Erik Fuglseth

Synthesis of 1-aryl-2-fluoroethanones and their use in the preparation of enantioenriched 1-aryl-2-fluoroethanols and 1-aryl-2-fluoroethylamines

Thesis for the degree of Philosophiae Doctor

Trondheim, August 2010

Norwegian University of Science and Technology
Faculty of Natural Sciences and Technology
Department of Chemistry

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Preface

The presented work has been conducted at the Department of Chemistry, Norwegian University of Science and Technology (NTNU) from April 2006 to May 2010. The funding has been provided by the Department of Chemistry.

Several people have during the last four years collaborated with me and made important contributions to this thesis. These efforts are described in the chapters where the work is presented and have all been greatly appreciated.

The work has been carried out under the supervision of Associate Professor Bård Helge Hoff. He has given me the room to let me pursue my own ideas but at the same time guided me in the right direction during times of frustration. Without his inspiring presence I am convinced that the road would have been much longer and more winding. I am especially thankful to Bård for the understanding he has shown when I have spent afternoons and weekends at home with my family instead of working in the lab.

Past and present members of the "Fluorine family", especially Associate Professor Eirik Sundby, are thanked for fruitful advice and discussions during group meetings, as well as for creating a social working environment. I regret not winning a single round of go-cart.

Christopher James Collyer, Frank Edward Collyer and PhD Christian Sperger are all gratefully acknowledged for their constructive suggestions and linguistic advice.

My colleagues among the PhD students at our department are thanked for creating a working environment where both meaningful and meaningless discussions are appreciated. I especially want to thank those that I have had the pleasure of sharing office with; Susana, for providing a female touch to the office, Jon Erik, for sharing his humorous views on life and Thor, for generously donating coffee whenever needed.

I am also grateful to my family for always supporting me during my time at the university.

Most of all I am thankful to Stine for making it possible for me to complete this thesis while being the father of two small girls. Thank you for always understanding and for creating a home I look forward to coming back to every day.

Erik Fuglseth
Trondheim, May 2010

Contents

Abstract

The synthesis of a series of 1-aryl-2-fluoroethanones and their use in the preparation of enantioenriched 1-aryl-2-fluoroethanols and 1-aryl-2-fluoroethylamines has been investigated. Several chiral analogues of the antimycotic agents Butenafine and Terbinafine have also been prepared and their antifungal activity assessed.

Starting with the corresponding 1-arylethanones, one nucleophilic and three electrophilic fluorination methods towards 1-aryl-2-fluoroethanones were compared. The target compounds containing electron donating aromatic substituents were isolated in high yields (91-76%) by fluorinating the trimethylsilyl ethers of the 1-arylethanones with Selectfluor®. For substrates bearing more electron withdrawing substituents, however, the microwave (MW) mediated Selectfluor® fluorination of 1-arylethanones in methanol gave the best results (86-41% yield). Compared to the thermal synthesis, the MW assisted method resulted in a significant reduction in reaction time and chemical consumption. For the nucleophilic fluorination of 1-aryl-2-bromoethanones using tetrabutylammonium bifluoride, moderate to poor yields were experienced (51-20%).

Following their synthesis, two approaches for the asymmetric reduction of eight 1-aryl-2-fluoroethanones were investigated. Catalysed by the proline based (*R*)-MeCBS in 1,2-dimethoxyethane, all the ketones were reduced with excellent to good enantioselectivity (99.5-91.5% ee). A ruthenium catalysed asymmetric transfer hydrogenation was also investigated. Four catalytic systems were tested, each constructed of a ruthenium complex coordinated to a chiral diamine ligand. The best results were achieved using $[RuCl_2(mesitylene)]_2$ coordinated to (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine in a formic acid/triethylamine mixture. The overall enantioselectivity (99.5-85.0% ee) was lower than for the (*R*)-MeCBS reductions. The absolute configuration of the products was determined by circular dichroism (CD) using the exciton chirality method.

A Mitsunobu inversion of the prepared (*R*)-1-aryl-2-fluoroethanols was employed in the synthesis of the corresponding (*S*)-1-aryl-2-fluoroethylamines. For six of the substrates, clean inversion of stereochemistry was observed. However, racemisation and low yields were the result when electron donating substituents were present at the aromatic ring of the substrates. When substituted with a cyano or a nitro group, fluorine elimination occurred, thereby limiting the yield for these transformations. To gain access to the (*R*)-1-aryl-2-fluoroethylamines, a Novozym 435 catalysed kinetic resolution of the racemic 1-aryl-2-fluoroethylamines was performed. This gave the (*R*)-amines in excellent to good

enantiomeric excess (99.0-96.0%). The absolute configuration of the amines was determined by CD.

Five chiral derivatives of both Butenafine and Terbinafine were synthesised and evaluated for their antifungal activity towards *Cryptococcus neoformans*. The most active Butenafine derivative, having a methyl substituent at the carbon connected to the central nitrogen atom, performed equally well as the parent compound. Testing each of the enantiomers of this compound against *Cryptococcus neoformans*, *Cryptococcus diffluens* and *Trichosporon cutaneum* revealed that most of the activity originated from the (*R*)-enantiomer. Against each of the test strains, the (*R*)-enantiomer showed equal or higher antifungal activity than Butenafine.

Appended papers

Paper I
Fuglseth, E., Thvedt, T. H. K., Møll, M. F., Hoff, B. H.
Electrophilic and nucleophilic side chain fluorination of *para*-substituted acetophenones
Tetrahedron **2008**, 64 (30-31), 7318-7323.

Paper II
Krane Thvedt, T.H., Fuglseth, E., Sundby, E., Hoff, B. H.
Microwave assisted fluorination: an improved method for side chain fluorination of substituted 1-arylethanones
Tetrahedron **2009**, 65 (46), 9550-9556.

Paper III
Fuglseth, E., Sundby, E., Bruheim, P., Hoff, B. H.
Asymmetric reduction using (*R*)-MeCBS and determination of absolute configuration of *para*-substituted 2-fluoroarylethanols
Tetrahedron: Asymmetry **2008**, 19 (16), 1941-1946.

Paper IV
Fuglseth, E., Sundby, E., Hoff, B. H.
Ruthenium-catalysed asymmetric transfer hydrogenation of *para*-substituted α-fluoroacetophenones
J. Fluorine Chem. **2009**, 130 (6), 600-603.

Paper V
Krane Thvedt, T.H., Fuglseth, E., Sundby, E., Hoff, B. H.
Enantioenriched 1-aryl-2-fluoroethylamines. Efficient lipase catalysed resolution and limitations to the Mitsunobu inversion protocol
Tetrahedron **2010**, 66 (34), 6733-6743.

Paper VI
Fuglseth, E., Otterholt, E., Høgmoen, H., Sundby, E., Charnock, C., Hoff, B. H.
Chiral derivatives of Butenafine and Terbinafine: synthesis and antifungal activity
Tetrahedron **2009**, 65 (47), 9807-9813.

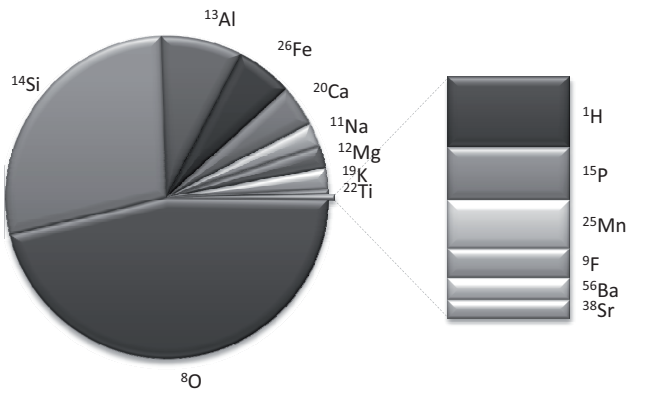
Abbreviations and symbols

Δε	Molar extinction
λ_{max}	Absorption maximum
ATH	Asymmetric transfer hydrogenation
Bn	Benzyl
CD	Circular dichroism
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DME	1,2-Dimethoxyethane
ECD	Electronic circular dichroism
ee	Enantiomeric excess
HPLC	High performance liquid chromatography
ICP-MS	Inductively coupled plasma mass spectroscopy
LiHMDS	Lithium hexamethyldisilazane
MeCBS	Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole
MeCN	Acetonitrile
MIC	Minimum inhibitory concentration
MM2	Molecular mechanical force field 2
MS	Mass spectroscopy
MTBE	Methyl *tert*-butyl ether
MW	Microwave
NFSI	*N*-Fluorobenzenesulfonimide
pK_a	Negative logarithm of the acid dissociation constant
SAAS	Semisolid agar antifungal susceptibility
TBABF	Tetrabutylammonium bifluoride
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TMSCl	Trimethylsilyl chloride
TsCYDN	*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine
TsDPEN	*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine
W	Watt

1. Introduction

1.1 Why organofluorine?

Despite the fact that fluorine is the 13th most abundant element in the earth's crust (Figure 1.1),[1] organic compounds containing fluorine are virtually absent in nature. No major biological pathways rely on fluorinated metabolites and there is only one known naturally occurring enzyme which catalyses carbon-fluorine bond formation.[2-4] This seemingly insignificant spot missed by nature means that organic chemists are now doing the work evolution has done over billions of years for the other elements in organic chemistry. This presents many great challenges but it also gives an entirely synthetic dimension to organic chemistry, with unique chemistry and novel materials with extreme properties discovered every day.[5]



Element	Abundance [%]
^{8}O	46,10
^{14}Si	28,20
^{13}Al	8,23
^{26}Fe	5,63
^{20}Ca	4,15
^{11}Na	2,36
^{12}Mg	2,33
^{19}K	2,09
^{22}Ti	0,57
^{1}H	0,14
^{15}P	0,11
^{25}Mn	0,10
^{9}F	0,06
^{56}Ba	0,04
^{38}Sr	0,04

Figure 1.1: The relative amounts of the 15 most abundant elements in the earth's crust.[1]

Incorporating one or more fluorine atoms into a molecule often has a profound effect on the physical, electronic and physiological properties of an organic compound. The usefulness of this effect, sometimes called "fluorine magic", can be visualised by looking at the vast range of advanced materials, pharmaceuticals and agrochemicals which owe their valuable properties to the presence of one or more fluorine atoms.

Due to the sometimes extreme effects it can have on the properties of organic compounds, fluorine is often referred to as "a small atom with a big ego". Some of these

effects can be rationalised and explained from a quantum chemical point of view, others are complicated by the cooperative work of these effects.[6] This section will present a brief overview of some of the most pronounced effects fluorine has on the physical, electronic and physiological properties of organic compounds, and how they are utilised in the design of new pharmaceuticals.

1.1.1 Physical properties

The physical properties of fluoroorganic compounds are mainly governed by two factors; (1) The combination of high electronegativity with moderate size and the excellent match between the fluorine 2s or 2p orbitals with the corresponding orbitals of carbon and (2) the resulting extremely low polarizability of fluorine.[7]

As a consequence of the low polarizability, perfluorinated compounds have very weak intermolecular dispersion interactions. This explains the perhaps most characteristic physical properties for most perfluorocarbons; their unusually low boiling points. Unlike most halogenated compounds which attain higher boiling points along with the increased number of halogens present, perfluorinated compounds are extremely volatile and must be handled with caution (Figure 1.2).

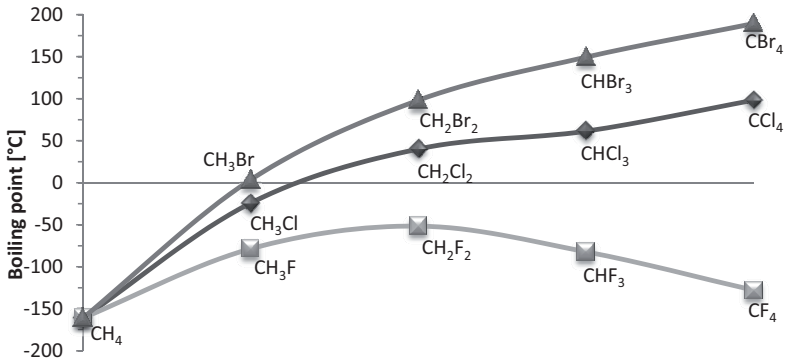


Figure 1.2: Boiling points of halomethanes.

Despite the very high electronegativity of fluorine (4.0 at the Pauling scale),[8] perfluorinated organic compounds are significantly more lipophilic compared to the non-fluorinated counterparts. This apparent contradiction is explained by the fact that all the local dipole moments cancel each other out, resulting in a global non-polar compound. This makes the introduction of perfluorinated moieties a useful tool when highly hydrophilic molecules need to be made more lipophilic.[6,9]

Perfluorinated carbon chains are far more stiff and rigid than the corresponding non-fluorinated chains. This phenomenon can be visualised when comparing the well known rigid Teflon® polymer (polytetrafluoroethene), used among other things as coating in frying pans, with the highly flexible plastic polyethene. The reason for this difference in physical properties is attributed to the larger size of fluorine compared to hydrogen. This makes the energy barrier for the internal rotation of the carbon-carbon bond higher for perfluorinated chains, thereby increasing the rigidity.[6]

1.1.2 Electronic properties

The electronic effect of a fluorine substituent is largely dependent on whether it is attached to a σ-electron system or to a π-electron system. As a consequence of the high electronegativity of the fluorine atom, fluorine substituents are strongly inductively electron withdrawing, thereby activating nearby reaction centres for nucleophilic attack. The lone-pair electrons of fluorine can, however, donate electrons back through π-bonds. This resonance effect, although weak, will affect the reaction rates and the regiochemistry of reactions such as electrophilic aromatic substitution reactions.[10,11]

As with other electronegative substituents, fluorine insertion increases the acidity of a molecule. However, due to the electron donating resonance effect discussed above, this increase in acidity is smaller compared to the other halogens when attached to π-electron systems.[12]

Unlike the fluorine atom, the trifluoromethyl group and perfluoroalkyl groups are always net electron withdrawing substituents. For perfluoroalkyl groups the inductive effect increases with increasing number of fluorine atoms until it levels off from CF_2CF_3. The trifluoromethyl group has an electron withdrawing effect comparable to nitro and cyano groups when attached to π-electron system. This effect is rationalised by the ability of these groups to delocalize lone-pair electrons by negative hyperconjugation as illustrated for the two *para*-substituted anilines in Figure 1.3.[6]

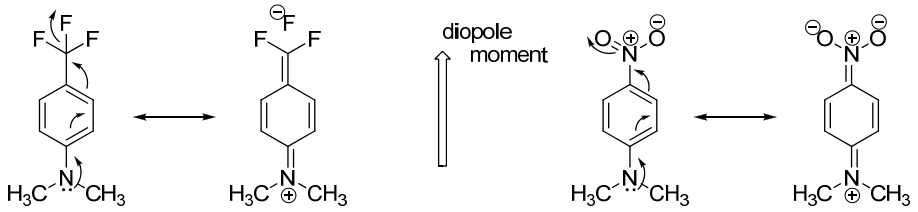


Figure 1.3: Negative hyperconjugation as explanation for the similarity in electron withdrawing effect between the CF_3 and NO_2 group.[6]

Negative hyperconjugation was proposed in 1950 to explain the strong *meta*-orienting influence of trifluoromethyl groups in electrophilic aromatic substitution reactions.[13] The phenomenon has been debated and an alternative interpretation of the experimental data has been proposed.[14] It is now, however, widely recognised that the hyperconjugation plays an important role in the stabilisation of the β-carbanion **A**, in the shortening and strengthening of the C_α-C_β bond in the systems **A**, **C** and **D**, and in the high reactivity of the C-F bond in system **D** (Figure 1.4).[6]

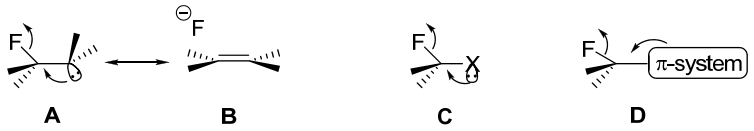


Figure 1.4: Some effects of negative hyperconjugation.[6]

The near optimum overlap between the 2s and 2p orbitals of fluorine with the corresponding orbitals of carbon makes the C-F bond extraordinarily stable. The bond length of a carbon-fluorine bond is typically 1.35 Å, making it the most stable bond between carbon and another element. As a consequence, fluorine is a poor leaving group for aliphatic nucleophilic substitution. Even when reacted with strong nucleophiles, alkylfluorides mostly react via elimination (E2 or $E1_{CB}$) rather than substitution (S_N2).[15]

1.1.3 Fluorine in pharmaceuticals

Over the past years fluorine has become a common substituent in pharmaceutical compounds.[16,17] Its unique ability to influence a molecule's properties combined with its small size makes fluorine a valuable tool in drug discovery. The effect in terms of physiological and pharmacological properties is often difficult to predict but the introduction of a fluorine atom rarely passes unnoticed.

Stability toward metabolic degradation is an important factor when designing a drug. Fluorine insertion has frequently been used as a tool to selectively block positions in a molecule prone to metabolic degradation.[18,19] Oxidation of aromatic rings can, for instance, be prevented by fluorination of the *para*-position (Figure 1.5). While other electron withdrawing elements may play the same role, the use of fluorine substitution has the advantage of avoiding large steric alterations in the molecule.[20]

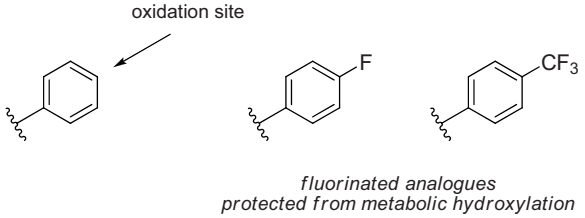


Figure 1.5: Prevention of biological oxidation of an aromatic ring by fluorination.

Drugs containing basic nitrogen atoms are often troubled by low oral bioavailability due to the high pK_a value of the nitrogen atom. Whether or not basic nitrogen atoms are protonated in the biological environment may not only be critical for binding potency at the target but also affects properties such as lipophilicity and membrane permeability. Introducing a fluorine atom in the molecule reduces the pK_a value and higher oral bioavailability is often the result.[21-23] The orally administered thrombine inhibitor shown in Figure 1.6 illustrates this by the elevated level of the drug found in the blood of rats (C_{max}) given the fluorinated drug analogue.[24]

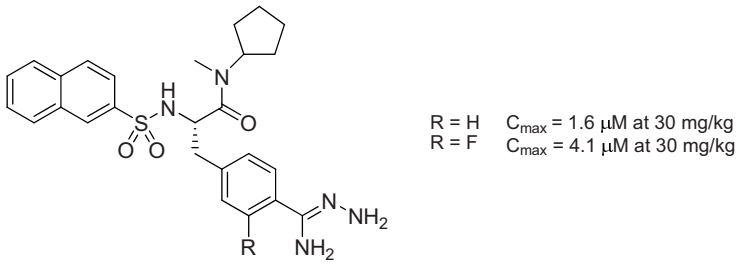


Figure 1.6: The effect of fluorine on the oral bioavailability.[24]

Bioisosteres are substituents or groups with similar physical or chemical properties and are frequently used in drug design. The reason for changing one bioisostere for another is to enhance the desired biological or physiological properties of a compound without

making significant changes in the chemical structure. Fluorine is involved in several bioisosteres, the most common being the well known hydrogen-fluorine replacements (Figure 1.7).[25,26] Other fluorine bioisosteres are fluoroalkenes for amides,[27] C-CF_3 groups for carbonyl groups[28] and fluorine for hydroxyl groups.[29,30]

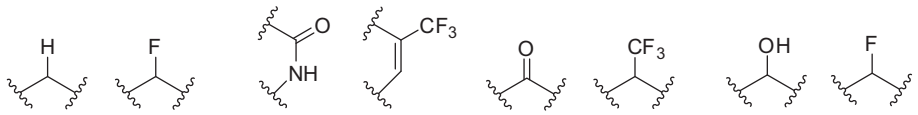


Figure 1.7: Some examples of bioisosteres involving fluorine.

"Suicide inhibition" is a term which describes the irreversible binding of a ligand to a protein followed by loss of the original activity. This is a common mode of action for a number of pharmaceuticals and there are several examples where fluorine is the active part in the inhibition process.[31,32]

More recently, an increased focus has been put on unveiling the interactions between fluorinated ligands and the active site in proteins. Fluorine substituents interact efficiently with peptide bonds (Figure 1.8) and, by performing so-called "fluorine scans" on lead drug candidates, the goal is to strengthen the protein-ligand binding. This would result in a more potent drug in terms of increased binding efficacy and selectivity.[33]

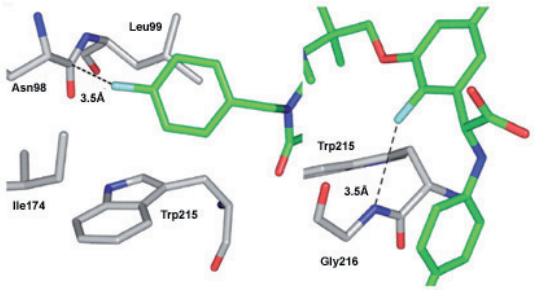


Figure 1.8: Interactions between peptidic C=O and N-H moieties in the enzyme thrombin and the C-F residue of two different inhibitors.[33]

1.2 Chirality

Chirality is a property associated with three-dimensional objects. An object is defined as chiral if it is non-superimposable with its own mirror image. The word chiral originates from the Greek word for hand (kheir) and perhaps the most recognisable way to illustrate chirality is by looking at our hands. They are mirror images of each other but not superimposable.

In chemistry, chirality is related to the three dimensional properties of molecules. Some molecules can exist in two forms which are constitutionally equal but the three dimensional arrangement of the atoms makes them into non-superimposable mirror images (Figure 1.9). These two forms of a molecule are referred to as enantiomers.

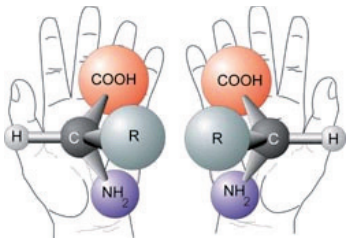


Figure 1.9: Illustration of the non-superimposable mirror images of chiral molecules.

The most common group of chiral compounds are molecules with stereogenic centres. These stereogenic centres are atoms, usually carbon, attached to four different groups. The majority of chiral compounds owe their chirality to such tetrahedral atoms but it can also originate from stereogenic axes or stereogenic planes.[34]

In an achiral environment, two enantiomers will have identical chemical and physical properties, except the ability to rotate plane polarized light in opposite directions. In chiral surroundings, however, the two enantiomers may behave differently.

1.2.1 Chirality in biological systems

Very often, living organisms utilise only one of the enantiomers of a chiral compound. Proteins are, for instance, exclusively made up of *L*-amino acids and nucleic acids are based on *D*-sugars.[35] Since biological systems are chiral, the two different enantiomers of a bioactive compound can interact differently with bio-receptors, giving rise to two different responses. Our sense of smell is a good illustration of such interactions, one

example being the chiral compound 3-methylthiobutanal, where the (*R*)-enantiomer smells like cooked potatoes while the (*S*)-enantiomer is odourless (Figure 1.10).[36]

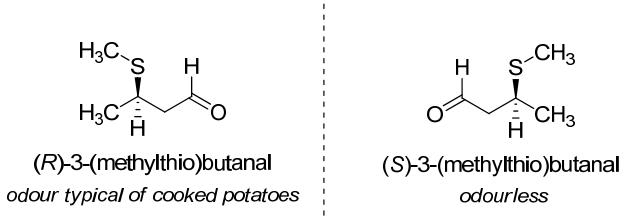


Figure 1.10: The different odours of the enantiomers of 3-methylthiobutanal.[36]

As a consequence of the ability of two enantiomers to interact differently with a biological system like the human body, the focus on chirality in medicinal chemistry has been increasing over the last decades. Many pharmaceuticals are chiral molecules and, often, the desired effect originates from only one of the enantiomers. The other enantiomer may be inactive but in worst case it has an inhibiting or harmful effect. This is illustrated by the drug penicillamine, where the (*S*)-enantiomer is used to treat Wilson´s disease and rheumatoid arthritis while the (*R*)-enantiomer is highly toxic (Figure 1.11). The drug is, therefore, sold as the enantiomerically pure (*S*)-form.[37] Even if it has no harmful effect, the unwanted enantiomer represents unnecessary strain enforced on the body's liver and kidneys. For this reason it is desirable to make enantiomerically pure pharmaceuticals. In 2005, single-enantiomer therapeutics had sales of $225 billion, representing 37% of the total final formulation pharmaceutical market.[38] The pharma companies' increased interest in single-enantiomer drugs is, however, also partly economically motivated. The time and costs to bring a drug to the market can be significantly reduced by turning an existing racemic drug into the single-enantiomer formulation. This "chiral switch" also prolongs the company´s patent protection for the drug.

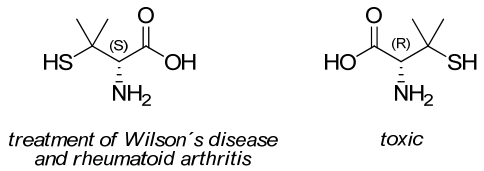


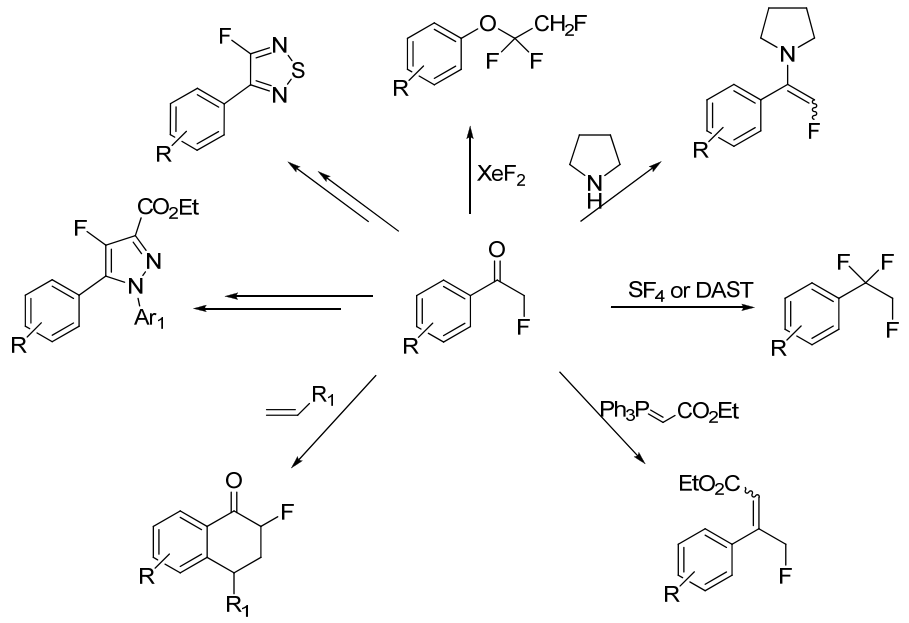
Figure 1.11: The biological effects of the enantiomers in penicillamine.

2. 1-Aryl-2-fluoroethanones

This chapter summarises Paper I and Paper II. Master of Science Thor Håkon Krane Tvedt is acknowledged for optimising the microwave assisted fluorination method, as well as for performing several of the fluorination reactions discussed in this chapter. Master of Technology Tor Arne Krakeli and Master of Technology Maria Førde Møll are acknowledged for their contributions regarding fluorination reactions performed on 1-acetonaphthone and on the 4-F and 4-CN substituted acetophenones.

