirring the reaction mixture for 30 min at 0 ^{o}C, the required amount of *N*-methylephedrine was added, and the required amount of diethylzinc was then added to the reaction mixture which was stirred for 4.5 h at 0 ^{o} C. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined and then washed with 1 M HCl (50 mL), brine (50 mL) and water (50 mL). After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to give the desired product as a colourless oil. The enantiomeric excess was determined by ^{19}F NMR spectroscopy and chiral HPLC.

General method for Table 2.2

N-methylephedrine (0.18 g, 1.0 mmol), ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol), benzaldehyde (0.1 mL, 0.1 g, 1.0 mmol) and tolyl ether (0.099 g, 0.5 mmol - only those reactions where conversion was determined by GC) were added to the required dry solvent (8 mL). After stirring the reaction mixture for 30 min at 0 ^{o}C, diethylzinc (2.1 mL, 1.0 M solution in hexane, 2.1 mmol) was added to the reaction mixture which was stirred for 4.5 h at 0 ^{o} C. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined and then washed with 1 M HCl (50 mL), brine (50 mL) and water (50 mL).

After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to give the desired product as a colourless oil. The enantiomeric excess was determined by chiral GC and chiral HPLC.

General methods for Tables 2.3, 2.6 and 2.7

Benzaldehyde (0.5 mL, 0.53 g, 5.0 mmol) and tolyl ether (0.495 g, 2.5 mmol) were dissolved in THF in a 10 mL volumetric flask under an inert atmosphere in a flush box and the mixture was transferred to a dry two neck round bottom flask. A three necked round bottom flask was flame dried and then THF (6 mL), the required amount of *N*-methylephedrine and ethyl bromodifluoroacetate, and 2 mL of the mixture of benzaldehyde and tolyl ether in THF were added at 0 ^{o}C. The reaction mixture was stirred for 30 minutes at 0 ^{o}C before the required amount of diethylzinc was added. The reaction mixture was stirred at 0 ^{o}C for 4.5 hours and was quenched with 1 M HCl (10 mL). Ethyl acetate (10 mL) was added and the organic layer was washed with 1 M HCl (10 mL), brine (10 mL) and water (10 mL) before drying over magnesium sulphate. The obtained mixture was eluted through a short silica column (around 1 cm of silica gel) and was analysed by GC in order to determine the conversion. The solvent was removed on a rotary evaporator and the crude product was analysed by ^{1}H and ^{19}F NMR spectroscopy and then purified by column chromatography (ethyl acetate/hexane = 4:1). The enantiomeric excess was determined by chiral GC and/or chiral HPLC.

General method for Table 2.4

N-Methylephedrine (0.18 g, 1.0 mmol), the required amount of ethyl bromodifluoroacetate and benzaldehyde (0.1 mL, 0.1 g, 1.0 mmol) were added to dry THF (8 mL). After stirring the reaction mixture for 30 min at 0 ^{o}C, the required amount of either diethylzinc or dimethylzinc was added. The reaction vessel was protected with a drying tube filled with calcium (II) chloride and air slowly replaced inert atmosphere. The reaction mixture was stirred for 4.5 h at 0 ^{o} C before it was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined and then washed with 1 M HCl (50 mL), brine (50 mL) and water (50 mL). After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to

give the desired product as a colourless oil. The enantiomeric excess was determined by chiral ^{19}F NMR spectroscopy and chiral GC.

6.2.3 Monitoring of the synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate (44) by GC.

Ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate was synthesised from ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol), *N*-methylephedrine (0.179 g, 1.0 mmol) and diethylzinc (2.01 mL, 1.0 M solution, 2.1 mmol) using the General Method for Tables 2.3 and 2.6. A small sample (0.5 mL) of the reaction mixture was collected by syringe every 30 minutes for 4.5 hours. The sample was quenched with 1 M HCl (0.5 mL), extracted and the organic layer was washed with 1 M HCl (1 mL), brine (1 mL) and water (1 mL) before being analysed by GC to determine the conversion.

Table 6.1 Monitoring of the Reformatsky reaction with benzaldehyde by GC

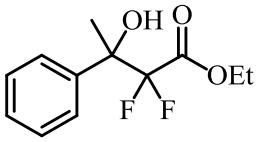
Time [h]	**Conversion[a] [%]**	**Time [h]**	**Conversion[a] [%]**
0.5	25	3.0	52
1.0	35	3.5	54
1.5	43	4.0	55
2.0	48	4.5	55
2.5	50		

[a] Conversion was determined by GC.

6.3 Synthetic procedures for Chapter three

6.3.1 Synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate (48)

Method 1.



The title compound was synthesised using Kumadaki's procedure.[1] Under a nitrogen atmosphere a dry three neck flask was charged with Wilkinson's catalyst (0.063 g, 0.07 mmol), acetonitrile (56 mL), ethyl bromodifluoroacetate (1.33 mL, 2.1 g, 10.5 mmol) and acetophenone (0.82 mL, 0.84 g, 7.0 mmol). After 30 min of stirring the reaction mixture at 0 ^{o}C, a 1.0 M solution of diethylzinc (10.5 mL, 10.5 mmol) was added and the reaction mixture was stirred for another 4.5 h at 0 ^{o}C. After quenching the reaction mixture with 1 M HCl (50 mL), it was extracted with ethyl acetate (2 x 50 mL). The

organic layer was washed with 1 M HCl (50 mL), brine (50 mL) and water (50 ml) before being dried over magnesium sulphate. The solvent was removed and the product was purified by silica gel column chromatography (EtOAc:hexane = 1:4) to give a colourless oil (1.06 g, 62 %). The characterisation data was in agreement with the literature.[2] δ_H ($CDCl_3$) 0.96 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.59 (3H, t, $^4J_{HF}$ 1.5 Hz, $CF_2C(OH)CH_3$), 2.93 (1H, br s, OH), 4.00 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 7.14-7.25 (3H, m, ArH), 7.37 (2H, d, $^3J_{HH}$ 6.7 Hz, ArH.); δ_F ($CDCl_3$) -115.05 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), -115.81 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.6 (CH_3), 23.3 (CH_3), 62.9 (CH_2) 75.9 (t, $^2J_{CF}$ 24.5 Hz, C), 114.8 (t, $^1J_{CF}$ 261.5 Hz, CF_2), 126.0 (CH), 128.1 (CH), 128.2 (CH), 139.6 (C), 163.5 (t, $^2J_{CF}$ 32.1 Hz, CO); m/z (FAB) 245.09886 (MH^+. $C_{12}H_{15}F_2O_3$ requires 245.09893). The enantiomers were separated on a chiralcel AS column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.80 min (enantiomer 1), 14.43 min (enantiomer 2) and a chiralcel OD-H column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 7.65 min (enantiomer 1), 8.35 min (enantiomer 2).

Method 2.

The title compound was prepared using a modification of Kumadaki's procedure.[1] Under an argon atmosphere a three neck round bottom flask was charged with ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol), acetophenone (0.12 mL, 0.12 g, 1.0 mmol) and dry THF (8 mL). After stirring the reaction mixture at 0 ^oC for 30 minutes, a 1.0 M solution of diethylzinc (1.5 mL, 1.5 mmol) was added and the reaction mixture was stirred for another 4.5 h at 0 ^oC. After quenching the reaction with a 1.0 M solution of HCl (10 mL), it was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with 1.0 M HCl (10 mL), brine (10 mL) and water (10 mL) before being dried over magnesium sulphate. The solvent was removed on a rotary evaporator to give the crude product which was analysed by ^1H NMR spectroscopy (100% conversion).

6.3.2 General method for asymmetric synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate (48)

General method for Table 3.1

Acetophenone (0.300 g, 2.5 mmol) and tolyl ether (0.248 g, 1.25 mmol) were dissolved in THF in a 5 mL volumetric flask under an inert atmosphere in a flush box and the mixture was transferred to a dry two neck round bottom flask. A three necked round bottom flask was flame dried and then THF (6 mL), the required amount of ethyl bromodifluoroacetate and 2 mL of the mixture of acetophenone and tolyl ether in THF were added at 0 ^{o}C. The reaction mixture was stirred for 30 minutes before the required amount of *N*-methylephedrine was added followed by a 1.0 M solution of diethylzinc. The reaction mixture was stirred at 0 ^{o}C for 4.5 hours and was then quenched with 1 M HCl (10 mL). Ethyl acetate (10 mL) was added and the organic layer was washed with 1 M HCl, brine and water before drying over magnesium sulphate. After eluting the sample through a short silica gel column made with a Pasteur pipette (around 1 cm of silica gel) with 20 % of ethyl acetate in hexane, a small amount of the mixture was analysed by GC and the solvent was removed from the rest of the sample on a rotary evaporator. The crude product was analysed by ^{1}H and ^{19}F NMR spectroscopy and was then purified on a silica gel column (ethyl acetate/hexane = 4:1). The conversion was determined by GC, and the enantiomeric excess was determined by chiral HPLC.

General method for Table 3.2

Acetophenone (0.600 g, 5.0 mmol) and tolyl ether (0.496 g, 2.5 mmol) were dissolved in THF using a 10 mL volumetric flask in the flushbox and were transferred into a Schlenk flask. A flamed dried 100 mL three neck round bottomed flask under argon was charged with THF (6 mL) and 2 mL of solution of acetophenone (0.120 g, 1.0 mmol) and tolyl ether (0.099 g, 0.5 mmol) in THF (~2 mL) before being cooled to 0 ^{o}C. Then ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol) and (1*S*,2*R*)-(+)-*N*-methylephedrine (0.18 g, 1.0 mmol) were added. After 30 minutes of stirring diethylzinc (2.0 mL, 1.0 M solution in hexane, 2.0 mmol) was added. Further aliquots of ethyl bromodifluoroacetate (0.06 mL, 0.10 g, 0.5 mmol,) followed by diethylzinc (0.5 mL, 1.0 M solution in hexane, 0.5 mmol) were added after two and four hours from the initial injection of diethylzinc. The reaction was quenched with 1 M HCl (10 mL) after

4.5 h after the first addition of diethylzinc and was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The conversion was determined by GC of the crude reaction mixture which had been eluted through silica gel. A short column was made from Pasteur pipette, cotton wool plug and approximately 1 cm of silica gel. The sample used on GC was reunited with the rest of the solution. The solvent was removed and the product was purified by silica gel column chromatography (EtOAc:hexane = 1:4) to give a colourless oil. The enantiomeric excess was determined by chiral HPLC.

General method for Tables 3.3

General method for Table 3.2 was also used for Table 3.3 except that the initial charge of ethyl bromodifluoroacetate was 2.0 mmol (0.25 mL, 0.40 g) and diethylzinc was 2.5 mmol (2.5 mL, 1.0 M solution in hexane).

General method for Table 3.6 and 3.9

A flamed dried 100 mL three neck round bottomed flask under argon was charged with THF (8 mL) and acetophenone (0.12 mL, 0.12 g, 1.0 mmol) before being cooled to 0 ^{o}C. Then ethyl iododifluoroacetate (0.22 mL, 1.5 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)1-propanol (0.2053 g, 1.0 mmol) were added. After 30 minutes of stirring at 0 ^{o}C, diethylzinc (2.0 mL, 1.0 M solution in hexane, 2.0 mmol) was added. Further aliquots of ethyl iododifluoroacetate (0.07 mL, 0.5 mmol) and diethylzinc (0.5 mL, 0.5 mmol) were added after two hours from the initial injection of diethylzinc. The reaction was quenched with 1 M HCl (10 mL) after 4.5 h after the initial addition of diethylzinc and was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The conversion was determined by GC on the crude reaction mixture which was eluted through silica gel. A short column was made from Pasteur pipette, cotton wool plug and approximately 1 cm of silica gel. The sample used on GC was reunited with the rest of the solution. The solvent was removed and the conversion was determined by ^{1}H NMR spectroscopy on the crude sample. The product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give a colourless oil.

General method for Table 3.14

Preparation of the solution of the Reformatsky reagent:

A flamed dried two neck round bottomed flask equipped with a condenser was filled with acid washed zinc dust (0.565 g, 5.7 mmol) and dry THF (15.2 mL). The temperature of the suspension was increased to 60 ^{o}C but heating was stopped before ethyl iododifluoroacetate (0.83 mL, 1.425 g, 5.7 mmol) was added dropwise (from syringe) over 2-3 minutes. The Reformatsky reagent was used after 2 minutes of stirring.

The Reformatsky reaction with acetophenone:

A flame dried three neck round bottomed flask was charged with THF (1 mL), acetophenone (0.12 mL, 0.12 g, 1.0 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)1-propanol and was cooled to 0 ^{o}C . The solution of the Reformatsky reagent (2.5 mmol in 7 ml of dry THF) was added. The reaction was stirred for 6.5 hours at 0 ^{o}C before it was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The solvent was removed and the product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give a colourless oil.

General method for Table 3.18

A flamed dried 100 mL three neck round bottomed flask under argon was charged with THF (8 mL) and acetophenone (0.12 mL, 0.12 g, 1.0 mmol) before being cooled to -40 ^{o}C. Then ethyl iododifluoroacetate (0.29 mL, 0.5 g, 2.0 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (0.205 g, 1.0 mmol) were added. After 30 minutes of stirring at -40 ^{o}C, diethylzinc (2.5 mL, 1.0 M solution in hexane, 2.5 mmol) was added. The reaction was quenched with 1 M HCl (10 mL) after 4.5 h and was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The solvent was removed and the product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give a colourless oil.

6.3.3 General method for the Reformatsky reaction with ketones (Table 3.8)

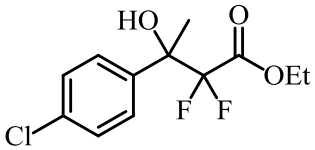
Method 1.

The compound was prepared using Kumadaki's procedure 1. A dry three neck round bottom flask was charged with Wilkinson's catalyst (0.036 g, 0.04 mmol), THF (32 mL), ethyl bromodifluoroacetate (0.76 mL, 1.2 g, 6.0 mmol) and the appropriate ketone (4.0 mmol). The mixture was cooled to 0 ^{o}C and was stirred for 30 min before a 1.0 M solution of diethylzinc in hexane (6 mL, 6.0 mmol) was added and the reaction mixture was stirred for another 4.5 h at 0 ^{o}C. After quenching the reaction with 1 M HCl (25 mL), it was extracted with ethyl acetate (2 x 25 mL). The organic layer was separated, washed with 1 M HCl (50 mL), brine (50 mL) and water (50 mL) before being dried over magnesium sulphate.

Method 2.

A dry three neck round bottomed flask was charged with THF (24 mL), ethyl bromodifluoroacetate (0.6 mL, 0.91 g, 4.5 mmol) or ethyl iododifluoroacetate (0.66 mL, 1.13 g, 4.5 mmol) and the appropriate ketone (3.0 mmol). The mixture was cooled to 0 ^{o}C for 30 min before a 1.0 M solution of diethylzinc in hexane (4.5 mL, 4.5 mmol) was added and the reaction mixture was stirred for another 4.5 hours at 0 ^{o}C. After quenching the reaction with 1 M HCl (25 mL), it was extracted with ethyl acetate (2 x 25 mL). The organic layer was separated, washed with 1 M HCl (50 mL), brine (50 mL) and water (50 mL) before being dried over magnesium sulphate.

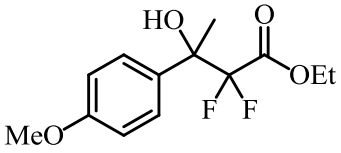
Preparation of ethyl 3-(4-chlorophenyl)-2,2-difluoro-3-hydroxybutanoate (51)



The title compound was prepared by Method 1. The crude product was purified by column chromatography (20 % EtOAc in hexane) to give a colourless oil (0.44 g, 52 %). The characterisation data was in agreement with literature.[3] (Found: C, 51.80; H, 4.63. Calc. for $C_{12}H_{13}ClF_2O_3$: C, 51.72; H, 4.70 %). δ_H ($CDCl_3$) 1.10 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.65 (3H, t, $^4J_{HF}$ 1.5 Hz, $CF_2C(OH)CH_3$), 3.03 (1H, s, O*H*), 4.12 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 7.27 (2H, dt, $^3J_{HH}$ 8.6 Hz, $^5J_{HF}$ 2.7 Hz, Ar*H*), 7.39 (2H, d, $^3J_{HH}$ 9.0 Hz, Ar*H*); δ_F ($CDCl_3$) -114.88 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), -115.83 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.7 (CH_3), 23.4 (CH_3), 63.1 (CH_2),

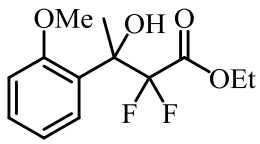
75.7 (t, $^{2}J_{CF}$ 24.1 Hz, C), 114.6 (t, $^{1}J_{CF}$ 261.6 Hz, CF_2), 127.6 (CH), 128.3 (CH), 134.3 (C), 138.2 (C), 163.4 (t, $^{2}J_{CF}$ 32.2 Hz, CO); m/z (EI) 278.5189 (M^+. $C_{12}H_{13}ClF_2O_3$ requires 278.5180), 278 (9%), 233 (3 %), 51 (100%). The enantiomers were separated on a chiralcel AS column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 10.17 min (enantiomer 1), 16.88 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)butanoate (52)



The title compound was prepared by Method 1. The crude product was purified by column chromatography (10 % EtOAc in hexane) to give the pure product as a colourless oil (0.48 g, 43 %). The characterisation data was in agreement with literature.[3] δ_H ($CDCl_3$) 1.20 (3H, t, $^{3}J_{HH}$ 7.0 Hz, CH_2CH_3), 1.74 (3H, t, $^{4}J_{HF}$ 3.1 Hz, $CF_2C(OH)CH_3$), 3.10 (1H, s, O*H*), 3.82 (3H, s, OCH_3), 4.20 (2H, q, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3), 6.91 (2H, d, $^{3}J_{HH}$ 9.0 Hz, ArH), 7.45 (2H, d, $^{3}J_{HH}$ 9.0 Hz, ArH); δ_F ($CDCl_3$) -115.84 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF_AF_B), -115.11 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.7 (CH_3), 23.4 (CH_3), 55.2 (CH_3), 62.9 (CH_2), 75.6 (t, $^{2}J_{CF}$ 24.6 Hz, C), 113.5 (CH), 114.9 (t, $^{1}J_{CF}$ 261.1 Hz, CF_2), 127.4 (CH), 131.7 (C), 159.5 (C), 163.6 (t, $^{2}J_{CF}$ 32.2 Hz, CO); m/z (EI) 274.10133 (M^+. $C_{13}H_{16}F_2O_4$ requires 274.10127), 151 (100 %). The enantiomers were separated on a chiralcel OD-H column eluted with 2 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 14.68 min (enantiomer 1), 16.41 min (enantiomer 2).

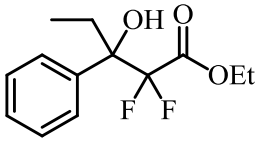
Preparation of ethyl-2,2-difluoro-3-hydroxy-3-(2-methoxyphenyl)butanoate (53)



The title compound was prepared by Method 2 with ethyl iododifluoroacetate. The crude product was purified by column chromatography (20 % EtOAc in hexane) to give a colourless oil (0.23 g, 83 %). δ_H ($CDCl_3$) 1.20 (3H, t, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.72 (3H, t, $^{4}J_{HF}$ 2.0 Hz, $CF_2C(OH)CH_3$), 3.84 (3H, s, OCH_3), 4.19 (2H, q, $^{3}J_{HH}$ 7.4 Hz, OCH_2CH_3), 5.88 (1H, s, O*H*), 6.89 (1H, dd, $^{3}J_{HH}$ 8.2 Hz, $^{4}J_{HH}$ 1.2 Hz, ArH), 6.92 (1H, td, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HH}$ 1.2 Hz, ArH), 7.22 (1H, d, $^{3}J_{HH}$ 8.2 Hz), 7.26 (1H, m, ArH); δ_F ($CDCl_3$) -113.50 (1F, d, $^{2}J_{FF}$ 246.5 Hz, CF_AF_B), -115.60 (1F, d, $^{2}J_{FF}$ 246.5 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 23.0 (CH_3), 56.2 (CH_3), 62.4 (CH_2), 77.8 (t, $^{2}J_{CF}$ 25.2 Hz, C), 112.3 (CH), 115.9 (t, $^{1}J_{CF}$ 260.6 Hz, CF_2), 121.5 (CH), 126.6 (C), 129.5 (CH), 130.0 (CH), 158.2 (C),

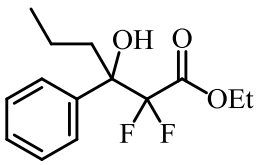
163.7 (t, $^{2}J_{CF}$ 32.2 Hz, C); m/z (FAB) 297.0918 (MNa^{+}. $C_{13}H_{16}F_2O_4Na$ requires 297.0914). The enantiomers were separated on a chiralcel OD-H column eluted with 2 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 19.95 min (enantiomer 1), 28.29 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-phenylpentanoate (54)



The title compound was prepared by Method 1. The crude product was purified by column chromatography (10 % EtOAc in hexane) to give colourless crystals (0.27 g, 26 %). M.p. 38-39 ^{o}C; (Found: C, 60.50; H, 6.34. Calc. for $C_{13}H_{16}F_2O_3$: C, 60.46; H, 6.24 %); δ_H ($CDCl_3$) 0.69 (3H, t, $^{3}J_{HH}$ 7.4 Hz, CH_2CH_3), 1.00 (3H, t, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3), 2.02 (1H, m, $CH_AH_BCH_3$), 2.13 (1H, m, $CH_AH_BCH_3$), 2.58 (1H, s, O*H*), 4.02 (2H, q, $^{3}J_{HH}$ 7.0, OCH_2CH_3), 7.21-7.34 (3H, m, Ar*H*), 7.36 (2H, d, $^{3}J_{HH}$ 7.0 Hz, Ar*H*); δ_F ($CDCl_3$) -116.14 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF_AF_B), -115.43 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 6.6 (CH_3), 13.6 (CH_3), 27.1 (CH_2), 62.8 (CH_2), 78.5 (t, $^{2}J_{CF}$ 23.6 Hz, C), 115.1 (t, $^{1}J_{CF}$ 261.6 Hz, CF_2), 126.5 (CH), 128.0 (CH), 128.1 (CH), 137.3 (C), 163.6 (t, $^{2}J_{CF}$ 32.2 Hz, CO); m/z (EI) 258.10641 (M^{+}. $C_{13}H_{16}F_2O_3$ requires 258.10635), 229 (18%), 201 (23 %), 135 (100%). Crystals suitable for X-ray crystallography were grown on the side of a round bottomed flask from pure product without using any solvent. The enantiomers were separated on a chiralcel OD-H column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 8.63 min (enantiomer 1), 9.26 min (enantiomer 2).

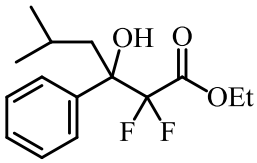
Preparation of ethyl-2,2-difluoro-3-hydroxy-3-phenylhexanoate (55)



The title compound was prepared by Method 2 with ethyl bromodifluoroacetate. The crude product was purified by column chromatography (10 % EtOAc in hexane) to yield colourless crystals (0.19 g, 35 %). M.p. 41-43 ^{o}C; (Found: C, 61.85; H, 6.65. Calc. for $C_{14}H_{18}F_2O_3$: C, 61.75; H, 6.66 %); δ_H ($CDCl_3$) 0.80 (3H, t, $^{3}J_{HH}$ 7.0 Hz, CH_2CH_3), 0.90 (1H, m, $CH_AH_BCH_3$), 1.00 (3H, t, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.31 (1 H, m, $CH_AH_BCH_3$), 1.94 (1H, m, $CH_CH_DCH_AH_B$), 2.07 (1H, tdt, $^{2}J_{HH}$ 12.5 Hz, $^{3}J_{HH}$ 7.0 Hz, $^{4}J_{FH}$ 4.6 Hz, $CH_CH_DCH_AH_B$), 2.96 (1H, s, O*H*), 4.04 (2H, q, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3), 7.21-7.31 (3H, m, ArH), 7.41 (2H, d, $^{3}J_{HH}$ 7.0 Hz, ArH); δ_F ($CDCl_3$) -115.46 (1F, d, $^{2}J_{FF}$ 257.4 Hz,

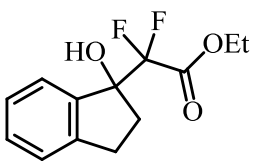
CF_AF$_B$), -116.16 (1F, d, $^2J_{FF}$ 257.4 Hz, CF$_A$$F_B$); δ_C ($CDCl_3$) 13.7 (CH_3), 14.3 (CH_3), 15.7 (CH_2), 36.4 (CH_2), 62.8 (CH_2), 78.3 (t, $^2J_{CF}$ 24.1 Hz, C), 115.0 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.4 (CH), 128.0 (CH), 128.1 (CH), 137.8 (C), 163.6 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (EI) 271.1141 (M^+. $C_{14}H_{18}F_2O_3$ requires 271.1146), 165 (10 %), 133 (100%). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from hexane. The enantiomers were separated on a chiralcel AS column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 5.76 min (enantiomer 1), 10.44 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate (56)



The title compound was prepared by Method 2 with ethyl bromodifluoroacetate. The crude product was purified by column chromatography (10 % EtOAc in hexane) to yield colourless crystals (0.10 g, 17 %). M.p. 63-64 ^oC; (Found: C, 63.08; H, 6.87. Calc. for $C_{15}H_{20}F_2O_3$: C, 62.92; H, 7.04 %); δ_H ($CDCl_3$) 0.61 (3H, d, $^3J_{HH}$ 6.7 Hz, CHCH_3), 0.86 (3H, d, $^3J_{HH}$ 6.7 Hz, CHCH_3), 0.98 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.50 (1H, m, CH(CH_3)$_2$), 1.82 (1H, dd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 7.4 Hz, CH_AH$_B$CH), 2.09 (1H, ddt, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 5.1 Hz, $^4J_{HF}$ 1.6 Hz, CH$_A$$H_B$CH), 2.95 (1H, s, OH), 4.02 (2H, q, $^2J_{HH}$ 7.0 Hz, OC$H_2$$CH_3$), 7.21-7.31 (3H, m, ArH), 7.40 (2H, d, $^3J_{HH}$ 7.0 Hz, ArH); δ_F ($CDCl_3$) -116.02 (2F, s, CF_2); δ_C ($CDCl_3$) 11.5 (CH_3), 23.5 (CH_3), 24.0 (CH_3), 24.4 (CH), 41.9 (CH_2), 66.8 (CH_2), 78.8 (t, $^2J_{CF}$ 23.1 Hz, C), 114.9 (t, $^1J_{CF}$ 263.6 Hz, CF_2), 126.6 (CH), 127.98 (CH), 128.02 (CH), 137.9 (C), 163.6 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (EI) 285.1311 (M^+. $C_{15}H_{20}F_2O_3$ requires 285.1302). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from hexane. The enantiomers were separated on a chiralcel AS column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 4.81 min (enantiomer 1), 7.14 min (enantiomer 2).

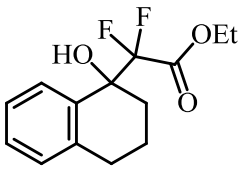
Preparation of ethyl-2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate (57)



The title compound was prepared by Method 1. The crude product was purified by column chromatography (2 % EtOAc in hexane) to yield colourless crystals (0.66 g, 64 %). M.p. 56-58 ^oC; (Found: C, 60.98; H, 5.48. Calc. For $C_{13}H_{14}F_2O_3$: C, 60.93; H,

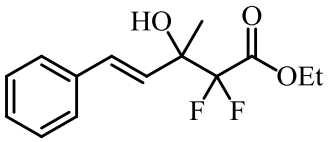
5.51 %); δ_H ($CDCl_3$) 1.23 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 2.11 (1H, m, $CH_AH_BCH_2Ar$), 2.72-3.04 (4H, m, $CH_AH_BCH_2Ar$ and OH), 4.25 (2H, m, OCH_2), 7.17-7.23 (2H, m, ArH), 7.27 (1H, t, $^3J_{HH}$ 7.4 Hz, ArH), 7.42 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH); δ_F ($CDCl_3$) -117.59 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), -114.57 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.8 (CH_3), 29.9 (CH_2), 35.7 (CH_2), 63.1 (CH_2), 84.7 (t, $^2J_{CF}$ 24.1 Hz, C), 115.3 (t, $^1J_{CF}$ 259.1 Hz, CF_2), 124.9 (CH), 125.1 (CH), 126.9 (CH), 129.8 (CH), 139.8 (C), 145.0 (C), 163.8 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (EI) 256.09065 (M^+. $C_{13}H_{14}F_2O_3$ requires 256.09075), 165 (10 %), 133 (100%). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from 20 % EtOAc in hexane. The enantiomers were separated on a chiralcel OD-H column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 8.40 min (enantiomer 1), 10.79 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (58)



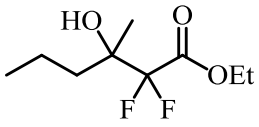
The title compound was prepared using Method 1. The crude product was purified by column chromatography (10 % EtOAc in hexane) to give a colourless oil (0.42 g, 39 %). (Found: C, 62.28: H, 5.97. Calc. for $C_{14}H_{16}F_2O_3$: C, 62.22; H, 5.97 %); δ_H ($CDCl_3$) 1.26 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.85 (1H, m, $CH_2CH_AH_BCOH$), 2.05 (2H, m, $CH_2CH_2CH_2$), 2.30 (1H, m, $CH_2CH_AH_BCOH$), 2.85 (3H, m, $ArCH_2$ and OH), 4.29 (2H, m, OCH_2CH_3), 7.16 (1H, m, ArH), 7.22-7.31 (2H, m, ArH), 7.69 (1H, d, $^3J_{HH}$ 7.4 Hz, ArH); δ_F ($CDCl_3$) -113.24 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), -111.58 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.7 (CH_3), 18.7 (CH_2), 29.5 (CH_2), 33.2 (CH_2), 63.0 (CH_2), 73.7 (t, $^2J_{CF}$ 22.6 Hz, C), 116.0 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.2 (CH), 127.9 (CH), 128.6 (CH), 129.1 (CH), 133.7 (C), 138.9 (C), 163.8 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (EI) 270.10642 (M^+. $C_{14}H_{16}F_2O_3$ requires 270.10635), 147 (100 %). The enantiomers were separated on a chiralcel OD-H column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 8.20 min (enantiomer 1), 9.88 min (enantiomer 2).

Preparation of (*E*)-ethyl-2,2-difluoro-3-hydroxy-3-methyl-5-phenylpent-4-enoate (59)



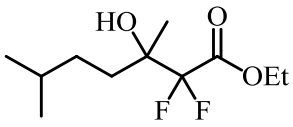
The title compound was prepared by Method 2 with ethyl iododifluoroacetate in acetonitrile. The crude product was purified by column chromatography (10 % EtOAc in hexane) to give a colourless oil (0.21 g, 78 %). The characterisation data was in agreement with literature.[4] (Found: C, 62.12; H, 5.87. Calc. for $C_{14}H_{16}F_2O_3$: C, 62.22; H, 5.97 %); δ_H ($CDCl_3$) 1.28 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.46 (3H, t, $^4J_{HF}$ 1.6 Hz, $CF_2C(OH)CH_3$), 2.50 (1H, br s, O*H*), 4.24 (2H, q, $^3J_{HH}$ 7.0, OCH_2CH_3), 6.21 (1H, dt, $^3J_{HH}$ 16.0 Hz, $^4J_{HF}$ 1.6 Hz, ArCH=C*H*C(OH)), 6.25 (1H, d, $^3J_{HH}$ 16.0 Hz, ArC*H*), 7.17-7.22 (1H, m, Ar*H*), 7.23-7.28 (2H, m, Ar*H*), 7.30-7.34 (2H, m, Ar*H*); δ_F ($CDCl_3$) -116.52 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), -117.82 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 21.8 (CH_3), 63.1 (CH_2), 75.1 (t, $^2J_{CF}$ 25.2 Hz, C), 114.8 (t, $^1J_{CF}$ 260.6 Hz, CF_2), 126.8 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 131.3 (CH), 136.0 (C), 163.6 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (FAB) 293.0960 (MNa^+. $C_{14}H_{16}F_2O_3Na$ requires 293.0965). The enantiomers were separated on a chiralcel OD-H column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 10.19 min (enantiomer 1), 11.55 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-hydroxy-3-methylhexanoate (60)



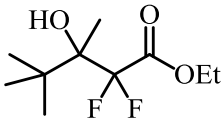
The title compound was prepared by Method 2 with ethyl bromodifluoroacetate. The crude product was purified by column chromatography (20 % EtOAc in hexane) to give a colourless oil (0.19 g, 30 %). The characterisation data was in agreement with literature.[5] δ_H ($CDCl_3$) 0.88 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.25 (3H, t, $^4J_{HF}$ 1.5 Hz, C(OH)C*H*$_3$), 1.30 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.40 (2H, m, CH_3CH_2), 1.52 (2H, m, $CH_2C(OH)CH_3$), 2.15 (1H, s, O*H*), 4.29 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3); δ_F ($CDCl_3$) -118.10 (1F, d, $^2J_{FF}$ 259.0 Hz, CF_AF_B), -117.00 (1F, d, $^2J_{FF}$ 259.0 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 14.5 (CH_3), 15.9 (CH_2), 19.8 (CH_3), 37.5 (CH_2), 62.9 (CH_2), 74.7 (t, $^2J_{CF}$ 24.1 Hz, C), 116.0 (t, $^1J_{CF}$ 259.6 Hz, CF_2), 163.8 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (EI) 209.09859 ($(M-H)^+$. $C_9H_{15}F_2O_3$ requires 209.09855). The enantiomers were separated by chiral GC on a G-TA column eluted with a flow of nitrogen at 100 ^oC. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.30 min (enantiomer 1), 9.91 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-hydroxy-3,6-dimethylheptanoate (61)



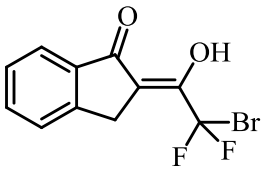
The title compound was prepared Method 2 with ethyl iododifluoroacetate. The crude product was purified by column chromatography (10 % EtOAc in hexane) to give a colourless oil (0.22 g, 31 %). (Found: C, 55.49; H, 8.35. Calc. for $C_{11}H_{20}F_2O_3$: C, 55.45; H, 8.46 %); δ_H ($CDCl_3$) 0.81 (3H, d, $^3J_{HH}$ 6.6 Hz, CHCH_3), 0.84 (3H, d, $^3J_{HH}$ 7.0 Hz, CHCH_3), 1.19 (1H, m, $(CH_3)_2$CHC$H_A$$H_B$), 1.24 (3H, t, $^4J_{HF}$ 1.7 Hz, CF_2C(OH)CH_3), 1.30 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.30 (1H, m, $(CH_3)_2$CHC$H_A$$H_B$)), 1.45 (1H, m, C$H$$(CH_3)_2$), 1.54 (2H, m, C$H_2$C(OH) CH_3), 2.10 (1 H, s, OH), 4.30 (2H, q, $^3J_{HH}$ 7.0 Hz, OC$H_2$$CH_3$); δ_F ($CDCl_3$) -118.00 (1F, d, $^2J_{FF}$ 257.4 Hz, C$F_A$$F_B$), -116.80 (1F, d, $^2J_{FF}$ 257.4 Hz, $CF_A$$F_B$); δ_C ($CDCl_3$) 13.9 (CH_3), 19.8 (CH_3), 22.4 (CH_3), 22.6 (CH_3), 28.4 (CH), 31.4 (CH_2), 33.1 (CH_2), 63.0 (CH_2), 74.7 (t, $^2J_{CF}$ 23.1 Hz, C), 116.1 (t, $^1J_{CF}$ 259.6 Hz, CF_2), 163.9 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (EI) 237.12971 ($(M-H)^+$. $C_{11}H_{20}F_2O_3$ requires 237.12975). The enantiomers were separated by chiral GC on a G-TA column eluted with a flow of nitrogen at 120 ^oC. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 10.49 min (enantiomer 1), 11.13 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-hydroxy-3,4,4-trimethylpentanoate (62)



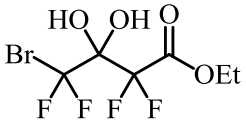
The title compound was prepared by Method 2 with ethyl bromodifluoroacetate. The crude product was purified by column chromatography (20 % EtOAc in hexane) to give a colourless oil (0.21 g, 31 %). δ_H ($CDCl_3$) 0.99 (9H, t, $^5J_{HF}$ 1.5 Hz, C(CH_3)$_3$), 1.28 (3H, t, $^4J_{HF}$ 2.0 Hz, C(OH)CH_3), 1.30 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 2.43 (1H, br s, OH), 4.27 (2H, q, $^3J_{HH}$ 7.0 Hz, OC$H_2$$CH_3$); δ_F ($CDCl_3$) -111.29 (1F, d, $^2J_{FF}$ 260.2 Hz, C$F_A$$F_B$), -108.08 (1F, d, $^2J_{FF}$ 260.2 Hz, $CF_A$$F_B$); δ_C ($CDCl_3$) 13.9 (CH_3), 18.6 (t, $^3J_{CF}$ 3.0 Hz, CH_3), 26.2 (CH_3), 37.7 (C), 63.0 (CH_2), 78.4 (t, $^2J_{CF}$ 22.1 Hz, C), 117.5 (t, $^1J_{CF}$ 262.6 Hz, CF_2), 164.6 (t, $^2J_{CF}$ 33.2 Hz, CO); HRMS (EI) 223.11426 ($(M-H)^+$. $C_{10}H_{17}F_2O_3$ requires 223.11415). The enantiomers could not be separated by either chiral GC or chiral HPLC.

Preparation of (*Z*)-2-(2-bromo-2,2-difluoro-1-hydroxyethylidene)-2,3-dihydro-1H-inden-1-one (63)



The title compound was prepared from indanone (0.132 g, 1.0 mmol) by the method used for Table 3.2 with addition of aliquots of ethyl bromodifluoroacetate (0.06 mL, 0.5 mmol) and diethylzinc (0.5 mL, 1.0 M solution in hexane, 0.5 mmol) after 2 h from start of the reaction. The crude product was purified by silica gel column chromatography (20 % EtOAc in hexane) to give brown crystals (0.10 g, 68 %). M.p. 56-58 ^{o}C. δ_H ($CDCl_3$) 3.74 (2H, s, ArCH_2), 7.39 (1H, t, $^3J_{HH}$ 7.4 Hz, ArH), 7.47 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH), 7.56 (1H, t, $^3J_{HH}$ 7.4 Hz, ArH), 7.77 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH); δ_F ($CDCl_3$) -58.64 (2F, s, CF_2Br); δ_C ($CDCl_3$) 31.3 (t, $^4J_{CF}$ 4.0 Hz, CH_2), 106.7 (C), 113.6 (t, $^1J_{CF}$ 310.9 Hz, CF_2Br), 123.3 (CH), 125.7 (CH), 127.8 (CH), 134.0 (CH), 136.0 (C), 147.8 (C), 170.4 (t, $^2J_{CF}$ 29.2 Hz, C), 190.1 (CO); m/z (FAB) 288.9671 (MH^+. $C_{11}H_7BrF_2O_2$ requires 288.9676).

Preparation of ethyl-4-bromo-2,2,4,4-tetrafluoro-3,3-dihydroxybutanoate (70)



The title compound was formed as a by-product in Method 2 of the Reformatsky reaction of ethyl bromodifluoroacetate with 3,3-dimethylbutan-2-one. The crude product was purified by column chromatography (20 % EtOAc in hexane) to give a colourless oil. δ_H ($CDCl_3$) 1.34 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.37 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.50 (2H, br s, $C(OH)_2$); δ_F ($CDCl_3$) -59.69 (2F, t, $^4J_{FF}$ 13.8 Hz, CF_2Br), -117.64 (2F, t, $^4J_{FF}$ 13.8 Hz, $C(OH)_2CF_2CO_2Et$); δ_C ($CDCl_3$) 13.7 (CH_3), 64.6 (CH_2), 93.5 (quintet, $^2J_{CF}$ 26.4 Hz, C), 110.0 (t, $^1J_{CF}$ 268.9 Hz, CF_2), 122.3 (t, $^1J_{CF}$ 318.2 Hz, CF_2Br), 163.2 (t, $^2J_{CF}$ 30.5 Hz, CO).

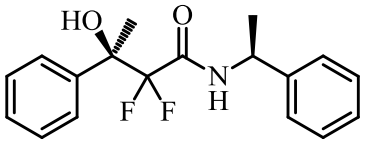
6.3.4 Determination of the absolute configuration of the new chiral centre

General method for the reaction of *α,α*-difluoro-*β*-hydroxy esters with (*S*)-(1-phenylethyl)amine[6]

Under an argon atmosphere a dry three neck flask was charged with THF (30 mL), (*S*)-(1-phenylethyl)amine (0.81 mL, 0.76 g, 6.3 mmol) and *n*-butyllithium (5.7 mL, 1.6 M solution in hexane 9.0 mmol). After 30 min of stirring at 0 ^{o}C, a solution of the

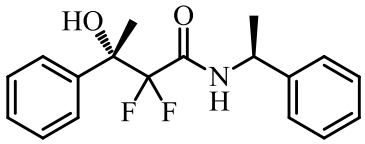
difluorinated ester (2.5 mmol) in THF (2 mL) was added. The dropping funnel was washed with THF (2 mL) and the reaction mixture was stirred for 24 h at 0 ^{o}C. After quenching the reaction mixture with water (10 mL), it was acidified to pH 5 with 1 M HCl and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over magnesium sulphate.

Preparation of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-propanamide (65)



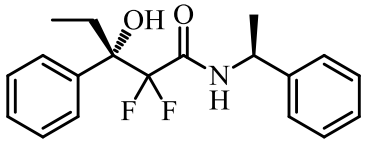
The title compound was synthesised using Braun's procedure.[6] Under an argon atmosphere a dry 250 mL three neck flask was charged with THF (30 mL), (*S*)-(1-phenylethyl)amine (0.81 mL, 0.76 g, 6.3 mmol) and *n*-butyllithium (5.7 mL, 1.6 M in hexane, 9.1 mmol). After 30 min of stirring at 0 ^{o}C, a solution of (*S*)-ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate (0.60 g, 2.5 mmol, 75 % ee) in THF (2 mL) was added. The dropping funnel was washed with THF (2 mL) and the reaction mixture was stirred for 24 h at 0 ^{o}C. After quenching the reaction with water (10 mL), it was acidified to pH 5 with 1 M HCl and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over magnesium sulphate. The solvent was removed and the crude product consisted of a 6:1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereoisomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (EtOAc:hexane = 15:85) to give the pure diastereoisomer 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-propanamide **(65a)** as colourless crystals (0.04 g, 5 %). M.p. 84-86 ^{o}C (Found: C, 67.6; H, 5.8; N, 4.2. Calc. for $C_{18}H_{19}F_2NO_2$: C, 67.7; H, 6.0; N, 4.4 %). δ_H ($CDCl_3$) 1.03 (3H, d, $^{3}J_{HH}$ 7.0 Hz, CHC*H*$_3$), 1.63 (3H, t, $^{4}J_{HF}$ 1.2 Hz, $CF_2C(OH)CH_3$), 4.49 (1H, br s, O*H*), 4.83 (1H, quintet, $^{3}J_{HH}$ 7.0 Hz, C*H*CH_3), 6.30 (1 H, br s, N*H*), 7.05-7.10 (2H, m, ArH), 7.16-7.30 (6H, m, ArH), 7.41-7.46 (2H, m, ArH); δ_F ($CDCl_3$) -116.55 (1F, d, $^{2}J_{FF}$ 257.4 Hz, C*F*$_A$F$_B$), -117.45 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF$_A$*F*$_B$); δ_C ($CDCl_3$) 20.6 (CH_3), 22.6 (CH_3), 48.9 (CH), 76.1 (t, $^{2}J_{CF}$ 24.0 Hz, C), 114.5 (t, $^{1}J_{CF}$ 262.6 Hz, CF_2), 126.1 (CH), 126.3 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.9 (CH), 140.1 (C), 141.2 (C), 163.3 (t, $^{2}J_{CF}$ 29.2 Hz, CO); m/z (FAB) 320.1465 (MH^+. $C_{18}H_{20}F_2NO_2$ requires 320.1462). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from a

solution of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)propanamide in 20 % EtOAc in hexane.



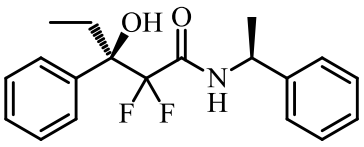
The pure diastereoisomer 2,2-difluoro-3(*S*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)propanamide **(65b)** was obtained as colourless crystals (0.50 g, 62 %). M.p. 81-85 ^{o}C. (Found: C, 67.85; H, 5.6; N, 4.3 %. Calc. for $C_{18}H_{19}F_2NO_2$: C, 67.7; H, 6.0; N, 4.4 %), δ_H ($CDCl_3$) 1.46 (3H, d, $^3J_{HH}$ 7.0 Hz, CHC*H*$_3$), 1.74 (3H, s, $CF_2C(OH)CH_3$), 4.72 (1H, s, O*H*), 4.96 (1H, quintet, $^3J_{HH}$ 7.0 Hz, C*H*CH_3), 6.40 (1H, br s, N*H*) 6.79-6.82 (2H, m, ArH), 7.19-7.25 (3H, m, ArH), 7.31-7.36 (3H, m, ArH), 7.49-7.53 (2H, m, ArH); δ_F ($CDCl_3$) -115.40 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF$_B$), -117.96 (1F, d, $^2J_{FF}$ 257.4 Hz, CF$_A$$F_B$); δ_C ($CDCl_3$) 20.9 (CH_3), 22.5 (CH_3), 48.7 (CH), 76.1 (t, $^2J_{CF}$ 24.1 Hz, C), 114.4 (t, $^1J_{CF}$ 262.6 Hz, CF_2), 125.7 (CH), 126.3 (CH), 127.5 (CH), 128.1 (CH), 128.3 (C), 128.7 (CH), 140.1 (C), 140.9 (C), 163.5 (t, $^2J_{CF}$ 29.2 Hz, CO); m/z (FAB) 320.1465 (MH^+. $C_{18}H_{20}F_2NO_2$ requires 320.1462).

Determination of the absolute configuration of the new chiral centre in ethyl-2,2-difluoro-3-hydroxy-3-phenylpentanoate (66)



The procedure above was repeated using (*S*)-(1-phenylethyl)amine (0.22 mL, 0.20 g, 1.7 mmol), *n*-butyllithium (1.6 mL, 1.6 M in hexane, 2.6 mmol), (*S*)-ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate (0.18 g, 0.7 mmol, 78 % ee) and THF (8 mL). The crude product consisted of a 7.3:1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereoisomers according to the ^{1}H NMR spectrum. The diastereomerically pure 2,2-difluoro-3(*S*)-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl) pentanamide **(66a)** was separated by silica gel column chromatography (10 % EtOAc in hexane) as colourless crystals (0.18 g, 77 %). M.p. 88-90 ^{o}C. δ_H ($CDCl_3$) 0.66 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.36 (3H, d, $^3J_{HH}$ 7.0 Hz, CHC*H*$_3$), 2.07 (2H, q, $^3J_{HH}$ 7.4 Hz, C*H*$_2$CH$_3$), 4.55 (1H, br s, O*H*), 4.83 (1H, quintet, $^3J_{HH}$ 7.4 Hz, C*H*CH_3), 6.29 (1H, br s, N*H*), 6.64-6.69 (2H, m, ArH), 7.07-7.16 (3H, m, ArH), 7.22-7.27 (3H, m, ArH), 7.36-7.41 (2H, m, ArH); δ_F ($CDCl_3$) -115.35 (1F, d, $^2J_{FF}$ 257.5 Hz, CF_AF$_B$), -118.65 (1F, d, $^2J_{FF}$ 257.5 Hz, CF$_A$$F_B$); δ_C ($CDCl_3$) 6.5 (CH_3), 20.9 (CH_3), 26.7 (CH_2), 48.6 (CH), 78.6 (t, $^2J_{CF}$ 23.1 Hz, C), 114.7 (t, $^1J_{CF}$ 263.6 Hz, CF_2), 125.7 (CH), 126.8 (CH), 127.5 (CH), 127.9 (CH), 128.3

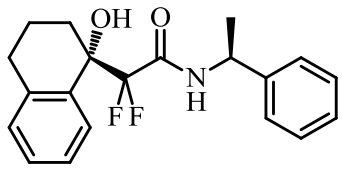
(CH), 128.7 (CH), 138.0 (C), 140.9 (C), 163.7 (t, $^{2}J_{CF}$ 28.2 Hz, CO); m/z (FAB) 334.1620 (MH^{+}. $C_{19}H_{22}F_{2}NO_{2}$ requires 334.1619).