2.1 Introduction

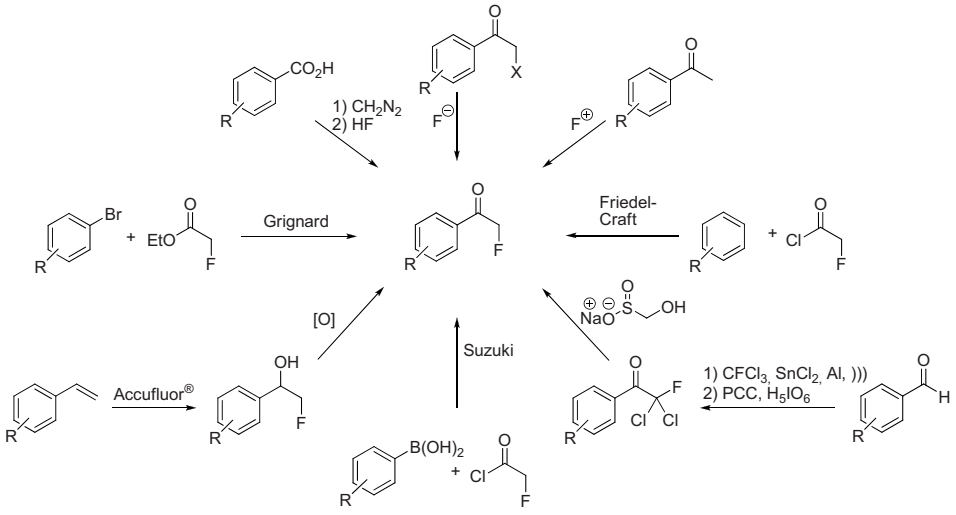
With very few fluorinated organic compounds occurring in nature, any fluorinated compound we wish to access have to be synthesised. Fluorinated building blocks which can be incorporated into larger structures are, therefore, highly valuable in the field of medicinal and material chemistry. 1-Aryl-2-fluoroethanones are a class of such building blocks and offer an excellent starting point for the synthesis of a wide range of fluorinated compounds. As Scheme 2.1 illustrates, reactions can be performed at the carbonyl group, the α-carbon or the aromatic ring, providing routes to, among others, fluorinated tetralones,[39] pyrozoles[40] and thiadiazoles.[41] 1-Aryl-2-fluoroethanones are also suitable starting materials for compounds such as 1,1,2-trifluoroethyl aryl ethers,[42] 1-aryl-2-fluoroenamines,[43] 1-aryl-1,1,2-fluoroethanes[44] and allylic fluorides.[45,46]



Scheme 2.1

2.1.1 Synthetic routes to 1-aryl-2-fluoroethanones

When this work was undertaken, no systematic study on the synthesis of 1-aryl-2-fluoroethanones had been conducted. Most of the reported work treated approaches targeting α-fluoroacetophenone (**1c**) as product and only a limited number of analogues had been synthesised. Various synthetic routes towards these compounds have been reported. Some of these routes are shown in Scheme 2.2 and discussed briefly below.



Scheme 2.2

The fluoride ion is a powerful nucleophile and the displacement of halogen atoms or other good leaving groups with a fluoride anion is a well known strategy for incorporating fluorine into a molecule. Starting with 1-aryl-2-bromoethanones, there are several reports on fluorinations having been performed with KF. The more classic conditions with phase transfer catalysis[47] have recently been improved by the use of ionic liquids[48,49] and various co-catalysts,[50,51] resulting in milder reaction conditions and enhanced activity of the fluoride ion. Introduced in 1987,[52] tetrabutylammonium bifluoride (TBABF) is another nucleophilic fluorinating agent. The reaction conditions for this reagent are generally mild and a few 1-aryl-2-fluoroethanones have been synthesised using TBABF.[53-55] The related tetrabutylammonium fluoride (TBAF) has also shown promising results as a fluorinating reagent for structurally similar compounds.[56]

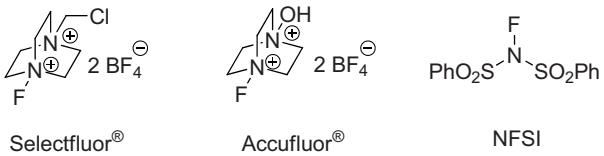
Friedel Crafts acylation is another common route to arylketones. It has been utilised successfully on benzene and some of its electron rich derivatives to synthesise 1-aryl-2-fluoroethanones.[57,58] Electron poor benzenes are, however, unreactive as the aromatic ring is deactivated towards electrophilic aromatic substitution. Naphthyl derivatives are also poor substrates for this reaction, resulting in complex mixtures of isomers.[59] Another drawback is the use of the highly toxic fluoroacetyl chloride, known to block the citric acid cycle in human metabolism.[60]

Reactions involving organometallic reagents like the Grignard reaction can also be used for the introduction of a fluoroacetyl functionality in aromatic compounds. Ethyl fluoroacetate, also highly toxic, has been used to prepare α-fluoroacetophenone (**1c**) in a moderate 63% yield,[61] while 88% yield was reported with the use of a Weinreb amide.[62]

A more cumbersome procedure, starting with a benzaldehyde, has previously been reported.[63] This three step reaction involves the reductive addition of $CFCl_3$ to the aldehyde followed by pyridinium chlorochromate oxidation of the alcohol before the α-fluoroacetophenone is released by dechlorination. Not surprisingly, the method was hampered by poor yields (35-25%).

Benzoic acid derivatives have also been used as substrates for making several 1-aryl-2-fluoroethanones.[43,64] They are inexpensive and readily available compounds but the method involves the use of diazomethane, which is explosive, and hydrogen fluoride which is highly toxic and corrosive.

More safe fluorinations can be performed using electrophilic fluorinating agents. Although early routes to 1-aryl-2-fluoroethanones involved the use of F_2-gas[65] and trifluoromethyl hypofluorite,[66] less hazardous reagents such as Accufluor®,[63,67,68] Selectfluor®[69,70] and *N*-fluorobenzenesulfonimide (NFSI)[71] (Figure 2.1) have later been developed. Using these reagents, several starting materials have been utilised to access 1-aryl-2-fluoroethanones, including trimethylsilyl enol ethers,[65,66,72] metal enolates,[73,74] enamines and imines.[71] The direct fluorination of 1-arylethanones using Selectfluor®[40,75] or Accufluor®[76] has also been performed, giving the corresponding α-fluoroketones in decent yields. Accufluor® has been used to fluorinate styrene, providing the corresponding fluorinated secondary alcohol in 90% yield.[63] The subsequent oxidation to α-fluoroacetophenone (**1c**) has not yet been reported but results from similar compounds make this a promising route.[77]



Selectfluor® Accufluor® NFSI

Figure 2.1: Structures of some electrophilic fluorinating agents.

Cross coupling reactions between various acyl chlorides and aryl boronic acids have been shown to produce acetophenones in decent yields.[78,79] Several trifluoroacetophenones have also been prepared from similar reactions.[80,81] However, no data has been reported on the monofluorinated analogues. This might be a useful approach to access the α-fluoroacetophenones, although involving the use of hazardous and expensive chemicals.

2.1.2 Microwave irradiation in organofluorine chemistry

Microwave irradiation is a powerful and easily controllable heating source. Its popularity in organic synthesis is primarily attributed to the rate acceleration that can be seen in many reactions, especially those involving polar transition states.[82-85] In addition to higher reaction rate, the use of microwave irradiation has been shown to give increased yields,[86] induction of regio- or chemoselectivity[87,88] and a change of reaction mechanism.[88]

Although no microwave assisted fluorinations of acetophenones had been reported as this project was started, there were several examples of successful fluorinations of other substrates. The earliest reports generally focused on nucleophilic approaches while,[89-93] more recently, an increased interest in electrophilic reagents such as Selectfluor® has emerged.[94-98]

2.2 Electrophilic and nucleophilic side chain fluorination of substituted 1-arylethanones

The initial goal of this project was to synthesise a series of eight *para*-substituted α-fluoroacetophenones (**1a-h**) (Figure 2.2). To reach this target, the original strategy was to perform a nucleophilic fluorination of the corresponding α-bromoacetophenones **2a-h** by using KF under classic phase transfer conditions.[47] Early experiments, however, revealed this route as unsuitable for these substrates and the use of the non-hazardous and mild fluorinating agent TBABF was instead investigated (Scheme 2.4). Reports in the literature proposed this as a promising route but, as the work commenced, it was realised that this strategy would not give the desired products in adequate yields.[55]

Thus, two new strategies were identified and examined. Trimethylsilyl enol ethers had previously been shown to readily undergo electrophilic fluorinations,[65,66,72] while the direct fluorination of acetophenones using Selectfluor® also appeared promising.[40] A possible improvement of the latter method by the use of microwave irradiation as the heating source was also investigated. The results from the different strategies are briefly described and compared below.

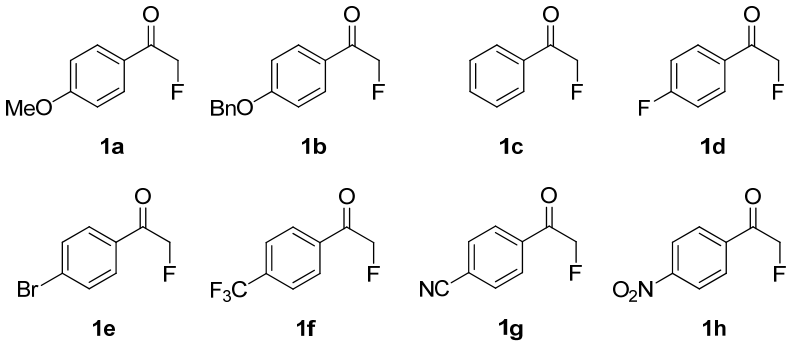


Figure 2.2: The initial target compounds for the fluorination reactions.

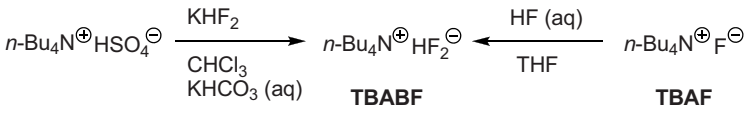
2.2.1 Nucleophilic displacement

The initial nucleophilic fluorination experiments were performed on the α-bromoacetophenones **2c-d** and **2g-h** using dry fine powdered KF[99] (2 equiv) and 18-crown-6 (0.08 equiv) in refluxing acetonitrile. Unfortunately, all the reactions were troubled by poor yields (37-8%) due to the formation of several by-products, the main type being the cyclopropane derivative **3** (Scheme 2.4). Based on these early results, it was concluded that this approach was not suitable for preparing the α-fluoroacetophenones **1a-h**.

Simultaneously with the KF fluorinations, attempts to fluorinate **2d** and **2g** with TBAF (2 equiv) in acetonitrile (60 °C) were performed. Unfortunately, these experiments also failed, yielding only traces of the fluoroketones **1d** and **1g**.

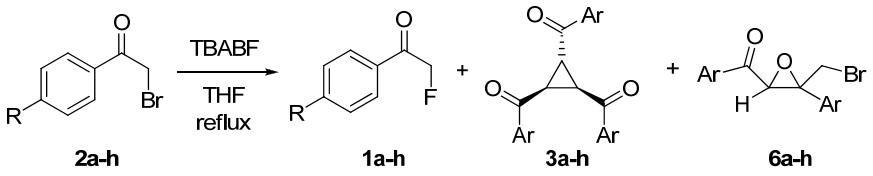
As the fluorinations with both KF and TBAF were unsuccessful, attention was turned to TBABF. Landini and co-workers had reported a procedure for preparing the reagent by an anion exchange reaction between tetrabutylammonium hydrogen sulphate and potassium bifluoride (Scheme 2.3).[100] After conducting this procedure, however, the obtained product had a dark red colour and showed poor activity in test reactions. The product also proved difficult to analyse, as it appeared to be pure by standard organic analysis methods (NMR, MS and IR). Attempts to analyse the product by titration and ICP-MS were also

made but no uniform results regarding its purity could be obtained. Following this, TBABF was attempted prepared by reacting TBAF with aqueous HF (Scheme 2.3).[101] The results were, however, similar to the former method. TBABF was, therefore, purchased as an acetonitrile solution.



Scheme 2.3

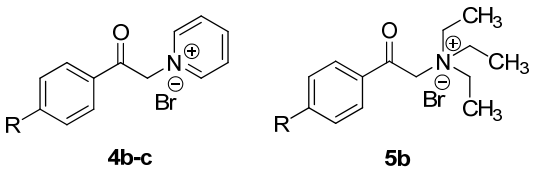
The original literature based set-up for the nucleophilic displacement of the α-bromoacetophenones **2a-h** with TBABF involved the addition of pyridine as a base.[54,55] In our hands, however, the use of either pyridine or triethylamine resulted in the formation of significant amounts of the ammonium salt by-products **4** and **5**, shown in Figure 2.3. The more sterically hindered 2,6-dimethylpyridine gave less by-product formation but no benefit could be found in the use of these bases. The best reaction conditions were eventually found to be refluxing the α-bromoacetophenones **2a-h** in THF with two equivalents of TBABF present (Scheme 2.4).



R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 2.4

The moderate to low yields (Table 2.1) experienced for these reactions could mainly be attributed to two different side-reactions. The main by-products were identified as the cyclopropanes **3a-h**, probably formed by a cycloaddition reaction.[102,103] ^{1}H NMR spectroscopy also indicated the formation of compounds **6a-h**, products of a Darzen type condensation.[104-106] The extent of both these side-reactions increased with the increasing electron withdrawing properties of the aromatic substituents of the substrates, lowering the yields significantly.

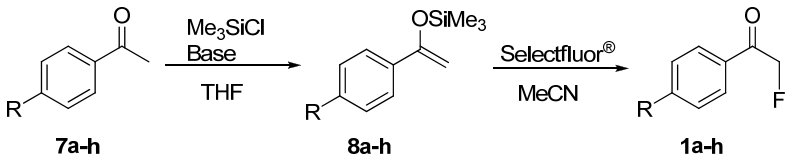


4b-c **5b**

Figure 2.3: Isolated by-products caused by addition of pyridine and triethylamine.

2.2.2 Electrophilic fluorination via trimethylsilyl enol ethers

As the nucleophilic fluorination of the α-bromoacetophenones **2a-h** failed to provide satisfactory results, the electrophilic fluorination of the corresponding enolates quickly emerged as an alternative approach. Lithium enolates had previously been fluorinated by electrophilic reagents but the acetophenone derivative was troubled by a competing dimerisation reaction.[73] Lal and co-workers had, however, reported a successful fluorination of trimethylsilyl enol ethers in a steroid synthesis.[107] The acetophenones **7a-g** were, therefore, transformed into the trimethylsilyl enol ethers **8a-g** by reacting them with lithium hexamethyldisilazane and trimethylsilyl chloride in THF at room temperature (Scheme 2.5). Due to insufficient conversion under these conditions, the preparation of **8h** was performed with DBU as base. The crude trimethylsilyl enol ethers **8a-h** were then treated with Selectfluor® (1.0-1.2 equiv) at ambient temperature in acetonitrile to give the 1-aryl-2-fluoroethanones **1a-h**.



7a-h **8a-h** **1a-h**

R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

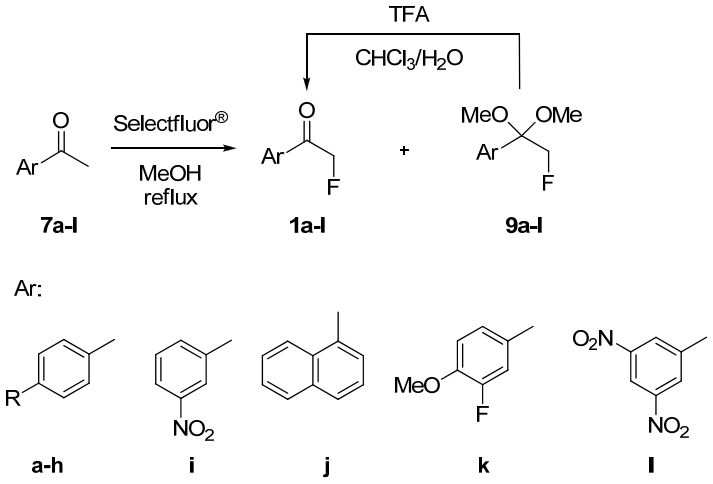
Scheme 2.5

As shown in Table 2.1, this strategy resulted in excellent to good yields for the 1-aryl-2-fluoroethanones **1a-f**. However, compounds **1g** and **1h**, bearing strongly electron withdrawing cyano and nitro groups, were isolated in rather poor yields. The reason for this loss in yield could mainly be attributed to the low stability of the corresponding trimethylsilyl enol ethers **8g** and **8h**. This resulted in product mixtures containing

significant amounts of starting material (**7g** and **7h**) and subsequent troublesome purification steps.

2.2.3 Electrophilic fluorination of 1-arylethanones

Parallel with the trimethylsilyl enol ether approach, a strategy with direct fluorination of the acetophenones **7a-h** was investigated. Again, Selectfluor® was the reagent of choice, using refluxing methanol as solvent. The procedure, which has the advantage of a very simple experimental setup, proved to be a two step reaction as the corresponding dimethyl acetals **9a-h** were formed in considerable amounts. These acetals could be hydrolysed to the 1-aryl-2-fluoroethanones **1a-h** by stirring with trifluoroacetic acid (TFA) in a chloroform/water mixture (Scheme 2.6).

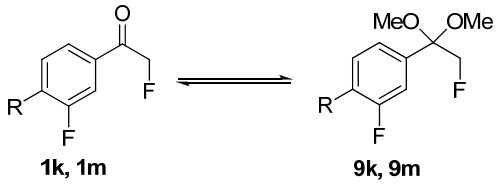


R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 2.6

Unlike the two previous routes, the yields of this approach were less dependent on the electronic properties of the substrates (Table 2.1). Due to their higher stability, elevated amounts of the dimethyl acetals were formed for the substrates containing electron withdrawing substituents but, as the acetals were effectively hydrolysed by TFA, this had no effect on the total yield of the reactions. The compounds containing the most electron donating groups, however, were troubled by a side-reaction giving the ring fluorinated ketones **1k** and **1m** and the corresponding dimethyl acetals **9k** and **9m** (Scheme 2.7).

Another drawback with the strategy was the prolonged reaction times required, especially for substrates containing electron withdrawing substituents.



1k, 1m **9k, 9m**

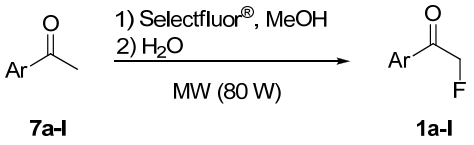
R = OMe, R' = H (**k**), R = OBn, R' = H (**m**)

Scheme 2.7

To investigate the scope and limitations to this method further, the four additional 1-arylethanones **7i-l** (Scheme 2.6) were also fluorinated. As expected, 1-acetonaphthone **7j** resulted in a complex mixture consisting of several ring fluorinated compounds. In terms of susceptibility towards aromatic fluorination, **7k** represented a borderline case and, as compared with compound **7a**, the additional fluorine in **7k** suppressed further ring fluorination. Not surprisingly, both the two nitro containing compounds **7i** and **7l** reacted very slowly under the given conditions. The dinitro compound **7l** clearly illustrates the limitation of this method, requiring five weeks to reach 39% conversion.

2.2.4 Microwave assisted electrophilic fluorination of 1-arylethanones

The use of microwave irradiation as a heating source is known to enhance the reaction rate for certain reactions in organic chemistry.[82,83] It was, therefore, considered worthwhile to investigate if it could reduce the reaction times for the electrophilic fluorination of the 1-arylethanones **7a-l** (Scheme 2.8). Preliminary experiments revealed promising results and a re-evaluation of the choice of solvent was performed. Among the six solvents tested, methanol was found to give the highest conversion. In this solvent, the most suitable irradiation effect was found to be 80 W.

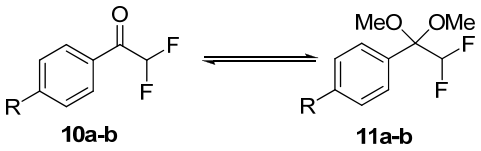


Structure elements **a-l**; see Scheme 2.6

Scheme 2.8

As hoped for, microwave irradiation reduced the reaction times significantly. The reaction which previously had taken five weeks to complete could now be performed in less than two hours. Moreover, it was discovered that the fluorination and hydrolysis could be performed in two subsequent steps in the same reaction vessel. By simply adding water to the reaction mixture and further irradiating, Selectfluor® was probably acting as a Lewis acid, catalysing the cleavage of the dimethyl acetals **9a-l** to give the 1-aryl-2-fluoroethanones **1a-l**.

Compared to the thermal process, the obtained yields did not change dramatically but the microwave method gave somewhat lower yields for the most electron rich compounds **1a-b** (Table 2.1). This was attributed to the elevated levels of ring fluorinated by-products (**1k** and **1m**), as well as the α,α-difluoroketones **10a-b** and the α,α-difluorodimethyl acetals **11a-b** shown in Scheme 2.9. The microwave method gave improved yields for the *p*-CF_3 (**1f**) and *p*-CN (**1g**) substituted derivatives. The dimethyl acetal **9f** is a highly volatile compound, and this probably caused a loss in yield in the thermal reaction. However, this was not the case in the microwave assisted reaction as no isolation of the acetal was required. The reason for the lower yield of **1g** in the thermal reaction could probably be attributed to side reactions taking place at the cyano group due to the prolonged reaction time.



10a-b **11a-b**

R = OMe (**a**), OBn (**b**)

Scheme 2.9

2.2.5 Summary

A systematic study of the synthesis of a series of 1-aryl-2-fluoroethanones (**1a-l**) has been performed. Starting with the corresponding 1-arylethanones and using non-hazardous procedures, one nucleophilic and three electrophilic approaches were compared. As can be seen from Table 2.1, the trimethylsilyl enol ethers **8a-d**, containing electron donating and moderately electron withdrawing aromatic substituents, were fluorinated in excellent to good yields. When moving further down the table, however, the yields of this method decrease. The direct electrophilic fluorination of the 1-arylethanones **7a-l** was not affected by the substituents in the same way. Consequently, this approach was more suitable for fluorinating compounds containing more electron withdrawing substituents. The microwave assisted procedure was superior to the thermal approach due to significantly shorter reaction times, simpler experimental setup and less chemical consumption. None of the tested approaches seemed suitable for fluorinating substrates with strongly electron withdrawing substituents.

Table 2.1: Isolated yields of **1a-l** for the compared fluorination strategies.

		Isolated yields [%]			
Product	**Ar**	Nucleophilic	Electrophilic via TMS enol ether	Electrophilic thermal	Electrophilic microwave
1a	4-OMe C_6H_4	48	91	67	46
1b	4-OBn C_6H_4	51	89	58	46
1j	1-Naphthyl	-	-	50	38
1k	3-F, 4-OMe C_6H_3	-	-	67	59
1c	C_6H_5	42	76	66	65
1d	4-F C_6H_4	36	74	25	74
1e	4-Br C_6H_4	33	69	77	81
1f	4-CF_3 C_6H_4	26	69	73	69
1g	4-CN C_6H_4	20	55	64	86
1h	4-NO_2 C_6H_4	20	44	70	82
1i	3-NO_2 C_6H_4	-	-	73	72
1l	3,5-di-NO_2 C_6H_3	-	-	39	41

3. Enantiomerically enriched 1-aryl-2-fluoroethanols

This chapter summarises results presented in Papers III-V. Master of Technology Maria Førde Møll is acknowledged for the early work performed with the MeCBS reductions of the α-fluoroacetophenones **1d** and **1g**.

3.1 Introduction

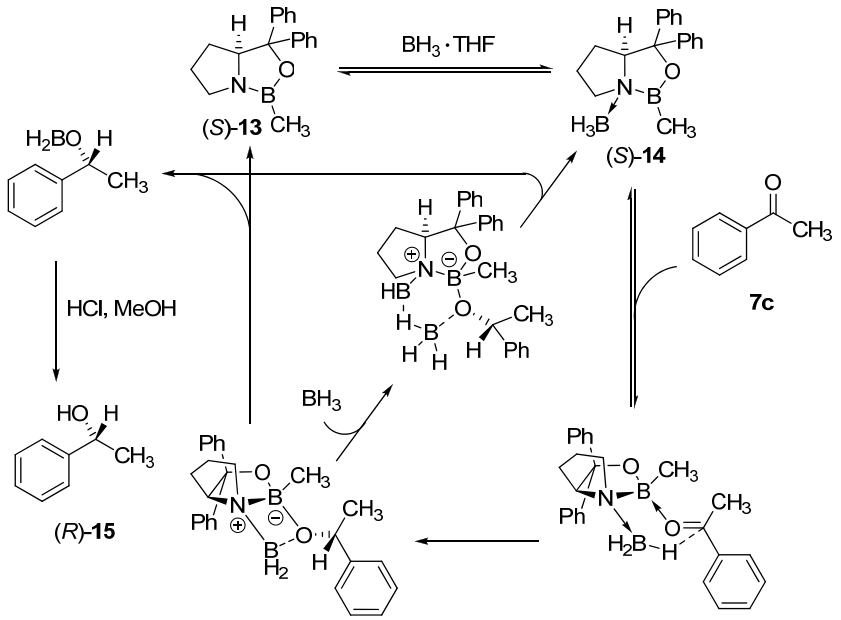
1-Arylethanols are frequently used motifs in both pharmaceuticals and agrochemicals.[108-112] The use of the fluorinated 1-aryl-2-fluoroethanols have, however, been far more limited. The reason for this can probably be attributed to their somewhat troublesome preparation but, as we had synthesised the 1-aryl-2-fluoroethanones **1a-h**, the corresponding 1-aryl-2-fluoroethanols **12a-h** (Scheme 3.4) were now easily accessible. Prochiral ketones are excellent substrates for asymmetric reductions and this is a well known route to enantiomerically enriched alcohols. Numerous catalytic systems have been developed and, compared to resolution methods, this method has the advantage of a 100% theoretical yield.[113]

3.1.1 Synthetic routes to enantiomerically enriched 1-aryl-2-fluoroethanols

When this project was started, surprisingly little work had been reported on the synthesis of enantioenriched 1-aryl-2-fluoroethanols. Among the target alcohols **12a-h**, both enantiomers of alcohol **12c** had been prepared by asymmetric reduction of the corresponding ketone **1c**, using several catalytic systems.[77,114-117] The fluoroketone **1e** had been reduced with Baker's yeast, giving (*R*)-**12e** in 94% ee, although in a moderate 46% yield.[77] No work had been reported on the remaining target alcohols **12a-b, 12d** and **12f-h**.

The chiral oxazaborolidine catalysed reduction of prochiral ketones is one of the classic reactions in asymmetric synthesis. It was developed by the pioneering work of Itsuno in 1983,[118] and further improved by Corey, Bakshi and Shibata.[119,120] Due to their broad substrate specificity and high turnover numbers, these proline based catalysts have become increasingly popular and have found several industrial applications.[121-123] A great number of catalysts have been developed and, methyl oxazaborolidine (**13**) (MeCBS) shown in Scheme 3.1, is among the most utilised versions. When exposed to a borane source it forms the borane complex **14** which is the active catalyst responsible for the

observed enantioselectivity. The proposed reaction mechanism for the reduction of acetophenone (**7c**) to (*R*)-1-phenylethanol ((*R*)-**15**) is shown in Scheme 3.1.[124]

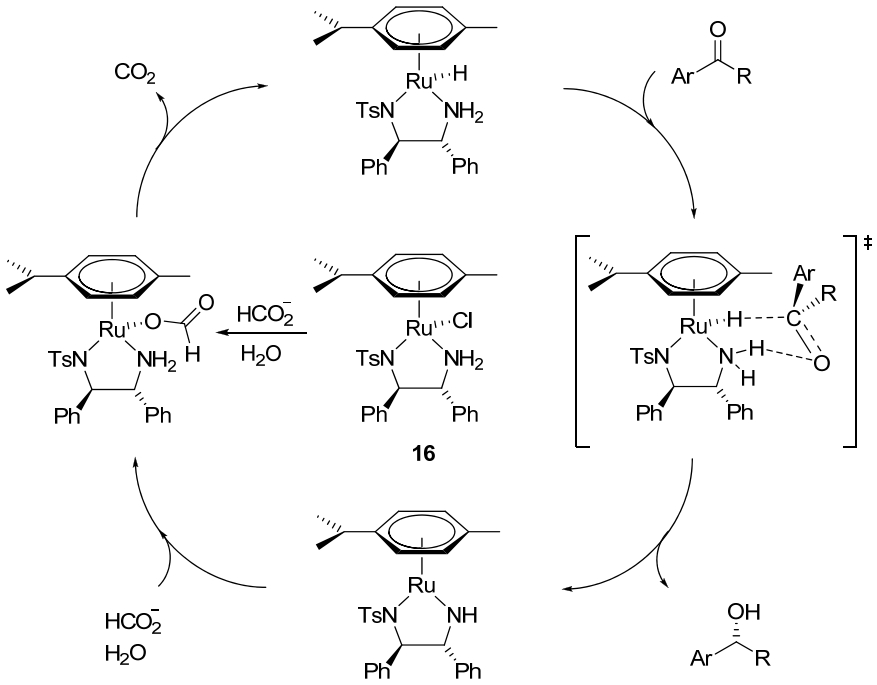


Scheme 3.1[124]

MeCBS (**13**) has previously been reported to reduce several acetophenone derivatives, providing the corresponding alcohols in high enantiomeric excess (ee).[125,126] Several studies have also been conducted regarding the effects of the solvent and the electronic character of the substrates on the enantioselectivity in MeCBS reductions.[127-129] Thus, the MeCBS catalyst **13** appeared as a promising starting point for the asymmetric reduction of the 1-aryl-2-fluoroethanones **1a-h**.

Although being more stable than many other CBS catalysts, MeCBS is sensitive to air and humidity and, consequently, requires inert atmosphere protection when handled. From an industrial point of view, a more robust and environmentally friendly reaction would, therefore, be more attractive. Asymmetric transfer hydrogenation (ATH) matches these specifications and has over the last years become an alternative to other asymmetric reduction methods.