The procedure above was repeated using (*S*)-(1-phenylethyl)amine (0.77 mL, 0.71 g, 5.9 mmol), *n*-butyllithium (5.4 mL, 1.6 M in hexane, 8.6 mmol), racemic ethyl 2,2-difluoro-3-hydroxy-3-phenyl-pentanoate (0.31 g, 1.2 mmol) and THF (28 mL). The crude product consisted of a 1:1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereoisomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (10 % EtOAc in hexane) to give diastereomerically pure 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)-pentanamide **(66b)** as colourless crystals (0.06 g (15 %). M.p. 131-132 ^{o}C. (Found: C, 67.73; H, 5.06; N, 3.82 %. Calc. for $C_{19}H_{21}F_{2}NO_{2}$: C, 68.45; H, 6.35; N, 4.20 %). δ_{H} ($CDCl_{3}$) 0.78 (3H, t, $^{3}J_{HH}$ 7.4 Hz, $CH_{2}CH_{3}$), 1.14 (3H, d, $^{3}J_{HH}$ 6.7 Hz, $CHCH_{3}$), 2.07-2.23 (2H, m, $CH_{2}CH_{3}$), 4.49 (1H, br s, O*H*), 4.91 (1H, quintet, $^{3}J_{HH}$ 7.0 Hz, $CHCH_{3}$), 6.34 (1H, br s, N*H*), 7.17-7.21 (2H, m, ArH), 7.27-7.42 (6H, m, ArH), 7.49-7.54 (2H, m, ArH); δ_{F} ($CDCl_{3}$) -116.69 (1F, d, $^{2}J_{FF}$ 254.7 Hz, $CF_{A}F_{B}$), -118.40 (1F, d, $^{2}J_{FF}$ 254.7 Hz, $CF_{A}F_{B}$); δ_{C} ($CDCl_{3}$) 6.6 (CH_{3}), 20.5 (CH_{3}), 26.6 (CH_{2}), 48.8 (CH), 78.6 (t, $^{2}J_{CF}$ 23.1 Hz, C), 114.8 (t, $^{1}J_{CF}$ 262.6 Hz, CF_{2}), 126.1 (CH), 126.9 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.9 (CH), 138.0 (C), 141.1 (C), 163.5 (t, $^{2}J_{CF}$ 28.2 Hz, CO); m/z (FAB) 334.1621 (MH^{+}. $C_{19}H_{22}F_{2}NO_{2}$ requires 334.1619). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)pentanamide in 10 % EtOAc in hexane.

Determination of the absolute configuration of the new chiral centre in ethyl-2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphtalen-1-yl)acetate (67)

The procedure above was repeated using (*S*)-(1-phenylethyl)amine (0.32 mL, 0.30 g, 2.5 mmol), *n*-butyllithium (2.3 mL, 1.6 M in hexane, 3.7 mmol), racemic ethyl 2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (0.14 g, 0.5 mmol) and THF (12 mL). The crude product consisted of a 1:1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereoisomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (10 % EtOAc in hexane) to give diastereomerically pure 2,2-difluoro-2-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-

yl)-*N*-((*S*)-1-phenylethyl)acetamide as colourless crystals (0.03 g, 17%). M.p. 153-155  °C. (Found: C, 69.43; H, 6.20; N, 4.05. Calc. for $C_{20}H_{21}F_2NO_2$: C, 69.55; H, 6.13; N, 4.05 %). δ_H ($CDCl_3$) 1.44 (3H, d, $^3J_{HH}$ 7.0 Hz, CH_3), 1.66-1.78 (1H, m, $CF_2C(OH)H_AH_B$), 1.88 (2H, d, $^3J_{HH}$ 11.0 Hz, $CH_2CH_2CH_2$), 2.24 (1H, m, $^3J_{HH}$ 9.0 Hz, $CF_2C(OH)H_AH_B$), 2.62-2.78 (2H, m, ArCH_2), 4.05 (1H, br s, O*H*), 5.04 (1H, quintet, $^3J_{HH}$ 7.0 Hz, C*H*CH_3), 6.52 (1H, br s, N*H*), 7.02-7.06 (2H, m, ArH), 7.12-7.32 (6H, m, ArH), 7.51 (2H, d, $^3J_{HH}$ 7.8 Hz, ArH); δ_F ($CDCl_3$) -112.76 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), -118.65 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 19.0 (CH_2), 21.2 (CH_3), 29.5 (CH_2), 33.2 (CH_2), 49.3 (CH), 73.7 (t, $^2J_{CF}$ 23.1 Hz, C), 115.7 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.2 (2 x CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 129.0 (CH), 134.0 (C), 139.1 (C), 141.4 (C), 163.6 (t, $^2J_{CF}$ 29.2 Hz, CO); m/z (FAB) 346.1628 (MH^+. $C_{20}H_{22}F_2NO_2$ requires 346.1619).

The procedure above was repeated using (*S*)-(1-phenylethyl)amine (0.28 mL, 0.27 g, 2.25 mmol), *n*-butyllithium (2.0 mL, 1.6 M in hexane, 3.2 mmol), (*S*)-ethyl 2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (0.24 g, 0.9 mmol, 88 % ee) and THF (11 mL). The crude product consisted of a 10:1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereoisomers according to the ^{1}H and ^{19}F NMR spectra. The direct comparison of ^{1}H and ^{19}F NMR spectra for the crude product with ^{1}H and ^{19}F NMR spectra for 2,2-difluoro-2-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)-acetamide confirmed that that this was the major product in the reaction.

6.3.5 Monitoring of the synthesis of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate (48) by GC.

Monitoring 1 – The reaction between ethyl bromodifluoroacetate and acetophenone in presence of diethylzinc and *N*-methylephedrine at 0 °C.

A dry round bottomed flask was charged with THF (8 mL), acetophenone (0.12 mL, 1.2 g, 1.0 mmol), tolyl ether (0.0991 g, 0.5 mmol), ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol) and *N*-methylephedrine (0.18 g, 1.0 mmol). The solution was stirred at 0 °C for 30 minutes before the addition of diethylzinc (2.0 mL, 1.0 M solution in hexane, 2.0 mmol). A small sample (0.5 mL) of the reaction mixture was collected by

syringe every 30 minutes for 4.5 hours. The sample was quenched with 1 M HCl (1.0 mL) and extracted with EtOAc (1 mL). The organic layer was washed with 1 M HCl (1 mL), brine (1 mL) and water (1 mL) before being dried over magnesium sulphate and analysed by GC to determine the conversion.

Table 6.2 Monitoring of the Reformatsky reaction with acetophenone by GC.

Time [h]	**Conversion[a] [%]**	**Time [h]**	**Conversion[a] [%]**
0.5	14	3.0	30
1.0	23	3.5	31
1.5	26	4.0	32
2.0	27	4.5	32
2.5	29	5.0	

[a] Conversion was determined by GC.

Monitoring 2 - The reaction between the Reformatsky reagent and acetophenone in the presence of (1*R*,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol

A flamed dried two neck round bottomed flask equipped with a condenser was charged with acid washed zinc dust (0.215 g, 3.3 mmol) and dry THF (7.5 mL). The temperature was increased to 60 ^{o}C but heating was stopped before ethyl iododifluoroacetate (0.49 mL, 0.83 g, 3.3 mmol) was added dropwise over 2 minutes. After stirring for 5 minutes the solution of the Reformatsky reagent (7 mL, 3.0 mmol) was added to the flask containing THF (2 mL), acetophenone (0.12 mL, 0.12 g, 1.0 mmol), tolyl ether (0.0991 g, 0.5 mmol) and (1*R*,*2*S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (0.205 g, 1.0 mmol) stirring at 0 ^{o}C. A small sample (0.75 mL) of the reaction mixture was collected by syringe every 30 minutes for 4.5 hours. The sample was quenched with 1 M HCl (1.0 mL) and extracted with EtOAc (1 mL). The organic layer was washed with 1 M HCl (1 mL), brine (1 mL) and water (1 mL) before being dried over magnesium sulphate and analysed by GC to determine the conversion.

Table 6.3 Monitoring of the asymmetric Reformatsky reaction with acetophenone.

Time [h]	Conversion[a] [%]	Time [h]	Conversion[a] [%]
0.5	9	3.0	52
1.0	16	3.5	58
1.5	26	4.0	64
2.0	35	4.5	68
2.5	44	5.0	70

[a] Conversion was determined by GC.

Monitoring 3 - The reaction between ethyl iododifluoroacetate and acetophenone in the presence of (1*R*,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol

The method used for monitoring of the Reformatsky reaction of ethyl iododifluoroacetate and diethylzinc with acetophenone was identical to the one used in Monitoring 1 but ethyl bromodifluoroacetate was replaced with ethyl iododifluoroacetate (0.22 mL, 0.38 g, 1.5 mmol).

Table 6.4 Monitoring of the Reformatsky reaction with acetophenone by GC.

Time [h]	Conversion[a] [%]	Time [h]	Conversion[a] [%]
0.5	56	3.0	60
1.0	59	3.5	60
1.5	59	4.0	61
2.0	60	4.5	61
2.5	60		

[a] Conversion was determined by GC.

Monitoring 4 - The reaction between ethyl iododifluoroacetate and acetophenone in the presence of diethylzinc and (1*R*,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol at - 40 ^{o}C

Six separate reactions were run to obtain the profile of the reaction. A 25 mL round bottomed flask was charged with THF (4 mL), acetophenone (0.06 mL, 0.5 mmol), ethyl iododifluoroacetate (0.15 mL, 0.25 g, 1.0 mmol) and (1*R*,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (0.103 g, 0.5 mmol). After 30 minutes of stirring at -40 ^{o}C, diethylzinc (1.25 mmol, 1.0 M solution in hexane, 1.25 mL) was added. The reaction was quenched and worked-up after a specified period of time (Table 6.5). The conversion was determined by ^{1}H NMR spectroscopy by comparison of the integrations

of the CH_3 signals for acetophenone and ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate.

Table 6.5 Monitoring of the Reformatsky reaction of ethyl iododifluoroacetate and diethylzinc with acetophenone at -40 ^{o}C.

Time [min]	**Conversion[a] [%]**	**Time [min]**	**Conversion[a] [%]**
10	16	120	87
30	28	180	96
60	56	270	99

[a] Conversion determined by ^{1}H NMR spectroscopy.

6.3.6 Observation of the active species in the Reformatsky reaction by ^{19}F NMR spectroscopy

Method 1

The Reformatsky reagent formed from ethyl bromodifluoroacetate and zinc dust, and modification of the Schlenk equilibrium by addition of zinc (II) bromide

A flame dried 25 mL RBF was charged with THF (7 mL) and zinc dust (0.1 g, 1.5 mmol). The temperature of the suspension was increased to 60 ^{o}C but heating was stopped before ethyl bromodifluoroacetate (0.19 mL, 0.30 g, 1.5 mmol) was added dropwise from a syringe over 2-3 minutes. Two Young's NMR tubes containing C_6D_6 lock tubes were charged with 1 mL of the solution of the Reformatsky reagent under an argon atmosphere. One of these NMR tubes contained $ZnBr_2$ (0.5 equivalents, 0.145 g, 0.14 mmol). The ^{19}F NMR spectroscopy experiments were run without delay.

Method 2

The Reformatsky reagent formed from ethyl iododifluoroacetate and zinc dust

The Reformatsky reagent was prepared according to Method 1 using ethyl iododifluoroacetate (0.22 mL, 0.38 g,1.5 mmol) and 1 mL of the solution was transferred to a Young's NMR tube containing a C_6D_6 lock tube.

Method 3

The Reformatsky reagent formed from ethyl iododifluoroacetate and diethylzinc

Under an argon atmosphere a flame dried three neck round bottom flask was charged with THF (4 mL) and ethyl iododifluoroacetate (0.07 mL, 0.13 g, 0.5 mmol) at 0 ^{o}C. After stirring the reaction mixture at 0 ^{o}C for 30 minutes, diethylzinc (0.5 mL, 1.0 M solution in hexane, 0.5 mmol) was added. The solution of the Reformatsky reagent was transferred to a Young's NMR tube containing a C_6D_6 lock tube.

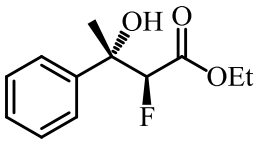
Method 4

The Reformatsky reagent formed from ethyl bromodifluoroacetate and diethylzinc

Under an argon atmosphere a flame dried three neck round bottom flask was charged with THF (4 mL) and ethyl bromodifluoroacetate (0.06 mL, 0.5 mmol) at 0 ^{o}C. After stirring the reaction mixture at 0 ^{o}C for 30 minutes, the required amount of diethylzinc (1.0 M solution in hexane) was added. The solution of the Reformatsky reagent was transferred to a Young's NMR tube containing a C_6D_6 lock tube and the ^{19}F NMR spectroscopy experiment was performed without delay.

6.4. Synthetic Procedures for Chapter four

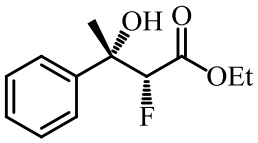
Preparation of ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate (81) (Table 4.10)



(2*S*,3*S*)

Under an argon atmosphere a dry three neck flask was charged with THF (8 mL), acetophenone (0.12 mL, 0.12 g, 1.0 mmol) and ethyl iodofluoroacetate (0.20 mL, 0.35 g, 1.5 mmol). After 30 min of stirring the reaction mixture at 0 ^{o}C, a 1.0 M solution of diethylzinc (1.5 mL, 1.5 mmol) was added and the reaction mixture was stirred for another 4.5 h at 0 ^{o}C. After quenching the reaction mixture with 1 M HCl (10 mL), it was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (10 mL), brine (10 mL) and water (10 ml) before being dried over magnesium sulphate. The solvent was removed and the product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give a colourless oil (0.22 g, 98 %). Crystals were formed from the pure product and were recrystallised from hexane to give the pure (2*R*,3*R*)/(2*S*,3*S*)-diastereoisomer as colourless crystals (0.12 g, 53 %). The characterisation data was in agreement with the literature.[7] M.p. 76-78 ^{o}C (lit.,[7] 76.5-78

^{o}C). δ_H ($CDCl_3$) 1.00 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.65 (3H, d, $^4J_{HF}$ 2.0 Hz, CH_3), 3.15 (1H, br s, O*H*), 4.02 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.84 (1H, d, $^2J_{HF}$ 47.7 Hz, C*H*F), 7.22 (1H, tt, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 7.29 (2H, tt, $^3J_{HH}$ 7.4, $^4J_{HH}$ 1.6 Hz, ArH), 7.40 (2H, dt, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz); δ_F ($CDCl_3$) -194.54 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.8 (CH_3), 25.4 (d, $^3J_{CF}$ 2.1 Hz, CH_3), 61.6 (CH_2), 74.7 (d, $^2J_{CF}$ 20.1 Hz, C), 92.9 (d, $^1J_{CF}$ 194.2 Hz, CH), 125.4 (CH), 127.7 (CH), 128.2 (CH), 142.1 (C), 168.0 (d, $^2J_{CF}$ 24.1 Hz, CO); m/z (FAB) 227.10787 (MH^+. $C_{12}H_{16}FO_3$ requires 227.10795). The enantiomers were separated on a chiralcel OD-H column eluted with 1 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 12.68 min (enantiomer 1), 14.90 min (enantiomer 2).



(2*R*,3*S*)

The pure sample of (2*R*,3*S*)/(2*S*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate was obtained as a colourless oil after purification on the chromatotron with 5 % Et_2O in hexane (0.012 g, 5 %). The characterisation data was in agreement with the literature.[7] δ_H ($CDCl_3$) 0.99 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.60 (3H, d, $^4J_{HF}$ 2.7 Hz, CH_3), 3.40 (1H, br s, O*H*), 4.00 (1H, dq, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, OCH_AH_B), 4.05 (1H, dq, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, CH_AH_B), 4.93 (1H, d, $^2J_{HF}$ 47.7 Hz, C*H*F), 7.21 (1H, tt, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.27 (2H, dt, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.41 (2H, dt, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.2 Hz, ArH); δ_F ($CDCl_3$) -192.00 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.8 (CH_3), 26.1 (d, $^3J_{CF}$ 2.1 Hz, CH_3), 61.8 (CH_2), 75.0 (d, $^2J_{CF}$ 20.1 Hz, C), 93.5 (d, $^1J_{CF}$ 199.2 Hz, CH), 125.1 (CH), 127.7 (CH), 128.3 (CH), 142.8 (C), 168.5 (d, $^2J_{CF}$ 23.1 Hz, CO); The enantiomers were separated on a chiralcel OD-H column eluted with 1 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.65 min (enantiomer 1), 11.27 min (enantiomer 2).

General methods for asymmetric synthesis of *α*-fluoro-*β*-hydroxy esters

Method 1 (Tables 4.11)

Preparation of the solution of the Reformatsky reagent:

Under an argon atmosphere a flame dried 25 mL two neck round bottomed flask equipped with a condenser was charged with acid washed zinc dust (0.228 g, 3.5 mmol) and dry THF (5.0 mL). The temperature of the suspension was increased to 60 ^{o}C but heating was stopped before the solution of ethyl bromofluoroacetate or ethyl

iododifluoroacetate (3.2 mmol) in THF (9.6 mL) was added dropwise from a pressure equalised dropping funnel over 6 minutes. The mixture was left to stir for 10 min before 7 mL of the solution was used in the reaction with acetophenone and the excess reagent was examined by ^{19}F NMR spectroscopy using a C_6D_6 lock tube.

The Reformatsky reaction with acetophenone:
A flame dried 25 mL two neck round bottomed flask was charged with THF (1 mL) and acetophenone (0.12 mL, 0.12 g, 1.0 mmol) or benzaldehyde (0.10 mL, 0.10 g, 1.0 mmol) at 0 ^oC. The solution of the Reformatsky reagent (1.5 mmol in 7 ml of dry THF) was added. The reaction was stirred for 6.5 hours at 0 ^oC before it was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The solvent was removed and the crude product was analysed by ^1H and ^{19}F NMR spectroscopy.

Method 2 (Table 4.13)

Under an argon atmosphere a dry three neck flask was charged with the required amount of Wilkinson's catalyst, THF (8 mL), acetophenone (0.12 mL, 0.12 g, 1.0 mmol) or benzaldehyde (0.10 mL, 0.10 g, 1.0 mmol) and ethyl bromofluoroacetate (0.18 mL, 0.276 g, 1.5 mmol). After 30 min of stirring at 0 ^oC, a 1.0 M solution of diethylzinc (1.5 mL, 1.5 mmol) was added and the reaction mixture was stirred for another 4.5 h at 0 ^oC. After quenching the reaction mixture with 1 M HCl (10 mL), it was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 ml) before being dried over magnesium sulphate. The solvent was removed and the crude product was examined by ^1H and ^{19}F NMR spectroscopy.

Method 3 (Tables 4.15 and 4.16)

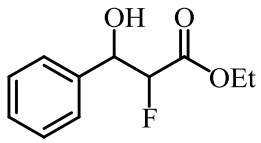
Under an argon atmosphere a dry three neck flask was charged with THF (8 mL), acetophenone (0.12 mL, 0.12 g, 1.0 mmol), the required amount of ethyl iodofluoroacetate and the required amount of (1*R*,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol. After 30 min of stirring at the stated temperature, the required amount of a 1.0 M solution of diethylzinc was added and the reaction mixture was left

to stir for another 4.5 h. After quenching the reaction mixture with 1 M HCl (10 mL), it was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 ml) before being dried over magnesium sulphate. The solvent was removed and the pure product was obtained after purification by silica gel column chromatography.

Method 4 (Table 4.24)

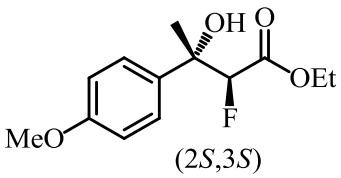
Under an argon atmosphere a dry three neck flask was charged with THF (8 mL), (1*R*,*2*S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (0.205g, 1.0 mmol), the required ketone (1.0 mmol) and ethyl iodofluoroacetate (2.0 mmol, 0.29 mL, 2.0 mmol). After 30 min of stirring at -40 ^{o}C, diethylzinc (3.5 mL, 1.0 M solution in hexane, 3.5 mmol) was added and the reaction mixture was left to stir for another 4.5 h. After quenching the reaction mixture with 1 M HCl (10 mL), it was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 ml) before being dried over magnesium sulphate. The solvent was removed and the pure product was obtained after purification by silica gel column chromatography.

Preparation of ethyl 2-fluoro-3-hydroxy-3-phenylpropanoate (77)



The title compound was prepared similarly to **(81)**, using benzaldehyde (0.1 mL, 0.1 g, 1.0 mmol). The pure product containing 63:37 mixture of diastereoisomers erythro:threo (63/37) was obtained after silica gel column chromatography (EtOAc in hexane 1:9) as a colourless oil (0.13 g, 61%). δ_H ($CDCl_3$) 1.13 (3H, t, $^3J_{HH}$ 7.1 Hz, OCH_2CH_3), 1.15 (3H, t, $^3J_{HH}$ 7.1 Hz, OCH_2CH_3), 2.49 (2H, br s, 2x O*H*), 4.13 (2H, q, $^3J_{HH}$ 7.1 Hz, OCH_2CH_3), 4.15 (2H, m, $^3J_{HH}$ 7.1 Hz, $OCH_AH_BCH_3$), 4.98 (1 H, dd, $^2J_{HF}$ 47.7 Hz, $^3J_{HH}$ 3.5 Hz, CH(OH)C*H*F), 5.00 (1 H, dd, $^2J_{HF}$ 48.1 Hz, $^3J_{HH}$ 5.1 Hz, CH(OH)C*H*F), 5.02-5.11 (2H, m, C*H*(OH)CHF), 7.23-7.36 (10H, m, ArH); δ_F ($CDCl_3$) -197.60 (1F, dd, $^2J_{FH}$ 48.0 Hz, $^3J_{FH}$ 17.4 Hz, CF), -202.60 (1F, dd, $^2J_{FH}$ 48.0 Hz, $^3J_{FH}$ 21.8 Hz, CF).

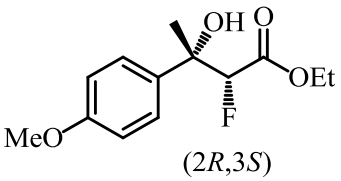
Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)-butanoate (83a)



(2*S*,3*S*)

The title compound was prepared similarly to **(81)**, using *p*-methoxyacetophenone (0.12 mL, 0.15 g, 1.0 mmol). The product was purified by silica gel column chromatography (10 % EtOAc in hexane) to give the title molecule containing 11 % of (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer. Colourless oil (0.154 g, 60 %). δ_H ($CDCl_3$) 1.15 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.69 (3H, d, $^4J_{HF}$ 2.0 Hz, CH_3), 3.21 (1H, s, O*H*), 3.83 (3H, s, OCH_3), 4.15 (2H, qd, $^3J_{HH}$ 7.0 Hz, $^5J_{HF}$ 1.2 Hz, OCH_2CH_3), 4.89 (1H, d, $^2J_{HF}$ 47.7 Hz, C*H*F), 6.89 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.41 (2H, d, $^3J_{HH}$ 9.0, ArH); δ_F ($CDCl_3$) -193.89 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.9 (CH_3), 25.3 (CH_3), 55.3 (CH_3), 61.7 (CH_2), 74.4 (d, $^2J_{CF}$ 21.1 Hz, C), 92.9 (d, $^1J_{CF}$ 194.2 Hz, CH), 113.6 (CH), 126.7 (CH), 134.3 (C), 159.1 (C), 168.2 (d, $^2J_{CF}$ 24.1 Hz, CO); The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 32.32 min (enantiomer 1), 37.30 min (enantiomer 2), 46.93 min (enantiomer 3), 67.96 min (enantiomer 4).

Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)-butanoate (83b)

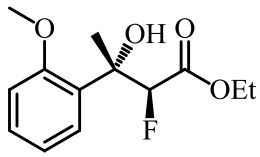


(2*R*,3*S*)

The title compound was prepared similarly to **(81)**, using *p*-methoxyacetophenone (0.12 mL, 0.15 g, 1.0 mmol). The sample was purified using the chromatotron (Et_2O:hexane = 1:5) after initial purification by silica gel column chromatography (EtOAc:hexane = 1:9). Colourless oil (0.064 g, 22 %). δ_H ($CDCl_3$) 1.12 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.67 (3H, d, $^4J_{HF}$ 2.7 Hz, CH_3), 3.43 (1H, br s, O*H*), 3.82 (3H, s, OCH_3), 4.09-4.17 (2H, m, $OCH_AH_BCH_3$), 4.98 (1H, d, $^3J_{HF}$ 48.1 Hz, C*H*F), 6.89 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.42 (2H, d, $^3J_{HH}$ 9.0, ArH); δ_F ($CDCl_3$) -191.86 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.9 (CH_3), 26.1 (CH_3), 55.2 (CH_3), 61.8 (CH_2), 74.7 (d, $^2J_{CF}$ 20.8 Hz, C), 92.5 (d, $^1J_{CF}$ 198.1 Hz, CH), 113.6 (CH), 126.4 (CH), 134.8 (C), 159.1 (C), 168.6 (d, $^2J_{CF}$ 24.0 Hz, CO); m/z (FAB) 256.11060 (M^+. $C_{13}H_{17}FO_4$ requires 256.11066). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t=

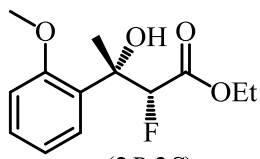
32.32 min (enantiomer 1), 37.30 min (enantiomer 2), 46.93 min (enantiomer 3), 67.96 min (enantiomer 4).

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-(2-methoxyphenyl)butanoate (84a)


(2*S*,3*S*)

The title compound was prepared similarly to **(81)**, using *o*-methoxyacetophenone (0.14 mL, 0.15 g, 1.0 mmol). The product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give colourless crystals (0.15 g, 62 %). M.p. 62 ^{o}C. δ_H ($CDCl_3$) 0.92 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.65 (3H, d, $^4J_{HF}$ 2.0 Hz, CH_3), 3.60 (1H, br s, O*H*), 3.82 (3H, s OCH_3), 3.92 (1H, dq, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 3.97 (1H, dq, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 5.43 (1H, d, $^2J_{HF}$ 48.5 Hz, C*H*F), 6.48 (1H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 6.90 (1H, td, $^3J_{HH}$ 7.4, $^4J_{HH}$ 1.2 Hz, ArH), 7.22 (1H, ddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 7.43 (1H, dd, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.6 Hz, ArH); δ_F ($CDCl_3$) -196.95 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.7 (CH_3), 25.7 (d, $^3J_{CF}$ 4.0 Hz, CH_3), 55.42 (CH_3), 61.0 (CH_2), 75.1 (d, $^2J_{CF}$ 21.1 Hz, C), 91.2 (d, $^1J_{CF}$ 188.1 Hz, CH), 111.1 (CH), 121.0 (CH), 127.2 (CH), 129.2 (CH), 130.2 (C), 156.3 (C), 168.0 (d, $^2J_{CF}$ 25.2 Hz, CO); m/z (FAB) 255.1032 $(M\text{-}H)^+$. $C_{13}H_{16}FO_4$ requires 255.1033). The enantiomers were separated on a chiralcel OD-H column eluted with 1 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 12.57 min (enantiomer 1), 15.33 min (enantiomer 2).

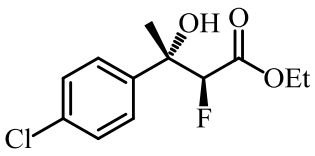
Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-3-(2-methoxyphenyl)-butanoate (84b)


(2*R*,3*S*)

The title compound was prepared similarly to **(81)**, using *o*-methoxyacetophenone (0.14 mL, 0.15 g, 1.0 mmol). The product was purified by Chromatotron (Et_2O:hexane = 5:95) to give a colourless oil (0.048 g, 22 %). δ_H ($CDCl_3$) 1.07 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.61 (3H, d, $^4J_{HF}$ 2.0 Hz, CH_3), 3.82 (3H, s OCH_3), 3.95 (1H, br s, O*H*), 3.90-4.11 (2H, m, OCH_2CH_3), 5.40 (1H, d, $^2J_{HF}$ 48.5 Hz, C*H*F), 6.85 (1H, d, $^3J_{HH}$ 7.4 Hz, ArH), 6.94 (1H, td, $^3J_{HH}$ 7.4, $^4J_{HH}$ 1.2 Hz, ArH), 7.22 (1H, ddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 7.37 (1H, dd, $^3J_{HH}$ 7.4, $^4J_{HH}$ 1.6 Hz, ArH); δ_F ($CDCl_3$) -195.08 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.9 (CH_3), 22.3 (d, $^3J_{CF}$ 5.0 Hz, CH_3), 55.5 (CH_3),

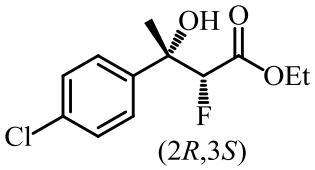
61.2 (CH_2), 75.9 (d, $^2J_{CF}$ 21.1 Hz, C), 92.5 (d, $^1J_{CF}$ 189.2 Hz, CH), 111.3 (CH), 121.2 (CH), 127.3 (CH), 129.4 (CH), 130.2 (C), 156.6 (C), 167.9 (d, $^2J_{CF}$ 24.1 Hz, CO); m/z (FAB) 255.1042 $(M-H)^+$. $C_{13}H_{16}FO_4$ requires 255.1033). The enantiomers were separated on a chiralcel OD-H column eluted with 1 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 22.08 min (enantiomer 1), 36.74 min (enantiomer 2).

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-3-(4-chlorophenyl)-2-fluoro-3-hydroxy-butanoate (85a)



The title compound was prepared similarly to **(81)**, using *p*-chloroacetophenone (0.13 mL, 0.15 g, 1.0 mmol). The product was purified by silica gel column chromatography (EtOAc:hexane 1:9) to give the product as colourless crystals (0.004 g, 5 %). M.p. 62-63 ^oC. δ_H ($CDCl_3$) 1.06 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.60 (3H, d, $^4J_{HF}$ 2.3 Hz, CH_3), 3.20 (1H, br s, O*H*), 4.07 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.79 (1H, d, $^2J_{HF}$ 47.3 Hz, C*H*F), 7.26 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.35 (2H, d, $^3J_{HH}$ 9.0, ArH); δ_F ($CDCl_3$) -194.45 (1F, s, C*F*H); δ_C ($CDCl_3$) 12.8 (CH_3), 24.3 (CH_3), 60.8 (CH_2), 73.4 (d, $^2J_{CF}$ 20.1 Hz, C), 91.6 (d, $^1J_{CF}$ 194.2 Hz, CH), 126.0 (CH), 127.3 (CH), 132.7 (C), 139.7 (C), 166.9 (d, $^2J_{CF}$ 24.1 Hz, CO), m/z (FAB) 259.0538 $(M-H)^+$. $C_{12}H_{13}ClFO_3$ requires 259.0537). The enantiomers were separated on a chiralcel AS column eluted with 10 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 6.66 min (enantiomer 1), 13.71 min (enantiomer 2).

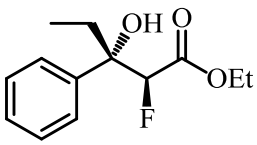
Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-3-(4-chlorophenyl)-2-fluoro-3-hydroxy-butanoate (85b)



The title compound was prepared similarly to **(81)**, using *p*-chloroacetophenone (0.13 mL, 0.15 g, 1.0 mmol). The product was purified by silica gel column chromatography (EtOAc:hexane 1:9) and then by chromatotron (Et_2O:hexane 1:19) to give a colourless oil (0.02 g, 9 %). δ_H ($CDCl_3$) 1.03 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.57 (3H, d, $^4J_{HF}$ 2.3 Hz, CH_3), 3.49 (1H, br s, O*H*), 4.07 (2H, m, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 4.89 (1H, d, $^2J_{HF}$ 47.7 Hz, C*H*F), 7.24 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.35 (2H, d, $^3J_{HH}$ 9.0, ArH); δ_F ($CDCl_3$) -191.88 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.8 (CH_3), 26.3

(d, $^{3}J_{CF}$ 3.0 Hz, CH_3), 62.0 (CH_2), 74.7 (d, $^{2}J_{CF}$ 19.1 Hz, C), 93.1 (d, $^{1}J_{CF}$ 199.2 Hz, CH), 126.7 (d, $^{4}J_{CF}$ 2.0 Hz, CH), 128.4 (CH), 133.7 (C), 141.4 (C), 168.5 (d, $^{2}J_{CF}$ 22.1 Hz, CO); m/z (FAB) 259.0539 $(M-H)^{+}$. $C_{12}H_{13}ClFO_3$ requires 259.0537). The enantiomers were separated on a chiralcel AD column eluted with 2 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 12.86 min (enantiomer 1), 15.53 min (enantiomer 2).

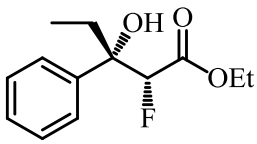
Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl 2-fluoro-3-hydroxy-3-phenylpentanoate (86a)



(2*S*,3*S*)

The title compound was prepared similarly to **(81)**, using propiophenone (0.13 mL, 0.13 g, 1.0 mmol). The product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give colourless crystals (0.13 g, 54 %). M.p. 60-61 ^{o}C. The characterisation data was in agreement with literature.[7] (Found: C, 64.89; H, 7.00 %. Calc. for $C_{13}H_{17}FO_3$: C, 64.98; H, 7.13 %). δ_H ($CDCl_3$) 0.69 (3H, t, $^{3}J_{HH}$ 7.4 Hz, CH_2CH_3), 0.93 (3H, t, $^{3}J_{HH}$ 7.4 Hz, OCH_2CH_3), 1.93 (2H, qd, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HF}$ 2.0 Hz, CH_2CH_3), 2.94 (1H, br s, O*H*), 3.97 (2H, q, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.88 (1H, d, $^{2}J_{HF}$ 47.7 Hz, C*H*F), 7.21 (1H, tm, $^{3}J_{HH}$ 7.4 Hz, ArH), 7.28 (2H, tm, $^{3}J_{HH}$ 7.4, ArH), 7.35 (2H, dt, $^{3}J_{HH}$ 7.0 Hz, $^{4}J_{HH}$ 2.0 Hz, ArH); δ_F ($CDCl_3$) -196.37 (1F, s, C*F*H); δ_C ($CDCl_3$) 7.0 (CH_3), 13.6 (CH_3), 30.4 (CH_2), 61.5 (CH_2), 77.4 (d, $^{2}J_{CF}$ 20.1 Hz, C), 93.0 (d, $^{1}J_{CF}$ 193.2 Hz, CH), 125.9 (CH), 127.5 (CH), 128.1 (CH), 139.7 (d, $^{3}J_{CF}$ 2.0 Hz, C), 167.9 (d, $^{2}J_{CF}$ 26.2 Hz, CO), m/z (FAB) 239.1084 $(M-H)^{+}$. $C_{13}H_{16}FO_3$ requires 239.1083). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 20.60 min (enantiomer 1), 23.18 min (enantiomer 2).

Preparation of (2*R*,3*S*)/(2*S*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylpentanoate (86b)

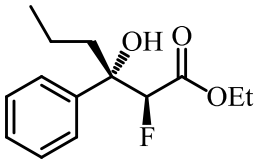


(2*R*,3*S*)

The title compound was prepared similarly to **(81)**, using propiophenone (0.13 mL, 0.13 g, 1.0 mmol). The product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give a colourless oil (0.097 g, 40 %). The characterisation data was in agreement with literature.[7] (Found: C, 64.86; H, 7.07 %. Calc. for $C_{13}H_{17}FO_3$: C, 64.98; H, 7.13 %). δ_H ($CDCl_3$) 0.80 (3H, t, $^{3}J_{HH}$ 7.4 Hz, CH_2CH_3), 0.95 (3H, t, $^{3}J_{HH}$ 7.4 Hz, OCH_2CH_3), 1.94 (2H, 2x qd, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HF}$ 1.6 Hz, CH_2CH_3),

3.48 (1H, br s, O*H*), 3.97 (1H, dq, $^{2}J_{HH}$ 11.0 Hz, $^{3}J_{HH}$ 7.4 Hz, OCH_AH$_B$), 4.02 (1H, dq, $^{2}J_{HH}$ 11.0 Hz, $^{3}J_{HH}$ 7.4 Hz, OCH$_A$$H_B$), 4.97 (1H, d, $^{2}J_{HF}$ 47.7 Hz, C*H*F), 7.19 (1H, tt, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HH}$ 1.2 Hz, ArH), 7.26 (2H, td, $^{3}J_{HH}$ 7.4, $^{4}J_{HH}$ 1.6 Hz, ArH), 7.38 (2H, dt, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HH}$ 1.6 Hz, ArH); δ_F ($CDCl_3$) -193.36 (1F, s, C*F*H); δ_C ($CDCl_3$) 7.2 (CH_3), 13.8 (CH_3), 31.4 (d, $^{3}J_{CF}$ 3.0 Hz, CH_2), 61.8 (CH_2), 77.0 (d, $^{2}J_{CF}$ 19.2 Hz, C), 92.3 (d, $^{1}J_{CF}$ 201.2 Hz, CH), 125.5 (CH), 127.5 (CH), 128.1 (CH), 141.5 (C), 169.2 (d, $^{2}J_{CF}$ 22.1 Hz, CO), m/z (FAB) 239.1076 $(M-H)^+$. $C_{13}H_{16}FO_3$ requires 239.1083). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.77 min (enantiomer 1), 10.86 min (enantiomer 2).

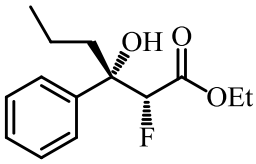
Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl 2-fluoro-3-hydroxy-3-phenylhexanoate (87a)



(2*S*,3*S*)

The title compound was prepared similarly to **(81)**, using 1-phenylbutan-1-one (0.15 mL, 0.15 g, 1.0 mmol). The product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) and contains less than 3 % of the (2*S*,3*R*)/(2*R*,3*S*)-diastereomer. Colourless crystals (0.14 g, 57 %). δ_H ($CDCl_3$) 0.79 (3H, t, $^{3}J_{HH}$ 7.4 Hz, CH_2CH_3), 0.87-1.00 (1H, m, CH_AH$_A$$CH_3$), 0.93 (3H, t, $^{3}J_{HH}$ 7.4 Hz, OCH_2CH_3), 1.24-1.36 (1H, m, CH$_A$$H_B$$CH_3$), 1.86-1.98 (2H, m, CH_2CH_2), 2.98 (1H, br s, O*H*), 3.95 (2H, q, $^{3}J_{HH}$ 7.0 Hz, OC$H_2$$CH_3$), 4.87 (1H, d, $^{2}J_{HF}$ 48.1 Hz, C*H*F), 7.20 (1H, tm, $^{3}J_{HH}$ 7.0 Hz, ArH), 7.28 (2H, tt, $^{3}J_{HH}$ 7.0, $^{4}J_{HH}$ 2.0 Hz, ArH), 7.35 (2H, dt, $^{3}J_{HH}$ 7.0 Hz, $^{4}J_{HH}$ 2.0 Hz, ArH); δ_F ($CDCl_3$) -196.15 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.6 (CH_3), 14.3 (CH_3), 16.1 (CH_2), 39.9 (CH_2), 61.5 (CH_2), 77.3 (d, $^{2}J_{CF}$ 19.2 Hz, C), 93.0 (d, $^{1}J_{CF}$ 193.3 Hz, CFH), 125.8 (CH), 127.4 (CH), 128.1 (CH), 140.1 (d, $^{3}J_{CF}$ 2.0 Hz, C), 167.9 (d, $^{2}J_{CF}$ 25.6 Hz, CO); m/z (FAB) 277.1216 (MNa^+. $C_{14}H_{19}FO_3Na$ requires 277.1216). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 17.52 min (enantiomer 1), 21.90 min (enantiomer 2).

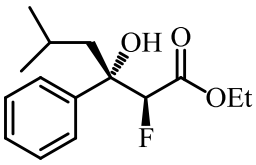
Preparation of (2*R*,3*S*)/(2*S*,3*R*)-ethyl-2-fluoro-3-hydroxy-3-phenylhexanoate (87b)



(2*R*,3*S*)

The title molecule was compound was prepared similarly to **(81)**, using 1-phenylbutan-1-one (0.15 mL, 0.15 g, 1.0 mmol). The product was purified using 5 % diethyl ether in hexane on the chromatotron. Colourless oil (0.030g, 12 %). δ_H ($CDCl_3$) 0.81 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 0.94 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.04-1.17 (1H, m, $CH_AH_BCH_2$), 1.31-1.45 (1H, m, $CH_AH_BCH_2$), 1.79-1.93 (2H, m, $CH_3CH_2CH_2$), 3.50 (1H, br s, O*H*), 3.95 (2H, m, $CH_AH_BCH_3$), 4.96 (1H, d, $^2J_{HF}$ 47.7 Hz, C*H*F), 7.18 (1H, tt, $^3J_{HH}$ 7.2 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.25 (2H, tm, $^3J_{HH}$ 7.0, ArH), 7.35 (2H, dt, $^3J_{HH}$ 7.2 Hz, $^4J_{HH}$ 1.2 Hz); δ_F ($CDCl_3$) -193.06 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.7 (CH_3), 14.2 (CH_3), 16.2 (CH_2), 40.8 (CH_2), 61.8 (CH_2), 76.9 (d, $^2J_{CF}$ 20.1 Hz, C), 92.5 (d, $^1J_{CF}$ 201.2 Hz, CH), 125.4 (CH), 127.5 (CH), 128.1 (CH), 141.8 (C), 169.1 (d, $^2J_{CF}$ 23.1 Hz, CO). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.57 min (enantiomer 1), 10.46 min (enantiomer 2).

Preparation of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate (88a)

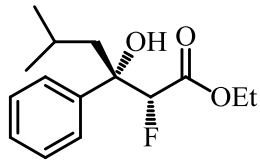


(2*S*,3*S*)

The title compound was prepared similarly to **(81)**, using 3-methyl-1-phenylbutan-1-one (0.17 mL, 0.16 g, 1.0 mmol). The product was purified by silica gel column chromatography (5 % EtOAc in hexane) to give colourless crystals (0.11 g, 46 %). M.p. 70-72 ^oC. δ_H ($CDCl_3$) 0.62 (3H, d, $^3J_{HH}$ 6.6 Hz, $CHCH_3$), 0.85 (3H, d, $^3J_{HH}$ 6.6 Hz, $CHCH_3$), 0.91 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.42-1.55 (1H, m, $CH(CH_3)_2$), 1.81 (1H, ddd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 7.4 Hz, $^4J_{HF}$ 2.3 Hz, $CH_AH_BCH(CH_3)_2$), 1.95 (1H, ddd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 4.7 Hz, $^4J_{HF}$ 1.2 Hz, $CH_AH_BCH(CH_3)_2$), 2.99 (1H, s, O*H*), 3.93 (2H, q, $^3J_{HH}$ 7.4 Hz, OCH_2CH_3), 4.80 (1H, d, $^2J_{HF}$ 48.1 Hz, C*H*F), 7.21 (1H, tt, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.28 (2H, tm, $^3J_{HH}$ 7.4, ArH), 7.36 (2H, dm, $^3J_{HH}$ 7.4 Hz, ArH); δ_F ($CDCl_3$) -195.35 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.6 (CH_3), 23.8 (CH_3), 23.9 (CH_3), 24.5 (CH), 45.6 (CH_2), 61.4 (CH_2), 77.8 (d, $^2J_{CF}$ 19.1 Hz, C), 93.4 (d, $^1J_{CF}$ 193.2 Hz, CH), 126.0 (CH), 127.4 (CH), 128.1 (CH), 140.2 (C), 167.8 (d, $^2J_{CF}$ 24.1 Hz, CO); m/z (FAB) 267.1389 $(M-H)^+$. $C_{15}H_{20}FO_3$ requires 267.1396). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate

of the mobile phase was set at 1.0 mL/min. R_t= 12.84 min (enantiomer 1), 14.75 min (enantiomer 2).

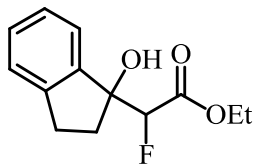
Preparation of (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate (88b)



(2*R*,3*S*)

The title compound was prepared similarly to **(81)**, using 3-methyl-1-phenylbutan-1-one (0.17 mL, 0.16 g, 1.0 mmol). The product was purified by silica gel column chromatography (5 % EtOAc in hexane) to give a colourless oil (0.058 g, 22 %). δ_H ($CDCl_3$) 0.66 (3H, d, $^3J_{HH}$ 6.6 Hz, CHCH_3), 0.88 (3H, d, $^3J_{HH}$ 6.6 Hz, CHCH_3), 0.93 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.56-1.66 (1H, m, CH(CH_3)$_2$), 1.74 (1H, ddd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 7.4 Hz, $^4J_{HF}$ 1.2 Hz, CH_AH$_B$CH$_3$), 1.93 (1H, ddd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 5.1 Hz, $^4J_{HF}$ 2.7 Hz, CH$_A$$H_BCH_3$), 3.55 (1H, br s, O$H$), 3.91-4.07 (2H, m, OC$H_A$$H_BCH_3$), 4.92 (1H, d, $^2J_{HF}$ 47.7 Hz, CHF), 7.16 (1H, m, ArH), 7.25 (2H, m, $^3J_{HH}$ 7.8 Hz, ArH), 7.39 (2H, dt, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.2 Hz, ArH); δ_F ($CDCl_3$) -192.14 (1F, s, CFH); δ_C ($CDCl_3$) 13.7 (CH_3), 23.8 (CH), 24.2 (CH_3), 24.4 (CH_3), 46.4 (CH_2), 61.8 (CH_2), 77.4 (d, $^2J_{CF}$ 17.1 Hz, C), 92.8 (d, $^1J_{CF}$ 201.2 Hz, CH), 125.2 (d, $^4J_{CF}$ 3.0 Hz, CH), 127.5 (CH), 128.1 (CH), 141.8 (C), 169.1 (d, $^2J_{CF}$ 23.1 Hz, CO), m/z (FAB) 267.1396 $(M-H)^+$. $C_{15}H_{20}FO_3$ requires 267.1396). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 7.88 min (enantiomer 1), 8.64 min (enantiomer 2).