Inspired by the work of Noyori and co-workers, ATH experienced a renaissance in the mid 1990s.[130,131] The main advantages of the method are the mild reaction conditions and the hydrogen sources used.[132-134] Traditional hydrogenation reactions normally require the use of hydrogen gas which, when performed on a large scale, represents a potential hazard. This hazard is eliminated in ATHs as they utilise much safer hydrogen sources such as sodium formate or isopropanol. As no hydrogen gas is used, the ATH method also has the advantage of requiring only a simple experimental setup. Moreover, asymmetric transfer hydrogenations can be performed in water and in the presence of air without significant loss in enantioselectivity.[135-139] This is in sharp contrast to most transition metal catalysed reactions. Recently, a reaction mechanism explaining the enantioselectivity for the RuCl-(*p*-cymene)-(*R*,*R*)-TsDPEN (**16**) catalysed ATH in water has been proposed (Scheme 3.2).[140]



Scheme 3.2[140]

A large number of ATH catalysts are available and the majority consist of a transition metal complex coordinated to a chiral ligand. The metal complexes are normally based on

an aromatic unit coordinated to either ruthenium (II), rhodium (III) or iridium (III). Chiral diamines and β-aminoalcohols have been shown to be the most effective ligands.[141,142]

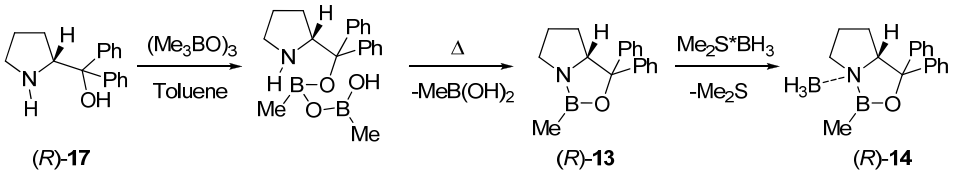
Acetophenones have been widely used as substrates for asymmetric transfer hydrogenations and the reactions have been shown to be influenced by factors such as temperature, catalyst species, solvent and pH.[134,142] Although some trifluoromethylketones had been used as substrates,[143] the ATH of monofluoroketones was an unexplored area as this project was undertaken.

3.2 Asymmetric reduction of 1-aryl-2-fluoroethanones

To obtain the 1-aryl-2-fluoroethanols **12a-h** in enantiomerically enriched form, the two different reduction systems discussed above were investigated. As only **12c** and **12e** had previously been reported and characterised as single enantiomers,[61,77] the absolute configuration of the remaining compounds had to be determined. This was achieved using circular dichroism (CD) and is described in Chapter V.

3.2.1 Asymmetric reduction using (*R*)-MeCBS

To synthesise the active catalyst (*R*)-**14**, (*R*)-α,α-diphenyl-2-pyrrolidinemethanol ((*R*)-**17**) and trimethylboroxine were stirred in toluene at ambient temperature. After the elimination of methylboronic acid and complexation to BH_3 from borane dimethyl sulphide, the MeCBS borane complex (*R*)-**14** could be obtained in 73% overall yield (Scheme 3.3).[125]



Scheme 3.3

Initial screening experiments with the synthesised catalyst (*R*)-**14** showed that the enantioselectivity in the asymmetric reduction of **1a** was strongly dependent on the solvent. Nine solvents were tested and, as Figure 3.1(A) shows, the reactions performed in ethers generally gave the best results. The only exception was diisopropyl ether, where significantly lower enantioselectivity was observed. This could probably be explained by the low solubility of both substrate and catalyst in the reaction medium. Following the initial experiments, the ketones **1b-h** were also reduced in three of the best solvents. The

results, illustrated in Figure 3.1(B), revealed that the overall highest enantioselectivity was obtained in DME.

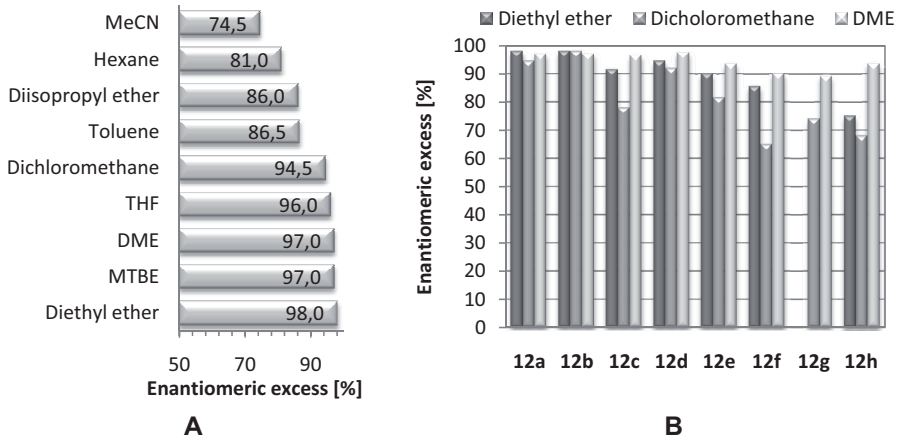


Figure 3.1: (**A**) Enantiomeric excess of the alcohol (*R*)-**12a** after MeCBS reductions of **1a** in different solvents. (**B**) Enantiomeric excess of the alcohols (*R*)-**12a-h** after MeCBS reductions of **1a-h** in diethyl ether, dichloromethane and DME. Low solubility of **1g** in diethyl ether resulted in low conversion.

In addition to being solvent dependent, the enantioselectivity of MeCBS reductions have also been known to be affected by both reaction temperature and the substrate addition time.[144] These effects were investigated closer for the reduction of **1a** by performing a series of reactions at different temperatures and with varying substrate addition times. The results, illustrated in Figure 3.2, revealed that, while the substrate addition time seemed less important, the ee of the product (*R*)-**12a** increased significantly as the temperature was lowered from 40 °C to -20 °C.

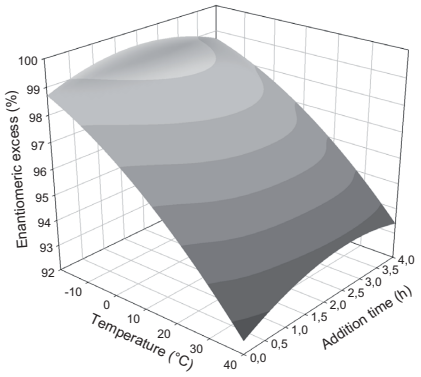
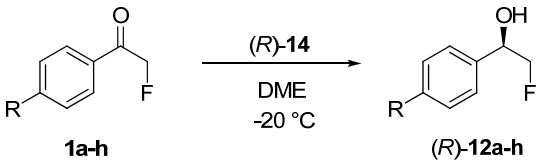


Figure 3.2: Surface plot showing the relationship between the enantiomeric excess of the product alcohol (*R*)-**12a**, the temperature and the substrate addition time in the (*R*)-MeCBS (**14**) catalysed reduction of **1a** in DME.

Based on the findings above and on literature reports stating that high catalyst loadings resulted in better enantioselectivity,[125] the α-fluoroacetophenones **1a-h** were reduced in DME at -20 °C with the MeCBS borane complex (*R*)-**14** in equimolar amounts (Scheme 3.4). As Table 3.1 shows, the products (*R*)-**12a-h** could be obtained in good yields and with excellent to good enantiomeric excess (99.5-91.5%). A slight decrease in the ee of the products was observed for the compounds bearing more electron withdrawing substituents at the aromatic ring. Similar observations have previously been rationalised by the decreased ability of the carbonyl oxygen atom in the electron deficient substrates to coordinate to the boron atom in the catalyst.[128] This could result in larger amounts of the substrate being reduced by free borane and a subsequent loss of enantioselectivity.



1a-h (*R*)-**12a-h**

R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 3.4

3.2.2 Asymmetric transfer hydrogenation

Although the MeCBS reductions gave the majority of the product alcohols (*R*)-**12a-h** in excellent enantiomeric excess, there was still room for improvement for the substrates bearing electron withdrawing substituents. Therefore, it was decided that a second reduction system should be examined. Asymmetric transfer hydrogenation was the method of choice and, to investigate this reaction thoroughly, a broad small scale screen was initially performed. Reducing the α-fluoroacetophenones **1a-h**, all combinations of two different ruthenium complexes coordinated to four different chiral diamine ligands (Figure 3.3) were tested in two different solvents (Scheme 3.5). The best conditions found from this screen were then used for gram scale reactions.

While the pre-catalyst $[RuCl_2(p\text{-cymene})]_2$ was commercially available, $[RuCl_2(\text{mesitylene})]_2$ had to be synthesised. This was accomplished by refluxing ruthenium(III)chloride hydrate and 1,3,5-trimethyl-1,4-cyclohexadiene in methanol according to literature procedures.[145] The catalysts **16** and **18-20** (Figure 3.3) were prepared in situ from the pre-catalysts $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2(\text{mesitylene})]_2$ and the ligands (*R,R*)-TsDPEN and (*R,R*)-TsCYDN. The (*R,R*)-configuration of the ligands was chosen for the small scale screening experiments as this was expected to give the (*S*)-enantiomers of the products **12a-h**, thereby, complementing the (*R*)-MeCBS reduction products. For the gram scale reactions, however, the need for the (*R*)-enantiomers of the alcohols as further building blocks had arisen. These reactions were, therefore, performed using the (*S,S*)-ligands. The results from the preparative scale reductions are shown in Table 3.1, while the screening experiments are shown in Figure 3.4 and Figure 3.5.

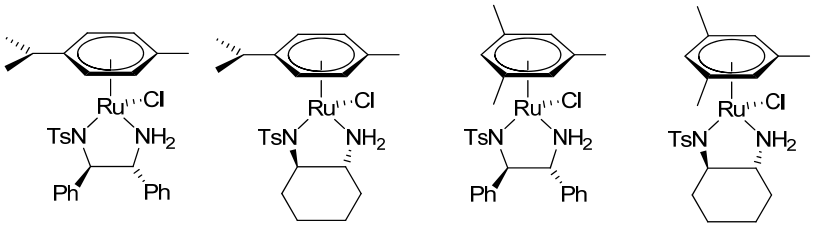
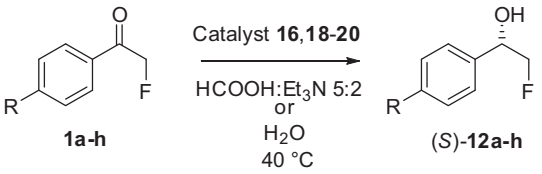


Figure 3.3: Catalysts used in the ATH of the α-fluoroacetophenones **1a-h.**

Based on numerous reports of the ATH of acetophenones, the reactions were performed with both water and formic acid/triethylamine (5/2) as solvents.[132,134] All reactions were conducted at 40 °C with a substrate/catalyst ratio of 100, without an inert atmosphere

protection. For the reactions performed in water, sodium formate was added as hydrogen source.



R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 3.5

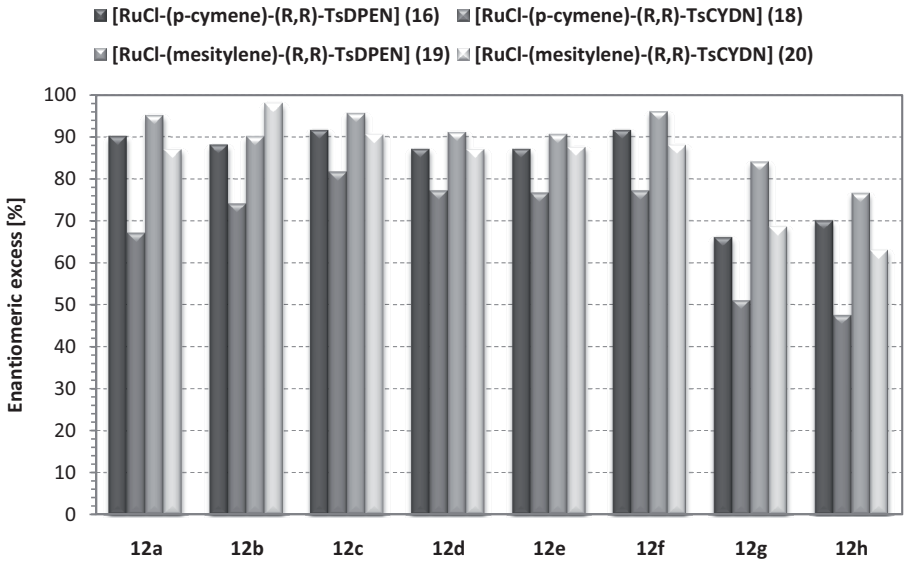


Figure 3.4: Enantiomeric excess of the alcohols (*S*)-**12a-h** after ATH of the α-fluoroacetophenones **1a-h** in water.

In both solvents, catalyst **19** gave the overall highest enantioselectivity. The reactions conducted in water (Figure 3.4) gave generally lower enantioselectivity compared to those in formic acid/triethylamine (Figure 3.5). The exceptions were the reactions with catalyst **20** which gave significantly higher enantioselectivity in water. The only substrate which

was reduced with the highest enantioselectivity in water was the *p*-CF_3 substituted alcohol **12f**, catalysed by [RuCl-(mesitylene)-(*R,R*)-TsDPEN] (**19**).

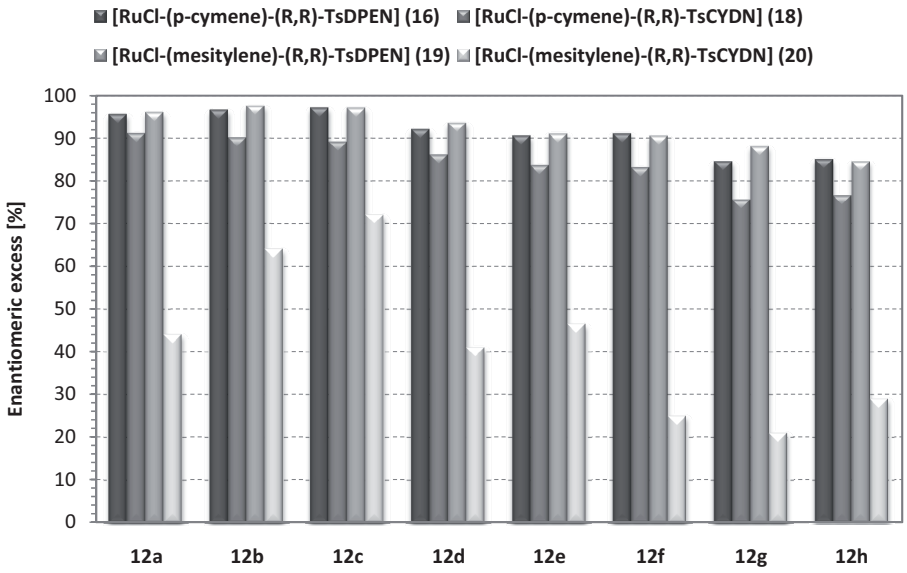


Figure 3.5: Enantiomeric excess of the alcohols (*S*)-**12a-h** after ATH of the α-fluoroacetophenones **1a-h** in formic acid/triethylamine (5/2).

Based on the results from the screening experiments, the best conditions for each substrate were used in gram scale reactions. The products were obtained in excellent to good ee (99.5-85.0%) and, compared to the small scale reactions, only minor deviations in enantioselectivity were experienced. The obtained yields were generally satisfactory but the reduction of **1f** in water gave only a moderate 52% yield (Table 3.1). The reason for this was not investigated but ^{1}H NMR spectroscopy of the crude product indicated the presence of some by-products, possibly formed by condensation reactions.

Similar to the MeCBS reductions, a loss in ee for the products bearing electron withdrawing substituents was experienced for all of the ATH reaction systems. These types of effects have been shown not to be related solely to electronic properties but also to changes in π-π interactions, solvation effects and dispersion interactions.[146]

Table 3.1: Isolated yields, enantiomeric excess and absolute configuration of the alcohols **12a-h** after asymmetric reduction of the α-fluoroacetophenones **1a-h** using (*R*)-MeCBS borane complex ((*R*)-**14**), and [RuCl-(mesitylene)-(*R,R*)-TsDPEN] (**19**) in water and formic acid/triethylamine (5/2).

Substrate		(*R*)-MeCBS ((*R*)-14)		Asymmetric transfer hydrogenation: Cat. 19 (water)		Cat. 19 (HCOOH:Et_3N 5:2)	
		Yield[a] [%] (min)	ee [%]	Conv.[b] [%] (h)	ee [%]	Yield[a] [%] (h)	ee [%]
1a	OMe	88 (30)	99.5 (*R*)	>99 (5)	95.0 (*S*)	76 (4)[c]	96.0 (*R*)
1b	OBn	88 (15)	97.0 (*R*)	71 (20)	90.0 (*S*)	61 (5)[c]	99.5 (*R*)
1c	H	84 (20)	96.5 (*R*)	>99 (2)	95.5 (*S*)	86 (6)[c]	98.0 (*R*)
1d	F	76 (20)	99.0 (*R*)	>99 (5)	91.0 (*S*)	79 (4)[c]	93.0 (*R*)
1e	Br	82 (20)	98.5 (*R*)	>99 (5)	90.5 (*S*)	79 (4)[c]	91.0 (*R*)
1f	CF_3	84 (20)	93.0 (*R*)	52 (10)[a,c]	92.5 (*R*)	>99 (2)[b]	90.5 (*S*)
1g	CN	74 (20)	91.5 (*R*)	45 (20)	84.0 (*S*)	85 (4)[c]	87.0 (*R*)
1h	NO_2	80 (20)	92.5 (*R*)	99 (20)	76.5 (*S*)	91 (4)[c]	85.0 (*R*)

[a] Isolated yield.
[b] Determined by HPLC (254 nm).
[c] [RuCl-(mesitylene)-(*S,S*)-TsDPEN] (**19**) used as catalyst.

3.2.3 Summary

As can be seen from the overall results shown in Table 3.1, the alcohols **12a-e** were obtained in excellent enantiomeric excess (99.5-98.0%) using either the MeCBS-reduction system or asymmetric transfer hydrogenation. Although decent enantioselectivity was achieved also for the alcohols containing more electron withdrawing aromatic substituents (**12f-h**) (93.0-91.5% ee), they are not satisfactory when high enantiomeric purity is the target. It seems, therefore, that the tested reduction systems are not suitable methods when reducing 1-aryl-2-fluoroethanones bearing electron withdrawing aromatic substituents. Recently, however, a diphenylprolinol derived catalyst has been reported to reduce 1-(4-nitrophenyl)ethanone (**7h**) with excellent selectivity.[147] This may indicate that improved results for the 1-aryl-2-fluoroethanones **12f-h** can be achieved using structural analogues of MeCBS (**13**).

When comparing the two reduction systems, the best overall results were obtained with (*R*)-MeCBS ((*R*)-**14**) as catalyst. These reactions were fast and gave the products in generally good yields and high enantiomeric excess. The experimental setup of the ATH reactions was, however, considerably simpler as the reactions were performed without inert atmosphere protection at 40 °C. The latter method is also highly tunable as a number of both ligands and metal complexes are available for adjusting the catalyst reactivity.

From an environmental point of view, ATH is also the better choice, an important argument when considering industrial processes.

4. Enantiomerically enriched 1-aryl-2-fluoroethylamines

This chapter summarises some of the results presented in Paper V. Master of Science Thor Håkon Krane Tvedt is acknowledged for the work with the reductive amination/kinetic resolution pathway which is a part of his currently ongoing PhD studies. Master of Science Svein Jacob Kaspersen is acknowledged for performing the experiments related to the potential tyrosine kinase inhibitors. This project is a part of his ongoing PhD studies.

4.1 Introduction

During the work with the 1-aryl-2-fluoroethanols it was realised that similar structural elements had been used in chiral bioactive compounds targeting tyrosine kinases in cancer therapy.[148,149] Two promising drug candidates, patented by Novartis,[150,151] were particularly interesting as they consist of a pyrrolopyrimidine skeleton linked to a benzylic amine (Figure 4.1). To investigate the usefulness of our prepared alcohols **12a-h** as chiral building blocks, we wanted to synthesise structural analogues of these tyrosine kinase inhibitors. The introduction of a fluorine atom close to the benzylic amine would lower its basicity and this could potentially have a positive effect on the bioavailability of the drugs.

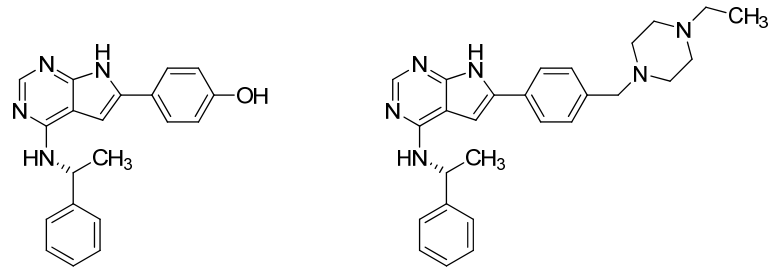
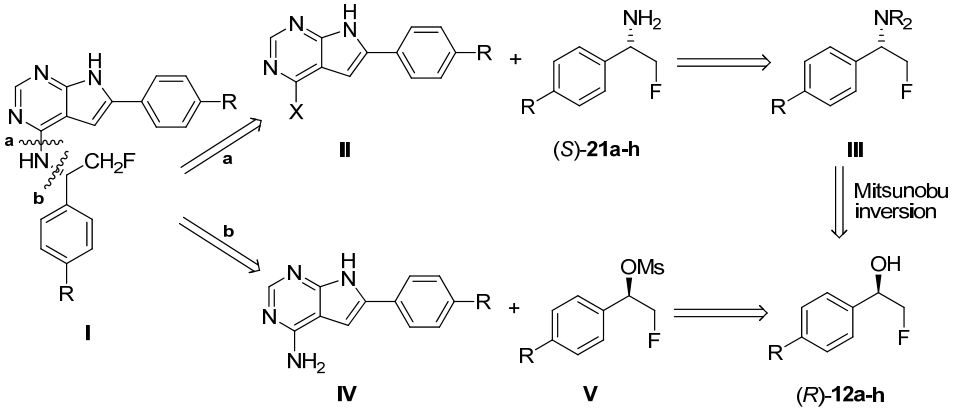


Figure 4.1: Examples of compounds with high inhibiting activity against tyrosine kinases.[148,149]

Reacting the enantiomerically enriched 1-aryl-2-fluoroethanols **12a-h** directly with the pyrrolopyrimidine moiety was considered at the early stages of the project. This would have provided the ether analogues of the drug candidates. However, as all reported similar tyrosine kinase inhibitors contained the amine functionality, it was considered important to keep this structural element. Two retrosynthetic approaches toward the drug analogues (**I**) are shown in Scheme 4.1. In path **a**, the bond between the

pyrrolopyrimidine moiety and the amino group is disconnected. This bond can be formed by a nucleophilic aromatic substitution reaction between the halogenated pyrrolopyrimidine **II** and the benzylic amines (*S*)-**21a-h**. The latter compounds can be made by performing a Mitsunobu inversion on the 1-aryl-2-fluoroethanols (*R*)-**12a-h**. Another possibility is disconnecting the benzylic amine bond (path **b**). This would give the amino group bearing pyrrolopyrimidine **IV** which can react via an S_N2 reaction with, for instance, the mesylated alcohols **V**.



Scheme 4.1

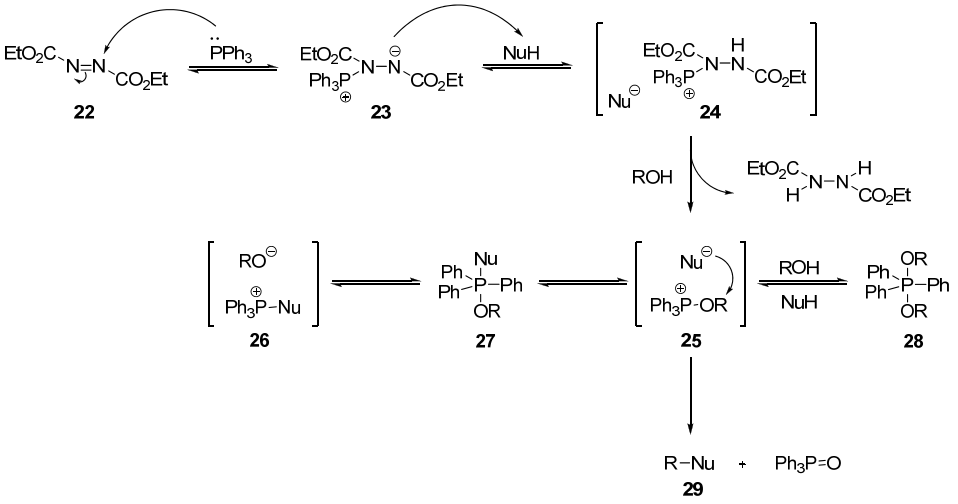
PKI-166 (Figure 4.1) has previously been synthesised in good yield by the nucleophilic aromatic substitution pathway (path **a**).[152,153] The analogue of **21d**, 1-(4-fluorophenyl)ethylamine, has also been successfully employed as substrate in the same strategy.[152] Although the fluorinated amines **21a-h** will have lower basicity than the non-fluorinated analogues, their nucleophilicity will not be influenced to the same extent.[154] They should, therefore, be suitable as substrates in nucleophilic aromatic substitution reactions. While path **a** employs previously reported pyrrolopyrimidines,[152,155] this is not the case for path **b**. Based on this, path **a** was selected as the preferred approach for synthesising the fluorinated drug analogues.

When starting with the alcohols (*R*)-**12a-h**, a Mitsunobu inversion was seen as the best strategy to make the amines (*S*)-**21**. Parallel with the work on this strategy, however, the research group also investigated the possibility of making the enantiomerically enriched amines by performing a kinetic resolution of the racemic amines **21a-h**. This approach was investigated by Master of Science Thor Håkon Krane Thvedt as a part of his ongoing PhD

project. The results from this work will, therefore, only be briefly summarised and not discussed in detail herein.

4.1.1 The Mitsunobu reaction in amine synthesis

Since its discovery in 1967,[156] the Mitsunobu reaction has become one of the classic reactions in synthetic organic chemistry. The main reasons for its popularity are attributed to the mild reaction conditions, the wide range of possible substrates and the stereospecifity which is observed. The Mitsunobu reaction is often used in the modification of primary and secondary alcohols with different nucleophiles. For chiral alcohols, the reaction normally proceeds with inversion of stereochemistry.[157] Although the reaction was discovered well over 40 years ago, the details of the reaction mechanism are still heavily debated.[158-160] For that reason, Scheme 4.2 presents just an overview of the mechanism, showing only intermediates which have been confirmed by experimental data.[161] The first step of the reaction is the nucleophilic attack of a phosphine (most often triphenylphosphine) on an azodicarboxylate (usually diethyl azodicarboxylate (**22**) (DEAD)). This results in the formation of the betain **23** which then deprotonates the pronucleophile (NuH). The resulting ionic species **24** then reacts with the alcohol (ROH) and generates the key alkoxyphosphonium salt **25**. Depending on the pK_a of the pronucleophile and on the polarity of the solvent, the different phosphorous intermediates **26-28** are present in variable amounts. The only pathway leading to the desired product **29**, however, is a nucleophilic attack (S_N2) of the nucleophile (Nu^-) on the alkoxyphosphonium ion **25**, liberating triphenylphosphine oxide.



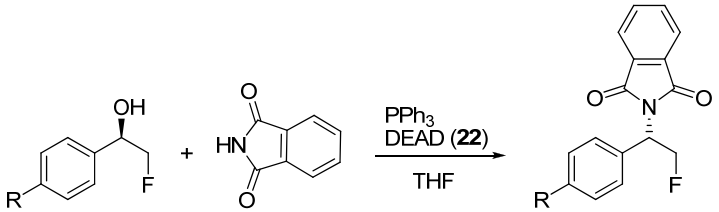
Scheme 4.2[161]

By utilising nucleophiles such as amides or azides, the Mitsunobu protocol can be a useful tool for transforming alcohols into amines. Among the amides, the activated phthalimide (**30**) is often used.[157] The resulting *N*-substituted phthalimides can easily be converted into the corresponding amines by hydrazinolysis.[162] Moreover, phthalimide is cheap and easy to handle.

Even though much work has been done on transforming alcohols to the corresponding amines, very few examples of the Mitsunobu inversion of 1-arylethanols to 1-arylethylamines have been reported. The majority of the few reports that do exist, utilise phthalimide (**30**) as pronucleophile and standard Mitsunobu conditions, with DEAD (**22**) and triphenylphosphine in tetrahydrofuran (THF). After hydrazinolysis with hydrazine, the corresponding amines could be obtained in decent yields.[163-165] Other pronucleophiles such as hydrogen azide[166] and a *p*-toluenesulfonamide[167] have also been used with good results. By replacing triphenylphosphine with a chiral phosphorous reagent, an enantioselective Mitsunobu reaction of a series of racemic 1-arylethanols has also been reported. Unfortunately, only moderate ee values were experienced.[168]

4.2 Mitsunobu inversion of enantioenriched (*R*)-1-aryl-2-fluoroethanols

Standard Mitsunobu reaction conditions using triphenylphosphine, DEAD (**22**) and THF were chosen for the first step in the transformation of the 1-aryl-2-fluoroethanols (*R*)-**12a-h** to the 1-aryl-2-fluoroethylamines (*S*)-**21a-h** (Scheme 4.3). Phthalimide (**30**) was used as pronucleophile. The reactions were performed by dissolving triphenylphosphine, phthalimide (**30**) and the substrate alcohols (*R*)-**12a-h** in THF under an inert atmosphere. DEAD (**22**) was then added and the reaction mixture was stirred at room temperature over night.

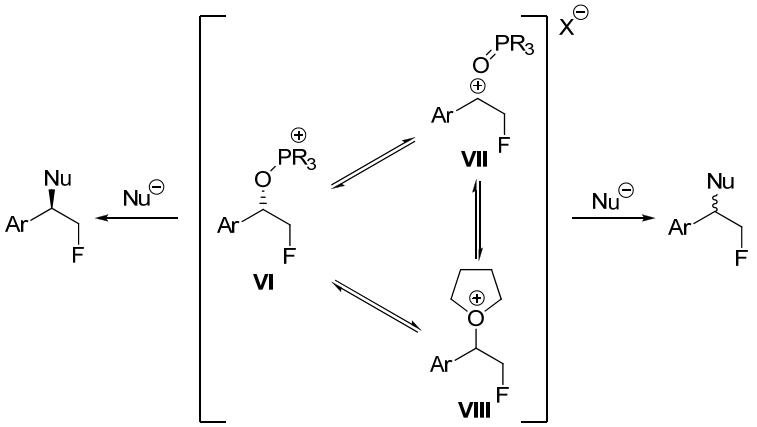


(*R*)-**12a-h** **30** (*S*)-**31a-h**

R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 4.3

As Table 4.1 shows, the Mitsunobu reactions gave the *N*-substituted phthalimides (*S*)-**31c-f** in good yields and with a clean inversion of stereochemistry. The compounds containing electron donating groups at the aromatic ring, (*S*)-**31a** and (*S*)-**31b**, were, however, troubled by racemisation and poor yields. This phenomenon has been observed previously when similar compounds have been subjected to Mitsunobu reaction conditions.[167,169,170] Hillier and co-workers have explained the loss in enantiomeric excess by the formation of the intermediate **VI**, shown in Scheme 4.4.[170] This compound can form intermediate **VII** via an S_N1 type pathway and then react with either the nucleophile to form the racemic product, or THF to form **VIII**. The low yields experienced indicate that these pathways may also be responsible for the formation of other by-products.



Scheme 4.4

The *N*-substituted phthalimides with the most electron withdrawing substituents, (*S*)-**31g** and (*S*)-**31h**, were also obtained in poor yields, though without racemisation. It is known that hydroxyl compounds with an acidic hydrogen atom adjacent to the hydroxyl group may undergo intramolecular dehydrations or elimination reactions under Mitsunobu reaction conditions.[157,158] Numerous examples of such by-products have been reported but none resulting from 1-arylethanols.[171-173]

Table 4.1: Enantiomeric excess and isolated yields of the *N*-substituted phthalimides (*S*)-**31a-h** and the amines (*S*)-**21a-h** following the Mitsunobu inversion of the alcohols (*R*)-**12a-h**.

Substrate			**Phthalimide (*S*)-31**		**Amine (*S*)-21**	
	R	ee [%]	Yield [%]	ee [%]	Yield [%]	ee [%]
(*R*)-**12a**	OMe	96.0	32	53.0	73	53.5
(*R*)-**12b**	OBn	99.5	37	60.0	72	60.0
(*R*)-**12c**	H	98.0	77	99.0	66	98.5
(*R*)-**12d**	F	93.0	77	[a]	75	92.5
(*R*)-**12e**	Br	91.0	83	90.0	66	90.5
(*R*)-**12f**	CF_3	92.5	78	92.0	71	91.5
(*R*)-**12g**	CN	87.0	66	87.5	75	87.5
(*R*)-**12h**	NO_2	85.0	34	84.0	80	84.0

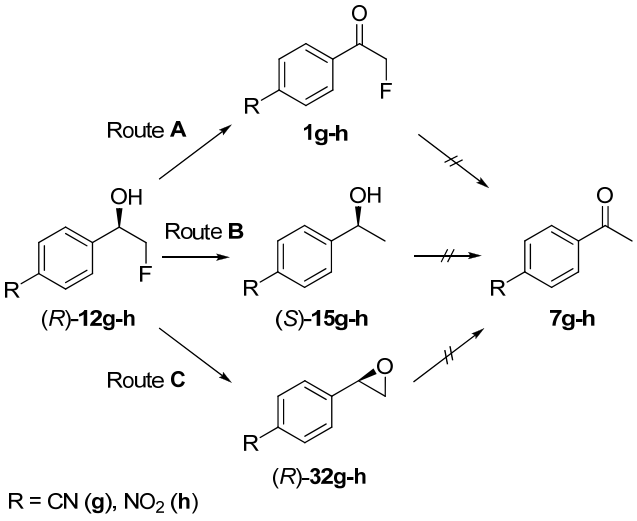
[a] Not determined

The main reason for the low yields obtained in the synthesis of (*S*)-**31g** and (*S*)-**31h** proved to be the formation of the corresponding acetophenones, **7g** and **7h**. In an attempt to

determine how these by-products were formed, some additional experiments were conducted.

The initial experiments showed that, in the absence phthalimide (**30**), the Mitsunobu inversion of the fluoroalcohols **12g-h** yielded the methylketones **7g-h** as the only major products. Mixing the fluoroalcohols **12g** or **12h** with either triphenylphosphine or DEAD (**22**) alone did not give any reactions, so both reagents had to be present for the by-products to be formed. In an attempt to identify possible reaction intermediates, the reaction with the fluoroalcohol **12h** was performed in THF-*d*8 and continuously monitored by ^{1}H NMR spectroscopy. Spectra were recorded each minute during the reaction but no distinct intermediates could be detected. As short-lived intermediates can be difficult to observe by ^{1}H NMR spectroscopy, the formation of reaction intermediates could, however, not be ruled out by this experiment.

The fluoroketones **1g-h**, the methylalcohols **15g-h** and the epoxides **32g-h** were all seen as possible reaction intermediates. It was, therefore, investigated if these compounds could be transformed into the methylketones **7g-h** under the given reaction conditions (Scheme 4.5).

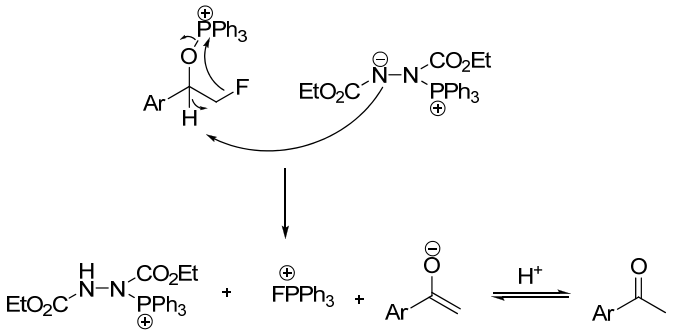


Scheme 4.5

DEAD (**22**) is an oxidising agent and could possibly convert the fluoroalcohols **12g-h** into the fluoroketones **1g-h**.[174] However, when the fluoroketone **1h** was subjected to DEAD

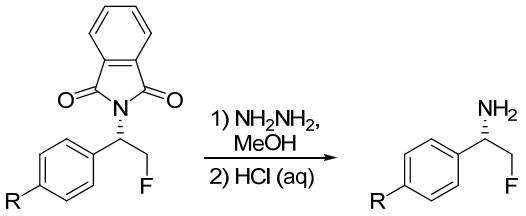
(**22**) and triphenylphosphine, the acetophenone **7h** was not formed, thus, Route A could be excluded. Another possible route to the acetophenones **7g-h** was the formation of epoxides ((*R*)-**32g-h**) followed by a subsequent rearrangement (Route C). This could, however, also be excluded since an experiment using 2-(4-nitrophenyl)oxirane (**32h**) as substrate failed to yield detectable amounts of **7h**. To test if the fluoroalcohols **12g-h** somehow could react via the methylalcohols **15g-h** (Route B), 1-(4-nitrophenyl)ethanol (**15h**) was subjected to the Mitsunobu conditions. This also resulted in no observable amounts of the by-product being formed.

The presence of an electron withdrawing substituent on the aromatic ring, along with the adjacent fluorine atom, will lower the pK_a of the proton at the stereogenic centre of the alcohols **12g** and **12h**, thereby making them susceptible to elimination reactions. This, along with the observations discussed above, makes the concerted mechanism shown in Scheme 4.6 a possible explanation for the formation of the acetophenones **7g** and **7h**. This mechanistic proposal is further strengthened by the fact that triphenylphosphine previously has been used as a defluorinating agent.[175]



Scheme 4.6

Following the Mitsunobu inversion, the enantioenriched amines (*S*)-**21a-h** were obtained by performing a hydrazinolysis of the *N*-substituted phthalimides (*S*)-**31a-h** (Scheme 4.7). This was achieved by stirring the substrates (*S*)-**31a-h** together with hydrazine in methanol at room temperature until the starting material had been consumed. Aqueous hydrochloric acid was then added and, after stirring over night, the amines (*S*)-**21a-h** were isolated in decent yields without alteration of the enantiomeric excess (Table 4.1). The absolute configuration of the products was determined by CD. This work is described in Chapter V.



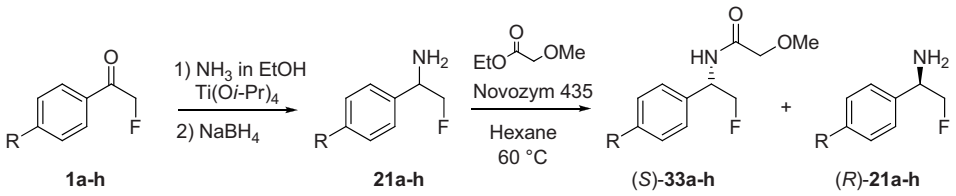
(*S*)-**31a-h** (*S*)-**21a-h**

R = OMe (**a**), OBn (**b**), H (**c**), F **(d)**, Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 4.7

4.3 Kinetic resolution of racemic 1-aryl-2-fluoroethylamines

To synthesise the racemic 1-aryl-2-fluoroethylamines **21a-h**, the α-fluoroacetophenones **1a-h** were treated with ammonia and titanium(IV) isopropoxide in ethanol, followed by sodium borohydride (Scheme 4.8). This produced the amines **21a-h** in 95-68% yield (Table 4.2).



1a-h **21a-h** (*S*)-**33a-h** (*R*)-**21a-h**

R=OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 4.8

The racemic amines **21a-h** were then resolved by a lipase catalysed kinetic resolution (Scheme 4.8). After conducting a number of small scale screening experiments, the best results were achieved with immobilised lipase B from *Candida antarctica* (Novozym 435) in hexane at 60 °C using equimolar amounts of ethyl methoxyacetate as acyl donor. The main results are summarised in Table 4.2.

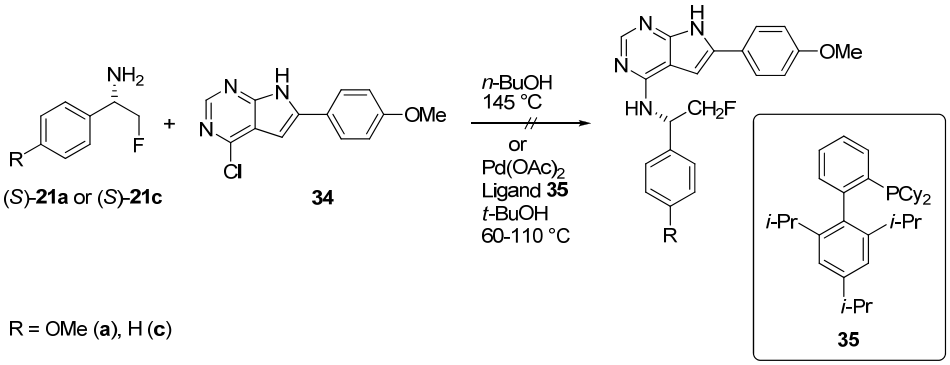
Table 4.2: Isolated yields of the racemic amines **21a-h** after the reductive amination of the α-fluoroacetophenones **1a-h**. Isolated yields, ee and absolute configuration of the methoxy acetamides (*S*)-**33a-h** and amines (*R*)-**21a-h** after kinetic resolution.

	Red. amination	**Kinetic resolution**			
R	Amine **21**	Methoxy acetamide (*S*)-**33**		Amine (*R*)-**21**	
	Yield [%]	Yield [%]	ee [%]	Yield [%]	ee [%]
OMe	89	35	>99.5 (*S*)	43	97.0 (*R*)
OBn	84	31	>99.5 (*S*)	34	96.0 (*R*)
H	93	32	>99.5 (*S*)	36	>99.5 (*R*)
F	95	40	>99.5 (*S*)	43	>99.5 (*R*)
Br	71	42	>99.5 (*S*)	39	>99.5 (*R*)
CF	68	35	>99.5 (*S*)	38	>99.5 (*R*)
CN	81	42	>99.5 (*S*)	37	99.0 (*R*)
NO_2	79	36	>99.5 (*S*)	43	>99.5 (*R*)

As Table 4.2 shows, the kinetic resolutions produced both the methoxy acetamides (*S*)-**33a-h** and the amines (*R*)-**21a-h** in good yields and in excellent enantiomeric excess.

4.4 Synthesis of potential tyrosine kinase inhibitors

To utilise the synthesised amines (*S*)-**21a-h** in the preparation of potential tyrosine kinase inhibitors, attempts were made to react (*S*)-**21a** and (*S*)-**21c** with the pyrrolopyrimidine **34** as shown in Scheme 4.9. Based on reports on successful syntheses using several non-fluorinated 1-arylethylamines,[176] two different methods were investigated. The first approach was a nucleophilic aromatic substitution performed in refluxing 1-butanol using the amines in a three fold excess.[177] The second method tested was a palladium catalysed Buchwald-Hartwig cross coupling reaction performed in *tert*-butyl alcohol. The catalyst was made in situ by mixing $Pd(OAc)_2$ (5 mol%) with the dialkylbiarylphosphine ligand **35** (10 mol%) and water (4 mol%) in *tert*-butyl alcohol at 110 °C. The reactions were carried out at 60 °C and 110 °C.[178]



Scheme 4.9

Unfortunately, none of the methods yielded the desired products. The nucleophilic aromatic substitution approach was troubled by low reaction rates and the formation of an unidentified by-product. This indicated that the adjacent fluorine atom had reduced the nucleophilic character of the amino group, thereby, preventing the reaction from taking place. The Buchwald-Hartwig cross coupling reactions also failed to afford the target compounds. In contrast to the aromatic substitution reactions, however, these reactions were fast (100% conversion within 15 minutes) and yielded two major by-products. The identity of the by-products has not been established but ^{1}H and ^{13}C NMR spectroscopy revealed that none of the compounds contained fluorine atoms. Further investigations are currently under way to solve the encountered problems.

4.5 Summary

When comparing the results of the two tested routes to the enantiomerically enriched 1-aryl-2-fluoroethylamines **21a-h**, an obvious advantage of the kinetic resolution approach was the excellent enantioselectivity observed. The asymmetric transfer hydrogenations reduced the ketones **1a-c** in almost matching selectivity but the inversions of (*R*)-**12a** and (*R*)-**12b** were hampered by racemisation under the Mitsunobu reaction. Therefore, only amine (*S*)-**21c** was produced in similar enantiomeric excess by the Mitsunobu approach.

The kinetic resolution approach requires only two steps to produce the target compounds, compared with three steps for the Mitsunobu approach. The drawback of a kinetic resolution is, however, the limitation of a maximum 50% yield of one enantiomer. The consequence of this can be seen when the overall yields of the amines **21a-h** from the 1-aryl-2-fluoroethanones **1a-h** are compared (Table 4.3). Despite the extra step, all the

amines except the ones containing electron donating substituents (**21a-b**) were produced in slightly higher yields by the Mitsunobu route.

Table 4.3: Overall yields, enantiomeric excess and absolute configuration of the enantioenriched amines **21a-h**, starting from the 1-aryl-2-fluoroethanones **1a-h**.

Substrate	Amine 21			
	Mitsunobu approach		Kinetic resolution	
	Yield [%]	ee [%]	Yield [%]	ee [%]
1a (OMe)	18	53.5 (*S*)	38	97.0 (*R*)
1b (OBn)	16	60.0 (*S*)	29	96.0 (*R*)
1c (H)	44	98.5 (*S*)	33	>99.5 (*R*)
1d (F)	46	92.5 (*S*)	41	>99.5 (*R*)
1e (Br)	43	90.5 (*S*)	28	>99.5 (*R*)
1f (CF_3)	29	91.5 (*S*)	26	>99.5 (*R*)
1g (CN)	42	87.5 (*S*)	29	99.0 (*R*)
1h (NO_2)	25	84.0 (*S*)	34	>99.5 (*R*)

It should be mentioned that kinetic resolutions, unlike asymmetric transfer hydrogenations, do not offer the possibility of choosing which enantiomer that should be synthesised. The methoxy acetamides (*S*)-**33a-h**, prepared in this case, can be converted into the amines (*S*)-**21a-h** but this will further diminish the yields. If the desired enantiomer is not the one being produced, this can be a significant drawback.

Seen from an environmental point of view, the Mitsunobu reaction route has serious disadvantages. Although ATH is considered to be an environmental friendly reaction, the Mitsunobu reaction is not. In addition to using the toxic and potentially explosive DEAD (**22**), the reaction generates two moles of waste for each mole of product formed. Hydrazine, used in the final hydrazinolysis step, is also an environmentally harmful and toxic compound. When considering the kinetic resolution route, the only serious drawback is the use of two equivalents of titanium(IV) isopropoxide in the reductive amination step. This problem can, however, be circumvented by employing another method towards the racemic amines **21a-h**.

In total, the results obtained from the kinetic resolution approach are superior to those achieved with the Mitsunobu route. Despite the lower yields experienced for some substrates, the enantioselectivity for all the reactions was better. This is a key factor which outweighs the slightly reduced yields. Another argument for this approach is the fact that

both steps were performed using a very simple experimental setup. Due to the higher yields achieved for the amine **21c**, the Mitsunobu approach could be chosen if very high enantiomeric purity is not crucial.

5. Determination of absolute configuration by circular dichroism

This chapter summarises some of the results presented in Paper III and V.

5.1 Introduction

The determination of the absolute configuration of an enantioenriched compound can be achieved by several different methods.[179] The most commonly used approaches include X-ray crystallography,[180] the use of chiral shift reagents in NMR spectroscopy[181] and circular dichroism.[182,183] Provided no racemisation takes place, synthesising a compound from chiral precursors with known absolute configuration is also a viable approach.[184]

Electronic circular dichroism (ECD) measurements have been performed routinely since around 1960.[185] The technique has been widely used for determining the absolute configuration of organic molecules and relies on the ability of enantiomers to rotate circularly polarised light in opposite directions. The early work was based on empirical rules associated with relatively simple molecules[185] but it has now been established as a non-empirical method, widely used for structural investigations of organic and inorganic compounds, polymers and biomacromolecules.[182,186]

One of the simplest and most versatile ECD-techniques is the "exciton chirality method".[187] This method relies on the spatial interaction between two or more strong chromophoric electric dipole transitions which are chirally arranged and close in energy. The dipoles will interact and give rise to an exciton split CD spectrum, known as a CD couplet, consisting of two Cotton effects of opposite signs. The sign of the CD couplet, defined by the longer wavelength component, reflects the absolute sense of twist between the two interacting chromophores. This sense of twist can be predicted by viewing the two chromophores along the direction connecting their centres. A negative sign is defined when an anticlockwise rotation makes the dipole in the front superimpose the dipole in the back and *vice-versa* (Figure 5.1). Provided that the relative orientation between the interacting dipoles and their spectroscopic properties are known, exciton coupled CD enables the unambiguous determination of absolute configuration.[186-188] The method is limited to compounds with at least two chromophores located at suitable positions in the molecule. Derivatisation is, therefore, often required before the desired information can be obtained.

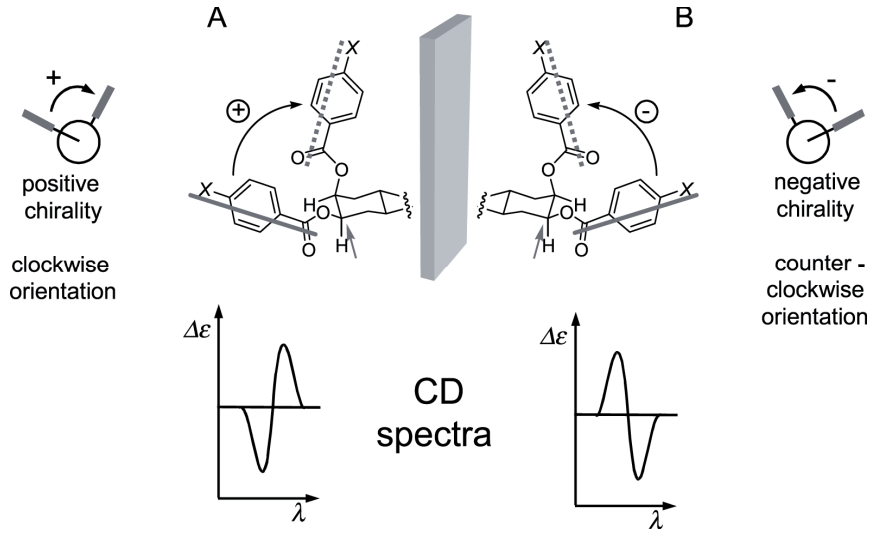


Figure 5.1: Illustration of the exciton chirality method, showing (**A**) clockwise and (**B**) counter-clockwise orientation of two identical chromophores and the two resulting CD spectra. (Reprinted with kind permission from Springer Science and Business Media.)[189]

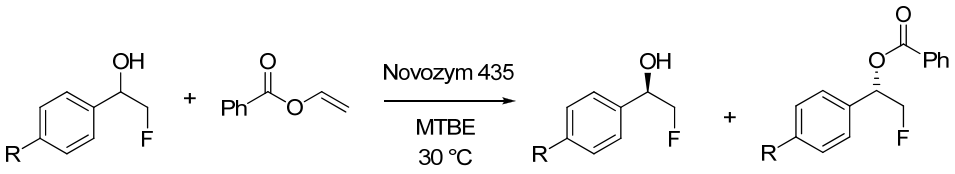
5.2 Determination of the absolute configuration of enantioenriched 1-aryl-2-fluorethanols

Among the synthesised 1-aryl-2-fluoroethanols **12a-h**, only **12c** and **12e** had previously been characterised in enantiomerically enriched form.[61,77] Therefore, the absolute configuration of the remaining alcohols had to be determined. As the CD exciton chirality method had previously been used for assigning the absolute configuration of similar compounds,[190] it was decided to investigate this approach.

Since the CD exciton chirality method requires the presence of at least two chromophores in a molecule, an additional chromophore had to be introduced in the 1-aryl-2-fluoroalcohols **12a-h**. The benzoate group has been frequently used for making secondary alcohols and primary amines eligible for CD measurements and was, therefore, selected as the additional chromophore.[189-191]

The benzoyl derivatisation was conducted by a Novozym 435 catalysed kinetic resolution of the racemic alcohols **12a-h**, using vinyl benzoate as acyl donor (Scheme 5.1). These robust reactions use a simple experimental setup and are performed under mild reaction

conditions, thus minimising the risk of racemisation. The benzoates (*S*)-**36a-h** were isolated in good to excellent enantiomeric excess (Table 5.1) but prolonged reaction time (1-2 weeks) was an obvious disadvantage for this approach.



12a-h (*R*)-**12a-h** (*S*)-**36a-h**

R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 5.1

Results from CD measurements can only be interpreted correctly when the most favoured conformation of the compound is known. Therefore, an energy minimisation calculation (MM2) of the benzoates (*S*)-**36a-h** was performed. In accordance with calculations previously performed on related compounds,[190] this showed that all the benzoates (*S*)-**36a-h** had similar preferred conformations, with the hydrogen at the stereogenic centre arranged in the same plane as the disubstituted aromatic ring. Figure 5.2(A) shows the most favoured conformation for (*S*)-**36h**.

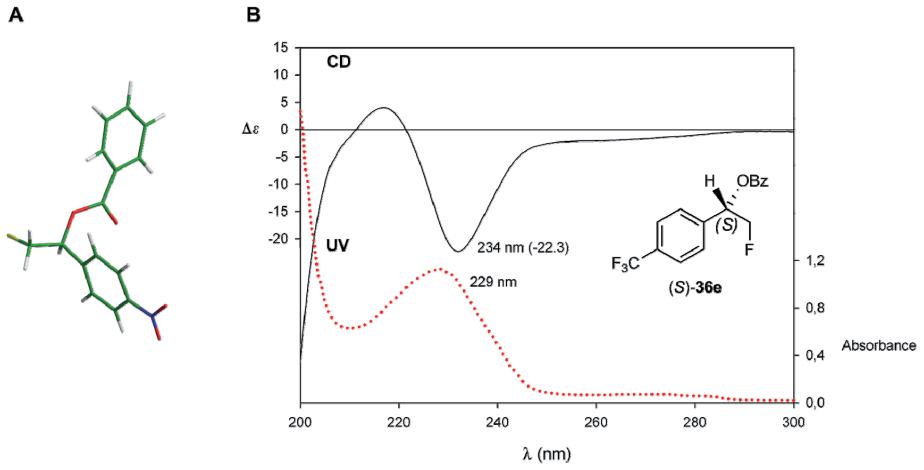


Figure 5.2: (**A**) The most favoured conformation for (*S*)-**36h** and (**B**) the CD and UV spectrum of (*S*)-**36e**.

As illustrated in Figure 5.2(A) for (*S*)-**36h**, an anticlockwise rotation of the disubstituted phenyl ring brings it onto the benzoate dipole. According to the exciton chirality rule, this predicts a negative first Cotton effect. This was confirmed by the CD measurements performed and the absolute configuration of the prepared benzoates **36a-h** could be assigned as (*S*). The CD and UV spectrum of (*S*)-**36e** is shown in Figure 5.2(B). The second Cotton effect was not observed because the CD spectrum was perturbed by other electronic transitions and effects caused by solvents. Based on the results from the benzoates, the 1-aryl-2-fluoroethanols **12a-h** left unreacted in the resolution reactions were assigned as (*R*). The molar extinction values (Δε) and λ_{max} of the benzoates (*S*)-**36a-h** are summarised in Table 5.1.

Table 5.1: Enantiomeric excess (ee), molar extinction (Δε) and λ_{max} of first Cotton effect for (*S*)-**36a-h**.

Compound	ee [%]	Δε	λ_{max} [nm]
(*S*)-**36a** (OMe)	73	-5.9	233
(*S*)-**36b** (OBn)	99	-14.2	234
(*S*)-**36c** (H)	88	-9.0	228
(*S*)-**36d** (F)	79	-7.1	228
(*S*)-**36e** (Br)	94	-22.3	232
(*S*)-**36f** (CF_3)	96	-6.0	227
(*S*)-**36g** (CN)	90	-19.6	237
(*S*)-**36h** (NO_2)	94	-9.0	265

5.3 Determination of the absolute configuration of enantioenriched 1-aryl-2-fluoroethylamines

Among the prepared 1-aryl-2-fluoroethylamines **21a-h**, only **21a**[192] and **21c**[192-194] had previously been characterised in enantiomerically enriched form. As for the 1-aryl-2-fluoroethanols **12a-h**, the absolute configuration of the amines **21a-h** was determined by using the CD exciton chirality method.

The phthalimide group chromophore has previously been used for CD measurements[195,196] and, as the *N*-substituted phthalimides (*S*)-**31a-h** were already available, they were utilised for determining the absolute configuration of the corresponding 1-aryl-2-fluoroethylamines (*S*)-**21a-h**.

The most favoured conformation of the *N*-substituted phthalimides (*S*)-**31a-h** was predicted by energy minimisation calculations. All the compounds had similar preferred conformations, with the hydrogen atom attached to the stereogenic centre arranged in the same plane as the phenyl ring. Figure 5.3(A) illustrates the most favoured conformation for (*S*)-**31f**.