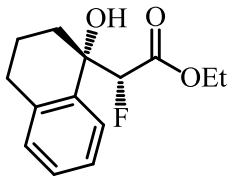
Preparation of ethyl-2-fluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate (89)



The title compound was prepared similarly to **(81)**, using indanone (0.13 g, 1.0 mmol). The pure product containing 54:46 mixture of (2*S*,3*S*)/(2*R*,3*R*):(2*S*,3*R*)/(2*R*,3*S*) diastereoisomers was obtained after silica gel column chromatography (EtOAc in hexane 1:9) as a colourless oil (0.20 g, 84 %). δ_H ($CDCl_3$) 1.41 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3) and 1.80 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 2.04-2.14 (2H, m, CHH), 2.51-2.66 (2H, m, CHH), 2.75-2.87 (2H, m, CHH), 2.93-3.03 (3H, m, CHH and OH), 3.15 (1H, br s, OH), 4.11 (4H, m, OC$H_A$$H_BCH_3$), 4.95 (1H, d, $^2J_{HF}$ 47.7 Hz, CHF) and 5.00 (1H, d, $^2J_{HF}$ 47.7 Hz, CHF), 7.15-7.26 (6H, m, ArH), 7.32 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH), 7.36 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH); δ_F ($CDCl_3$) -193.48 (1F, s, CFH) and -196.39 (1F, s, CFH); δ_C

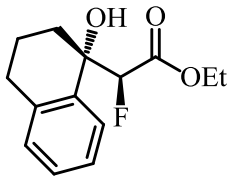
($CDCl_3$) 13.9 and 14.0 (CH_3), 29.5 and 29.7 (CH_2), 35.9 (CH_2) and 36.5 (d, $^3J_{CF}$ 3.0 Hz, CH_2), 61.8 and 61.9 (CH_2), 77.0 (d, $^2J_{CF}$ 32.2 Hz, C) and 77.2 (d, $^2J_{CF}$ 31.2 Hz, C), 90.7 (d, $^1J_{CF}$ 193.2 Hz, CH) and 92.3 (d, $^1J_{CF}$ 192.2 Hz, CH), 123.7 (CH), 124.4 (CH), 124.4 (CH), 125.0 (CH), 126.8 (CH), 129.3 (CH), 141.9 (C), 142.5 (C), 143.8 (C), 144.1 (C), 167.9 (d, $^2J_{CF}$ 24.1 Hz, CO) and 168.5 (d, $^2J_{CF}$ 24.1 Hz, CO); m/z (FAB) 221 $(M\text{-}OH)^+$, 201 $(M\text{-}OH\text{-}HF)^+$. The enantiomers were separated on a chiralcel OD-H column eluted with 1 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 17.56 min (enantiomer 1), 19.09 min (enantiomer 2), 22.14 min (enantiomer 3), 24.70 min (enantiomer 4),

Preparation of ethyl-2-fluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (90b)



(2*R*,3*S*)

The title compound was prepared similarly to **(81)**, using tetralone (0.13 mL, 0.15 g, 1.0 mmol). The pure product containing 54:46 mixture of diastereoisomers was obtained after silica gel column chromatography (EtOAc in hexane = 1:9) (0.24 g, 96 %). The pure sample of the (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer was separated by chromatotron (Et_2O:hexane 1:4) as a colourless oil (0.055 g, 22 %). δ_H ($CDCl_3$) 1.21 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.75-1.89 (3H, m, CH_2CHH), 2.09-2.17 (1H, m, CH*H*), 2.65-2.80 (2H, m, CH_2), 3.08 (1H, br s, O*H*), 4.18 (1H, dq, $^2J_{HH}$ 13.7 Hz, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 4.25 (1H, dq, $^2J_{HH}$ 13.7 Hz, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 5.07 (1H, d, $^2J_{HF}$ 47.3 Hz, C*H*F), 7.03-7.07 (1H, m, ArH), 7.14-7.18 (2H, m, ArH), 7.44-7.49 (1H, m, ArH); δ_F ($CDCl_3$) -191.36 (1F, s, C*F*H); δ_C ($CDCl_3$) 14.1 (CH_3), 18.9 (CH_2), 29.4 (CH_2), 33.1 (CH_2), 62.0 (CH_2), 72.4 (d, $^2J_{CF}$ 21.1 Hz, C), 91.8 (d, $^1J_{CF}$ 196.2 Hz, CH), 126.3 (CH), 126.6 (CH), 128.1 (CH), 129.1 (CH), 136.1 (C), 138.4 (C), 169.0 (d, $^2J_{CF}$ 24.1 Hz, CO); m/z (FAB) 235 $(M\text{-}OH)^+$, 215 $(M\text{-}OH\text{-}HF)^+$. The spectral properties of (2*S*,3*S*)/(2*R*,3*R*)-ethyl-2-fluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate



(2*S*,3*S*)

(90a) were assigned from the second fraction still containing 35 % of (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer. δ_H ($CDCl_3$) 0.98 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.74-1.96 (3H, m, $CH_2CH_AH_B$), 2.12-2.20 (1H, m, CH_AH_B), 2.58-2.80 (3H, m, CH_2 and O*H*), 3.98 (1H, dq, $^2J_{HH}$ 17.2 Hz, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 4.05 (1H, dq, $^2J_{HH}$ 17.2 Hz, $^3J_{HH}$ 7.0 Hz, $OCH_AH_BCH_3$), 5.09 (1H, d, $^2J_{HF}$ 48.1 Hz, C*H*F), 7.02-7.07 (1H, m, ArH),

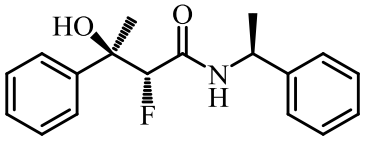
7.12-7.19 (2H, m, ArH), 7.44-7.51 (1H, m, ArH); δ_F ($CDCl_3$) -198.13 (1F, s, C*F*H); δ_C ($CDCl_3$) 13.7 (CH_3), 19.3 (CH_2), 29.6 (CH_2), 33.0 (d, $^3J_{CF}$ 4.0 Hz, CH_2), 61.4 (CH_2), 73.2 (d, $^2J_{CF}$ 21.1 Hz, C), 93.6 (d, $^1J_{CF}$ 191.2 Hz, CH), 126.1 (CH), 127.8 (CH), 128.2 (CH), 129.0 (CH), 135.9 (C), 137.7 (C), 167.5 (d, $^2J_{CF}$ 25.2 Hz, CO); m/z (FAB) 235 $(M\text{-}OH)^+$, 215 $(M\text{-}OH\text{-}HF)^+$. The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 35.82 min (enantiomer 1), 44.38 min (enantiomer 2), 68.02 min (enantiomer 3), 78.87 min (enantiomer 4)

Determination of the absolute configuration of the new chiral centres in ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate (81)

General method for the reaction of (*S*)-(1-phenylethyl)amine with ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate (81)[6]

The two diastereoisomers of ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate **(81a)** and **(81b)** were separated and for each reaction the pure racemic diastereoisomer was used. A dry 25 mL two neck round-bottomed flask was cooled to 0 ^oC and charged with the required amount of THF, (*S*)-(1-phenylethyl)amine and *n*-butyllithium (1.6 M solution in hexane). After 30 minutes of stirring at 0 ^oC, the solution of ester in THF (1 mL) was added. The reaction was quenched with water (5 mL) after 16 hours. After acidifying to pH 5 with 1 M HCl, the solution was extracted with diethyl ether (3 x 5 mL). The organic fractions were combined and dried over $MgSO_4$ before the solvent was removed. The crude product was purified by silica gel column chromatography.

Preparation of (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-butanamide (82b)

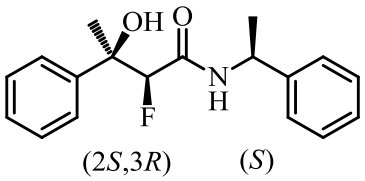


(2*R*,3*R*) (*S*)

The title compound was prepared by a modification of Braun's method[6] using racemic (2*R*,3*R*)/(2*S*,3*S*)-ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate (0.05 g, 0.22 mmol), THF (3 mL), (*S*)-(1-phenylethyl)amine (0.07 mL, 0.07 g, 0.55 mmol) and *n*-butyllithium (0.5 mL, 1.6 M solution in hexane, 0.8 mmol). The crude product was purified by silica gel column chromatography (5 % EtOAc in

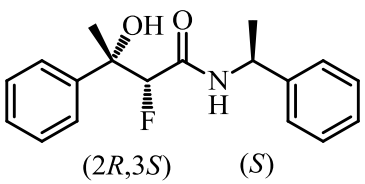
hexane) to give colourless crystals (0.023 g, 8 %). M.p. 114-116 ^{o}C. δ_H ($CDCl_3$) 1.46 (3H, s, CH_3), 1.47 (3H, d, $^3J_{HH}$ 5.9 Hz, CH_3), 4.68 (1H, d, $^2J_{HF}$ 47.7 Hz, C*H*F), 4.70 (1H, br s, O*H*), 5.11 (1H, quintet, $^3J_{HH}$ 7.0 Hz, C*H*), 6.60 (1H, br s, N*H*), 7.22-733 (8H, m, ArH), 7.43-7.47 (2H, dt, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.6 Hz, ArH); δ_F ($CDCl_3$) -191.67 (1F, s, C*F*H); δ_C ($CDCl_3$) 21.6 (CH_3), 22.8 (CH_3), 48.8 (CH), 79.9 (d, $^2J_{CF}$ 19.2 Hz, C), 93.1 (d, $^1J_{CF}$ 196.5 Hz, CHF), 126.0 (CH), 126.1 (CH), 127.7 (CH), 127.8 (CH), 128.1 (CH), 128.9 (CH), 142.2 (C), 143.0 (C), 168.8 (CO); m/z (FAB) 302.1558 (MH^+. $C_{18}H_{21}FNO_2$ requires 302.1556). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from hexane. The second expected isomer was not isolated.

Preparation of (2*S*,3*R*) and (2*R*,3*S*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide and (82c) and (82d)



(2*S*,3*R*) (*S*)

The titled compound was prepared using racemic (2*S*,3*R*)/(2*R*,3*S*)-ethyl-2-fluoro-3-hydroxy-3-phenyl-butanoate (0.09 g, 0.4 mmol), THF (5 mL), (*S*)-(1-phenylethyl)amine (0.13 mL, 0.12 g, 1.0 mmol) and *n*-butyllithium (1.0 mL, 1.0 M solution in hexane, 1.6 mmol). The diastereoisomers **(82c)** and **(82d)** were separated by silica gel column chromatography (Et_2O:hexane 40:60). (2*S*,3*R*)-2-Fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-butanamide **(82c)** was obtained as colourless crystals (0.016 g, 13 %). M.p. 140-142 ^{o}C. δ_H ($CDCl_3$) 0.87 (3H, d, $^3J_{HH}$ 7.0 Hz, CH_3), 1.63 (3H, d, $^4J_{HF}$ 2.3 Hz, CH_3), 4.75 (1H, quintet, $^3J_{HH}$ 7.4 Hz, C*H*), 4.81 (1H, d, $^2J_{HF}$ 48.5 Hz, C*H*F), 4.99 (1H, s, O*H*), 6.13 (1H, br s, N*H*), 7.09 (2H, d, $^3J_{HH}$ 6.4 Hz, ArH), 7.15-7.31 (6H, m, ArH), 7.41 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH); δ_F ($CDCl_3$) -191.28 (1F, s, C*F*H); δ_C ($CDCl_3$) 20.6 (CH_3), 26.6 (d, $^3J_{CF}$ 3.0 Hz, CH_3), 48.1 (CH), 74.4 (d, $^2J_{CF}$ 18.0 Hz, C), 93.8 (d, $^1J_{CF}$ 201.2 Hz, CHF), 125.5 (d, $^4J_{CF}$ 3.0 Hz CH), 126.1 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.8 (CH), 141.6 (C), 142.5 (C), 168.4 (d, $^2J_{CF}$ 19.1 Hz, CO); m/z (FAB) 302.1552 (MH^+. $C_{18}H_{21}FNO_2$ requires 302.1556). Crystals suitable for X-ray crystallography were obtained by recrystallisation from Et_2O/hexane solution (40:60). The sample of (2*R*,3*S*)-2-fluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide **(82d)** contained 14 % of the distereoisomer **(82c)**. Colourless oil (0.034 g, 28 %). δ_H ($CDCl_3$) 1.33 (3H, d, $^3J_{HH}$ 7.0 Hz, CH_3), 1.61 (3H, d, $^4J_{HF}$ 1.6 Hz, CH_3), 4.81 (1H,



(2*R*,3*S*) (*S*)

quintet, $^{3}J_{HH}$ 7.4 Hz, C*H*), 4.87 (1H, d, $^{2}J_{HF}$ 48.5 Hz, C*H*F), 5.09 (1H, s, O*H*), 6.25 (1H, br s, N*H*), 6.50 (2H, d, $^{3}J_{HH}$ 7.4 Hz, ArH), 7.01-7.11 (3H, m, ArH), 7.16-7.24 (3H, m, ArH), 7.35 (2H, dt, $^{3}J_{HH}$ 7.8 Hz, $^{4}J_{HH}$ 1.6 Hz, ArH); δ_F ($CDCl_3$) -191.53 (1F, s, C*F*H); δ_C ($CDCl_3$) 21.1 (CH_3), 26.6 (d, $^{3}J_{CF}$ 2.0 Hz, CH_3), 47.8 (CH), 74.4 (d, $^{2}J_{CF}$ 18.1 Hz, C), 93.8 (d, $^{1}J_{CF}$ 201.2 Hz, CHF), 125.56 (d, $^{4}J_{CF}$ 5.0 Hz CH), 125.58 (CH), 127.1 (CH), 127.5 (CH), 128.2 (CH), 128.5 (CH), 141.3 (C), 142.4 (C), 168.5 (d, $^{2}J_{CF}$ 19.1 Hz, CO).

Determination of the absolute configuration of the new chiral centre in ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate (81)

The diastereoisomers of enantiomeric ethyl-2-fluoro-3-hydroxy-3-phenylbutanoate **(81)** were isolated by silica gel column chromatography (20 % Et_2O in hexane). The procedure above was repeated separately with (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer (86 % ee) and (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer (73 % ee) using (*S*)-(1-phenylethyl)amine (0.2 mL, 0.19 g, 1.5 mmol), *n*-butyllithium (1.4 mL, 1.6 M in hexane, 2.2 mmol), THF (6 mL) and the ester **(81)** (0.11 g, 0.5 mmol). The crude product obtained in the reaction with (2*S*,3*S*)/(2*R*,3*R*)-diastereoisomer consisted of a 91:9 mixture of (2*S*,3*S*)- and (2*R*,3*R*)-diastereoisomers of **(82)** according to the ^{19}F NMR spectrum. The crude product obtained in the reaction with (2*S*,3*R*)/(2*R*,3*S*)-diastereoisomer consisted of a 88:12 mixture of (2*R*,3*S*)- and (2*S*,3*R*)-diastereoisomers of **(82)** according to the ^{19}F NMR spectrum.

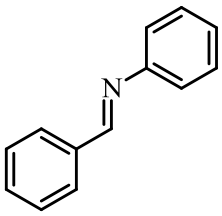
6.5 Synthetic Procedures for Chapter 5

6.5.1 Synthesis of imines

Method 1

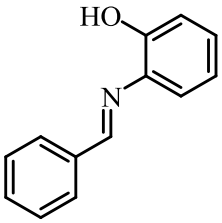
The imines were prepared by a modified method reported by Quirion.[8] A 100 mL round bottomed flask was charged with benzaldehyde (2.06 g, 2.05 mL, 19.5 mmol), the required amount of amine (19.5 mmol) and dry DCM (5 mL) before adding $MgSO_4$ (1 g). After refluxing the reaction mixture for 3 hours, the solvent was removed and the crude product was recrystallised from hexane. Finally, the product was distilled in a Kugelröhr oven under oil pump vacuum to give the pure imine.

Preparation of (*E*)-*N*-benzylideneaniline (93)



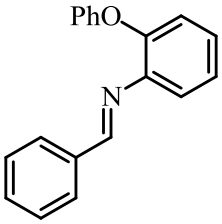
Grey solid (5.78 g, 58 %). The characterisation data was in agreement with literature. M.p. 50-51 ^{o}C (lit.,[9] 50.9-51.7 ^{o}C). δ_H ($CDCl_3$) 7.23-7.29 (3H, m, ArH), 7.43 (2H, t, $^3J_{HH}$ 7.8 Hz, ArH), 7.47-7.54 (3H, m, ArH), 7.92-7.96 (2H, m, ArH), 7.49 (1H, s, *H*C=N); δ_C ($CDCl_3$) 120.88 (CH), 125.94 (CH), 128.79 (CH), 128.83 (CH), 129.16 (CH), 131.38 (CH), 136.27 (C), 152.13 (C), 160.40 (CH); m/z (FAB) 182.0966 (MH^+. $C_{19}H_{12}N$ requires 182.0970).

Preparation of (*E*)-2-(benzylideneamino)phenol (94)



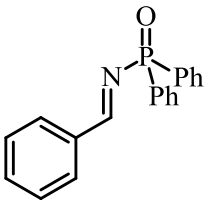
Yellow solid (1.78 g, 36 %). The characterisation data was in agreement with literature. M.p. 90-91 ^{o}C (lit.,[10] 92 ^{o}C). δ_H ($CDCl_3$) 6.83 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 6.94 (1H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.5 Hz, ArH), 7.12 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 7.22 (1H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.5 Hz, ArH), 7.28 (1H, br s, O*H*), 7.38-7.44 (3H, m, ArH), 7.82-7.86 (2H, m, ArH), 8.62 (1H, s, *H*C=N); δ_C ($CDCl_3$) 115.0 (CH), 115.9 (CH), 120.1 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 131.7 (CH), 135.5 (C), 135.9 (C), 152.4 (C), 157.1 (CH); m/z (FAB) 198.0913 (MH^+. $C_{13}H_{12}NO$ requires 198.0919).

Preparation of (*E*)-*N*-benzylidene-2-phenoxyaniline (95)



Grey solid (3.27 g, 65 %). The characterisation data was in agreement with literature. Mp 84-86 ^{o}C (lit.,[11] 84-86 ^{o}C). δ_H ($CDCl_3$) 6.97-7.11 (4H, m ArH), 7.15-7.23 (3H, m, ArH), 7.26-7.32 (2H, m, ArH), 7.39-7.49 (3H, m, ArH), 7.77-7.81 (2H, m, ArH), 8.48 (1H, s, *H*C=N); δ_C ($CDCl_3$) 117.8 (CH), 121.1 (CH), 121.4 (CH), 122.47 (CH), 124.7 (CH), 126.6 (CH), 128.6 (CH), 128.9 (CH), 129.5 (CH), 131.4 (CH), 136.3 (C), 144.4 (C), 148.6 (C), 158.2 (C), 161.8 (CH); m/z (FAB) 274.1240 (MH^+. $C_{19}H_{16}NO$ requires 274.1232).

Preparation of (*E*)-*N*-benzylidene-P,P-diphenylphosphinic amide (97)

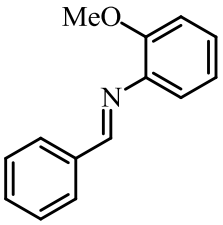


The title compound was prepared by using Desrosiers's methodology.[12] The characterisation data was in agreement with literature.[13] A 100 mL flask was charged with diphenylphosphinoamide (1.74 g, 8.0 mmol), dry DCM (13.5 mL) and dry diethyl ether (66 mL). After five minutes of stirring benzaldehyde (1.2 mL, 11.0 mmol) and *p*-toluenesulfinic acid (1.87 g, 12.0 mmol) were added and the reaction mixture was stirred at room temperature for 48 h. A white suspension was formed. The solid was filtered, washed with diethyl ether and dried under vacuum. The (diphenylphosphorylamino)-(phenyl)methyl benzenesulfinate was obtained as a white solid (3.43 g, 93 %). A flame dried 100 mL round bottomed flask was charged with (diphenylphosphorylamino)-(phenyl)methyl benzenesulfinate (3.37 g, 7.5 mmol), potassium carbonate (5.00 g) and acetonitrile (60 mL). The reaction mixture was filtered through a sintered glass funnel after 12 h of stirring at room temperature and the solvent was removed from the filtrated to give a white solid (1.99 g, 89 %). M.p. 134-138 ^{o}C (lit.,[14] 140-141 ^{o}C). δ_H ($CDCl_3$) 7.44-7.66 (9H, m, ArH), 7.61 (1H, td, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 7.94-8.06 (5H, m, ArH), 9.35 (1H, d, $^3J_{HP}$ 32.1 Hz, C*H*N); δ_P ($CDCl_3$) 24.94 (1P, s, *P*OPh_2); δ_C ($CDCl_3$) 128.5 (d, J_{CP} 12.1 Hz, CH), 128.9 (CH), 130.2 (CH), 131.6 (d, J_{CP} 9.1 Hz, CH), 131.6 (d, J_{CP} 3.0 Hz, CH), 132.4 (C), 133.6 (CH), 135.8 (d, $^1J_{CP}$ 25.8 Hz, C), 173.8 (d, $^2J_{CP}$ 7.0 Hz, CH); m/z (FAB) 306.1041 (MH^+. $C_{19}H_{17}NOP$ requires 306.1048).

Method 2

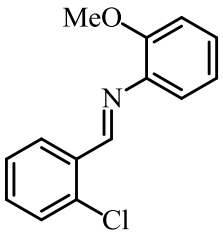
The imines were synthesised using Bartsch's methodology.[15] The required aldehyde (30.0 mmol) and 2-methoxyaniline (3.70 g, 3.4 mL, 36.0 mmol) were dissolved in dry toluene (15 mL) before molecular sieves were added (12.0 g). The reaction mixture was stirred for 24 hours at room temperature before the solvent was removed and the crude product was distilled in a Kugelröhr oven under oil pump vacuum to give the pure product.

Preparation of (*E*)-*N*-benzylidene-2-methoxyaniline (96)



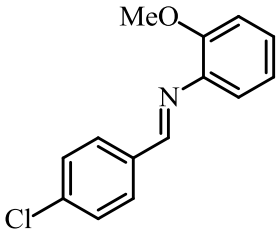
Yellow oil (2.42 g, 37 %). The characterisation data was in agreement with literature.[15] δ_H ($CDCl_3$) 3.91 (3H, s, OC*H*$_3$), 6.97-7.05 (3H, m, ArH), 7.19-7.24 (1H, m, ArH), 7.47-7.51 (3H, m, ArH), 7.93-7.97 (2H, m, ArH), 8.50 (1H, s, *H*C=N); δ_C ($CDCl_3$) 55.9 (CH_3), 111.6 (CH), 120.3 (CH), 121.1 (CH), 126.6 (CH), 128.7 (CH), 128.9 (CH), 131.3 (CH), 136.4 (C), 142.0 (C), 152.3 (C), 161.4 (CH); m/z (FAB) 212.1070 (MH^+. $C_{14}H_{14}NO$ requires 212.1075).

Preparation of (*E*)-*N*-(2-chlorobenzylidene)-2-methoxyaniline (105)



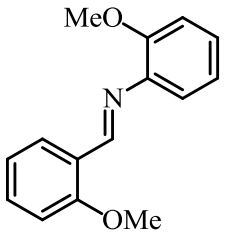
Yellow oil (2.95 g, 81 %). δ_H ($CDCl_3$) 3.82 (3H, s, OC*H*$_3$), 6.88-6.98 (3H, m, ArH), 7.14 (1H, ddd, $^3J_{HH}$ 7.8 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.25-7.36 (3H, m, ArH), 8.25 (1H, dd, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 8.86 (1H, s, C*H*N); δ_C ($CDCl_3$) 55.9 (CH_3), 111.6 (CH), 121.5 (CH), 121.6 (CH), 127.07 (CH), 127.12 (CH), 128.9 (CH), 129.8 (CH), 132.1 (CH), 133.5 (C), 136.0 (C), 141.7 (C), 152.4 (C), 157.9 (CH); m/z (FAB) 246.0680 (MH^+. $C_{14}H_{13}ClNO$ requires 246.0686).

Preparation of (*E*)-*N*-(4-chlorobenzylidene)-2-methoxyaniline (106)



Yellow crystals (3.31 g, 90 %). M.p. 66-68 (lit.,[9] 63.8-65.7 ^oC). δ_H ($CDCl_3$) 3.80 (3H, s, OC*H*$_3$), 6.86-6.95 (3H, m, ArH), 7.12 (1H, ddd, $^3J_{HH}$ 7.8 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.36 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 7.78 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 8.36 (1H, s, C*H*N); δ_C ($CDCl_3$) 55.9 (CH_3), 111.7 (CH), 120.3 (CH), 121.1 (CH), 126.9 (CH), 129.0 (CH), 130.0 (CH), 134.9 (C), 137.3 (C), 141.5 (C), 152.3 (C), 159.8 (CH); m/z (FAB) 246.0685 (MH^+. $C_{14}H_{13}ClNO$ requires 246.0686).

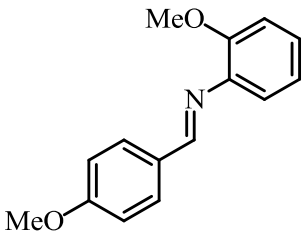
Preparation of (*E*)-2-methoxy-*N*-(2-methoxybenzylidene)aniline (107)



Yellow oil (3.18 g, 88 %). δ_H ($CDCl_3$) 3.78 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 6.83-6.97 (5H, m, ArH), 7.08 (1H, ddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 7.33 (1H, ddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 8.12 (1H, dd, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 8.82 (1H, s, C*H*N); δ_C ($CDCl_3$) 55.6 (CH_3), 55.9 (CH_3), 111.0

(CH), 111.5 (CH), 120.3 (CH), 120.8 (CH), 121.0 (CH), 125.0 (C), 126.4 (CH), 127.9 (CH), 132.6 (CH), 142.8 (C), 152.5 (C), 157.3 (CH), 159.5 (C); m/z (FAB) 242.1186 (MH^+. $C_{15}H_{16}NO_2$ requires 242.1181).

Preparation of (*E*)-2-methoxy-*N*-(4-methoxybenzylidene)aniline (108)



Yellow oil (1.16 g, 45 %). δ_H ($CDCl_3$) 3.79 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 6.85-6.93 (5H, m, ArH), 7.09 (1H, ddd, $^3J_{HH}$ 7.8 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.79 (2H, d, $^3J_{HH}$ 8.6 Hz, ArH), 8.31 (1H, s, C*H*N); δ_C ($CDCl_3$) 55.4 (CH_3), 55.9 (CH_3), 111.5 (CH), 114.1 (CH), 120.3 (CH), 121.1 (CH), 126.2 (CH), 129.5 (C), 132.0 (CH), 142.3 (C), 152.3 (C), 160.6 (CH), 162.2 (C); m/z (FAB) 242.1188 (MH^+. $C_{15}H_{16}NO_2$ requires 242.1181).

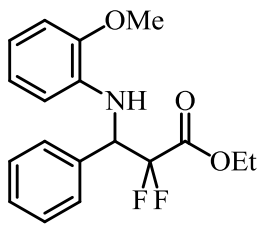
6.5.2 Products of the Reformatsky reaction with imines

General Method

Method 1

Ethyl iododifluoroacetate (0.22 mL, 0.375 g, 1.5 mmol) and imine (1.0 mmol) were added to dry THF (8 mL). After stirring the reaction mixture for 30 min at 0 ^oC, diethylzinc (1.5 mL, 1.0 M solution in hexane, 1.5 mmol) was added to the reaction mixture which was stirred for 4.5 h at 0 ^{o} C. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and then washed with 1 M HCl (50 mL), brine (50 mL) and water (50 mL). After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel to give the desired product.

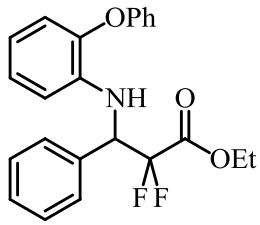
Preparation of ethyl-2,2-difluoro-3-(2-methoxyphenylamino)-3-phenylpropanoate (98)



Purification by silica gel column chromatography (EtOAc:hexane = 1:9). Colourless crystal (0.21 g, 63 %). M.p. 49-52 ^oC. δ_H ($CDCl_3$) 1.19 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 3.80 (3H, s, OC*H*$_3$), 4.20 (2H, q, $^3J_{HH}$ 7.0 Hz, OC*H*$_2$CH$_3$), 5.04 (1H, dd, $^3J_{HF}$ 18.8 Hz, $^3J_{HF}$ 7.8 Hz, C*H*CF$_2$), 6.47 (1H, dd, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz,

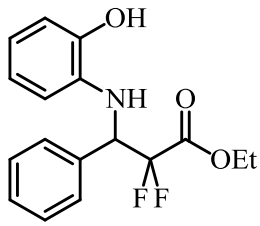
ArH), 6.58-6.63 (1H, m, ArH), 6.64-6.71 (2H, m, ArH), 7.21-7.30 (3H, m, ArH), 7.32-7.36 (2H, m, ArH); δ_F ($CDCl_3$) -108.97 (1F, d, $^2J_{FF}$ 254.7 Hz, CF_AF$_B$), -119.21 (1F, d, $^2J_{FF}$ 254.7 Hz, CF$_A$$F_B$); δ_C ($CDCl_3$) 13.8 (CH_3), 55.6 (CH_3), 59.9 (dd, $^2J_{CF}$ 27.2, $^2J_{CF}$ 22.4 Hz, CH), 63.1 (CH_2), 109.9 (CH), 110.9 (CH), 114.6 (t, $^1J_{CF}$ 255.6 Hz, CF_2), 118.3 (CH), 121.1 (CH), 128.4 (CH) 128.6 (CH), 128.7 (CH), 134.0 (C), 135.3 (C), 147.4 (C), 163.6 (t, $^2J_{CF}$ 31.2 Hz, CO); m/z (FAB) 336.1414 (MH^+. $C_{18}H_{20}F_2NO_3$ requires 336.1411). The enantiomers were separated on a chiralcel OD-H column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 10.38 min (enantiomer 1), 11.57 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-(2-phenoxyphenylamino)-3-phenylpropanoate (99)



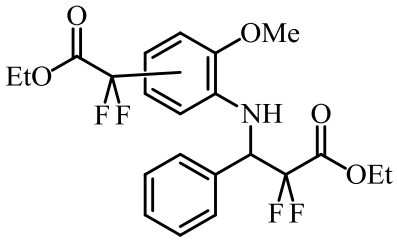
Purification by silica gel column chromatography (EtOAc:hexane = 1:19). Reddish oil (0.28 g, 70 %). δ_H ($CDCl_3$) 1.23 (3H, t, $^3J_{HH}$ 7.0 Hz, $CH_2C\mathit{H}_3$), 4.15-4.30 (2H, m, O$C\mathit{H}_A\mathit{H}_BCH_3$), 5.18 (1H, dd, $^3J_{HF}$ 19.2 Hz, $^3J_{HF}$ 7.8 Hz, CHCF$_2$), 6.70 (2H, tt, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 6.74 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH), 6.96 (1H, td, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 7.00 (2 H, dt, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 0.8 Hz, ArH), 7.13 (1 H, tt, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.32-7.42 (7H, m, ArH); δ_F ($CDCl_3$) -108.76 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF$_B$), -119.47 (1F, d, $^2J_{FF}$ 257.4 Hz, CF$_A$$F_B$); δ_C ($CDCl_3$) 13.8 (CH_3), 60.0 (dd, $^2J_{CF}$ 27.2 Hz, $^2J_{CF}$ 22.1 Hz, CH), 63.1 (CH_2), 113.2 (CH), 114.5 (t, $^1J_{CF}$ 255.6 Hz, CF_2), 117.8 (CH), 118.8 (CH), 119.3 (CH), 123.1 (CH), 124.6 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129.8 (CH), 133.8 (C), 137.6 (C), 144.2 (C), 157.4 (C), 163.5 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (FAB) 398.1564 (MH^+. $C_{23}H_{22}F_2NO_3$ requires 398.1568). The enantiomers were separated on a chiralcel OD-H column eluted with 2 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 5.29 min (enantiomer 1), 5.97 min (enantiomer 2).

Preparation of ethyl 2,2-difluoro-3-(2-hydroxyphenylamino)-3-phenylpropanoate (100)



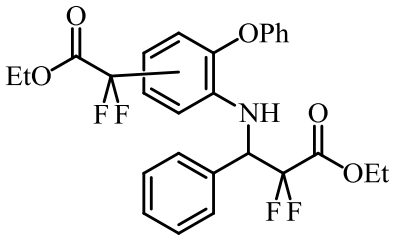
The title molecule was prepared in a two-step Reformatsky reaction. Preparation of the solution of the Reformatsky reagent: A flamed dried two neck round bottomed flask equipped with condenser was charged with acid washed zinc dust (0.221 g, 3.4 mmol) and dry THF (15.5 mL). The temperature of the suspension was increased to 60 ^{o}C but heating was stopped before ethyl iododifluoroacetate (0.85 g, 0.5 mL, 3.4 mmol) was added dropwise from a syringe over 2-3 minutes. The Reformatsky reagent was used after 2 minutes of stirring. A flame dried 25 mL RBF was charged with imine (0.197 g, 1.0 mmol) and THF (1 mL) at 0 ^{o}C. The solution of Reformatsky reagent (1.5 mmol in 7 mL) was added and the reaction mixture was stirred for 4.5 h at 0 ^{o}C before it was quenched with 1 M HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic solvents were combined and washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The crude product was purified by silica gel column chromatography (EtOAc:hexane= 1:9) to give the pure product as a colourless liquid (0.16 g, 51 %). δ_H ($CDCl_3$) 1.19 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.22 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3,), 4.60 (1H, br s, O*H*), 4.95 (1H, dd, $^3J_{HF}$ 18.8 Hz, $^3J_{HF}$ 7.8 Hz, $CHCF_2$), 5.30 (1H, br s, N*H*), 6.47 (1H, dd, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 6.57-6.68 (3H, m, ArH), 7.23-7.31 (3H, m, ArH), 7.32-7.37 (2H, m, ArH); δ_F ($CDCl_3$) -108.90 (1F, d, $^2J_{FF}$ 254.7 Hz, CF_AF_B), -119.05 (1F, d, $^2J_{FF}$ 254.7 Hz, CF_AF_B); δ_C ($CDCl_3$) 12.8 (CH_3), 59.8 (t, $^2J_{CF}$ 23.1 Hz, CH), 62.3 (CH_2), 113.6 (t, $^1J_{CF}$ 257.6 Hz, CF_2), 113.8 (CH), 114.0 (CH), 119.0 (CH), 120.3 (CH), 127.4 (CH), 127.6 (CH), 127.8 (CH), 132.8 (C), 132.9 (C), 143.8 (C), 163.9 (t, $^2J_{CF}$ 29.2 Hz, CO); m/z (FAB) 322.1257 (MH^+. $C_{17}H_{18}F_2NO_3$ requires 322.1255). The enantiomers were separated on a chiralcel AS column eluted with 5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 8.17 min (enantiomer 1), 9.74 min (enantiomer 2).

Preparation of ethyl-3-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methoxy-phenylamino)-2,2-difluoro-3-phenylpropanoate (101)



The title compound was isolated as a co-product in the synthesis of ethyl 2,2-difluoro-3-(2-methoxy-phenylamino)-3-phenylpropanoate as a colourless oil (0.02 g, 0.9 %). δ_H ($CDCl_3$) 1.15 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.21 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 4.15-4.22 (4H, m, OCH_2CH_3), 5.04 (1H, dd, $^3J_{HF}$ 17.2 Hz, $^3J_{HF}$ 8.2 Hz, CH), 5.30 (1H, br s, NH), 6.44 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH), 6.88-6.93 (2H, m, ArH), 7.24-7.35 (5H, m, ArH); δ_F ($CDCl_3$) -102.0 (2F, s, $ArCF_2$), -109.86 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), -118.11 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 12.8 (CH_3), 12.9 (CH_3), 54.8 (CH_3), 58.6 (t, $^2J_{CF}$ 26.7 Hz, CH), 61.9 (CH_2), 62.2 (CH_2), 105.64 (t, $^3J_{CF}$ 6.4 Hz, CH), 109.1 (CH), 112.6 (t, $^1J_{CF}$ 251.9 Hz, CF_2), 113.3 (t, $^1J_{CF}$ 258.1 Hz, CF_2), 117.8 (t, $^3J_{CF}$ 6.6 Hz, CH), 120.9 (t, $^2J_{CF}$ 26.0 Hz, C), 127.2 (CH), 127.7 (CH), 128.0 (CH), 132.4 (C), 136.6 (C), 145.8 (C), 162.3 (t, $^2J_{CF}$ 31.5 Hz, CO), 163.5 (t, $^2J_{CF}$ 36.6 Hz, CO); m/z (FAB) 458.1575 (MH^+. $C_{22}H_{24}F_4NO_5$ requires 458.1591).

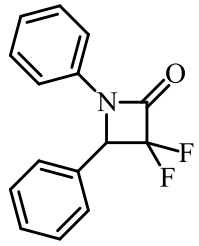
Preparation of ethyl-3-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-phenoxyphenyl-amino)-2,2-difluoro-3-phenylpropanoate (102)



The title compound was isolated as a co-product in the synthesis of ethyl 2,2-difluoro-3-(2-phenoxy-phenylamino)-3-phenylpropanoate as a colourless oil (0.03 g, 10 %**).** δ_H ($CDCl_3$) 1.11 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.15 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.05-4.19 (4H, m, OCH_2CH_3), 5.07 (1H, dd, $^3J_{HF}$ 17.2 Hz, $^3J_{HF}$ 7.8 Hz, CH), 5.30 (1H, br s, NH), 6.59 (1H, d, $^3J_{HH}$ 8.7 Hz, ArH), 6.89-6.93 (2H, m, ArH), 6.96 (1H, d, $^4J_{HH}$ 2.0 Hz, ArH), 7.04-7.10 (2H, m, ArH), 7.24-7.31 (7H, m, ArH); δ_F ($CDCl_3$) -101.97 (2F, s, $ArCF_2$), -109.72 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), -118.16 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.78 (CH_3), 13.83 (CH_3), 59.7 (t, $^2J_{CF}$ 26.2 Hz, CH), 62.9 (CH_2), 63.3 (CH_2), 110.7 (CH), 113.2 (t, $^1J_{CF}$ 252.6 Hz, CF_2), 114.2 (t, $^1J_{CF}$ 256.6 Hz, CF_2), 116.0 (t, $^3J_{CF}$ 6.0 Hz, CH), 118.2 (CH), 121.9 (t, $^3J_{CF}$ 7.0 Hz, CH), 122.6 (t, $^2J_{CF}$ 27.2 Hz, C), 123.9 (CH), 128.3 (CH), 128.8 (CH), 129.1 (CH), 130.0 (CH),133.2 (C), 139.7 (C),

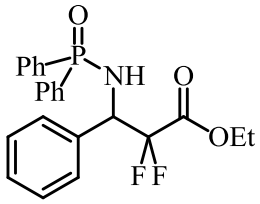
144.0 (C), 156.6 (C), 163.2 (t, $^{2}J_{CF}$ 31.2 Hz, CO), 164.2 (t, $^{2}J_{CF}$ 35.2 Hz, CO); m/z (FAB) 520.1742 (MH^{+}. $C_{27}H_{26}F_{4}NO_{5}$ requires 520.1747).

Preparation of 3,3-difluoro-1,4-diphenylazetidin-2-one (103)



The product was purified by silica gel column chromatography (EtOAc:hexane = 1:9) to give the product as colourless crystals (0.13 g, 53 %). M.p. 132-138 ^{o}C (lit.,[16] 135 ^{o}C). δ_{H} ($CDCl_{3}$) 5.33 (1H, dd, $^{3}J_{HF}$ 7.4 Hz, $^{3}J_{HF}$ 2.0 Hz, C*H*CF_{2}), 7.09 (1H, tt, $^{3}J_{HH}$ 7.0 Hz, $^{4}J_{HH}$ 1.6 Hz, ArH), 7.21-7.30 (6H, m, ArH), 7.34-7.38 (3H, m, ArH); δ_{F} ($CDCl_{3}$) -113.90 (1F, d, $^{2}J_{FF}$ 227.0 Hz, C$F_{A}F_{B}$), -119.56 (1F, d, $^{2}J_{FF}$ 227.0 Hz, $CF_{A}F_{B}$); δ_{C} ($CDCl_{3}$) 68.1 (t, $^{2}J_{CF}$ 25.2 Hz, CH), 117.2 (CH), 118.5 (t, $^{1}J_{CF}$ 288.8 Hz, CF_{2}), 124.7 (CH), 126.5 (CH), 128.2 (CH), 128.4 (CH), 128.8 (CH), 134.68 (C), 156.9 (t, $^{2}J_{CF}$ 31.2 Hz, CO); One quaternary carbon is missing possibly because it overlaps with another signal. m/z (FAB) 260.0884 (MH^{+}. $C_{15}H_{12}F_{2}NO$ requires 260.0887). The enantiomers were separated on a chiralcel OD-H column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_{t}= 5.84 min (enantiomer 1), 6.84 min (enantiomer 2).

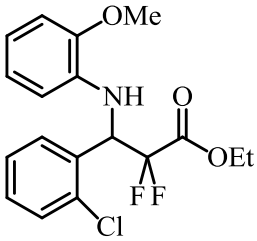
Preparation of ethyl-3-(diphenylphosphorylamino)-2,2-difluoro-3-phenyl-propanoate (104)



White solid (0.19 g, 45 %). M.p. 162-163 ^{o}C. δ_{H} ($CDCl_{3}$) 1.26 (3H, t, $^{3}J_{HH}$ 7.0 Hz, $CH_{2}CH_{3}$), 3.80 (1H, dd, $^{2}J_{HP}$ 11.0 Hz, $^{3}J_{HH}$ 8.6 Hz, N*H*), 4.12-4.27 (2H, m, O$CH_{A}H_{B}CH_{3}$), 4.66-4.79 (1H, m, C*H*), 7.16-7.21 (2H, m, ArH), 7.22-7.30 (5H, m, ArH), 7.35-7.41 (3H, m, ArH), 7.43-7.49 (1H, m, ArH), 7.55-7.62 (2H, m, ArH), 7.70-7.77 (2H, m, ArH); δ_{F} ($CDCl_{3}$) -110.96 (1F, d, $^{2}J_{FF}$ 254.7 Hz, C$F_{A}F_{B}$), -115.88 (1F, d, $^{2}J_{FF}$ 254.7 Hz, $CF_{A}F_{B}$); δ_{P} 24.00 (1P, s, *P*OPh_{2}), δ_{C} ($CDCl_{3}$) 13.8 (CH_{3}), 57.2 (t, $^{2}J_{CF}$ 26.2 Hz, CH), 63.4 (CH_{2}), 114.4 (td, $^{1}J_{CF}$ 256.6 Hz, $^{3}J_{CP}$ 6.3 Hz, CF_{2}), 128.2 (CH), 128.4 (d, J_{CP} 12.9 Hz, CH), 128.59 (d, J_{CP} 12.9 Hz, CH), 128.61 (CH), 128.8 (CH), 131.1 (d, $^{1}J_{CP}$ 47.3 Hz, C), 132.0 (d, J_{CP} 9.8 Hz, CH), 132.1 (CH), 132.26 (CH), 132.31 (d, J_{CP} 9.8 Hz, CH), 132.34 (d, $^{1}J_{CP}$ 46.3 Hz, C), 134.8 (C), 163.1 (t, $^{2}J_{CF}$ 31.2 Hz, CO); m/z (FAB) 430.1371 (MH^{+}. $C_{23}H_{23}F_{2}NO_{3}P$ requires 430.1384). The enantiomers were separated on a chiralcel AD column eluted with 10 % IPA in hexane. The flow rate of

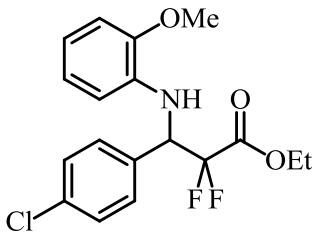
the mobile phase was set at 1.0 mL/min. R_t= 18.05 min (enantiomer 1), 23.21 min (enantiomer 2).

Preparation of ethyl-3-(2-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)-propanoate (109)



Colourless crystals with a green impurity on the surface were obtained after purification by column chromatography (EtOAc:hexane = 1:9) followed by recrystallisation from hot hexane (0.09 g, 25 %). M.p. 88-91 ^{o}C. δ_H ($CDCl_3$) 1.21 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 3.78 (3H, s, OCH_3), 4.18-4.30 (2H, m, OCH_2CH_3), 5.04 (1H, s, N*H*), 5.76 (1H, dd, $^3J_{HF}$ 20.3 Hz, $^3J_{HF}$ 5.5 Hz, $CHCF_2$), 6.50 (1H, dd, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 6.59-6.64 (1H, m, ArH), 6.66-6.72 (2H, m, ArH), 7.14-7.20 (2H, m, ArH), 7.29-7.34 (1H, m, ArH), 7.36-7.41 (1H, m, ArH); δ_F ($CDCl_3$) -108.72 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), -120.11 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.8 (CH_3), 55.3 (t, $^2J_{CF}$ 21.1 Hz, CH), 55.6 (CH_3), 63.2 (CH_2), 109.9 (CH), 111.4 (CH), 114.5 (t, $^1J_{CF}$ 257.6 Hz, CF_2), 118.5 (CH), 121.2 (CH), 127.2 (CH), 129.1 (CH), 129.6 (CH), 129.9 (CH), 132.3 (C), 134.8 (C), 135.3 (C), 147.3 (C), 163.2 (t, $^2J_{CF}$ 33.6 Hz, CO); m/z (FAB) 370.1021 (MH^+. $C_{18}H_{19}ClF_2NO_3$ requires 370.1022). The enantiomers were separated on a chiralcel OD column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.62 min (enantiomer 1), 12.41 min (enantiomer 2).

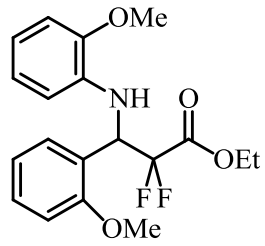
Preparation of ethyl-3-(4-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)-propanoate (110)



Brown oil (0.19 g, 51 %) δ_H ($CDCl_3$) 1.16 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 3.75 (3H, s, OCH_3), 4.18 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 4.89 (1H, s, N*H*), 5.01 (1H, dd, $^3J_{HF}$ 19.1 Hz, $^3J_{HF}$ 7.4 Hz, $CHCF_2$), 6.39 (1H, dd, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 6.57-6.66 (3H, m, ArH), 7.21 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.28 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH); δ_F ($CDCl_3$) -108.29 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), -119.72 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 55.6 (CH_3), 76.1 (dd, $^2J_{CF}$ 27.2 Hz, $^2J_{CF}$ 23.1 Hz, CH), 63.3 (CH_2), 110.0 (CH), 111.6 (CH), 114.4 (t, $^1J_{CF}$ 257.6 Hz, CF_2), 118.7 (CH), 121.1 (CH), 128.9 (CH), 129.8 (CH), 132.7 (C), 134.8

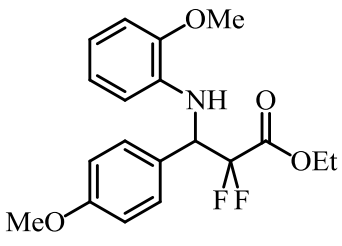
(C), 134.9 (C), 147.4 (C), 163.6 (t, $^{2}J_{CF}$ 32.2 Hz, CO); m/z (FAB) 370.1016 (MH^{+}. $C_{18}H_{19}ClF_2NO_3$ requires 370.1022). The enantiomers were separated on a chiralcel OD column eluted with 0.5 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 8.81 min (enantiomer 1), 10.53 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-(2-methoxyphenyl)-3-(2-methoxyphenylamino)-propanoate (111)



Colourless crystals (0.18 g, 49 %). M.p. 74-76 ^{o}C. δ_H ($CDCl_3$) 1.28 (3H, t, $^{3}J_{HH}$ 7.0 Hz, CH_2CH_3), 3.86 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.29 (2H, q, $^{3}J_{HH}$ 7.4 Hz, OCH_2CH_3), 5.25 (1H, br s, N*H*) 5.76 (1H, dd, $^{3}J_{HF}$ 20.0 Hz, $^{3}J_{HF}$ 7.4 Hz, $CHCF_2$), 6.68 (2H, m, ArH), 6.75-6.82 (2H, m, ArH), 6.93 (1H, dd, $^{3}J_{HH}$ 8.2, $^{4}J_{HH}$ 1.2 Hz, ArH), 6.96 (1H, td, $^{3}J_{HH}$ 7.4, $^{4}J_{HH}$ 1.2 Hz, ArH), 7.30 (1H, ddd, $^{3}J_{HH}$ 8.2 Hz, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HH}$ 2.0 Hz, ArH), 7.39 (1H, dt, $^{3}J_{HH}$ 7.8 Hz, $^{4}J_{HH}$ 1.6 Hz, ArH); δ_F ($CDCl_3$) -109.50 (1F, d, $^{2}J_{FF}$ 254.7 Hz, CF_AF_B), -118.92 (1F, d, $^{2}J_{FF}$ 254.7 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.83 (CH_3), 52.8 (dd, $^{2}J_{CF}$ 28.8 Hz, $^{2}J_{CF}$ 22.4 Hz, CH), 55.6 (CH_3), 55.8 (CH_3), 62.9 (CH_2), 109.84 (CH), 110.9 (CH), 111.3 (CH), 115.1 (t, $^{1}J_{CF}$ 257.6 Hz, CF_2), 117.9 (CH), 128.9 (CH), 121.1 (CH), 122.7 (C), 128.9 (CH), 129.7 (CH), 135.6 (C), 147.4 (C), 158.1 (C), 163.8 (t, $^{2}J_{CF}$ 33.2 Hz, CO); m/z (FAB) 366.1508 (MH^{+}. $C_{19}H_{22}F_2NO_4$ requires 366.1517). The enantiomers were separated on a chiralcel OD column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 6.15 min (enantiomer 1), 10.76 min (enantiomer 2).