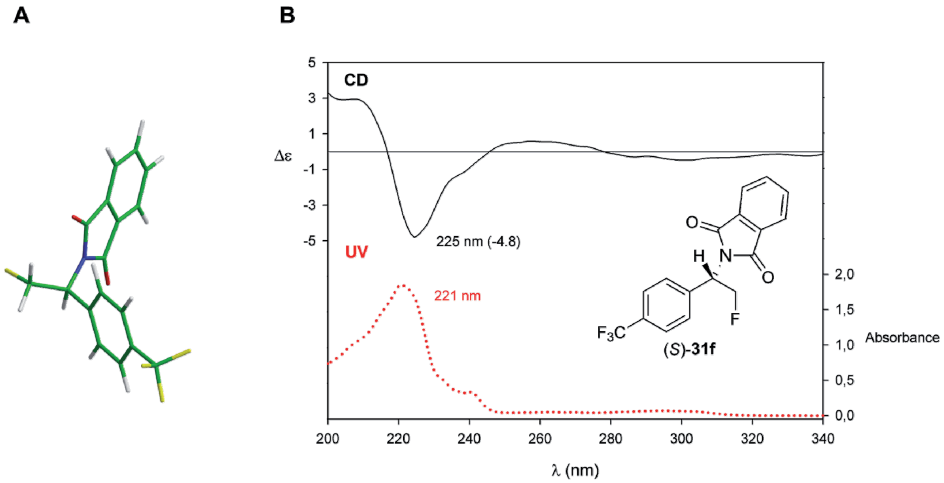


Figure 5.3: (**A**) The most favoured conformation for (*S*)-**31f** and (**B**) the CD and UV spectrum of (*S*)-**31f**.

Based on the conformation shown for (*S*)-**31f** in Figure 5.3(A), a negative negative first Cotton effect was expected for the *N*-substituted phthalimides (*S*)-**31a-h**. This was

confirmed by the CD measurements as illustrated for (*S*)-**31f** in Figure 5.3(B). The results for all the *N*-substituted phthalimides (*S*)-**31a-h** are summarised in Table 5.2.

Table 5.2: Enantiomeric excess (ee), molar extinction (Δε) and λ_{max} of first Cotton effect for (*S*)-**31a-h**.

Compound	ee [%]	Δε	λ_{max} [nm]
(*S*)-**31a** (OMe)	53.0	-1.3	232
(*S*)-**31b** (OBn)	60.0	-3.8	234
(*S*)-**31c** (H)	99.0	-3.5	223
(*S*)-**31d** (F)	[a]	-1.6	223
(*S*)-**31e** (Br)	90.0	-3.9	230
(*S*)-**31f** (CF_3)	92.0	-4.8	225
(*S*)-**31g** (CN)	87.5	-2.7	237
(*S*)-**31h** (NO_2)	84.0	-1.4	228

[a] Not determined

5.4 Summary

By applying the CD exciton chirality method, the absolute configuration of the benzoates (*S*)-**36a-h** and *N*-substituted phthalimides (*S*)-**31a-h** has been unambiguously determined. Based on these results, the absolute configuration of the alcohols (*R*)-**12a-h** and the amines (*S*)-**21a-h** could also be assigned.

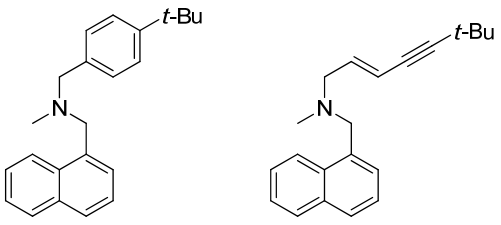
As can be seen from Table 5.1 and Table 5.2, the molar extinction values (Δε) for the *N*-substituted phthalimides (*S*)-**31a-h** were considerably lower than the values for the benzoates (*S*)-**36a-h**. This was expected, as the exciton coupling between two equal chromophores will give a higher Δε-value.[182] Even though lower molar extinction values were experienced, they were still large enough to provide reliable and reproducible results. As anticipated, the phthalimide group and the benzoate group were confirmed as good alternatives as an extra chromophore when the absolute configuration of 1-aryl-2-fluoroethanols and 1-aryl-2-fluoroethylamines is to be determined by the CD exciton chirality method.

6. Chiral derivatives of Butenafine and Terbinafine

This chapter summarises the results presented in Paper VI. Master of Technology Hanne Høgmoen is acknowledged for the work with the di- and trifluorinated compounds. Master of Science Eli Otterholt and Associate Professor Colin Charnock are acknowledged for the work related to the biological activity screens.

6.1 Introduction

Butenafine (**37**) and Terbinafine (**38**) (Figure 6.1) are part of a well established class of antimycotic agents referred to as allylamines. They are used among others in topical treatment of dermatocytes invading skin and nails and act by preventing the synthesis of ergosterol in fungal cells. Ergosterol is an essential membrane component and a lack of this compound causes the fungal cells to lyse. In the biosynthesis of ergosterol, the allylamines inhibit the enzyme squalene epoxidase responsible for converting squalene into squalene 2,3-epoxide. In addition to the lack of ergosterol, the accumulation of squalene also plays a role in the fungicidal action of these pharmaceuticals.[197]



Butenafine (**37**) Terbinafine (**38**)

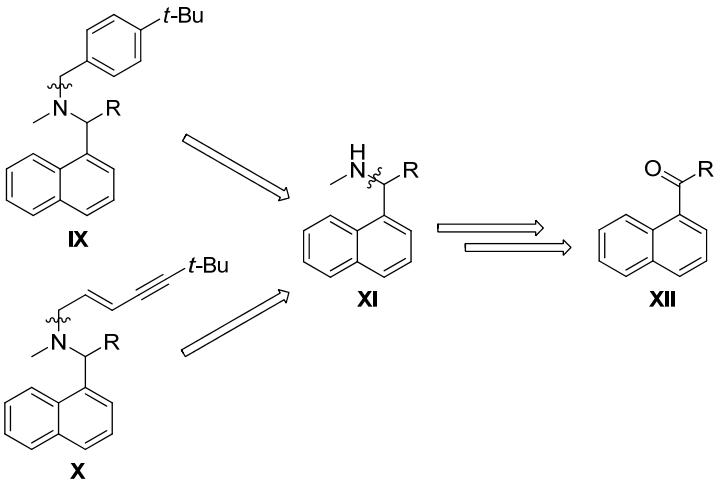
Figure 6.1: The structure of the antimycotic agents Butenafine (**37**) and Terbinafine (**38**).

As can be seen from Figure 6.1, both Butenafine (**37**) and Terbinafine (**38**) are achiral compounds consisting of a tertiary amine located in the benzylic position of a naphthyl group. The antifungal activity of a number of achiral derivatives of these compounds have previously been investigated.[198-204] However, derivatives containing a stereogenic centre adjacent to the central nitrogen atom have been substantially less studied. Both the 1-acetonaphthone derived compounds **39a** and **40a** (Figure 6.2) have previously been shown to have antifungal activity,[205-207] while the usefulness of (*R*)-**40b** has been indicated by comparative molecular field analysis.[208]

Elderly and immunocompromised patients are an increasing part of the world's population and, as a result of this, an increased use of antimycotics for treatment of fungal infections has occurred. Following this increase, pathogenic fungal strains showing resistance against the available antifungal agents are emerging as a serious problem.[209-211] Although many fungal infections are either harmless or give only minor symptoms, some fungal strains can cause potentially lethal infections. The *Cryptococcus neoformans* species is, for instance, known to cause the potentially fatal infection cryptococcosis in a large number of AIDS patients.[212-214] The same species is also responsible for causing a severe form of meningitis, especially frequent in the developing world.[215,216] *Cryptococcus diffluens* is from the same genus as *Cryptococcus neoformans* and, although being less pathogenic, it is a common cause of the eczema atopic dermatitis.[217] *Trichosporon cutaneum* (syn. *T. Beigelii*)[218] is a fungal strain which is normally found in soil but it can also inhabit humans. To healthy human beings it is harmless, although in some cases it can cause the hair infection white piedra. To immunocompromised patients, however, it represents a potential life threatening pathogen and responds poorly to antifungal agents.[219]

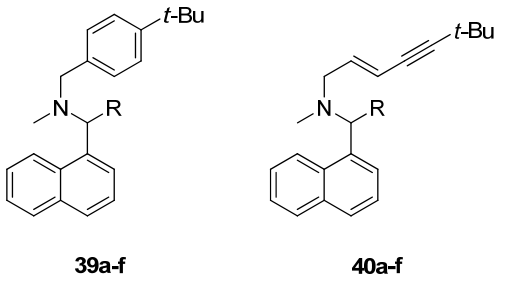
6.2 Synthesis of chiral derivatives of Butenafine and Terbinafine

A simple retrosynthetic analysis shows that chiral derivatives of Butenafine (**37**) and Terbinafine (**38**) could potentially be made starting from 1-naphthylethanones (**XII**) (Scheme 6.1). By disconnecting one of the amine bonds of the target compounds **IX** and **X**, the shown route utilises the resulting secondary methylamines **XI** as key intermediates. These intermediates can be accessed by a number of routes, one being the reductive amination of the corresponding 1-naphthylethanones **XII**.



Scheme 6.1

By employing 1-naphthyl-2-fluoroethanones as starting compounds, fluorinated amines could be produced. The amino group of these compounds would have lower basicity than the non-fluorinated analogues and, to investigate if this would affect the antifungal activity, the Butenafine and Terbinafine analogues **39a-f** and **40a-f** were targeted (Figure 6.2).



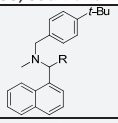
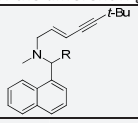
R = Me (**a**), Et (**b**), CH_2F (**c**), CHF_2 (**d**), CF_3 (**e**), CN (**f**)

Figure 6.2: Potential bioactive target compounds.

The mono-, di- and trifluorinated analogues **39c-e** and **40c-e** would have lower pK_a values than the existing drugs, while the methyl and ethyl substituted derivatives **39a-b** and **40a-b** would be slightly more basic (Table 6.1). To separate a possible size effect from an electronic effect, the cyano substituted compounds **39f** and **40f** were also included in the

study. The cyano group is close to CHF_2 and CF_3 in respect of electronic properties but it is smaller than a methyl group in size (Table 6.1).

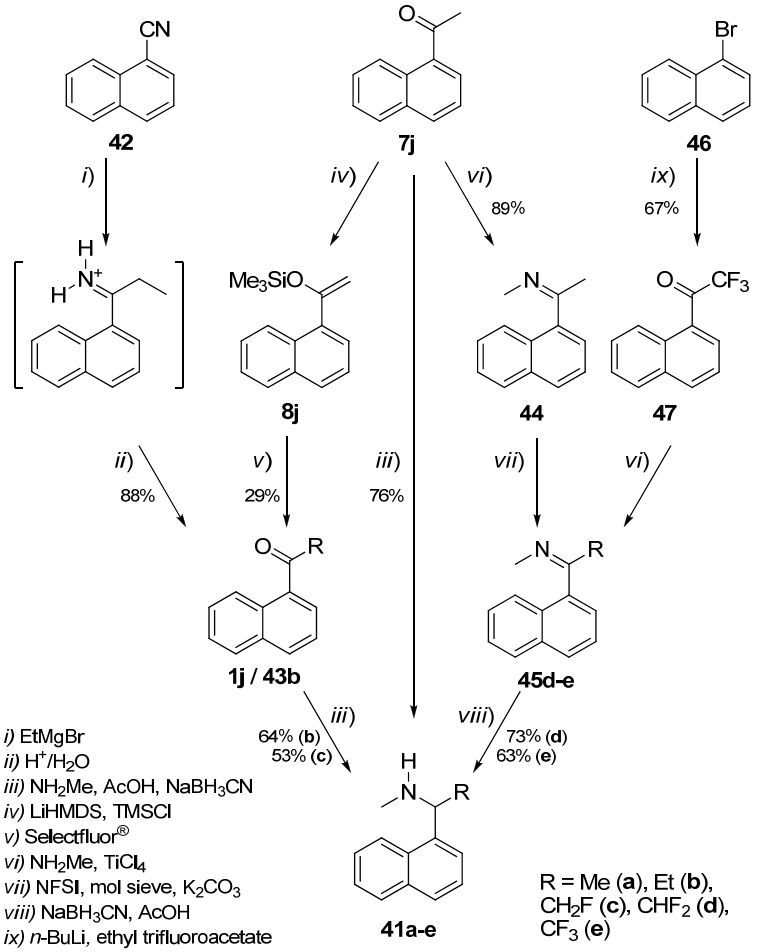
Table 6.1: Calculated pK_a-values of **37**, **38**, **39a-f** and **40a-f** and the relative sizes of the different R-groups.

					
R	**Rel. size**[a]	**Compound**	**Calcd. pK_a**[b]	**Compound**	**Calcd. pK_a**[b]
H	0	**37**	9.2	**38**	8.9
Me	0.52	**39a**	9.5	**40a**	9.2
Et	0.56	**39b**	9.5	**40b**	9.5
CH_2F	0.62	**39c**	9.5	**40c**	7.6
CHF_2	0.68	**39d**	9.8	**40d**	5.8
CF_3	0.91	**39e**	7.9	**40e**	2.9
CN	0.40	**39f**	6.1	**40f**	5.1

[a] Charton volume from tabulated values.[208,220]
[b] The pK_a-values were calculated using the Marvin program suite.

6.2.1 Synthesis of secondary methylamine intermediates

The secondary methylamines **41a-e** were synthesised as shown in Scheme 6.2. The cyano derivative **41f** was considered made via the Strecker synthesis[221] but as it was commercially available it was instead purchased.



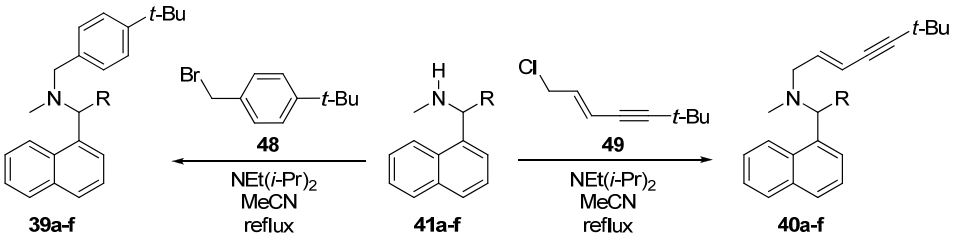
Scheme 6.2

The secondary methylamine **41a** was obtained in good yield after the reductive amination of 1-acetonaphtone (**7j**) using methylamine, acetic acid and sodium cyanoborohydride. A Grignard reaction between 1-cyanonaphthalene (**42**) and ethylmagnesium bromide followed by hydrolysis of the imine intermediate yielded the ketone **43b** which, by a reductive amination, gave the ethyl substituted secondary methylamine **41b**. To obtain the monofluorinated methylamine **41c**, electrophilic fluorination of the crude trimethylsilyl enol ether **8j** using Selectfluor® was employed. This reaction suffered from the formation of ring fluorinated by-products, resulting in a poor 29% yield of the α-

fluoroketone **1j**. The subsequent reductive amination provided the secondary methylamine **41c** in a mediocre 53% yield. The difluorinated methylamine **41d** was most conveniently synthesised from 1-acetonaphthone (**7j**) via the imine **44**. This was difluorinated with NFSI to provide the imine **45d**, which then was reduced directly to the methylamine **41d** in a decent 65% overall yield. Finally, the trifluorinated derivative **41e** was synthesised by transforming 1-bromonaphthalene (**46**) to 1-lithiumnaphthalene which subsequently was treated with ethyl trifluoroacetate. The trifluorinated ketone **47** was converted to the imine **45e** which then was reduced to the target compound **41e** in decent yield.

6.2.2 *N*-alkylation of secondary methylamines

To synthesise the final drug analogues **39a-f** and **40a-f**, the secondary methylamines **41a-f** were alkylated with the commercially available 1-(bromomethyl)-4-*tert*-butylbenzene (**48**) and (*E*)-1-chloro-6,6-dimethylhept-2-en-4-yne (**49**) (Scheme 6.3). The reactions were performed in refluxing acetonitrile, with *N*,*N*-diisopropylethylamine as the base.



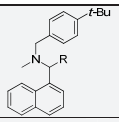
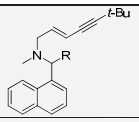
R = Me (**a**), Et (**b**), CH_2F (**c**), CHF_2 (**d**), CF_3 (**e**), CN (**f**)

Scheme 6.3

The yield of the reactions depended both on the nature of the R-groups and on the alkylating agent. As Table 6.2 shows, the Butenafine analogues **39a-f** were isolated in generally higher yields than the Terbinafine analogues **40a-f**. In addition to the better leaving group ability of the bromide compared to the chloride anion, the observed trend could also be attributed to the fact that the alkylating agent **49** contained 4% of the Z-isomer. This resulted in more complex reaction mixtures and troublesome purifications for the Terbinafine analogues **40a-f**. When inspecting the summarised results, a trend could also be seen between the nature of R-groups and the reaction times. As the number of fluorine atoms increased, the reaction time was extended from a few hours to several days. This effect was expected and can be explained by the decreasing nucleophilicity of

the amine moiety of **39d-e** and **40d-e**. For the synthesis of the cyano substituted analogues **39f** and **40f**, ^{1}H NMR spectroscopy indicated that the nitrile group had partially hydrolysed into the carboxylic acid and this probably explains the lower yields experienced for these reactions.

Table 6.2: Isolated yields and reaction times of **39a-f** and **40a-f** following the *N*-alkylation of **41a-f** using **48** and **49** as alkylating agents.

						
R	**Compound**	**Reaction time [h]**	**Isolated yield [%]**	**Compound**	**Reaction time [h]**	**Isolated yield [%]**
Me	**39a**	2	81	**40a**	2	61
Et	**39b**	2	82	**40b**	2	55
CH_2F	**39c**	4	86	**40c**	2	41
CHF_2	**39d**	48	90	**40d**	144	63
CF_3	**39e**	120	82	**40e**	240	44
CN	**39f**	4	75	**40f**	120	45

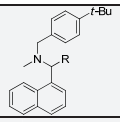
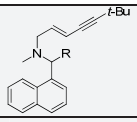
Starting with enantiomerically pure (*R*)-**41a** (99.5% ee) and (*S*)-**41a** (98.5% ee), (*R*)-**39a** and (*S*)-**39a** were also synthesised according to the same procedure as described for the racemic analogue **39a**.

6.3 Antifungal activity

The antifungal activity testing was performed at the Oslo University College by Master of Science Eli Otterholt as a part of her PhD project. The results from this work will, therefore, only be briefly discussed and summarised in this chapter.

Initially, the antifungal activity of the drug analogues **39a-f** and **40a-f** towards the microorganism *C. neoformans* was evaluated. For comparison, Butenafine (**37**) and Terbinafine (**38**) were also included in the test. The evaluation was performed by employing the semisolid agar antifungal susceptibility (SAAS) method and the resulting minimum inhibitory concentration (MIC) values are shown in Table 6.3.

Table 6.3: Antifungal activity (MIC values) of **37**, **38**, **39a-f**, **40a-f** towards *C. neoformans*, determined by the SAAS method.

R	Compound	MIC_{50} [µg/mL]	MIC_{75} [µg/mL]	Compound	MIC_{50} [µg/mL]	MIC_{75} [µg/mL]
H	**Butenafine (37)**	0.125	0.25	**Tebinafine (38)**	0.25	0.5
Me	**39a**	0.125	0.25	**40a**	0.5	1.0
Me	(*R*)-**39a**	<0.031	0.031	-	-	-
Me	(*S*)-**39a**	0.5[a]	1-8[a]	-	-	-
Et	**39b**	0.25-4[a]	8	**40b**	2-8[a]	16
CH_2F	**39c**	>16	>16	**40c**	>16	>16
CHF_2	**39d**	>16	>16	**40d**	>16	>16
CF_3	**39e**	>16	>16	**40e**	>16	>16
CN	**39f**	>16	>16	**40f**	>16	>16

[a] Trailing growth complicated assignment of MIC values.

The testing revealed that the racemic methyl substituted Butenafine derivative **39a** had higher activity than Terbinafine (**38**) and the same activity as Butenafine (**37**). By testing both the enantiomers (*R*)-**39a** and (*S*)-**39a** separately, the activity was proved mainly to originate from the (*R*)-enantiomer, as this was significantly more potent than both Butenafine (**37**) and the (*S*)-enantiomer. The racemic methyl substituted Terbinafine derivative **40a** was less efficient than the parent compound **38**. When the methyl substituent was replaced by an ethyl substituent, the antifungal activity of both the Butenafine analogue **39b** and the Terbinafine analogue **40b** dropped. For the analogues containing fluorine or a cyano group (**39c-f** and **40c-f**), no antifungal activity towards *C. neoformans* was observed.

Although less fungal growth inhibition was observed when the size of the R-group was increased from methyl, via ethyl to the fluorinated substituents, the observations could not solely be explained by steric effects. The lack of antifungal activity observed for the cyano substituted **39f** and **40f** indicated that electronic effects were of equal importance as steric effects. As no structural information currently is available for the squalene epoxidases of the tested organisms, it is difficult to explain the results at a molecular level.

To verify the main results from the SAAS testing, Butenafine (**37**) and the methyl substituted derivatives **39a**, (*R*)-**39a** and (*S*)-**39a** were also evaluated using the broth microdilution method.[222] To further investigate the usefulness of the compounds as antifungal agents, two additional fungal species (*C. diffluens* and *T. cutaneum*) were

included in the investigation. The results are summarised in Table 6.4 and show that all the compounds tested inhibited fungal growth. Although the MIC values obtained from the broth microdilution method of *C. neoformans* varied slightly from the SAAS values, the relative activities were the same. The testing against *C. diffluens* was troubled by trailing growth but (*R*)-**39a** was identified as the most active derivative, with a MIC_{50} value half of that for Butenafine (**37**). Against the *T.cutaneum* strain, Butenafine (**37**) and the analogues **39a** and (*R*)-**39a** were equally efficient. Although still being the least efficient compound, the relative activity of (*S*)-**39a** was higher against *T.cutaneum* when compared to the other organisms. This could indicate a more flexible inhibitor binding site.

Table 6.4: Antifungal activity of **37**, **39a,** (*R*)-**39a** and (*S*)-**39a** towards *C. neoformans*, *C. diffluens* and *T. cutaneum*, determined by the broth microdilution method.

Compound	*C. neoformans*		*C. diffluens*		*T. cutaneum*	
	MIC_{50} [µg/mL]	MIC_{75} [µg/mL]	MIC_{50} [µg/mL]	MIC_{75} [µg/mL]	MIC_{50} [µg/mL]	MIC_{75} [µg/mL]
37	0.5	1.0	0.5[a]	4.0[a]	0.5	1.0
39a	0.25	0.5	0.5[a]	2.0[a]	0.5	1.0
(*R*)-**39a**	0.125	0.25	0.25[a]	1.0[a]	0.5	1.0
(*S*)-**39a**	1.0[a]	2.0[a]	4.0[a]	>16[a]	1.0[a]	2.0[a]

[a] Trailing growth complicated assignment of MIC values.

6.4 Summary

The compounds **39a-f** and **40a-f**, structurally related to the antimycotic agents Butenafine (**37**) and Terbinafine (**38**), have been synthesised and their antifungal activity against *C. neoformans* have been evaluated. The compound displaying the highest activity was found to be **39a**, being equally as efficient as Butenafine (**37**). By testing each of the enantiomers (*R*)-**39a** and (*S*)-**39a** separately, it was revealed that the main activity originated from the (*R*)-enantiomer, which was significantly more active than Butenafine. When the methyl substituent at the stereogenic centre was replaced by more electron withdrawing substituents, the antifungal activity towards *C. neoformans* dropped below detectable limits. This may indicate that the basicity of the nearby amino group plays a crucial role in the antifungal action of these compounds. By applying the broth microdilution method, it was confirmed that the enantiomerically enriched methyl derivative (*R*)-**39a** had similar or better antifungal activity than Butenafine (**37**) against *C. neoformans*, *C. diffluens* and *T. cutaneum*. These results suggest that antimycotic agents based on this compound can potentially offer improvements of the existing Butenafine based formulations used today.

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Paper I

Fuglseth, E., Thvedt, T. H. K., Møll, M. F., Hoff, B. H.

Electrophilic and nucleophilic side chain fluorination of *para*-substituted acetophenones

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Electrophilic and nucleophilic side chain fluorination of *para*-substituted acetophenones

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ABSTRACT

para-Substituted α-fluoroacetophenones have been synthesised by three different routes. Electrophilic fluorination of trimethylsilyl enol ethers of acetophenones using Selectfluor (F–TEDA–BF_4, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate)) gave high to moderate yield depending on the electronic properties of the substituents. F–TEDA–BF_4 mediated fluorination of acetophenones in methanol resulted in a mixture of α-fluoroacetophenones and the corresponding 2-fluoro-1,1-dimethyl acetals. The dimethyl acetals were hydrolysed using trifluoroacetic acid in water to maximise the yield of the product. Nucleophilic fluorination of α-bromoacetophenones using tetrabutylammonium hydrogen bifluoride (TBABF) led to moderate yield when having electron-donating substituents, whereas low yields were experienced when more electron-withdrawing substituents were introduced.

1. Introduction

The importance of fluorinated compounds in pharmaceuticals, agrochemicals and material sciences has been thoroughly recognised.[1–5] As a consequence fluorinated building blocks are required. α-Fluoroacetophenones can give access to a number of interesting molecules by reaction at the keto-group, the α-carbon or the aromatic ring. Examples include synthesis of fluorinated tetralones,[6] pyrozoles[7] and thiadiazoles.[8] α-Fluoroacetophenones are also suitable starting materials for fluorochemicals such as 1,1,2-trifluoroethyl aryl ethers,[9] 1,2-difluoroethylaryls[10] and 1,1,2-trifluoroethylaryls.[11]

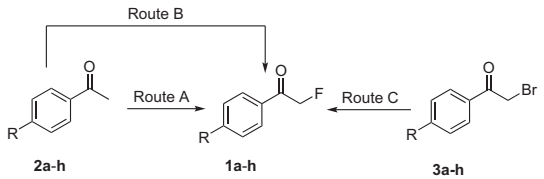
Various methods can be used for synthesis of α-fluoroacetophenones, including nucleophilic displacement,[11–16] electrophilic fluorination,[7,17–21] Friedel–Crafts chemistry,[22,23] coupling chemistry[24] and reaction via diazo ketones.[25,26] Some of these methods have drawbacks due to the use of hazardous and toxic chemicals.

Being in need of a series of α-fluoroacetophenones, it was recognised that the literature mainly covers reactions towards the parent compound 2-fluoro-1-phenylethanone, and no systematic study on the effect of substrate structure on yield had been performed. Therefore, the aim of the work was to compare the usefulness of two electrophilic and one nucleophilic strategies for the preparation of eight different *para*-substituted α-fluoroacetophenones. Targeting nonhazardous procedures, Selectfluor (F–TEDA–BF_4) and tetrabutylammonium hydrogen bifluoride (TBABF) were selected as fluorination reagents. F–TEDA–BF_4 is a stable crystalline solid with low hydroscopicity and toxicity, suited for safe fluorination.[27] TBABF is a nucleophilic fluorine source, claimed to be noncorrosive, possessing good solubility properties, and having a high thermal stability.[12]

2. Results and discussion

2.1. Comparison of the routes

The three routes investigated for the synthesis of α-fluoroacetophenones, **1a–h**, are shown in Scheme 1.



Scheme 1. Route A: (1) Base/TMSCl, (2) F–TEDA–BF_4. Route B: (1) F–TEDA–BF_4, (2) TFA. Route C: TBABF. R=OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**) and NO_2 (**h**).

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In route A, acetophenones were converted to the corresponding trimethylsilyl enol ethers, and reacted with F–TEDA–BF_4. The fluorination was performed in acetonitrile at room temperature. In route B,[7,17] electrophilic fluorination of the acetophenones, **2a**–**h**, was performed using 2 equiv of F–TEDA–BF_4 in refluxing methanol. The reaction yielded the fluorinated ketones **1a**–**h** and their corresponding 2-fluoro-1,1-dimethyl acetals. Hydrolysis under acidic conditions was required to convert the acetals to the α-fluoroacetophenones, **1a**–**h**. For the nucleophilic approach (route C), the α-bromoacetophenones, **3a**–**h**, were reacted with 2 equiv of TBABF in refluxing THF. The isolated yields for the three strategies are summarised in Table 1.

Table 1
Isolated yields for the routes A–C

R	Product	Isolated yield (%)		
		Route A	Route B	Route C
OMe	**1a**	91	67	48
OBn	**1b**	89	58	51
H	**1c**	76	66	42
F	**1d**	74	25	36
Br	**1e**	69	77	33
CF_3	**1f**	69	73	26
CN	**1g**	55	64	20
NO_2	**1h**	44	70	20

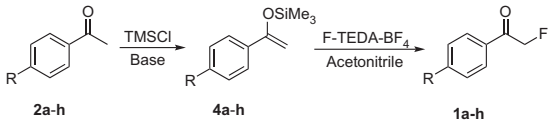
Electrophilic fluorination via the trimethylsilyl enol ethers (route A) provided on average the highest yield. The process was especially suited for substrates bearing electron-donating substituents. A decrease in yield was observed as more electron-withdrawing groups were introduced, and only a moderate 44% yield was obtained for the 4-nitro derivative, **1h**.

Fluorination of acetophenones in methanol (route B) gave yields in the range of 25–77%. Fluorination of **2a**–**b** also led to ring fluorinated by-products, which complicated the purification step. Of the methods tested, route B gave the highest yields of **1e**–**h**.

Nucleophilic fluorination of **3a**–**h** using TBABF (route C) gave moderate to low yield, depending on substrate structure. The best yields for route C were obtained when reacting α-bromoacetophenones having electron-donating substituents, whereas for substrates bearing electron-withdrawing substituents low yields were experienced.

2.2. Electrophilic fluorination via trimethylsilyl enol ethers (route A)

In the first step, the acetophenones (**2a**–**h**) were converted to the trimethylsilyl enol ethers **4a**–**h**, Scheme 2. For preparation of **4a**–**g**, lithium hexamethyldisilazane (LiHMDS) and trimethylsilyl chloride (TMSCl) were used, giving a conversion of >98%. Compound **4h** proved to be more difficult to prepare in decent purity by this method. Changing the base to DBU improved the synthesis, and a conversion of 95% could be obtained.

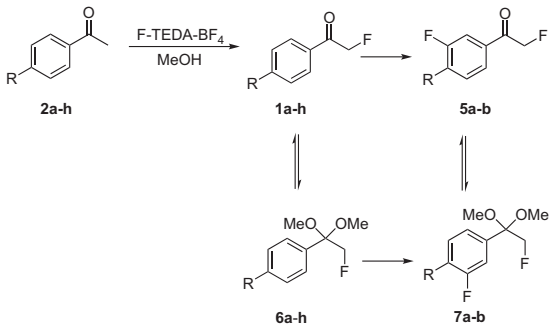


Scheme 2. Synthesis of **1a**–**h** via the trimethylsilyl enol ethers, **4a**–**h**, using F–TEDA–BF_4.

The crude trimethylsilyl enol ethers, **4a**–**h**, were treated with F–TEDA–BF_4 at room temperature in acetonitrile. The reaction progress was monitored by ^{1}H NMR spectroscopy. Some reactions failed to go to completion, but addition of 0.1–0.3 additional equivalents of F–TEDA–BF_4 allowed for full conversion (>98%). Of the substrates tested, only fluorination of **4h** failed to reach full conversion after additional F–TEDA–BF_4 had been added. The highest conversion obtained for **1h** via route A was 91%.

2.3. Electrophilic fluorination in methanol (route B)

Treating the acetophenones, **2a**–**h**, with 2 equiv of F–TEDA–BF_4 in refluxing methanol[7] gave the products **1a**–**h** and the corresponding 2-fluoro-1,1-dimethyl acetals, **6a**–**h**, Scheme 3. For substrates bearing electron-donating substituents, the ring fluorinated ketones, **5a**–**b**, and their 2-fluoro-1,1-dimethyl acetals, **7a**–**b**, were also formed. The chemoselectivity (aliphatic/aromatic) was found to be dependent on the degree of conversion, with higher conversion leading to increased levels of **5a**–**b** and **7a**–**b**.



Scheme 3. Products formed in fluorination of acetophenones using F–TEDA–BF_4 in methanol.

Table 2 summarises the reaction time, degree of conversion and product distribution for the reactions prior to acetal cleavage. The reaction time varied from 48 h for **2a** to 11 days for **2h**.

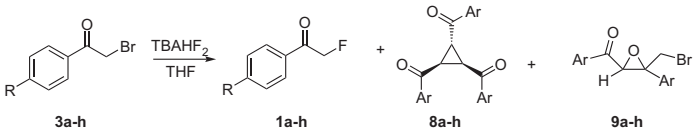
The ketone to dimethyl acetal product ratio depended on substrate structure, the dimethyl acetal form being favoured by electron-withdrawing groups. This is in agreement with ketone–dimethyl acetal equilibrium constants found for acetophenones.[28] ^{1}H NMR spectroscopy also indicated trace amounts of α,α-difluoroacetophenones and α-chloroacetophenones being present at high conversions. The formation of the latter is most likely due to electrophilic chlorine impurities in the commercial reagent.

Treating the ketone/dimethyl acetal mixture under acidic conditions, converted **6a**–**h** and **7a**–**b** to the corresponding α-fluoroacetophenones, **1a**–**h** and **5a**–**b**. The yield of **1a**–**h** varied between 25 and 77%. The low yield in the case of **1d** is explained by the volatility of the intermediate 2-fluoro-1,1-dimethyl acetal, **6d**. A test distillation performed at atmospheric pressure, revealed that both **6d** and **1d** co-distilled with methanol at 66–67 °C.

The hydrolytic stability of the dimethyl acetals was also dependent on the aromatic substituents. Electron-withdrawing

Table 2
Reaction time, conversion and product distribution (^{1}H NMR spectroscopy) for fluorination of acetophenones, **2a**–**h**, using F–TEDA–BF_4 in methanol

Substrate	Reaction time (h)	Conv. (%)	Product distribution (%)			
			1	**5**	**6**	**7**
2a	48	98	67	13	11	7
2b	72	96	57	6	24	9
2c	96	98	36	0	62	0
2d	96	99	38	0	61	0
2e	125	98	26	0	72	0
2f	144	99	7	0	92	0
2g	192	99	13	0	86	0
2h	261	99	7	0	92	0



Scheme 4. Synthesis of α-fluoroketones, **1a**–**h**, via α-bromoketones **3a**–**h**, using TBABF.

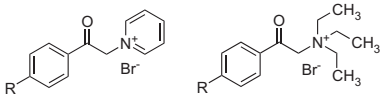
groups increased the stability. Compound **6h** proved to be particularly stable and could not be cleaved by several protocols.[29–31] However, refluxing with 10% aqueous hydrochloric acid in THF, or trifluoroacetic acid/water/chloroform,[32] provided full conversion within 20 h. The use of HCl had the drawback of formation of small amounts of the corresponding α-chloroacetophenone. The mechanistic rational behind this transformation has not been investigated.

2.4. Nucleophilic displacement (route C)

The yield of the nucleophilic displacement reaction using TBABF depended on the aromatic ring substituents. Moderate outcome was observed for substrates having electron-donating groups, whereas only 20% isolated yield was obtained for **1g**–**h**. The decrease in reaction yield through the series parallels the increasing electron-withdrawing property and acidity of the acetophenones.[33] The main by-products in these reactions were *trans*-1,2,3-tri-(benzoyl)cyclopropanes, **8a**–**h**, Scheme 4.

In the case of **3c**–**e**, ca. 20% of the substrates were consumed in this side reaction. Compounds **8c**–**e** were isolated and characterised. The stereochemistry of **8c**–**e** was evident from the ^{1}H NMR spectra, which contained a one proton triplet at ca. 4.2 ppm and a two proton doublet at ca. 3.7 ppm, both with a coupling constant of ca. 5.6 Hz. These compounds are most likely formed via the *trans*-1,2-dibenzoylethylenes, by a cycloaddition reaction of ionic character.[34,35] ^{1}H NMR spectroscopy also indicated compounds **9a**–**h**, products of Darzen-type condensations,[36–38] to be formed under these conditions.

Pyridine and triethylamine have previously been used in fluorinations of α-bromoacetophenones using TBABF.[15,39] The method was tested in fluorination of **3b** using both pyridine and triethylamine, and in reaction of **3c** using pyridine. However, this led to further loss in yield due to formation of compounds **10b**, **11b** and **10c**, Scheme 5.



Scheme 5. By-products caused by pyridine or triethylamine.

3. Conclusion

Using three different methods, eight α-fluoroacetophenones have been prepared. Three of these have previously not been characterised (**1b**, **1f** and **1g**). In general, electrophilic fluorination via the trimethylsilyl enol ethers, **4a**–**h**, using F–TEDA–BF_4, gave higher yields than that for the other methods tested. The yield depended on the aromatic ring substituents, with substrates bearing electron-donating groups giving higher yield. In contrast to molecular fluorine and trifluoromethyl hypofluorite,[18,20] the use of F–TEDA–BF_4 enables the fluorination to take place at room temperature in conventional media. Fluorination of acetophenones with F–TEDA–BF_4 in methanol gave the α-fluoroacetophenones, **1a**–**h**, and the corresponding 2-fluoro-1,1-dimethyl acetals, **6a**–**h**. The dimethyl acetals were hydrolysed to **1a**–**h** using trifluoroacetic acid. The method is experimentally simple, and the yields were independent of the electronic properties of the aromatic substituents. The protocol suffers from low chemoselectivity for substrates bearing electron-donating groups, prolonged reaction times and the requirement of 2 equiv of F–TEDA–BF_4. However, the method gave the highest yields for compounds **1e**–**h**. Nucleophilic displacement of α-bromoacetophenones containing electron-donating substituents gave moderate yields. For substrates bearing electron-withdrawing groups, condensation reactions led to complex mixtures and low yields. Compared to the electrophilic fluorinations, this method is of less value.

4. Experimental

4.1. General

The acetophenones **2a**, **2c** and **2f**–**h**, the α-bromoacetophenones **3a** and **3c** and tetrabutylammonium hydrogen bifluoride (50% solution) were purchased from Fluka. LiHMDS, Selectfluor (F–TEDA–BF_4) and trimethylsilyl chloride were purchased from Aldrich. Column chromatography was performed using silica gel 60A from Fluka, pore size 40–63 μm. 1-(4-Benzyloxyphenyl)ethanone (**2b**) was prepared from 4-hydroxyacetophenone using benzyl chloride and potassium carbonate in *N*,*N*-dimethylformamide as solvent. 1-(4-Fluorophenyl)ethanone (**2d**) was prepared as described by Olah et al.[40] The α-bromoacetophenones **3b** and **3d**–**h** were prepared by bromination of the corresponding acetophenones using molecular bromine. NMR spectra and high resolution mass spectra were in accordance with proposed structures. Compounds **6b**, **6e**–**h** and **7b** were isolated by column chromatography after synthesis according to route B (4.41 mmol scale), omitting the hydrolytic step.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^{1}H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. For ^{1}H and ^{13}C NMR chemical shifts are in parts per million relative to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. NMR resonance assignment was aided by the HMBC technique.[41] MS (EI/70 eV): Finnigan MAT 95 XL, MS (ESI): Waters QTOF II and MS (CI): Waters Prospec Q. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument.

4.3. Electrophilic fluorination via trimethylsilyl enol ethers (route A)

The trimethylsilyl enol ethers, **4a**–**g**, were prepared as described by Wiles et al.[42] starting with 20 mmol of the acetophenones. Compound **4h** was prepared according to Schumacher and Reissig.[43] ^{1}H NMR spectra were in accordance with that reported previously: **4a**,[44] **4b**,[44] **4c**,[45] **4d**,[18] **4f**,[43] **4g**[46] and **4h**.[43] Compound **4e**: ^{1}H NMR ($CDCl_3$) δ: 0.26 (s, 9H), 4.44 (d, J=1.9 Hz, 1H), 4.89 (d, J=1.9 Hz, 1H) and 7.44 (m, 4H).

The crude trimethylsilyl enol ether **4** (20 mmol) dissolved in dry acetonitrile (50 mL) was added to a suspension of F–TEDA–BF_4 (20 mmol) in dry acetonitrile (150 mL). The reaction mixture was

stirred at room temperature and monitored by ^{1}H NMR spectroscopy until complete consumption of the trimethylsilyl enol ether. Additional F–TEDA–BF_4 (0.1–0.2 equiv) was added in cases where complete conversion was not obtained. A solvent switch from acetonitrile to EtOAc (100 mL) was performed. The organic phase was washed with water (2×100 mL) and brine (100 mL), and dried over Na_2SO_4 before the solvent was evaporated under reduced pressure. The crude products were purified as follows: **1a**, silica gel chromatography (pentane/EtOAc, 5:2); **1b**, crystallisation (*i*-PrOH); **1c**, bulb to bulb distillation (94–96 °C at 1.5×10^{-2} mbar); **1d**, silica gel chromatography (cyclohexane/acetone, 5:1); **1e**, silica gel chromatography (pentane/acetone, 10:1); **1f**, bulb to bulb distillation (83–85 °C at 7.5×10^{-2} mbar); **1g**, crystallisation (EtOH) and **1h**, silica gel chromatography ($CHCl_3$).

4.4. Electrophilic fluorination in methanol (route B)

The acetophenone (8.84 mmol) and F–TEDA–BF_4 (2 equiv) were mixed in methanol (64 mL) and stirred at reflux for 2–11 days. The reaction mixture was cooled to room temperature, and the methanol was removed under reduced pressure. The residue was diluted with dichloromethane (150 mL). The organic fraction was washed with water (2×30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was mixed with chloroform (15 mL), trifluoroacetic acid (3 mL) and water (3 mL). The acetals **6a–e** were cleaved at room temperature, whereas compounds **6f–h** were hydrolysed by refluxing for 20 h. Trifluoroacetic acid was neutralised by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with chloroform (3×25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Compounds were purified as follows **1a**: silica gel chromatography (pentane/EtOAc, 5:2), **1b**: crystallisation (*i*-PrOH), **1c**: silica gel chromatography (CH_2Cl_2), **1d**: silica gel chromatography (cyclohexane/acetone, 5:1), **1e**: silica gel chromatography (pentane/acetone, 10:1), **1f**: silica gel chromatography (CH_2Cl_2), **1g**: crystallisation (EtOH), **1h**: crystallisation (*i*-PrOH).

4.5. Nucleophilic displacement (route C)

Tetrabutylammonium hydrogen bifluoride (10 mmol in acetonitrile) was treated under a stream of nitrogen gas to remove acetonitrile prior to dilution with freshly distilled THF (25 mL). The α-bromoacetophenone (5 mmol) was dissolved in THF (25 mL) and added drop wise to the TBABF solution under a nitrogen atmosphere. The mixture was refluxed until TLC analysis indicated complete conversion. The reaction mixture was then diluted with diethyl ether (50 mL) and washed with dilute HCl (0.1 M, 3×20 mL) and water (2×30 mL). The water phase was back extracted twice with diethyl ether. The combined organic fractions were dried over $MgSO_4$, concentrated, and then subjected to purification by silica gel column chromatography (CH_2Cl_2/MeOH, 100:1).

4.6. Analytical data for α-fluoroacetophenones

4.6.1. 2-Fluoro-1-(4-methoxyphenyl)ethanone (**1a**)[47]

White solid, mp 79–80 °C (78–79 °C).[7] ^{1}H, ^{13}C and ^{19}F NMR were in accordance with that reported by Funabiki et al.[48] IR was in accordance with Barkakaty et al.[47] MS (EI, *m*/*z*, %): 168 (M^+, 6), 127 (8), 71 (6) and 43 (100). HRMS (EI): 168.0580 (calcd 168.0587).

4.6.2. 1-(4-Benzyloxyphenyl)-2-fluoroethanone (**1b**)

White solid, mp 110–111 °C. ^{1}H NMR ($CDCl_3$) δ: 5.14 (s, 2H), 5.46 (d, J=47.0 Hz, 2H), 7.02–4.04 (m, 2H), 7.36–7.43 (m, 5H) and 7.87–7.89 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 70.2, 83.5 (d, J=181.1 Hz), 115.0 (2C), 127.0, 127.5 (2C), 128.4, 128.8 (2C), 130.3 (d, J=2.9 Hz, 2C), 135.9, 163.4 and 191.9 (d, J=15.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −230.4 (t, J=47.0 Hz). IR (KBr, cm^{-1}): 2940, 1700, 1599, 1242, 1174, 1082, 1007, 975, 834 and 755. MS (EI, *m*/*z*, %): 244 (M^+, 3), 91 (100) and 65 (7). HRMS (EI): 244.0895 (calcd 244.0990).

4.6.3. 2-Fluoro-1-phenylethanone (**1c**)[14]

Clear oil, which solidified upon storage, mp 25–26 °C (26 °C).[49] NMR[14,50] and IR-spectra[21] were in accordance with that reported previously. MS (EI, *m*/*z*, %): 138 (M^+, 9), 105 (100) and 77 (64). HRMS (EI): 138.0483 (calcd 138.0481).

4.6.4. 2-Fluoro-1-(4-fluorophenyl)ethanone (**1d**)[19]

White solid, mp 49–51 °C (48–50 °C).[19] ^{1}H NMR ($CDCl_3$) δ: 5.49 (d, J=46.9 Hz, 2H), 7.15–7.21 (m, 2H) and 7.83–7.98 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 83.5 (d, J=186.7 Hz), 116.1 (d, J=22.0 Hz, 2C), 130.2 (dd, J=4.2 and 1.1 Hz), 130.7 (dd, J=12.1 and 3.1 Hz, 2C), 166.2 (d, J=255.0 Hz) and 192.0 (d, J=15.8 Hz). ^{19}F NMR ($CDCl_3$) δ: −103.3 (m) and −230.0 (t, J=47.0 Hz). IR (KBr, cm^{-1}): 2951, 1686, 1600, 1236, 1161, 1083, 976 and 835. MS (EI, *m*/*z*, %): 156 (M^+, 1), 123 (42), 95 (27) and 75 (10). HRMS (EI): 156.0379 (calcd 156.0387).

4.6.5. 1-(4-Bromophenyl)-2-fluoroethanone (**1e**)[25]

White solid, mp 72–73 °C (71–72 °C).[25] ^{1}H NMR was in agreement with Ying et al.[51] ^{13}C and ^{19}F NMR corresponded with that reported by Bridge et al.[25] IR was in accordance with Barkakaty et al.[47] MS (EI, *m*/*z*, %): 216/218 (M^+, 7), 183/185 (100), 155/157 (50) and 104 (40). HRMS (EI): 215.9585 (calcd 215.9586).

4.6.6. 2-Fluoro-1-(4-trifluoromethylphenyl)ethanone (**1f**)

White solid, mp 35–36 °C. ^{1}H NMR ($CDCl_3$) δ: 5.52 (d, J=46.8 Hz, 2H), 7.76–7.79 (m, 2H) and 8.02–8.04 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 83.8 (d, J=184.3 Hz), 123.4 (q, J=273 Hz), 126.0 (q, J=3.8 Hz, 2C), 128.6 (d, J=3.1 Hz, 2C), 135.4 (q, J=32.9 Hz), 136.5 (m) and 192.9 (d, J=16.4 Hz). ^{19}F NMR ($CDCl_3$) δ: −63.9 (s, 3F) and −230.2 (t, J=47.0 Hz). IR (KBr, cm^{-1}): 2937, 1707, 1418, 1330, 1175, 1066, 976 and 836. MS (EI, *m*/*z*, %): 206 (M^+, 0.1), 173 (35), 145 (100), 125 (29), 95 (17) and 75 (9). HRMS (EI): 206.0360 (calcd 206.0355).

4.6.7. 1-(4-Cyanophenyl)-2-fluoroethanone (**1g**)

White solid, mp 104–105 °C. ^{1}H NMR ($CDCl_3$) δ: 5.51 (d, J=46.8 Hz, 2H), 7.81 (m. 2H) and 8.02 (m, 2H). ^{13}C NMR ($CHCl_3$) δ: 83.8 (d, J=183.5 Hz), 117.4, 117.6, 128.6 (d, J=3.3 Hz, 2C), 132.7 (2C), 136.7 (d, J=1.1 Hz) and 192.7 (d, J=16.9 Hz). ^{19}F NMR ($CDCl_3$) δ: −229.6 (t, J=47.0 Hz). IR (KBr, cm^{-1}): 3095, 2932, 2231, 1709, 1437, 1232, 1083, 979 and 839. MS (EI, *m*/*z*, %): 163 (M^+, 2), 130 (100), 102 (56), 76 (11) and 75 (17). HRMS (EI): 163.0437 (calcd 163.0433).

4.6.8. 2-Fluoro-1-(4-nitrophenyl)ethanone (**1h**)[25]

Off-white solid, mp 96–97 °C (90–92 °C).[25] ^{1}H, ^{13}C and ^{19}F NMR corresponds with that of Bridge et al.,[25] except the C–F coupling constant for the carbonyl: 192.8 (d, J=17.0 Hz). IR (KBr, cm^{-1}): 3119, 2934, 1709, 1607, 1526, 1346, 1227, 1091, 973, 857 and 799. MS (EI, *m*/*z*, %): 183 (M^+, 1), 150 (100), 104 (33), 92 (15) and 76 (20). HRMS (EI): 183.0339 (calcd 183.0332).

4.7. Analytical data for impurities and intermediates

4.7.1. 2-Fluoro-1-(3-fluoro-4-methoxyphenyl)ethanone (**5a**)[7]

Synthesis according to route B. Compound **5a** was isolated by silica gel chromatography (pentane/EtOAc, 5:2) as a white solid mp 84–85 °C (82–84 °C).[7] ^{1}H NMR was in accordance with that reported previously.[7] ^{13}C NMR ($CDCl_3$) δ: 56.5, 83.8 (dd, J=182.9 and 0.7 Hz), 112.8 (d, J=2.0 Hz), 115.9 (dd, J=19.3 and 3.2 Hz), 125.7 (t, J=3.5 Hz), 127.1 (dd, J=5.3 and 1.2 Hz), 152.3 (dd, J=249.0 and 0.5 Hz), 153.0 (d, J=10.8 Hz) and 191.5 (dd, J=16.0 and 2.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −133.3 (m) and −230.0 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2925, 2852, 1697, 1612, 1519, 1280, 1084, 1012 and 995. MS

(EI, *m*/*z*, %): 186 (M^+, 45), 153 (100), 125 (37), 110 (48), 95 (63) and 82 (47). HRMS (EI): 186.0497 (calcd 186.0492).

*4.7.2. 1-(4-(Benzyloxy)-3-fluorophenyl)-2-fluoroethanone (**5b**)*

Synthesis according to route B. The mother liquor after crystallisation of **1b** was concentrated, and compound **5b** was isolated by silica gel chromatography (CH_2Cl_2) yielding a white solid, mp 90–92 °C. ^{1}H NMR ($CDCl_3$) δ: 5.22 (s, 2H), 5.42 (d, J=47.0 Hz, 2H), 7.05 (m, 1H), 7.33–7.44 (m, 5H), 7.64 (m, 1H) and 7.68 (dd, J=11.5 and 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 71.4, 83.7 (dd, J=183.0 and 0.7 Hz), 114.6 (d, J=1.9 Hz), 116.2 (dd, J=19.5 and 3.2 Hz), 125.6 (t, J=3.4 Hz), 127.6 (2C), 128.7, 129.0 (2C), 130.5 (d, J=5.2 Hz), 135.6, 152.0 (d, J=10.8 Hz), 152.6 (dd, J=249.4 and 0.5 Hz) and 191.5 (dd, J=16.0 and 2.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −132.7 (m) and −230.0 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2933, 1707, 1687, 1608, 1517, 1275, 1081 and 994. MS (EI, *m*/*z*, %): 262 (M^+, 2), 139 (7), 91 (100) and 65 (8). HRMS (EI): 262.0804 (calcd 262.0805).

*4.7.3. 1-(2-Fluoro-1,1-dimethoxyethyl)-4-methoxybenzene (**6a**)*

Compound **6a** was synthesised from **1a** according to Ranu et al.[30] Compound hydrolysed during work-up yielding only 4 mg (5%) after silica gel chromatography (hexane/EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ: 3.27 (s, 6H), 3.82 (s, 3H), 4.48 (d, J=47.2 Hz, 2H), 6.91 (m, 2H) and 7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 49.1 (2C), 55.3, 83.5 (d, J=178.1 Hz), 100.4 (d, J=20.1 Hz), 113.6 (2C), 128.5 (d, J=0.9 Hz, 2C), 130.2 (d, J=0.9 Hz) and 159.7. ^{19}F NMR ($CDCl_3$) δ: −228.7 (t, J=47.4 Hz). IR (KBr, cm^{-1}): 2942, 2837, 1612, 1513, 1250, 1071 and 1038. MS (EI, *m*/*z*, %): 214 (M^+, 6), 183 (62), 181 (100), 149 (40), 135 (88), 121 (25) and 107 (41). HRMS (EI): 214.1000 (calcd 214.1005).

*4.7.4. 1-(Benzyloxy)-4-(2-fluoro-1,1-dimethoxyethyl)benzene (**6b**)*

Compound **6b** was purified by silica gel chromatography (pentane/EtOAc, 9:1) yielding a white sold, mp 64.5–66.5 °C. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 6H), 4.51 (d, J=47.3 Hz, 2H), 5.10 (s, 2H), 7.02 (m, 2H), 7.36 (m, 2H) and 7.40–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 49.3 (2C), 70.2, 83.7 (d, J=178.2 Hz), 100.6 (d, J=20.0 Hz), 114.6 (2C), 127.7 (2C), 128.2, 128.8 (2C), 128.8 (2C), 130.6, 137.1 and 159.1. ^{19}F NMR ($CDCl_3$) δ: −228.7 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2935, 2830, 1610, 1514, 1454, 1247, 1098 and 1038. MS (EI, *m*/*z*, %): 291 (M^++1, 4), 260 (24), 259 (50), 258 (73), 169 (5), 167 (5), 92 (34), 91 (100) and 65 (26). HRMS (EI): 290.1305 (calcd 290.1318).

*4.7.5. 1-Bromo-4-(2-fluoro-1,1-dimethoxyethyl)benzene (**6e**)*

The dimethyl acetal **6e** was purified by silica gel chromatography (CH_2Cl_2) yielding a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 3.27 (s, 6H), 4.47 (d, J=47.1 Hz, 2H), 7.40 (m, 2H) and 7.52 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 49.3 (2C), 83.2 (d, J=178.2 Hz), 100.4 (d, J=20.4 Hz), 123.0, 129.3 (d, J=0.9 Hz, 2C), 131.6 (2C) and 137.5 (d, J=0.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −229.8 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2944, 2836, 1592, 1485, 1394, 1290, 1071, 826 and 743. MS (EI, *m*/*z*, %): 264 (35), 262 (36), 245 (36), 243 (32), 234 (64), 233 (86), 232 (82), 231 (100), 230 (78), 229 (93), 216 (31), 201 (7), 199 (9), 105 (10) and 91 (17). HRMS (EI): 262.0006 (calcd 262.0005).

*4.7.6. 1-(2-Fluoro-1,1-dimethoxyethyl)-4-(trifluoromethyl)-benzene (**6f**)*

The dimethyl acetal **6f** was purified by silica gel chromatography (pentane/acetone, 7:1) yielding a clear oil. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 6H), 4.51 (d, J=47.0 Hz, 2H) and 7.66 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 49.2 (2C), 82.9 (d, J=178.2 Hz), 100.2 (d, J=20.6 Hz), 124.1 (q, J=272.3 Hz), 125.2 (q, J=3.8 Hz, 2C), 127.8 (d, J=0.9 Hz, 2C), 130.7 (q, J=32.4 Hz) and 142.3 (m). ^{19}F NMR ($CDCl_3$) δ: −63.2 (s) and −230.3 (t, J=47.0 Hz). IR (KBr, cm^{-1}): 2949, 2839, 1620, 1411, 1327, 1166 and 845. MS (EI, *m*/*z*, %): M^+—missing, 221 (32), 219 (100), 173 (47), 159 (17), 145 (31) and 109 (24). HRMS (EI): not obtained, molecular ion unstable.

*4.7.7. 4-(2-Fluoro-1,1-dimethoxyethyl)benzonitrile (**6g**)*

The dimethyl acetal **6g** was purified by silica gel chromatography ($CHCl_3$) yielding colourless oil. ^{1}H NMR ($CDCl_3$): 3.27 (s, 6H), 4.48 (d, J=47.0 Hz, 2H) and 7.67 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 49.4 (2C), 82.6 (d, J=178.2 Hz), 100.2 (d, J=19.8 Hz), 112.6, 118.8, 128.4 (d, J=1.0 Hz, 2C), 132.2 (2C) and 143.7. ^{19}F NMR ($CDCl_3$) δ: −230.7 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2943, 2843, 2232, 1610, 1294, 1067 and 1034. MS (EI, *m*/*z*, %): 209 (M^+, 6), 179 (43), 178 (95), 177 (76), 176 (100), 146 (8), 130 (64) and 104 (5). HRMS (EI): 209.0855 (calcd 209.0852).