Preparation of ethyl-2,2-difluoro-3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)-propanoate (112)



Brown solid (0.12 g, 34 %). M.p. 80-81 ^{o}C. δ_H ($CDCl_3$) 1.29 (3H, t, $^{3}J_{HH}$ 7.0 Hz, CH_2CH_3), 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.30 (2H, q, $^{3}J_{HH}$ 7.0 Hz, OCH_2CH_3,), 5.09 (1H, br s, N*H* and 1H, dd, $^{3}J_{HF}$ 18.8 Hz, $^{3}J_{HF}$ 8.2 Hz, $CHCF_2$), 6.56 (1H, dd, $^{3}J_{HH}$ 7.8 Hz, $^{4}J_{HH}$ 1.6 Hz, ArH), 6.68-6.73 (1H, m, ArH), 6.75-6.80 (2H, m, ArH), 6.89 (2H, d, $^{3}J_{HH}$ 8.6 Hz, ArH), 7.36 (2H, d, $^{3}J_{HH}$ 8.6 Hz, ArH); δ_F ($CDCl_3$) -109.21 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF_AF_B), -119.25 (1F, d, $^{2}J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 55.2 (CH_3), 55.6 (CH_3), 59.4 (t,

$^{2}J_{CF}$ 23.1 Hz, CH), 63.0 (CH_2), 109.9 (CH), 111.6 (CH), 114.0 (CH), 114.7 (t, $^{1}J_{CF}$ 256.6 Hz, CF_2), 118.2 (CH), 121.1 (CH), 125.9 (C), 129.5 (CH), 135.4 (C), 147.4 (C), 159.9 (C), 163.7 (t, $^{2}J_{CF}$ 30.2 Hz, CO); m/z (FAB) 366.1528 (MH^+. $C_{19}H_{22}F_2NO_4$ requires 366.1517). The enantiomers were separated on a chiralcel AD column eluted with 4 % IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL/min. R_t= 9.84 min (enantiomer 1), 11.76 min (enantiomer 2).

General methods for asymmetric synthesis with imines

General method 1 (Tables 5.14 and 5.15)

Two reactions were run simultaneously in two 25 mL two-neck round bottomed flasks in one cryogenic flask. The imine (0.5 mmol) was dissolved in dry THF (4 mL) and the mixture was cooled to 0 ^{o}C. Ethyl iododifluoroacetate (0.25 g, 0.15 mL, 1.0 mmol) and *N*-methylephedrine (0.090 g, 0.5 mmol) were added. After 30 minutes diethylzinc (1.25 mL, 1.0 M solution in hexane, 1.25 mmol) was added and the reaction mixture was stirred at stated temperature for 4.5 hours. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layers were combined and then washed with 1 M HCl (10 mL), brine (10 mL) and water (10 mL). After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel to give the desired product. The enantiomeric excess was determined by chiral HPLC.

General method 2 (Table 5.17)

Preparation of the Reformatsky reagent:

A flamed dried two neck round bottomed flask equipped with condenser was charged with acid washed zinc dust (0.275 g, 4.2 mmol) and dry THF (7 mL). The temperature of the suspension was increased to 60 ^{o}C but the heating was stopped before ethyl iododifluoroacetate (0.5 mL, 0.85 g, 3.5 mmol) was added dropwise from a syringe over 2-3 minutes. The Reformatsky reagent was used after 2 minutes of stirring.

The Reformatsky reaction with imines:

A flame dried three neck round bottomed flask was charged with THF (1 mL), imine (0.5 mmol) and (1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)1-propanol (0.5 mmol, 0.10 g) and

was cooled to 0 ^{o}C . The solution of the Reformatsky reagent (1.5 mmol in 3 ml of dry THF) was added. The reaction was stirred for 6.5 hours at the same temperature before it was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulphate. The solvent was removed and the product was purified by silica gel column chromatography.

General method 3 (Table 5.18)

A flamed dried 25 mL two-neck RBF was charged with imine (0.5 mmol) and THF (4 mL) and the mixture was cooled to the required temperature. The required amounts of ethyl iododifluoroacetate and *N*-methylephedrine were added. After 30 minutes the required amount of diethylzinc was added and the reaction mixture was stirred at the stated temperature for 4.5 hours. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layers were combined and then washed with 1 M HCl (20 mL), brine (20 mL) and water (20 mL). After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel to give the desired product.

General method 4 (Table 5.22)

A flamed dried 25 mL two-neck RBF was charged with imine (0.5 mmol), *N*-methylephedrine (0.5 mmol, 0.09 g), THF (4 mL) and the required amount of ethyl iododifluoroacetate, before the mixture was cooled to the required temperature. After 30 minutes the required amount of diethylzinc (1.0 M solution in hexane) was added and the reaction mixture was stirred at the stated temperature for 4.5 hours. The reaction mixture was quenched with 1 M HCl (10 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layers were combined and then washed with 1 M HCl (20 mL), brine (20 mL) and water (20 mL). After drying over magnesium sulphate, the solvent was removed. The crude product was purified by column chromatography on silica gel to give the desired product.

6.6 References

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Appendix

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Appendix

A1

Determination of the amount of ethyl-2,2-difluoro-3-hydroxy-3-phenyl propanoate (44) and benzaldehyde by GC assay

An internal standard, di-*p*-tolyl ether, was added to the reaction mixture in order to calculate the conversion of benzaldehyde to product in its reaction with the fluorinated Reformatsky reagent. Since the Reformatsky reaction has to be quenched and extracted with ethyl acetate, the volume of solvent and the product/starting material concentrations change before the sample can be analysed by GC, so the relative amounts of benzaldehyde and product were calculated by GC assay. By comparing the relative amounts of benzaldehyde and ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate to the amount of di-*p*-tolyl ether by GC, it was possible to determine the conversion of the starting material to product. A BD-M column also enabled the enantiomers to be separated and the enantiomeric excess to be determined from the areas of the respective peaks.

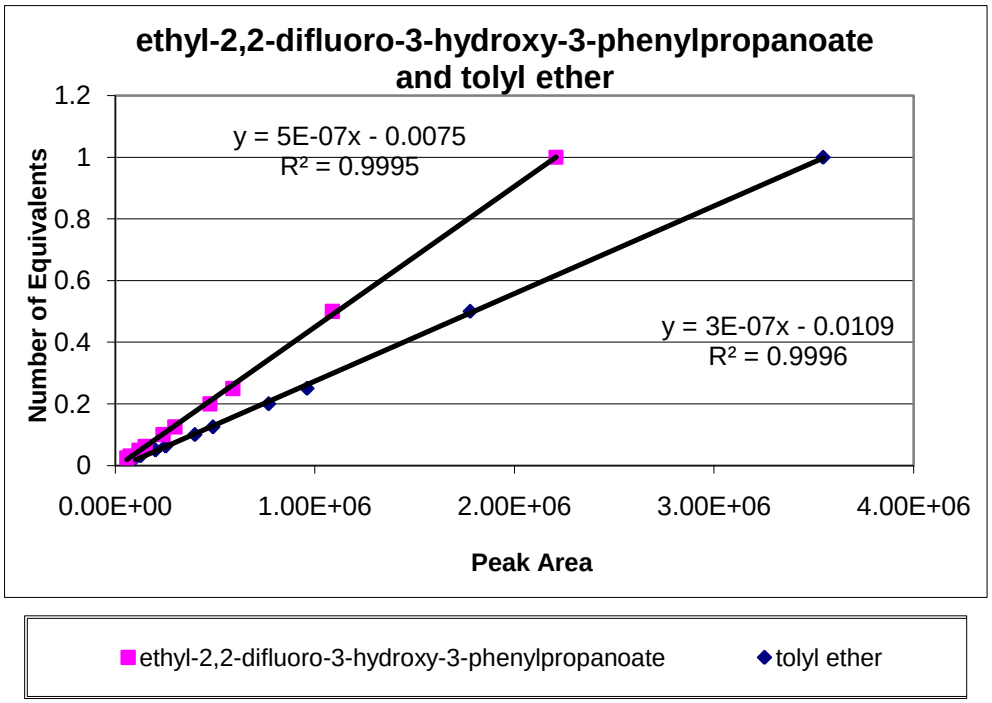
To determine the conversion in the reaction it was necessary to confirm that the area of each of the corresponding peaks was changing linearly with the change of concentration for each of the three compounds. A series of samples were prepared using an analytical balance (0.0001 g accuracy) for weighing out the small amounts of di-*p*-tolyl ether (0.198 g, 0.1 mmol), benzaldehyde (0.106 g, 0.1 mmol, 0.1 mL) and ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate (0.230 g, 0.1 mmol) which were placed in a 10 mL volumetric flask and dissolved in ethyl acetate (Sample 1, Table 1). Samples of that mixture (2 and 5 mL) were transferred to separate 10 mL volumetric flasks and ethyl acetate was added in order to prepare samples 4 and 2 respectively. Further samples (5 mL) were taken from samples 2 and 4, and were diluted in 10 mL volumetric flasks. This procedure was repeated several times in order to obtain a series of different concentrations and the samples were then analysed by gas chromatography (Table 1). The advantage of this procedure was that low concentrations of all three components could be obtained without weighing extremely small quantities of materials that would lead to larger errors. Simultaneously dissolving mixtures from two different flasks gave a control to check that no mistakes were made. If it was, or correlations from the series of concentrations were not linear, an error would be visible after plotting the graphs and displaying R^2 values.

Table 1 Peak areas obtained for benzaldehyde, ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate **(44)** and di-*p*-tolyl ether by GC analyses.

Sample	Equivalent in the reaction	Benzaldehyde	(44)	di-*p*-Tolyl ether
1	1.0	1711953	2208315	3547331
2	0.5	874758	1087663	1778607
3	0.25	471503	589056	961159
4	0.2	373946	474704	768640
5	0.125	237527	298526	489783
6	0.1	193016	239410	399113
7	0.0625	122069	149850	252607
8	0.05	96736	119632	201784
9	0.03125	61090	73517	127241
10	0.025	48655	58590	101404

Using the data from Table 1, Figures 1 and 2 were prepared. As well as showing how the area of the peaks depends on the concentration, the corresponding equations were also calculated. To determine the amount of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate, the area for the internal standard and equation for di-*p*-tolyl ether was first calculated from Figure 1 (Equation 1). The amount of internal standard can be different from the calculated value because of the response factor which is calculated by dividing the amount of internal standard used by the calculated value (Equation 2). This factor (f) is then used to calculate accurately the number of equivalents of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate in Equation 3 and simple multiplication by a hundred gives the conversion to product (Equation 4).

Figure 1 Number of equivalents of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate and di-*p*-tolyl ether plotted against peak areas.



Equation 1

$$E_{ct} = 3*10^{-7} A_t - 0.0109$$

E_{ct}- calculated equivalent of di-*p*-tolyl ether

A_t- area of di-*p*-tolyl ether

Equation 2

$$f = \frac{E_{ut}}{E_{ct}}$$

f- factor

E_{ut}- number of equivalent of di-*p*-tolyl ether used in experiment

E_{ct}- calculated equivalent of di-*p*-tolyl ether

Equation 3

$$E_p = 5*10^{-7} * f * A_p - 0.0075$$

E_p- number of equivalent of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate

f- factor

A_p- area of ethyl -2,2-difluoro-3-hydroxy-3-phenylpropanoate

Equation 4

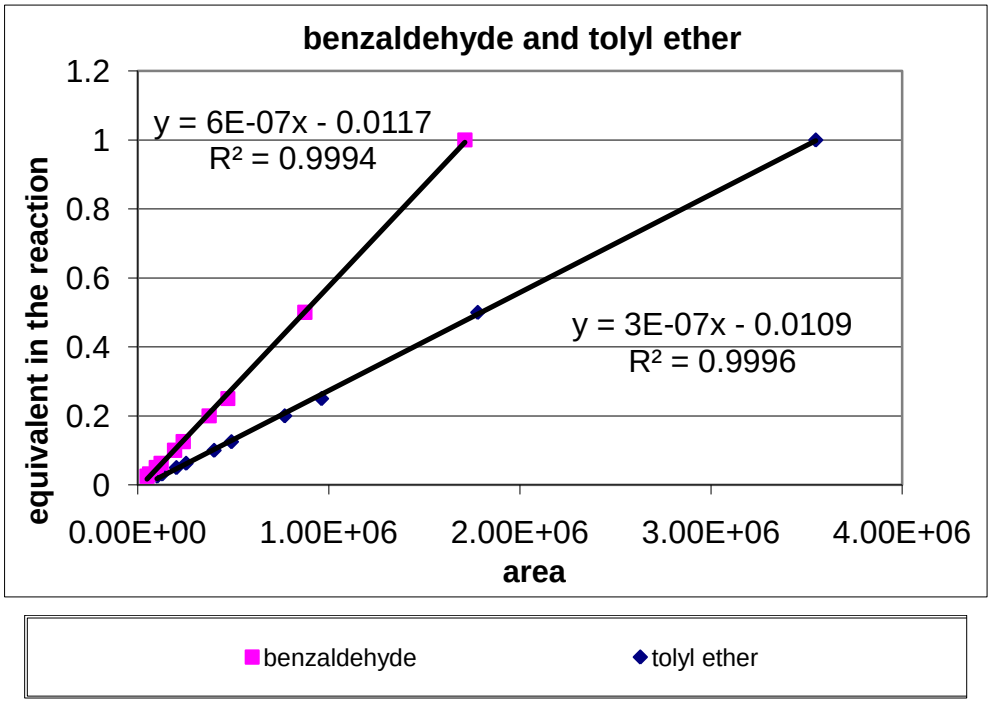
$$C_p = E_p * 100$$

C_p- conversion of benzaldehyde to ethyl -2,2-difluoro-3-hydroxy-3-phenylpropanoate

E_p- equivalent of ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate

Using the same process the number of equivalents of benzaldehyde can be calculated from Figure 2 and Equation 5. The response factor is identical to the calculations for ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate.

Figure 2 Number of equivalents of benzaldehyde and di-*p*-tolyl ether plotted against peak areas.



Equation 5

$$E_b = 6*10^{-7} * f * A_b - 0.0117$$

E_b- number of equivalent of benzaldehyde

f- factor

A_b- area of benzaldehyde

Before the method was used, a series of samples containing a known amount of benzaldehyde, product and internal standard were made (Table 2). The samples were analysed by GC (Table 3, results 1a-3a) and the results were used to determine the error in this technique. The same series of samples were then eluted through a short silica gel column, in the same way that the real samples are purified during work up, to make sure that it has no impact on the final analysis (Table 3, samples 1b-3b). Table 4 demonstrates that the method is extremely accurate for determining the amount of product present, but is less accurate for measuring the amount of benzaldehyde, especially when only small amounts are present.

Table 2 A series of samples (**1a**-**3a**) containing known amounts of benzaldehyde, product and di-*p*-tolyl ether.

Sample	Equivalent[a] of Benzaldehyde	Equivalent of Product	Equivalent of di-*p*-tolyl ether
1a	0. 75	0. 25	0. 78
2a	0. 5	0. 5	0. 78
3a	0. 25	0. 75	0. 78

[a] Equivalents calculated according to the amount of benzaldehyde used in the Reformatsky reaction.

Table 3 GC peak areas obtained for samples **(1a-3a)** before and after elution through a short column of silica gel.

	Benzaldehyde	**Product**	**di-*p*-Tolyl ether**
1a[a]	1599101	679021	3477201
2a[a]	928944	1166910	3030178
3a[a]	519104	1970400	3398141
1b[b]	1564885	662944	3448780
2b[b]	973582	1234162	3245220
3b[b]	440520	1720869	3000720

[a] Results for samples (**1a-3a**) obtained from the stock solutions, [b] results obtained for samples **(1a-3a)** after elution through a short silica gel column with ethyl acetate.

Table 4 Results of GC analyses for samples (**1a-3a**) before and after elution through a short silica gel column.

	Benzaldehyde[c]	**Error [%]**	**Product**[c]	**Error [%]**
1a[a]	0.713 (0.75)	5.3	0.249 (0.25)	0.4
2a[a]	0.472 (0.50)	6.0	0.499 (0.50)	0.2
3a[a]	0.229 (0.25)	8.0	0.754 (0.75)	0.5
1b[b]	0.704 (0.75)	6.1	0.245 (0.25)	2.0
2b[b]	0.493 (0.5)	1.4	0.462 (0.5)	7.6
3b[b]	0.22 (0.25)	12	0.747 (0.75)	0.4

[a] Results for samples **(1a-3a)** obtained from the stock solutions, [b] results obtained for samples **(1a-3a)** after elution through a short silica gel column, [c] calculated and used (in parenthesis) equivalents of the compounds.

A2

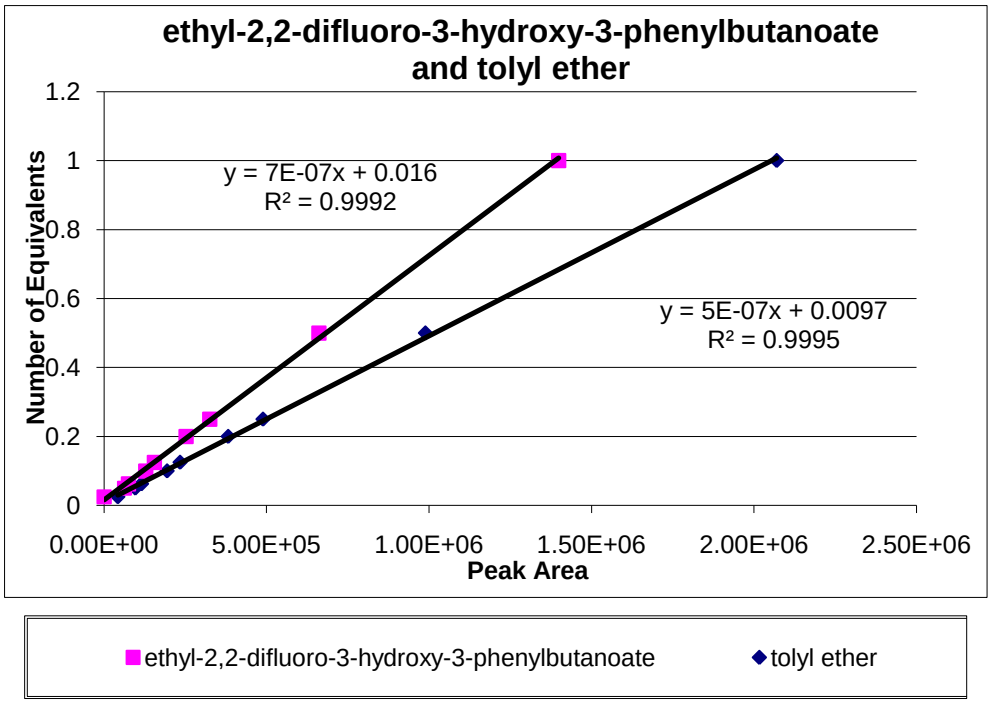
Determination of the amount of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate (48) and acetophenone by GC assay

Exactly the same GC assay protocol as that used for benzaldehyde was used to determine the conversion of acetophenone to ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate except that the PE-5 column did not allow for the separation of the enantiomers. A standard stock solution containing acetophenone (0.120 g, 0.1 mL, 0.1 mmol), ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate (0.244 g, 0.1 mmol) and di-*p*-tolyl ether (0.198 g, 0.1 mmol) was made up in a 10 mL volumetric flask. Samples were then taken and diluted in order to prepare a series of different samples as shown in Table 5. The results from Table 5 were used to plot Figures 3 and 4 which demonstrated clearly that the peak areas for each of the three compounds changes linearly with the change in concentration. After plotting Figure 3, the equations were used to calculate the amount of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate present in the samples (Equations 6-9) using the same process as for benzaldehyde. Figure 4 was also plotted from the data in Table 5 and the linear equations were used to determine the amount of acetophenone present (Equation 10).

Table 5 Peak areas obtained for acetophenone, ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate and di-*p*-tolyl ether by GC analyses

Sample	**Equivalent in the reaction**	**Acetophenone**	**(48)**	**di-*p*-Tolyl ether**
1	1.0	1195840	1398854	2069764
2	0.5	554930	661076	989023
3	0.25	262666	325152	489380
4	0.2	207080	252487	382258
5	0.125	126929	154951	234276
6	0.1	104809	128360	194361
7	0.0625	61499	75393	115671
8	0.05	49957	62908	96489
9	0.025	22261	28749	42786

Figure 3 Number of equivalents of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate and di-*p*-tolyl ether plotted against peak areas



Equation 6

$$E_{ct} = 5*10^{-7} A_t + 0.0097$$

E_{ct}- calculated equivalent of di-*p*-tolyl ether

A_t- area of di-*p*-tolyl ether

Equation 7

$$f = \frac{E_{ut}}{E_{ct}}$$

f- factor

E_{ut}- equivalent of di-*p*-tolyl ether used in experiment

E_{ct}- calculated equivalent of di-*p*-tolyl ether

Equation 8

$$E_p = 7*10^{-7} * f * A_p + 0.016$$

E_p- equivalent of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate

f- factor

A_p- area of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate

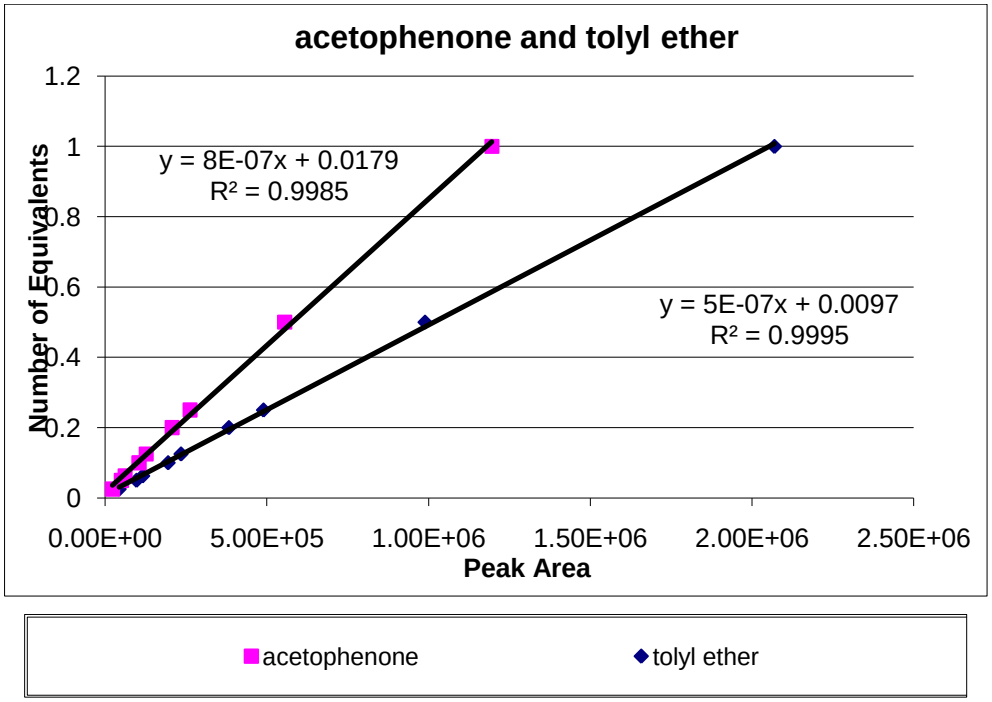
Equation 9

$$C_p = E_p * 100$$

C_p- conversion of acetophenone to ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate

E_p- equivalent of ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate

Figure 4 Number of equivalents of acetophenone and di-*p*-tolyl ether plotted against peak areas.