*4.7.8. 1-(Fluoro-1,1-dimethoxyethyl)-4-nitrobenzene (**6h**)*

The dimethyl acetal **6h** was purified by silica gel chromatography ($CHCl_3$), yielding a with solid, mp 45–46 °C. ^{1}H NMR ($CDCl_3$) δ: 3.29 (s, 6H), 4.50 (d, J=47.0 Hz, 2H), 7.72 (m, 2H) and 8.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 49.4, 82.6 (d, J=178.1 Hz), 100.2 (d, J=20.8 Hz), 123.5 (2C), 128.7 (2C), 145.6 (d, J=3.5 Hz) and 148.2. ^{19}F NMR ($CDCl_3$) δ: −230.8 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 3001, 2941, 1609, 1522, 1354, 1288, 1090 and 1071. MS (CI, CH_4–Cl, *m*/*z*, %): 231 (M^++2, 11) and 230 (M^++1, 100). HRMS (CI, CH_4–Cl): 230.0821 (calcd for $C_{10}H_{13}FNO_4^+$ 230.0823).

*4.7.9. 1-(Benzyloxy)-2-fluoro-4-(2-fluoro-1,1-dimethoxyethyl)benzene (**7b**)*

Compound **7b** was isolated by silica gel chromatography (pentane/EtOAc, 9:1) yielding a yellowish oil. ^{1}H NMR ($CDCl_3$) δ: 3.29 (s, 6H), 4.47 (d, J=47.4 Hz, 2H), 5.16 (s, 2H), 7.20 (m, 1H), 7.29 (dd, J=12.5 and 2.0 Hz, 1H) and 7.32–7.49 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 49.4 (2C), 71.5, 83.3 (d, J=178.2 Hz), 100.1 (dd, J=20.8 and 1.7 Hz), 115.2 (d, J=2.0 Hz), 115.8 (d, J=20.4 Hz), 123.3 (d, J=2.9 Hz), 127.6 (2C), 128.4, 128.9 (2C), 132.0 (d, J=5.4 Hz), 136.7, 147.0 (d, J=10.8 Hz) and 152.8 (d, J=245.9 Hz). ^{19}F NMR ($CDCl_3$) δ: −134.3 (m) and −229.3 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2943, 2836, 1601, 1515, 1276, 1072 and 1036. MS (EI, *m*/*z*, %): 308 (M^+, 31), 277 (58), 276 (53), 275 (88), 257 (53), 186 (27), 183 (18) and 91 (100). HRMS (EI): 308.1218 (calcd 308.1224).

*4.7.10. trans-1,2,3-Tribenzoylcyclopropane (**8c**)[35]*

Compound **8c** was isolated after synthesis according to route C by silica gel chromatography (CH_2Cl_2/MeOH, 100:1) and re-crystallised from EtOAc yielding a white solid, mp 216–217 °C (216–217 °C).[52] ^{1}H NMR corresponds with that of Fuhrmann et al.[36] ^{13}C NMR ($CDCl_3$) δ: 30.4, 36.4 (2C), 128.5 (4C), 128.7 (4C), 128.8 (2C), 128.9 (2C), 133.6 (2C), 134.0, 136.5 (3C), 193.0 (2C) and 196.0. IR (KBr, cm^{-1}): 3066, 3042, 2999, 1685, 1672, 1596, 1447, 1330, 1220 and 715. MS (EI, *m*/*z*, %): 354 (M^+, 1), 249 (32), 233 (9), 105 (100) and 77 (38). HRMS (EI): 354.1262 (calcd 354.1256).

*4.7.11. trans-1,2,3-Tri(4-fluorobenzoyl)cyclopropane (**8d**)*

trans-1,2,3-Tri(4-fluorobenzoyl)cyclopropane (**8d**) was isolated after synthesis according to route C by silica gel chromatography (CH_2Cl_2). White solid, mp 200–202 °C. ^{1}H NMR ($CDCl_3$) δ: 3.69 (d, J=5.6 Hz, 2H), 4.15 (t, J=5.6 Hz, 1H), 7.09–7.13 (m, 4H), 7.18–7.22 (m, 2H), 8.01–8.03 (m, 4H) and 8.21–8.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 30.3, 36.0 (2C), 116.0 (d, J=22.0 Hz, 4C), 116.1 (d, J=22 Hz, 2C), 131.4 (d, J=9.5 Hz, 4C), 131.5 (d, J=9.6 Hz, 2C), 132.8 (d, J=2.7 Hz, 2C), 132.8 (d, J=2.7 Hz), 166.1 (d, J=256.1 Hz, 2C), 166.4 (d, J=256.8 Hz), 191.3 (2C) and 194.1. IR (KBr, cm^{-1}): 3068, 3018, 1684, 1665, 1597, 1506, 1227, 1156 and 849. MS (EI, *m*/*z*, %): 408 (M^+, 7), 409 (2), 286 (55), 285 (92), 269 (57), 124 (65), 123 (100) and 95 (90). HRMS (EI): 408.0977 (calcd 408.0973).

*4.7.12. trans-1,2,3-Tri(4-bromobenzoyl)cyclopropane (**8e**)[53]*

trans-1,2,3-Tri(4-bromobenzoyl)cyclopropane (**8e**) was isolated after synthesis according to route C by silica gel chromatography (CH_2Cl_2/MeOH, 100:1). White solid, mp 198–200 °C. ^{1}H NMR ($CDCl_3$) δ: 3.69 (d, J=5.6 Hz, 2H), 4.13 (t, J=5.6 Hz, 1H), 7.59–7.61 (m, 4H), 7.67–7.70 (m, 2H), 7.85–7.87 (m, 4H) and 8.03–8.06 (m, 2H). ^{13}C NMR

($CDCl_3$) δ: 30.3, 36.1 (2C), 129.1 (2C), 129.6, 129.9 (4C), 130.2 (2C), 132.1 (4C), 132.3 (2C), 135.0 (3C), 191.8 (2C) and 194.6. IR (KBr, cm^{-1}): 3052, 1693, 1670, 1397, 1317, 1296, 1204, 1072 and 1008. MS (EI, *m*/*z*, %): 589/591 (M^+, 1), 406 (17), 185 (59), 183 (58), 157 (14), 155 (14) and 28 (100). HRMS (EI): 589.8529 (calcd for $C_{24}H_{15}O_3^{79}Br^{81}Br_2$: 589.8551).

*4.7.13. (3-(Bromomethyl)-3-(4-fluorophenyl)oxiran-2-yl)(4-fluorophenyl)methanone (**9d**)*

Compound **9d** was isolated after synthesis according to route C by column chromatography (CH_2Cl_2) starting with **3d**. ^1H NMR ($CDCl_3$) δ: 3.67 (d, *J*=11.1 Hz, 1H), 3.80 (d, *J*=11.1 Hz, 1H), 4.38 (s, 1H), 7.11–7.23 (m, 4H), 7.55–7.60 (m, 2H) and 8.04–8.09 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 31.4, 64.8, 116.0 (d, *J*=21.8 Hz, 2C), 116.4 (d, *J*=22.1 Hz, 2C), 128.3 (d, *J*=8.4 Hz, 2C), 131.4 (d, *J*=9.6 Hz, 2C), 132.2 (d, *J*=3.1 Hz), 132.4 (d, *J*=3.3 Hz), 163.1 (d, *J*=248.8 Hz), 166.5 (d, *J*=257.3 Hz) and 190.2.

*4.7.14. 1-(2-(4-(Benzyloxy)phenyl)-2-oxoethyl)pyridinium bromide (**10b**)*

1-(2-(4-(Benzyloxy)phenyl)-2-oxoethyl)pyridinium bromide precipitated from the reaction mixture upon fluorination of **3b** using TBABF in the presence of pyridine. It was also synthesised from **3b**. 1-(4-Benzyloxyphenyl)-2-bromoethanone (**3b**) (1.5 g, 4.9 mmol) dissolved in THF (25 mL) was treated with pyridine (0.93 g, 12 mmol) and stirred at 45 °C for 5 h. THF was removed and the residue was re-crystallised from ethanol utilising diethyl ether as anti solvent, yielding 1.2 g (64%) of a slight yellowish solid, mp 198–200 °C. ^1H NMR (DMSO) δ: 5.29 (s, 2H), 6.44 (s, 2H), 7.26–7.28 (m, 2H), 7.36–7.50 (m, 5H), 8.03–8.05 (m, 2H), 8.27 (t, 2H), 8.73 (t, 1H) and 8.99 (d, 2H). ^{13}C NMR ($CDCl_3$) δ: 66.5, 70.3, 115.9 (2C), 127.1 (2C), 128.4 (2C), 128.7, 129.1 (2C), 131.3 (2C), 136.8, 146.9 (2C), 163.9 and 189.5. IR (KBr, cm^{-1}): 3028, 2939, 1690, 1670, 1636, 1599, 1492, 1240, 1173, 990, 834, 752 and 686. HRMS (ESI): 304.1331 (calcd for $C_{20}H_{18}NO_2^+$: 304.1332).

*4.7.15. 1-(2-Oxo-2-phenylethyl)pyridinium bromide (**10c**)*[54]

Compound **10c** was isolated as described for **10b**. ^1H and ^{13}C NMR were in accordance with Szwajca et al.[54]

*4.7.16. 2-(4-(Benzyloxy)phenyl)-N,N,N-triethyl-2-oxoethanaminium bromide (**11b**)*

The identity of **11b** was confirmed by synthesis of a reference sample. 1-(4-Benzyloxyphenyl)-2-bromoethanone (**3b**) (1.5 g, 4.9 mmol) in THF (25 mL) was mixed with triethylamine (1.0 g, 10 mmol) and heated at 50 °C. After 5 h the reaction mixture was cooled to room temperature and diethyl ether (25 mL) was added. The solid material obtained after filtration was re-crystallised from isopropanol, yielding 1.51 g (75%) of a white solid, mp 162–164 °C. ^1H NMR ($CDCl_3$) δ: 1.41 (t, *J*=7.3 Hz, 9H), 3.87 (q, *J*=7.3 Hz, 6H), 5.13 (s, 2H), 5.45 (s, 2H), 7.05–7.07 (m, 2H), 7.35–7.40 (m, 5H) and 8.34–8.36 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 8.4 (3C), 54.6 (3C), 59.9, 70.2, 115.2 (2C), 126.7, 127.4 (2C), 128.2, 128.6 (2C), 131.6 (2C), 135.7, 164.2 and 189.5. IR (KBr, cm^{-1}): 2974, 2913, 1687, 1601, 1576, 1456, 1237, 1006, 833 and 755. HRMS (ESI): 326.2116 (calcd for $C_{21}H_{28}NO_2^+$ 326.2115).

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Paper II

Krane Thvedt, T.H., Fuglseth, E., Sundby, E., Hoff, B. H.

Microwave assisted fluorination: an improved method for side chain fluorination of substituted 1-arylethanones

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Microwave assisted fluorination: an improved method for side chain fluorination of substituted 1-arylethanones

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ABSTRACT

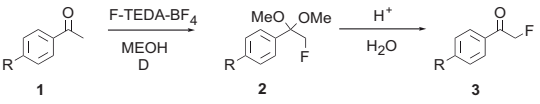
A two-step, one-pot microwave (MW) assisted fluorination of 1-arylethanones to their corresponding 1-aryl-2-fluoroethanones has been developed. The first step utilises Selectfluor™ as a fluorinating agent in methanol forming 1-aryl-2-fluoroethanones and their corresponding dimethyl acetals. In the second step, water is added and Selectfluor™ acts as a Lewis acid in the hydrolytic cleavage of the dimethyl acetals. Compared to the thermal synthesis, the MW assisted method leads to a reduction in reaction time both in the fluorination and for the dimethyl acetal cleavage. Moreover, the one-pot procedure reduces reagent and solvent consumption. The method is best suited for the preparation of 1-aryl-2-fluoroethanones containing substituents that deactivates electrophilic aromatic substitution, however highly electron deficient ketones such as 1-(3,5-dinitrophenyl)ethanone reacts more slowly. Reactions using electron rich aromatic ketones had a low regioselectivity, and also produced fluoroaromatic products.

1. Introduction

Microwave irradiation (MW) is a powerful and easily controllable heating source. For a number of reactions, especially those involving polar transition states, significant rate acceleration can be achieved compared to conventional heating.[1–4]

The use of microwaves has also been applied in various forms of fluorination.[5–13] Selectfluor™ (F-TEDA-BF_4) is a relatively stable electrophilic fluorinating agent,[14] and microwave assisted reactions on 1,3-dicarbonyl compounds,[13] aromatic compounds,[5] and 1-aryl-1-nitromethanes,[11] have been reported. Moreover, F-TEDA-BF_4 has also been applied as a Lewis acid in MW assisted synthesis.[15]

α-Fluoroacetophenones can be synthesised by nucleophilic displacement,[16–21] electrophilic fluorination of ketones, imines or enamines,[22–30] Friedel/Crafts acylation,[31,32] coupling chemistry,[33] and reaction via diazo ketones.[34,35] However, some of these methods have drawbacks due to the use of hazardous and toxic chemicals or the involvement of unstable intermediate compounds. We have recently compared three methods using conventional heating for the preparation of α-fluoroacetophenones.[36] A simple method using only F-TEDA-BF_4 in methanol enabled acetophenones to be fluorinated in decent yields. The method consists of two steps; fluorination yielding the target α-fluoroketone, **3**, its dimethyl acetal, **2**, and subsequent hydrolysis to convert **2** into **3**, Scheme 1.



1 2 3

Scheme 1. Fluorination of acetophenones using F-TEDA-BF_4 in methanol.

Although being very simple, an obvious drawback of the thermal method was the prolonged reaction times, especially for substrates containing electron withdrawing substituents. Moreover, several of the dimethyl acetals, **2**, required heating to reflux in the presence of trifluoroacetic acid for several hours for complete conversion to **3**.

To improve the usefulness of the method, we have investigated the use of microwaves to increase the reaction rates and yields in conversion of 1-arylethanones, **1** to the corresponding 1-aryl-2-fluoroethanones, **3**.

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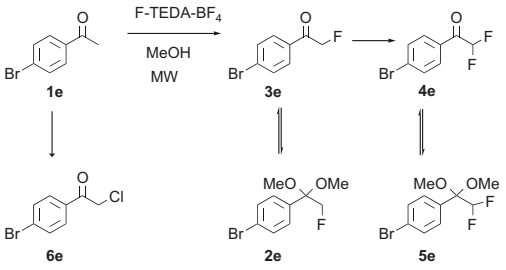
2. Results and discussion

2.1. MW assisted fluorination: solvent, effect (*W*) and reaction time

The reaction rate in the thermal fluorination of acetophenones using F-TEDA-BF_4 in MeOH was very dependant on the electronic properties of the substituents.[36] Therefore, initial experiments using MW as a heating source were performed using 1-(4-bromophenyl)ethanone (**1e**), which was intermediate with respect to electronic character. An Anton Paar 3000 microwave instrument equipped with a magnetic stirrer device was used. The reactions were performed in sealed Teflon tubes.

Running the reaction at 120 W using two equivalents of F-TEDA-BF_4 in methanol revealed that fluorination took place. However, several other fluorinated compounds and undefined substances were present in the discoloured reaction mixture. ^{1}H NMR spectroscopy was used for the identification of reaction components. The ^{1}H NMR chemical shifts of **1**–**3e** (Scheme 2) were known from a previous study.[36] The presence of 1-(4-bromophenyl)-2,2-difluoroethanone (**4e**) could be confirmed by the characteristic triplet at 6.24 ppm (J_{HF}=53.5 Hz). In addition, a triplet with comparable coupling constant was observed at 5.82 ppm (J_{HF}=55.3 Hz). Analysis after hydrolytic treatment revealed that this substance was converted to **4e**, and was therefore assigned as the dimethyl acetal, **5e**. Trace amounts of 1-(4-bromophenyl)-2-chloroethanone (**6e**),[37] was also observed. It is currently unclear if formation of **6e** is due to impurities in F-TEDA-BF_4 or decomposition reactions leading to electrophilic chlorine sources. A chlorinated by-product has previously been reported in fluorination of thiazole using F-TEDA-BF_4.[38]



Scheme 2. Reaction products after fluorination of **1e** in methanol using F-TEDA-BF_4.

Follow-up experiments revealed a positive effect both on conversion and colour of the reaction mixture when the effect was in the range of 80–100 W. Having found a suitable effect (*W*), the choice of reaction medium was reevaluated. If possible, it would be beneficial to avoid the formation of the intermediate dimethyl acetal, **2e**. Moreover, a change in solvent might affect conversion rates due to temperature effects. The fluorination was performed in six different solvents and reacted for 60 min at 80 W. The degree of conversion and product distribution after fluorination are given in Table 1.

Table 1
The conversion (conv.) and product distribution after fluorination of **1e** in different solvents at 80 W for 60 min

Solvent	Conv.[a] (%)	**1e** (%)	**2e** (%)	**3e** (%)	**4e** (%)	**5e** (%)	**6e** (%)
Acetonitrile	36	64	NA	34	0	0	2
t-BuOH	0	100	—	0	0	—	0
i-PrOH	0	100	—	0	0	—	0
EtOH	12	88	[b]	11	0	[a]	1
MeOH	97	3	30	54	11	5	1
Water	8	92	NA	6	—	—	2

[a] Conversion was measured by ^{1}H NMR spectroscopy.
[b] Ethyl acetals were not observed by ^{1}H NMR spectroscopy.

The degree of conversion was highly dependant on the solvent used. No fluorination was observed in *t*-BuOH or *i*-PrOH, while reactions in water and ethanol gave 8 and 12% conversion respectively. The reaction in acetonitrile gave a 36% conversion, whereas 97% was obtained using methanol as reaction solvent. In addition to the α-fluoroketone, **3e**, and its dimethyl acetal, **2e**, the difluoro-compounds **4e** and **5e** were observed. Although, aliphatic difluorination appeared in methanol, the reaction proceeded much faster than in any of the other solvents tested. One could speculate that methanol shifts the keto/enol equilibrium more to the enol side and that this is the reason for the solvent dependant rate acceleration.

Further experiments were undertaken to study how the effect and reaction time influenced the degree of conversion and product distribution using **1e** as substrate. The effect was varied between 60 and 100 W, and the reaction time was varied between 60 and 100 min. The results are summarised in Table 2.

Table 2
Conversion (conv.) and product distribution after fluorination of **1e** in MeOH varying MW effect (W) and reaction time

Entry	Effect (W)	Time (min)	Conv.[a] (%)	**3e**+**2e** (%)	**4e**+**5e** (%)
1	60	60	65	64	0
2	60	100	91	87	3
3	80	80	>99	87	11
4	100	60	97	89	7
5	100	100	98	85	14

[a] Conversion was measured by ^{1}H NMR spectroscopy.

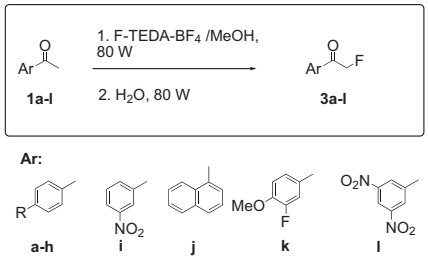
The degree of conversion measured by amount of residual 1-(4-bromophenyl)ethanone (**1e**) versus fluorinated products depended on both effect (*W*) and reaction time. Full conversion was not obtained at 60 W (Entries 1 and 2), due to insufficient reaction time. The incomplete conversion at 100 W was probably due to a thermal decomposition of F-TEDA-BF_4 as it was noted that the reaction mixture turned black. At 80 W, full conversion was obtained without discolouration of the reaction mixture. As full conversion and the absence of coloured by-products allowed for easier product purification, 80 W was selected as the preferred irradiation effect in the fluorinations.

To maximise the yield of the α-fluoroketone **3e**, its dimethyl acetal, **2e** needed to be hydrolysed. F-TEDA-BF_4 has previously been used as a Lewis acid.[15] We therefore tested if cleavage of the dimethyl acetal **2e** could be performed by simply adding water to the crude reaction mixture followed by MW irradiation. This proved to be the case, and **2e** was readily cleaved by addition of water and irradiating the reaction mixture at 80 W for 20 min. This enabled the preparation of **3e** using a one-pot two-step procedure.

2.2. Scope and limitations: substrate structure

To investigate the scope and limitations of the method with respect to substrate structure, a series of 1-arylethanones, **1a**–**l**, were fluorinated, see Scheme 3.

Both substrates with electron donating and withdrawing substituents were investigated. Compound **1k** was included in the study to investigate if one fluorine atom was sufficient to reduce ring fluorination as compared to **1a**. Compound **1l** was used to investigate the effects of two strong electron withdrawing groups on the fluorination and the hydrolysis steps. Both steps were performed at 80 W, and the reaction time was varied to obtain high conversions. Table 3 summarises the conversions and product distributions after fluorination, the conversions obtained in the hydrolytic step, and the yields for **3a**–**l**. The optimised reaction



R= **a** (OMe), **b** (OBn), **c** (H), **d** (F), **e** (Br), **f** (CF_3), **g** (CN), **h** (NO_2)

Scheme 3. Fluorination of **1a–l** using F-TEDA-BF_4.

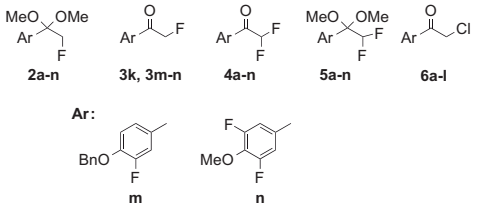


Figure 1. By-products and intermediates observed in preparation of **3a–l**. For structure elements **a–l** see Scheme 3.

times at 80 W for the two steps are given in Table 4 and the structures of the by-products are shown in Figure 1.

The MW assisted fluorination of the electron rich 1-arylethanones **1a–b** (Table 3, Entries 1–2) gave low yields of the target products **3a–b**. This was due to the formation of additional ring fluorinated by-products, **3k** and **3m**, high amounts of α,α-difluoroketones, **4a–b** and their corresponding dimethyl acetals, **5a–b**. Especially difficult was fluorination of 1-acetonaphthone (**1j**) (Entry 3), which led to at least three different α-fluoroketones, their corresponding dimethyl acetals and α,α-difluorides. ^1H and ^{19}F NMR spectroscopic analysis of the crude product mixture suggested that ring fluorination had taken place. These three substrates exemplify limitations of the method in general. Due to the complexity of the reaction mixtures, purifications were not attempted.

In terms of susceptibility towards aromatic fluorination, 1-(3-fluoro-4-methoxyphenyl)ethanone (**1k**), (Entry 4), represents a borderline case. As compared to fluorination of **1a**, the extra *m*-fluorine in **1k** suppressed ring fluorination, and only 5% of **3n** and **4n** was observed. Aliphatic difluorination leading to compound **4k** and **5k** (19%) was however still significant, reducing the isolated yield to 59%.

Fluorination of **1c** and **1d** and subsequent hydrolysis gave 65 and 74% isolated yield of **3c** and **3d** respectively. In the case of **1c**, unidentified by-products were detected, explaining the lower yield.

Table 3
MW assisted fluorination and hydrolysis using F-TEDA-BF_4: conversion (conv.) and product distribution after fluorination, conversion after hydrolysis and yields of **3a–l**. Isolated yields are reported unless otherwise stated. For reaction times see Table 4

Entry	Substrate	Fluorination					Hydrolysis		
		Conv.[a] (%)	2 (%)	3 (%)	4+5 (%)	Others (%)	Conv. (%)	Yield (%)	Product
1	*p*-MeO (**1a**)	>99	11	44	18	27 (**2k**+**3k**)	>99	46[b]	**3a**
2	*p*-BnO (**1b**)	>99	12	46	18	24 (**2m**+**3m**)	>99	46[b]	**3b**
3	1-Naphthyl (**1j**)	90	6	40	nd	Multiple[c]	>99	38[b]	**3j**
4	*m*-F, *p*-OMe (**1k**)	>99	23	53	19	5 (**2n**+**3n**)	>99	59	**3k**
5	H (**1c**)	>99	26	61	12	1 (**6c**)	>99	65	**3c**
6	*p*-F (**1d**)	>99	23	67	9	1 (**6d**)	>99	74	**3d**
7	*p*-Br (**1e**)	>99	24	63	11	1 (**6e**)	>99	81	**3e**
8	*p*-CF_3 (**1f**)	>99	41	52	6	1 (**6f**)	>99	69	**3f**
9	*p*-CN (**1g**)	99	30	62	6	1 (**6g**)	>99	86	**3g**
10	*p*-NO_2 (**1h**)	>99	70	24	5	<1 (**6h**)	>99	82	**3h**
11	*m*-NO_2 (**1i**)	98	58	36	4	1 (**6i**)	>99	72	**3i**
12	3,5-di-NO_2 (**1l**)	94	88	3	3	3 (**7l**)	97	41	**3l**

[a] Conversion was measured by ^1H NMR spectroscopy.
[b] Reaction yield of α-fluoroketone as quantified by ^1H NMR spectroscopy using 1-(4-methoxyphenyl)ethanone as standard.
[c] Not identified.

Table 4
Comparison of the MW (80 W) and thermal process for the preparation of **3a–l** (reaction time and yield)

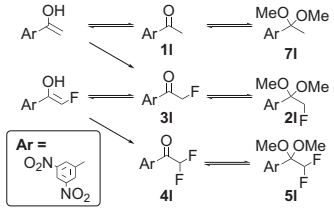
Entry	Substrate	MW			Thermal		
		Rx. time fluorination (min)	Rx. time hydrolysis (min)	Yield (%)	Rx. time fluorination (h)	Rx. time hydrolysis (h)	Yield (%)
1	*p*-MeO (**1a**)	60	15	46[a]	48	1 (rt)	67[b]
2	*p*-BnO (**1b**)	60	15	46[a]	72	1 (rt)	58[b]
3	1-Naphthyl (**1j**)	60	15	38[a]	144	1 (rt)	50[a]
4	*m*-F, *p*-OMe (**1k**)	60	15	59	96	3.5 (rt)	67
5	H (**1c**)	60	15	65	96	3.5 (rt)	66[b]
6	*p*-F (**1d**)	60	20	74	96	3.5 (rt)	25[b]
7	*p*-Br (**1e**)	80	15	81	125	24 (rt)	77[b]
8	*p*-CF_3 (**1f**)	85	25	69	144	20 (reflux)	73[b]
9	*p*-CN (**1g**)	80	30	86	192	20 (reflux)	64[b]
10	*p*-NO_2 (**1h**)	50	30	82	261	20 (reflux)	70[b]
11	*m*-NO_2 (**1i**)	60	30	72	336	20 (reflux)	73
12	3,5-di-NO_2 (**1l**)	120	30	41	500[c]	336[d] (reflux)	39

[a] Reaction yield quantified by ^1H NMR spectroscopy using 1-(4-methoxyphenyl)ethanone as standard.
[b] Results from previous study.[36]
[c] 82% conv.
[d] 63% conv.

In the fluorination of **1d–i** (Entries 5–11), aromatic fluorination was not observed. Moreover, moving down Table 3, as the electronic withdrawing character of the substituents increases, the level of the α,α-difluorides, **4** and **5** observed was also reduced. Higher yields were experienced, and the products could be obtained in 69–86% isolated yield. Electron withdrawing groups on the aromatic ring increased both the amounts and the stability of the dimethyl acetals. As a consequence, the reaction time in the hydrolytic step had to be increased from 15 to 30 min.

Another limitation to the presented method is exemplified by fluorination of 3,5-dinitroacetophenone (**1l**), (Entry 12). This substrate required prolonged reaction time, however, a 94% conversion was obtained by applying 80 W for 2 h.

The main product of the reaction was **2l** (88%) and formation of the dimethyl acetal **7l**,[39] was also noticed (Scheme 4). Such side products were not observed in fluorination of the other substrates.



Scheme 4. Products and assumed reaction intermediates in fluorination of **1l**.

The major challenge in the synthesis of **3l** by this process resides in the hydrolytic step. Somewhat surprisingly, fluorination continued during hydrolysis, resulting in the formation of three difluorinated compounds, including **4l**, **5l** and a unknown compound (δ: 5.79, J_{HF}=55.1 Hz).

The reaction progress for **1l** can be rationalised by referring to Scheme 4. When acetophenones are substituted with electron withdrawing groups, the ketone/dimethyl acetal equilibrium position is shifted towards the dimethyl acetal side.[40] This is especially pronounced in the case of **1l** due to the presence of two nitro groups. It can be assumed that fluorination takes place via the enol form of the ketone, and due to the limited amount of the ketone **1l**, and thereby its enol, a reduction in the reaction rate is experienced. Once formed, the α-fluoroketone, **3l** has an even higher tendency to react with methanol, forming **2l**. As evident from Table 3, the amount of **3l** in the reaction is very low, and further fluorination is therefore difficult. When water is added, the equilibrium position is shifted towards **3l** and its enol form, enabling fluorination to continue. The reason why α,α-difluorination during hydrolysis appears only for **3l** is not understood.

Attempts to fluorinate **1l** in water (80 W, 60 min) gave a complex mixture and a conversion of approximately 30%. The dominating products were **3l**, **4l** and the previous mentioned compound with shift value of 5.79 ppm.

2.3. Comparison of the MW and thermal fluorination methods

A comparison of the MW and the thermal process, with respect to reaction times and yields are shown in Table 4.