Equation 10

$$E_a = 8*10^{-7} * f * A_a + 0.0179$$

E_a- equivalent of acetophenone

f- factor

A_a- area of acetophenone

A3
Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate (54)

Empirical formula	C13 H16 F2 O3	
Formula weight	258.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.052(2) Å	α= 90°.
	b = 7.8441(18) Å	β= 106.959(3)°.
	c = 17.153(4) Å	γ = 90°.
Volume	1293.8(5) $Å^3$	
Z	4	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.111 mm^{-1}	
F(000)	544	
Crystal size	0.22 x 0.16 x 0.13 mm^3	
Theta range for data collection	2.12 to 25.00°.	
Index ranges	-11<=h<=11, -9<=k<=9, -20<=l<=20	
Reflections collected	8916	
Independent reflections	2286 [R(int) = 0.1658]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2286 / 0 / 166	
Goodness-of-fit on F^2	1.086	
Final R indices [I>2sigma(I)]	R1 = 0.0622, wR2 = 0.1330	
R indices (all data)	R1 = 0.0994, wR2 = 0.1463	
Largest diff. peak and hole	0.270 and -0.199 $e.Å^{-3}$	

A4
Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate (55)

Empirical formula	C14 H18 F2 O3	
Formula weight	272.28	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 7.046(3) Å	α= 90°.
	b = 16.235(7) Å	β= 90°.
	c = 24.642(11) Å	γ = 90°.
Volume	2819(2) $Å^3$	
Z	8	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F(000)	1152	
Crystal size	0.31 x 0.22 x 0.17 mm^3	
Theta range for data collection	2.51 to 25.00°.	
Index ranges	-8<=h<=8, -19<=k<=19, -28<=l<=29	
Reflections collected	18732	
Independent reflections	2484 [R(int) = 0.0929]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9822 and 0.9679	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2484 / 0 / 175	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0498, wR2 = 0.1087	
R indices (all data)	R1 = 0.0712, wR2 = 0.1184	
Largest diff. peak and hole	0.211 and -0.184 $e.Å^{-3}$	

A5
Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate (56)

Empirical formula	C15 H20 F2 O3	
Formula weight	286.31	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.953(3) Å	α= 90°.
	b = 20.190(8) Å	β= 93.291(9)°.
	c = 9.179(4) Å	γ = 90°.
Volume	1471.4(10) $Å^3$	
Z	4	
Density (calculated)	1.292 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	608	
Crystal size	0.21 x 0.09 x 0.05 mm^3	
Theta range for data collection	2.02 to 25.00°.	
Index ranges	-9<=h<=9, -23<=k<=24, -10<=l<=10	
Reflections collected	10577	
Independent reflections	2591 [R(int) = 0.4355]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9948 and 0.9783	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2591 / 0 / 185	
Goodness-of-fit on F^2	0.846	
Final R indices [I>2sigma(I)]	R1 = 0.0886, wR2 = 0.1417	
R indices (all data)	R1 = 0.2035, wR2 = 0.1847	
Largest diff. peak and hole	0.364 and -0.299 $e.Å^{-3}$	

A6

Crystal Data and Structure Refinement for ethyl 2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate (57)

Identification code	08013	
Empirical formula	C13 H14 F2 O3	
Formula weight	256.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.556(2) Å	α= 90°.
	b = 14.418(3) Å	β= 101.806(3)°.
	c = 13.450(2) Å	γ = 90°.
Volume	2383.6(7) $Å^3$	
Z	8	
Density (calculated)	1.428 Mg/m^3	
Absorption coefficient	0.120 mm^{-1}	
F(000)	1072	
Crystal size	0.27 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.66 to 26.00°.	
Index ranges	-15<=h<=15, -17<=k<=17, -16<=l<=16	
Reflections collected	18192	
Independent reflections	4684 [R(int) = 0.1454]	
Completeness to theta = 26.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4684 / 0 / 329	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0574, wR2 = 0.1198	
R indices (all data)	R1 = 0.0894, wR2 = 0.1317	
Largest diff. peak and hole	0.321 and -0.215 $e.Å^{-3}$	

A7
Crystal Data and Structure Refinement for (*Z*)-2-(2-bromo-2,2-difluoro-1-hydroxyethylidene)-2,3-dihydro-1H-inden-1-one (63)

Empirical formula	C11 H7 Br F2 O2	
Formula weight	289.08	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.4232(14) Å	α= 90°.
	b = 14.107(3) Å	β= 99.687(3)°.
	c = 10.0068(19) Å	γ = 90°.
Volume	1033.0(3) $Å^3$	
Z	4	
Density (calculated)	1.859 Mg/m^3	
Absorption coefficient	3.988 mm^{-1}	
F(000)	568	
Crystal size	0.21 x 0.10 x 0.04 mm^3	
Theta range for data collection	2.52 to 24.98°.	
Index ranges	-8<=h<=8, -16<=k<=16, -11<=l<=11	
Reflections collected	7292	
Independent reflections	1808 [R(int) = 0.0588]	
Completeness to theta = 24.98°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.862 and 0.478	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1808 / 0 / 146	
Goodness-of-fit on F^2	0.982	
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.0955	
R indices (all data)	R1 = 0.0616, wR2 = 0.1013	
Largest diff. peak and hole	1.174 and -0.508 e.$Å^{-3}$	

A8

Crystal Data and Structure Refinement for (*R*)-2,2-difluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide (65b)

Empirical formula	C18 H19 F2 N O2	
Formula weight	319.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.402(3) Å	α= 90°.
	b = 9.710(4) Å	β= 90°.
	c = 19.088(7) Å	γ = 90°.
Volume	1557.3(10) $Å^3$	
Z	4	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	672	
Crystal size	0.19 x 0.16 x 0.10 mm^3	
Theta range for data collection	2.13 to 24.99°.	
Index ranges	-9<=h<=9, -11<=k<=11, -22<=l<=22	
Reflections collected	11336	
Independent reflections	2739 [R(int) = 0.1280]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.569	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2739 / 0 / 211	
Goodness-of-fit on F^2	0.912	
Final R indices [I>2sigma(I)]	R1 = 0.0512, wR2 = 0.0862	
R indices (all data)	R1 = 0.0692, wR2 = 0.0919	
Absolute structure parameter	-1.5(9)	
Largest diff. peak and hole	0.244 and -0.261 e.$Å^{-3}$	

A9

Crystal Data and Structure Refinement for (*R*)-2,2-difluoro-3-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide (66b)

Empirical formula	C19 H21 F2 N O2	
Formula weight	333.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.8405(17) Å	α= 90°.
	b = 9.7476(19) Å	β= 90°.
	c = 19.684(4) Å	γ = 90°.
Volume	1696.3(6) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	704	
Crystal size	0.36 x 0.25 x 0.13 mm^3	
Theta range for data collection	2.07 to 25.00°.	
Index ranges	-10<=h<=10, -11<=k<=11, -22<=l<=23	
Reflections collected	12172	
Independent reflections	2987 [R(int) = 0.1351]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9873 and 0.9653	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2987 / 0 / 220	
Goodness-of-fit on F^2	1.007	
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.0995	
R indices (all data)	R1 = 0.0603, wR2 = 0.1055	
Absolute structure parameter	-0.1(9)	
Largest diff. peak and hole	0.214 and -0.269 $e.Å^{-3}$	

A10

Crystal Data and Structure Refinement for 2,2-difluoro-2-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)acetamide (67a)

Empirical formula	C20 H21 F2 N O2	
Formula weight	345.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.5802(18) Å	α= 90°.
	b = 9.972(2) Å	β= 90°.
	c = 19.406(4) Å	γ = 90°.
Volume	1660.4(6) $Å^3$	
Z	4	
Density (calculated)	1.382 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	728	
Crystal size	0.28 x 0.20 x 0.18 mm^3	
Theta range for data collection	2.10 to 26.00°.	
Index ranges	-10<=h<=10, -12<=k<=12, -23<=l<=23	
Reflections collected	12918	
Independent reflections	3247 [R(int) = 0.0714]	
Completeness to theta = 26.00°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9816 and 0.9715	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3247 / 0 / 227	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.0990	
R indices (all data)	R1 = 0.0511, wR2 = 0.1022	
Absolute structure parameter	0.1(7)	
Largest diff. peak and hole	0.347 and -0.271 e.$Å^{-3}$	

A11

Crystal Data and Structure Refinement for (2*S*,3*S*)/(2*R*,3*R*)-ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate (81)

Empirical formula	C12 H15 F O3	
Formula weight	226.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.8252(14) Å	α= 66.584(3)°.
	b = 9.0477(16) Å	β= 72.676(4)°.
	c = 9.1771(17) Å	γ = 84.422(3)°.
Volume	569.02(18) $Å^3$	
Z	2	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	240	
Crystal size	0.19 x 0.14 x 0.05 mm^3	
Theta range for data collection	2.45 to 25.00°.	
Index ranges	-9<=h<=9, -10<=k<=10, -10<=l<=10	
Reflections collected	4163	
Independent reflections	1999 [R(int) = 0.0754]	
Completeness to theta = 25.00°	99.4 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.469	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1999 / 0 / 147	
Goodness-of-fit on F^2	0.907	
Final R indices [I>2sigma(I)]	R1 = 0.0561, wR2 = 0.1160	
R indices (all data)	R1 = 0.0874, wR2 = 0.1277	
Largest diff. peak and hole	0.324 and -0.252 $e.Å^{-3}$	

A12

Crystal Data and Structure Refinement for (2*R*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)butanamide (82b)

Empirical formula	C18 H20 F N O2	
Formula weight	301.35	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 19.119(6) Å	α= 90°.
	b = 5.5114(16) Å	β= 109.351(6)°.
	c = 15.207(4) Å	γ = 90°.
Volume	1511.9(8) $Å^3$	
Z	4	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	640	
Crystal size	0.20 x 0.10 x 0.04 mm^3	
Theta range for data collection	2.23 to 26.00°.	
Index ranges	-23<=h<=23, -6<=k<=6, -18<=l<=18	
Reflections collected	5986	
Independent reflections	1648 [R(int) = 0.1603]	
Completeness to theta = 26.00°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.412	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1648 / 1 / 203	
Goodness-of-fit on F^2	0.833	
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.0792	
R indices (all data)	R1 = 0.1328, wR2 = 0.0937	
Absolute structure parameter	1(10)	
Largest diff. peak and hole	0.217 and -0.220 e.$Å^{-3}$	

A13

Crystal Data and Structure Refinement for (2*S*,3*R*)-2-fluoro-3-hydroxy-3-phenyl-N-((*S*)-1-phenylethyl)butanamide (82c)

Empirical formula	C18 H20 F N O2	
Formula weight	301.35	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 19.119(6) Å	α= 90°.
	b = 5.5114(16) Å	β= 109.351(6)°.
	c = 15.207(4) Å	γ = 90°.
Volume	1511.9(8) $Å^3$	
Z	4	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	640	
Crystal size	0.20 x 0.10 x 0.04 mm^3	
Theta range for data collection	2.23 to 26.00°.	
Index ranges	-23<=h<=23, -6<=k<=6, -18<=l<=18	
Reflections collected	5986	
Independent reflections	1648 [R(int) = 0.1603]	
Completeness to theta = 26.00°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.412	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1648 / 1 / 203	
Goodness-of-fit on F^2	0.826	
Final R indices [I>2sigma(I)]	R1 = 0.0608, wR2 = 0.0819	
R indices (all data)	R1 = 0.1326, wR2 = 0.0972	
Absolute structure parameter	0(10)	
Largest diff. peak and hole	0.214 and -0.220 e.$Å^{-3}$	

A14
Crystal Data and Structure Refinement for 3-(4-chlorophenyl)-2-fluoro-3-hydroxybutanoate (85)

Empirical formula	C12 H14 Cl F O3	
Formula weight	260.68	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 13.326(4) Å	α= 90°.
	b = 5.5683(19) Å	β= 92.031(7)°.
	c = 17.049(6) Å	γ = 90°.
Volume	1264.3(7) $Å^3$	
Z	4	
Density (calculated)	1.369 Mg/m^3	
Absorption coefficient	0.308 mm^{-1}	
F(000)	544	
Crystal size	0.29 x 0.11 x 0.08 mm^3	
Theta range for data collection	1.53 to 25.00°.	
Index ranges	-15<=h<=15, -6<=k<=6, -20<=l<=20	
Reflections collected	8734	
Independent reflections	2236 [R(int) = 0.0788]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.617	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2236 / 0 / 156	
Goodness-of-fit on F^2	0.981	
Final R indices [I>2sigma(I)]	R1 = 0.0675, wR2 = 0.1519	
R indices (all data)	R1 = 0.0951, wR2 = 0.1654	
Largest diff. peak and hole	1.119 and -0.327 $e.Å^{-3}$	

A15
Crystal Data and Structure Refinement for ethyl 2-fluoro-3-hydroxy-3-phenylpentanoate (86)

Empirical formula	C13 H17 F O3	
Formula weight	240.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.166(4) Å	α= 90°.
	b = 8.639(3) Å	β= 101.599(6)°.
	c = 12.008(4) Å	γ = 90°.
Volume	1236.4(7) $Å^3$	
Z	4	
Density (calculated)	1.291 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	512	
Crystal size	0.32 x 0.25 x 0.10 mm^3	
Theta range for data collection	1.71 to 25.00°.	
Index ranges	-14<=h<=14, -10<=k<=10, -14<=l<=14	
Reflections collected	8620	
Independent reflections	2181 [R(int) = 0.0571]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.706	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2181 / 0 / 156	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.1112	
R indices (all data)	R1 = 0.0621, wR2 = 0.1187	
Largest diff. peak and hole	0.246 and -0.188 $e.Å^{-3}$	

A16
Crystal Data and Structure Refinement for ethyl 2-fluoro-3-hydroxy-5-methyl-3-phenylhexanoate (88)

Empirical formula	C15 H21 F O3	
Formula weight	268.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.882(3) Å	α= 90°.
	b = 5.6391(17) Å	β= 97.418(6)°.
	c = 26.369(8) Å	γ = 90°.
Volume	1457.1(8) $Å^3$	
Z	4	
Density (calculated)	1.223 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	576	
Crystal size	0.21 x 0.17 x 0.08 mm^3	
Theta range for data collection	2.12 to 25.00°.	
Index ranges	-11<=h<=11, -6<=k<=6, -31<=l<=31	
Reflections collected	9992	
Independent reflections	2573 [R(int) = 0.0892]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9927 and 0.9810	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2573 / 0 / 176	
Goodness-of-fit on F^2	0.947	
Final R indices [I>2sigma(I)]	R1 = 0.0557, wR2 = 0.1156	
R indices (all data)	R1 = 0.0853, wR2 = 0.1256	
Largest diff. peak and hole	0.230 and -0.189 $e.Å^{-3}$	

A17
Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-(2-methoxyphenylamino)-3-phenylpropanoate (98)

Empirical formula	C18 H19 F2 N O3	
Formula weight	335.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.296(14) Å	α= 90.48(3)°.
	b = 16.281(19) Å	β= 100.03(2)°.
	c = 17.14(2) Å	γ = 93.13(2)°.
Volume	3374(7) $Å^3$	
Z	8	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	1408	
Crystal size	0.31 x 0.21 x 0.18 mm^3	
Theta range for data collection	1.68 to 25.00°.	
Index ranges	-14<=h<=14, -19<=k<=19, -20<=l<=20	
Reflections collected	24669	
Independent reflections	11785 [R(int) = 0.1438]	
Completeness to theta = 25.00°	99.1 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9815 and 0.9684	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11785 / 0 / 873	
Goodness-of-fit on F^2	0.916	
Final R indices [I>2sigma(I)]	R1 = 0.0868, wR2 = 0.1968	
R indices (all data)	R1 = 0.1437, wR2 = 0.2301	
Largest diff. peak and hole	0.787 and -0.507 $e.Å^{-3}$	

A18
Crystal Data and Structure Refinement for 3,3-difluoro-1,4-diphenylazetidin-2-one (103)

Empirical formula	C15 H11 F2 N O	
Formula weight	259.25	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 18.024(7) Å	α= 90°.
	b = 5.793(2) Å	β= 103.599(6)°.
	c = 23.796(9) Å	γ = 90°.
Volume	2415.0(16) $Å^3$	
Z	8	
Density (calculated)	1.426 Mg/m^3	
Absorption coefficient	0.111 mm^{-1}	
F(000)	1072	
Crystal size	0.30 x 0.20 x 0.14 mm^3	
Theta range for data collection	1.76 to 25.00°.	
Index ranges	-21<=h<=21, -6<=k<=6, -28<=l<=28	
Reflections collected	8222	
Independent reflections	2124 [R(int) = 0.0717]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9847 and 0.9675	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2124 / 0 / 172	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0473, wR2 = 0.1195	
R indices (all data)	R1 = 0.0568, wR2 = 0.1248	
Largest diff. peak and hole	0.275 and -0.247 $e.Å^{-3}$	

A19

Crystal Data and Structure Refinement for ethyl 3-(diphenylphosphorylamino)-2,2-difluoro-3-phenylpropanoate (104)

Empirical formula	C23 H22 F2 N O3 P	
Formula weight	429.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 23.093(17) Å	α= 90°.
	b = 8.611(7) Å	β= 98.12(2)°.
	c = 10.556(8) Å	γ = 90°.
Volume	2078(3) $Å^3$	
Z	4	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.175 mm^{-1}	
F(000)	896	
Crystal size	0.22 x 0.08 x 0.04 mm^3	
Theta range for data collection	0.89 to 25.00°.	
Index ranges	-27<=h<=27, -10<=k<=10, -12<=l<=12	
Reflections collected	14610	
Independent reflections	3658 [R(int) = 0.2977]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9930 and 0.9625	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3658 / 0 / 272	
Goodness-of-fit on F^2	0.922	
Final R indices [I>2sigma(I)]	R1 = 0.0987, wR2 = 0.2034	
R indices (all data)	R1 = 0.1999, wR2 = 0.2502	
Largest diff. peak and hole	0.419 and -1.010 $e.Å^{-3}$	

A20

Crystal Data and Structure Refinement for ethyl 3-(2-chlorophenyl)-2,2-difluoro-3-(2-methoxyphenylamino)propanoate (109)

Empirical formula	C18 H18 Cl F2 N O3	
Formula weight	369.78	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.513(3) Å	α= 88.100(6)°.
	b = 13.263(4) Å	β= 86.908(8)°.
	c = 16.012(5) Å	γ = 85.729(7)°.
Volume	1799.4(10) $Å^3$	
Z	4	
Density (calculated)	1.365 Mg/m^3	
Absorption coefficient	0.248 mm^{-1}	
F(000)	768	
Crystal size	0.35 x 0.16 x 0.06 mm^3	
Theta range for data collection	1.27 to 25.00°.	
Index ranges	-10<=h<=10, -15<=k<=15, -19<=l<=19	
Reflections collected	13155	
Independent reflections	6283 [R(int) = 0.1068]	
Completeness to theta = 25.00°	99.3 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.574	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6283 / 0 / 455	
Goodness-of-fit on F^2	0.825	
Final R indices [I>2sigma(I)]	R1 = 0.0640, wR2 = 0.1139	
R indices (all data)	R1 = 0.1454, wR2 = 0.1403	
Largest diff. peak and hole	0.298 and -0.286 $e.Å^{-3}$	

A21

Crystal Data and Structure Refinement for ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)propanoate (112)

Empirical formula	C19 H21 F2 N O4	
Formula weight	365.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.982(2) Å	α= 61.903(3)°.
	b = 10.289(2) Å	β= 84.003(4)°.
	c = 10.844(3) Å	γ = 66.636(4)°.
Volume	897.3(4) $Å^3$	
Z	2	
Density (calculated)	1.352 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	
F(000)	384	
Crystal size	0.40 x 0.20 x 0.17 mm^3	
Theta range for data collection	2.14 to 25.00°.	
Index ranges	-11<=h<=11, -12<=k<=12, -12<=l<=12	
Reflections collected	6453	
Independent reflections	3123 [R(int) = 0.0524]	
Completeness to theta = 25.00°	98.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.411	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3123 / 0 / 238	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(I)]	R1 = 0.0524, wR2 = 0.1298	
R indices (all data)	R1 = 0.0646, wR2 = 0.1366	
Largest diff. peak and hole	0.285 and -0.302 $e.Å^{-3}$	

A22 Lecture Courses Attended

Advanced Structure Determination, Prof. E. Hope

Organic Strategies, Dr. P. Jenkins/ Dr. S. Handa

A23 Conferences Attended

Organic Synthesis Symposium. University of Loughborough, October 2007

Introduction to Process Chemistry. GSK Stevenage, October 2007

Postgrad. RSC fluorine Subject Group Meeting, University of Leicester, September 2007

Sheffield Stereochemistry Meeting. University of Sheffield, January 2008

Organic Synthesis Symposium. University of Loughborough, October 2008

Postgrad. RSC Fluorine Subject Group Meeting. Newcastle University, September 2008

Sheffield Stereochemistry Meeting. University of Sheffield, January 2009

Meeting of the Organic Division of the RSC. University of Birmingham, April 2009

19th International Symposium on Fluorine Chemistry. Jackson Hole, Wyoming, USA, August 2009

Postgrad. RSC Fluorine Subject Group Meeting. University of Southampton, September 2009

Organic Synthesis Symposium. University of Loughborough, October 2009

Sheffield Stereochemistry Meeting. University of Sheffield, January 2010

East Midlands Organic Symposium - University of Leicester, April 2010

Postgrad. RSC Fluorine Subject Group Meeting. University of Durham, September 2010

A24 Presentations

Poster- 'A One-Pot Asymmetric Reformatsky Reaction of Ethyl Bromodifluoroacetate.' Presented at RSC meeting on Fluorine Chemistry at the University of Leicester.

Poster- 'A One-Pot Asymmetric Reformatsky Reaction of Ethyl Bromodifluoroacetate.' Presented at Postgrad. RSC Fluorine Subject Group Meeting. Newcastle University.

Poster- 'Asymmetric Reformatsky Reaction of Ethyl Iododifluoroacetate with Aromatic Ketones.' Presented at the Liverpool Summer School on Catalysis.

Poster- 'Asymmetric Reformatsky Reaction of Ethyl Iododifluoroacetate with Aromatic Ketones.'(Updated). Presented at the University of Southampton.

Poster- ‘Asymmetric Reformatsky Reaction of Ethyl Iododifluoroacetate with Aromatic Ketones’ M. Fornalczyk, A. M. Stuart. Presented at 19th Intl Symposium on Fluorine. Jackson Hole, Wyoming, USA.

Presentation- ‘A One-Pot Asymmetric Reformatsky Reaction of Ethyl Iododifluoroacetate with Aromatic Ketones’ M. Fornalczyk, A. M. Stuart. Presented at the Annual Departmental Research Day at the University of Leicester.

Presentation- ‘A One-Pot Asymmetric Reformatsky Reaction of Ethyl Iododifluoroacetate with Aromatic Ketones’ M. Fornalczyk, A. M. Stuart. Presented at Fluorine Subject Group Meeting at the University of Durham.