The MW assisted reactions benefit from shorter reaction times; fluorination proceeds in 60–120 min, whereas hydrolysis could be performed in 15–30 min. The corresponding thermal fluorinations required several days or weeks for complete conversion. The MW assisted method was inferior to the thermal reaction for the selective aliphatic fluorination of electron rich aromatic ketones (Entries 1–4), due to the formation of high levels of α,α-difluoroketones.

Compared to the thermal process, higher or comparable yields were obtained in the MW assisted fluorination and hydrolysis starting with **1c–i**. The largest difference in yield when comparing the two methods is seen in preparation of **3d** and **3g**.

The dimethyl acetal **2d** was previously found to be highly volatile, and this limited the isolated yield of the reported thermal reaction.[36] The volatility is not a problem in the MW process, as the isolation of **2d** is not required. The lower yield of **3g** in the thermal process is probably due to side reactions at the cyano-group, taking place during the prolonged reaction time.

The MW assisted fluorination of **1l** was hampered by a low reaction rate, and α,α-difluoride formation during hydrolysis. This gave 41% of **3l**. By comparison, the thermal process from **1l** also gave a moderate 39% isolated yield after a total of 5 weeks reaction time.

The reaction rate in the thermal fluorination was correlated with the electronic properties of the substituents. For the MW assisted fluorination, an increase in reaction time was needed for **1e–1g**, compared to **1a–d**. However, this was not seen for the nitro-derivatives, **1h–i**. Nitro groups are known to be efficient absorbers of MW energy, and the observation suggests that specific microwave effects are operating.

The MW process gave a higher ketone to dimethyl acetal ratio and higher amounts of α,α-difluorinated compounds than was the case in the thermal process. It is assumed that fluorination by F-TEDA-BF_4 takes place on the enol form of the ketone, (Scheme 4). As less α-fluoroketones are trapped as dimethyl acetals in the MW process, they are more available for further fluorination. This could explain the elevated levels of the α,α-difluoroketones in the microwave process as compared to the thermal method.

3. Conclusion

A one-pot, two-step MW assisted fluorination of 1-arylethanones has been developed. The main benefit of the MW strategy is a reduction of the reaction time from several days to 1.5–2 h. Moreover, a simplification of the dimethyl acetal cleavage step has been developed, reducing the number of operations, chemical consumption and time.

The method has its main advantage in the fluorination of moderately deactivated acetophenones **1c–i**, leading to the production of the 1-aryl-2-fluoroethanones in 65–86% isolated yield.

Electron rich 1-arylethanones are not selectively fluorinated in the side chain, but also forms fluoroaromatic derivatives. 1-(3-Fluoro-4-methoxyphenyl)ethanone (**1k**) represents a borderline case, where aromatic fluorination is starting to be suppressed.

Another limitation to the fluorination method is in the reaction of 1-arylethanones having two strongly electron withdrawing substituents. Although the fluorination takes place at a reduced rate, the hydrolysis led to the formation of aliphatic α,α-difluorinated compounds, reducing the yield significantly.

4. Experimental

4.1. General

The 1-arylethanones **1a**, **1g–h**, **1l**, and 1,3-dichloro-5,5-dimethylhydantoin were purchased from Fluka. Selectfluor™ (F-TEDA-BF_4), **1c–f**, **1j–k,** and *N*-fluorobisbenzenesulfonimide were from Aldrich. 1-(3-Nitrophenyl)ethanone (**1i**) was from Acros Organics, while 1-(4-bromophenyl)-2-chloroethanone (**6e**) was from Sigma–Aldrich. Methanol was from VWR (HPLC grade, 0.03% water). Column chromatography was performed using silica gel 60A from Fluka, pore size 40–63 μm. 1-(4-(Benzyloxy)phenyl)ethanone (**1b**) was prepared from 4-hydroxyacetophenone using benzyl chloride and potassium carbonate in *N*,*N*-dimethylformamide as solvent.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^{1}H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. For ^{1}H and ^{13}C NMR chemical shifts are in ppm rel to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. MS (EI/70 eV) Finnigan MAT 95 XL. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into the MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. The microwave experiments were performed using an Anton Paar 3000 instrument with a magnetic stirrer device.

4.3. General procedure MW assisted fluorination

To a Teflon reaction tube containing a magnetic stirrer bar 1-arylethanone (2.21 mmol), Selectfluor™ (4.42 mmol) and methanol (5 mL) were added. The reaction chamber was sealed and treated at 80 W for the times specified in Table 4. After cooling, water (5 mL) was added and the mixture was hydrolysed at 80 W with the reaction times specified in Table 4. After cooling, water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (4×15 mL). The dichloromethane layer was then washed with brine (15 mL), dried over Na_2SO_4 and evaporated to dryness. The 1-aryl-2-fluoroethanones were purified by the methods specified for each single compound.

4.4. Thermal fluorination in methanol

Thermal fluorination of the 1-arylethanones (1 equiv) in MeOH using F-TEDA-BF_4 (2 equivalents) was performed as described previously.[36]

4.5. 1-Aryl-2-fluoroethanones

*4.5.1. 2-Fluoro-1-(4-methoxyphenyl)ethanone (**3a**)*[22,36]. The identity of compound **3a** was verified by comparison of ^{1}H NMR shifts with a previous study.[36] ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H), 5.45 (d, J=47.2, 2H), 6.96 (m, 2H), 7.89 (m, 2H).

*4.5.2. 1-(4-(Benzyloxy)phenyl)-2-fluoroethanone (**3b**)*[36]. The identity of compound **3b** was verified by comparison of ^{1}H NMR shifts with a previous study.[36] ^{1}H NMR ($CDCl_3$) δ: 5.14 (s, 2H), 5.46 (d, J=47.0, 2H), 7.02–4.04 (m, 2H), 7.36–7.43 (m, 5H) and 7.87–7.89 (m, 2H).

*4.5.3. 2-Fluoro-1-phenylethanone (**3c**)*[19,36]. Compound **3c** was prepared as described in Section 4.3 starting with **1c** (265 mg, 2.21 mmol). Fluorination was performed for 60 min, and hydrolysis was done in 15 min. Purification by silica gel chromatography (pentane/EtOAc, 85/15) gave 198 mg (1.43 mmol, 65%) of **3c** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 5.53 (d, J=47.0, 2H), 7.50 (m, 2H), 7.63 (m, 1H), 7.90 (m, 2H).

*4.5.4. 2-Fluoro-1-(4-fluorophenylethanone) (**3d**)*[25,36]. Compound **3d** was prepared as described in Section 4.3 starting with **1d** (305 mg, 2.21 mmol). Fluorination was performed for 60 min, and hydrolysis was done in 20 min. Purification by silica gel chromatography (pentane/EtOAc, 85/15) gave 255 mg (1.63 mmol, 74%) of **3d** as a white solid mp 49–51 °C. ^{1}H NMR ($CDCl_3$) δ: 5.49 (d, J=46.9, 2H), 7.15–7.21 (m, 2H) and 7.83–7.98 (m, 2H).

*4.5.5. 1-(4-Bromophenyl)-2-fluoroethanone (**3e**)*[34,36]. Compound **3e** was prepared as described in Section 4.3 starting with **1e** (440 mg, 2.21 mmol). Fluorination was performed for 80 min, and hydrolysis was done in 15 min. Purification by silica gel chromatography (pentane/EtOAc, 85/15) gave 387 mg (1.78 mmol, 81%) of **3e** as a white solid mp 72–73 °C. ^{1}H NMR ($CDCl_3$) δ: 5.46 (d, J=46.9, 2H), 7.64 (m, 2H) and 7.77 (m, 2H).

*4.5.6. 2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethanone (**3f**)*[36]. Compound **3f** was prepared as described in Section 4.3 starting with **1f** (415 mg, 2.21 mmol). Fluorination was performed for 85 min, and hydrolysis was done in 25 min. Purification by silica gel chromatography (CH_2Cl_2) gave 312 mg (1.52 mmol, 69%) of **3f** as a white solid mp 36–37 °C. ^{1}H NMR ($CDCl_3$) δ: 5.52 (d, J=46.8, 2H), 7.77 (m, 2H), 8.03 (m, 2H).

*4.5.7. 4-(2-Fluoroacetyl)benzonitrile (**3g**)*[36]. Compound **3g** was prepared as described in Section 4.3 starting with **1g** (321 mg, 2.21 mmol), Fluorination was performed for 80 min, and hydrolysis was done in 30 min. Purification by silica gel chromatography (pentane/acetone, 7/3) gave 312 mg (1.90 mmol, 86%) of **3g** as a white solid mp 104–105 °C. ^{1}H NMR ($CDCl_3$) δ: 5.51 (d, J=46.8, 2H), 7.81 (m, 2H) and 8.02 (m, 2H).

*4.5.8. 2-Fluoro-1-(4-nitrophenyl)ethanone (**3h**)*[36]. Compound **3h** was prepared as described in Section 4.3 starting with **1h** (365 mg, 2.21 mmol), Fluorination was performed for 50 min, and hydrolysis was done in 30 min. Purification by silica gel chromatography (pentane/acetone, 7/3) gave 333 mg (1.81 mmol, 82%) of **3h** as a white solid mp 96–97 °C. ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, J=46.8, 2H), 8.11 (m, 2H) and 8.35 (m, 2H).

*4.5.9. 2-Fluoro-1-(3-nitrophenyl)ethanone (**3i**)*[41]. Compound **3h** was prepared as described in Section 4.3 starting with **1h** (370 mg, 2.21 mmol), Fluorination was performed for 60 min, and hydrolysis was done in 30 min. Purification by crystallisation from ethanol gave 293 mg (1.60 mmol, 72%) of **3h** as a white solid mp 83–84 °C. ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, J=46.7, 2H), 7.72–7.77 (m, 1H), 8.27–8.29 (m, 1H), 8.48–8.51 (m, 1H), 8.75–8.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 83.9 (d, J=184.7), 123.1 (d, J=3.9), 128.3, 130.3, 133.8 (d, J=3.5), 135.0 (d, J=1.4), 148.5, 192.0 (d, J=17.0). ^{19}F NMR ($CDCl_3$) δ: −229.7 (t, J=46.8). IR (neat, cm^{-1}): 3101, 1712, 1630, 1537, 1438, 1239, 1080, 1021, 901, 730.

*4.5.10. 2-Fluoro-1-(naphthalen-1-yl)ethanone (**3j**)*[42]. For identification purpose, compound **3j** was synthesised from **1j** (3.64 g, 21 mmol) via the trimethylsilyl enol ether as described by Fuglseth et al.[36] The product was purified by silica gel column chromatography (CH_2Cl_2) giving an oil. A following crystallisation from EtOAc/pentane yielded 1.10 g (5.83 mmol, 29%) of a white solid mp 44–45 °C. The ^{1}H, ^{13}C and ^{19}F NMR spectra corresponded with that reported.[42] ^{1}H NMR ($CDCl_3$) δ: 5.60 (d, J=47.2, 2H), 7.50–7.61 (m, 2H), 7.65 (m, 1H), 7.80 (m, 1H), 7.89 (m, 1H), 8.05 (d, J=8.3, 1H), 8.71 (m, 1H).

*4.5.11. 2-Fluoro-1-(3-fluoro-4-methoxyphenyl)ethanone (**3k**)*[22,36]. Compound **3k** was prepared as described in Section 4.3 starting with **1k** (370 mg, 2.21 mmol). Fluorination was performed for 60 min, and hydrolysis was done in 15 min. Purification by silica gel column chromatography (pentane/EtOAc, 5/2) gave 241 mg (1.30 mmol, 59%) of **3k** as a white solid mp 84–85 °C. ^{1}H NMR ($CDCl_3$) δ: 3.97 (s, 3H), 5.44 (d, J=47.0, 2H), 7.04 (m, 1H), 7.70 (m, 2H).

*4.5.12. 1-(3,5-Dinitrophenyl)-2-fluoroethanone (**3l**).* Compound **3l** was prepared as described in Section 4.3 starting with **1l** (464 mg,

2.21 mmol). Fluorination was performed for 120 min, and hydrolysis was done in 30 min. Compound **3l** was purified by crystallisation from chloroform giving 204 mg (0.89 mmol, 41%) of a white solid, mp 111–112 °C. ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, J=47.0, 2H), 9.04–9.05 (m, 2H), 9.28–9.30 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 84.3 (d, J=186.9), 123.0, 128.3 (d, J=4.9, 2C), 136.5 (d, J=2.0), 149.0 (2C), 190.7 (d, J=18.4). ^{19}F NMR ($CDCl_3$) δ: −227.3 (t, J=46.9). HRMS (ESI): 227.0106 (calcd 227.0110, M−H$^+$). IR (neat, cm^{-1}): 3116, 3084, 2942, 1709, 1612, 1525, 1349, 1230, 1074, 975, 805, 736.

*4.5.13. 1-(3,5-Difluoro-4-methoxyphenyl)-2-fluoroethanone (**3n**).* Compound **3n** was isolated after a thermal fluorination protocol as described previously,[36] starting with **1k** (1.49 mg, 8.84 mmol). Fluorination was performed for 96 h., while hydrolysis in TFA/water/$CHCl_3$ was performed for 3.5 h. The by-product, **3n**, was isolated by silica gel chromatography (pentane/EtOAc, 7/3) giving 14 mg (0.07 mmol, 1%) of a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 4.14 (t, J=1.8, 3H), 5.40 (d, J=46.9, 2H), 7.47–7.52 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 61.7 (t, J=4.2), 83.6 (d, J=184.4), 112.6 (ddd, J=3.9, 7.4, 16.6, 2C), 117.2 (d, J=1.4), 141.6, 154.9 (dd, J=5.7, 256.4, 2C), 190.7 (d, J=16.0). ^{19}F NMR ($CDCl_3$) δ: −127.2 (d, J=8.0), −229.2 (t, J=46.9). HRMS (ESI): 205.0473 (calcd 205.0471, M+H$^+$). IR (neat, cm^{-1}): 2946, 2847, 1708, 1517, 1432, 1330, 1081, 1040, 992, 707.

4.6. 1-Aryl-1,1-dimethoxyethylfluorids (2)

Seven 1-aryl-2,2-dimethoxyethylfluorides were characterised in the previous study.[36] The identity of the dimethyl acetals **2d** and **2n** was assumed from their ^{1}H NMR shifts and coupling constants, and their conversion to the corresponding 1-aryl-2-fluoroethanones by hydrolysis.

*4.6.1. 1-(2-Fluoro-1,1-dimethoxyethyl)-3-nitrobenzene (**2i**).* Compound **2i** was synthesised from **1i** (370 mg, 2.21 mmol) by MW fluorination at 80 W for 60 min, omitting the hydrolytic step. Purification by silica gel chromatography (pentane/acetone, 7/3), gave 137 mg (0.60 mmol, 27%) of a slightly yellowish solid, mp 57–59 °C. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 6H), 4.52 (d, J=47.0, 2H), 7.58 (m, 1H), 7.86 (m, 1H), 8.22 (m, 1H) and 8.42 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 49.3 (2C), 82.5 (d, J=178.4), 99.9 (d, J=20.8), 122.8 (d, J=1.1), 123.6, 129.3, 133.5 (d, J=1.1), 140.8, 148.5. ^{19}F NMR ($CDCl_3$) δ: −231.7 (t, J=47.0). HRMS (ESI): 252.0643 (calcd 252.0648, M+Na$^+$). IR (neat, cm^{-1}): 3097, 1543, 1348, 1070, 730, 695.

*4.6.2. 1-(2-Fluoro-1,1-dimethoxyethyl)-3,5-dinitrobenzene (**2l**).* Compound **2l** was synthesised from **1l** (464 mg, 2.21 mmol) by MW fluorination at 80 W for 120 min, omitting the hydrolytic step. Purification by silica gel chromatography (pentane/acetone, 7/3), gave 157 mg (0.57 mmol, 26%) of a slightly yellowish solid, mp 87–91 °C. ^{1}H NMR ($CDCl_3$) δ: 3.34 (s, 6H), 4.56 (d, J=46.8, 2H), 8.72 (d, J=2.1, 2H) and 9.05 (t, J=2.1, 1H). ^{13}C NMR ($CDCl_3$) δ: 49.5 (2C), 81.7 (d, J=178.7), 99.6 (d, J=21.2), 119.0, 127.9 (d, J=1.1, 2C), 143.5, 148.6 (2C). ^{19}F NMR ($CDCl_3$) δ: −232.2 (t, J=46.9). IR (neat, cm^{-1}): 3086, 1528, 1347, 1064, 703.

4.7. 1-Aryl-2,2-difluoroketones (4)

The ^{1}H NMR chemical shift and the coupling constants of the difluoromethylene groups in the α,α-difluoroketones were compared by that reported previously for **4a**,[29,43] **4c**,[29] **4e**,[43] and **4h**.[28] Selected compounds were isolated or synthesised. The compounds **4i** and **4j** could not be isolated in a sufficiently pure form for characterisation.

*4.7.1. 2,2-Difluoro-1-phenylethanone (**4c**)[29].* Compound **4c** was prepared as described for **3c** using MW heating. Purification by silica gel chromatography (pentane/acetone, 85/15) gave 41 mg (0.26 mmol, 12%) of **4c** as an oil. ^{1}H NMR data corresponded with that reported previously.[29] ^{1}H NMR ($CDCl_3$) δ: 6.29 (t, J=53.6, 1H), 7.54 (m, 2H), 7.68 (m, 1H), 8.08 (m, 2H).

*4.7.2. 2,2-Difluoro-1-(4-fluorophenyl)ethanone (**4d**)[44].* Compound **4d** was prepared as described for **3d** using MW heating. Purification by silica gel chromatography (pentane/acetone, 85/15) gave 63 mg (0.36 mmol, 16%) of **4d** as an oil. ^{1}H NMR ($CDCl_3$) δ: 6.24 (t, J=53.6, 1H), 7.21 (m, 2H) and 8.13 (m, 2H).

*4.7.3. 1-(4-Bromophenyl)-2,2-difluoroethanone (**4e**)[43].* Compound **4e** was prepared as described for **3e** using MW heating. Purification by silica gel chromatography (pentane/acetone, 85/15) gave 85 mg (0.36 mmol, 16%) of **4e** as an oil. ^{1}H NMR data corresponded with that reported previously.[43] ^{1}H NMR ($CDCl_3$) δ: 6.24 (t, J=53.5, 1H), 7.69 (m, 2H), 7.95 (m, 2H).

*4.7.4. 2,2-Difluoro-1-(4-trifluoromethylphenyl)ethanone (**4f**).* Compound **4f** was prepared as described for **3f** using MW heating. Purification by silica gel chromatography (CH_2Cl_2) gave 87 mg (0.38 mmol, 17%) of **4f** as an oil. ^{1}H NMR ($CDCl_3$) δ: 6.27 (t, J=53.4, 1H), 7.81 (m, 2H) and 8.21 (m, 2H).

*4.7.5. 2,2-Difluoro-1-(4-nitrophenyl)ethanone (**4h**)[28].* Compound **4h** was synthesised as described by Peng et al.[28] starting with **1h** (2.07 g, 12.53 mmol). The crude product obtained (1.65 g, contaminated with **3h**) had an ^{1}H NMR spectra, which corresponded well with that reported. ^{1}H NMR ($CDCl_3$) δ: 6.28 (t, J=53.3, 1H), 8.27 (m, 2H), 8.39 (m, 2H).

*4.7.6. 2,2-Difluoro-1-(naphthalen-1-yl)ethanone (**4j**)[42].* Compound **4j** was synthesised based on the method reported by Verniest et al.[30] starting with **1j** (2.30 g. 13.54 mmol). Compound **1j** was first converted to its corresponding methyl imine, followed by fluorination using *N*-fluorobisbenzenesulfonimide. The difluorinated imine formed was hydrolysed using HCl. This gave after purification by silica gel column chromatography (CH_2Cl_2) 1.34 g, (6.50 mmol, 48%) of a pale yellow oil. The ^{1}H, ^{13}C and ^{19}F NMR spectra corresponded with that reported.[42] ^{1}H NMR ($CDCl_3$) δ: 6.42 (t, J=53.9, 1H), 7.54–7.63 (m, 3H), 7.68 (m, 1H), 7.91 (d, J=8.0, 1H), 8.14 (d, J=8.0, 1H), 8.19 (m, 1H), 8.85 (d, J=8.0, 1H).

4.8. 1-Aryl-2-chloroethanones (6)

Trace impurities of 1-aryl-2-chloroethanoes were observed after most fluorinations. The identity of selected compounds was verified by isolation or synthesis.

*4.8.1. 1-(4-(Benzyloxy)phenyl)-2-chloroethanone (**6b**)[45].* 1-(4-Benzyloxyphenyl)ethanone (**1b**) (5.49 g, 19.0 mmol) and *p*-TsOH (2.31 g, 12.1 mmol) were suspended in methanol (500 mL) at 40 °C. Then 1,3-dichloro-5,5-dimethylhydantoin (3.59 g, 18.2 mmol) was added in portions over 1 h, followed by agitation of the reaction mixture at 40 °C for 22 h. Methanol was then distilled off until crystallisation started, followed by slow addition of water (200 mL). The suspension formed was then stirred for 45 min followed by isolation of the solid material. The crude product was recrystallised from EtOAc/ethanol. This gave 4.03 g (63%) of a white solid, mp 111–112 °C (Lit.[45] 109–110 °C). ^{1}H and ^{13}C NMR spectra corresponded with that reported.[45] ^{1}H NMR ($CHCl_3$) δ: 4.62 (s, 2H), 5.13 (s, 2H), 7.01 (m, 2H), 7.30–7.42 (m, 5H), 7.92 (m, 2H).

*4.8.2. 1-(4-Bromophenyl)-2-chloroethanone (**6e**)[37].* The identity of **6e** was verified by HPLC co-eluation with a commercial sample of **6e**. Column: Symmetry C8 3.5 μm, 4.6×150 mm, (Waters Corp.,

Massachusetts, USA); gradient elution starting with H_2O/acetonitrile/diethylamine (98/2/0.1, vol %), to H_2O/acetonitrile/diethylamine (30/70/0.1, vol%) after 70 min; flow rate: 1.0 mL/min; detection at 220 nm, retention time **6e**: 57.3 min.

*4.8.3. 2-Chloro-1-(trifluoromethylphenyl)ethanone (**6f**)*[46]. Following a thermal fluorination of **1f** (1.58 g, 8.84 mmol) in methanol using F-TEDA-BF_4, and acetal cleavage using trifluoroacetic acid as described previously,[36] 9 mg (0.04 mmole, 0.5%) of **6f** as an oil was isolated by silica gel column chromatography (CH_2Cl_2). ^{1}H NMR data in DMSO-d_6 corresponded with that reported.[46] ^{1}H NMR (DMSO-d_6) δ: 5.28 (s, 2H), 7.94 (m, 2H), 8.17 (m, 2H).

*4.8.4. 2-Chloro-1-(4-nitrophenyl)ethanone (**6h**)*[37]. Compound **6h** were obtained after a thermal fluorination a of **1h** (2.92 g, 17.68 mmol) in methanol for 11 days, followed by acetal cleavage using hydrochloric acid (10%, 20 mL) in THF (80 mL) at 65 °C overnight. After work-up, the resulting solid was crystallised from $CHCl_3$. The resulting mother liquor was then purified by silica gel chromatography ($CHCl_3$) yielding 30 mg (0.02 mmol, 1%) of an off-white solid, mp 87–91 °C. ^{1}H and ^{13}C NMR data corresponded with that reported.[47] ^{1}H NMR ($CDCl_3$) δ: 4.72 (s, 2H), 8.15 (m, 2H), 8.36 (m, 2H).

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Paper III

Fuglseth, E., Sundby, E., Bruheim, P., Hoff, B. H.

Asymmetric reduction using (*R*)-MeCBS and determination of absolute configuration of *para*-substituted 2-fluoroarylethanols

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Asymmetric reduction using (*R*)-MeCBS and determination of absolute configuration of *para*-substituted 2-fluoroarylethanols

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ABSTRACT

The asymmetric reduction of eight α-fluoroacetophenones has been investigated using (*R*)-MeCBS as a catalyst in various media. Based on a solvent screen, 1,2-dimethoxyethane, diethyl ether and dichloromethane were used in reductions of the α-fluoroacetophenones. The enantiomeric excess of the products depended on the solvent and the electronic character of the aromatic substituents. Higher enantioselectivity and less solvent dependency were observed in the reduction of substrates bearing electron donating substituents, whereas the opposite was the case for reduction of the substrates with electron withdrawing substituents. The (*R*)-2-fluoro-1-arylethanols were obtained with enantiomeric excesses in the range of 91–99% using 1,2-dimethoxyethane as a solvent. Six of the alcohols produced are new chemical entities. The absolute configurations of the (*R*)-2-fluoro-1-arylethanols were determined by circular dichroism using the exciton chirality method of the (*S*)-benzoate esters of the alcohols. The (*S*)-benzoate esters were obtained by lipase-catalysed resolution using Novozym 435.

1. Introduction

The importance of fluorinated compounds has been well documented and there is a fast growing demand of optically active fluorinated building blocks, for example, in medicinal chemistry, biochemistry and material science.[1–4] Approximately 20% of drugs on the market contain fluorine, a number expected to grow.[5] The 1-arylethanol-skeleton is a frequently encountered structural element in bioactive molecules.[6–9] However, applications of 1-aryl-2-fluoroethanols are not numerous.

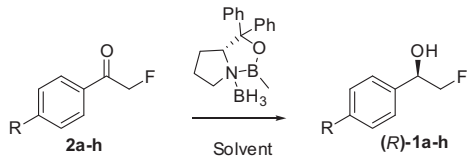
Enantioenriched (*R*)- and (*S*)-2-fluoro-1-phenylethanol are well known and have been prepared by microbial reductions,[10–13] reduction using DIP-Chlorine and Alpine-borane,[14] asymmetric epoxide opening[15,16] and hydrolase catalysed resolutions.[17–19] Also, (*R*)-1-(4-bromophenyl)-2-fluoroethanol has been prepared by Baker's yeast reduction.[10]

Chiral oxazaborolidine-catalysed borane reduction of prochiral ketones to chiral secondary alcohols is one of the most important methods in asymmetric synthesis. The present work deals with the asymmetric reduction and solvent selection for a series α-fluoroacetophenones using (*R*)-MeCBS.[20] The MeCBS catalyst had previously been used for the reduction of structurally related acetophenones, giving the corresponding alcohols in high enantiomeric excess (ee).[21,22] Mathre et al.,[21] compared the effect of three solvents on ee in reductions of a series of *para*-substituted acetophenones. Solvent effects have also been investigated experimentally by Gilmore et al.,[23] Xu et al.[24] and Corey et al.[25] whilst Xu et al.,[26] have investigated substrate electronic effects on the enantioselectivity in oxazaborolidine-catalysed reductions. Several theoretical studies of the catalyst have also been performed.[27–30]

2. Result and discussion

2.1. Asymmetric reduction

In order to find suitable conditions for the asymmetric reduction of a series of α-fluoroacetophenones, **2a**–**h** (Scheme 1), a solvent screen was performed. The investigation was carried out using nine different solvents, **2a** as the model substrate and



R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 1. Asymmetric reduction of **2a**–**h** using (*R*)-MeCBS in various solvents.

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(*R*)-MeCBS as the catalyst (Table 1). The catalyst was prepared from (*R*)-α,α-diphenyl-2-pyrrolidinemethanol,[21] and was used as the borane complex in equimolar amounts.

Table 1
Effect of solvent on ee (%) in reduction of **2a** at 25 °C

Solvent	ee (%)	Absolute configuration
Diethyl ether	98.0	(*R*)
t-BuOMe	97.0	(*R*)
DME	97.0	(*R*)
THF	96.0	(*R*)
CH_2Cl_2	94.5	(*R*)
Toluene	86.5	(*R*)
i-Pr ether	86.0	(*R*)
Hexane	81.0	(*R*)
MeCN	74.5	(*R*)

The enantioselectivity of the reductions depended on the solvent. The product (*R*)-**1a** was obtained in high ee when the reaction was performed in diethyl ether, *tert*-butyl methyl ether (*t*-BuOMe) and 1,2-dimethoxyethane (DME). Acyclic ethers had previously been found to be suitable solvents for the asymmetric reduction of structurally related ketones.[31,32] The reductions of **2a** in dichloromethane and THF also gave acceptable ee-values, whereas the reductions in the other solvents resulted in moderate enantioselectivity. Surprisingly, reductions in diisopropyl ether gave low selectivity. The reason for this is not clear; however, both the catalyst and the substrate had a low solubility in the reaction medium.

To investigate the effect of solvents on the enantioselectivity further, the whole series of substrates, **2a–2h,** were reduced in diethyl ether, dichloromethane and DME. *t*-BuOMe was not included due to the low solubility of the catalyst in this medium. Dichloromethane was included to ensure a larger variability in solvent properties. The reductions of **2a**–**h** in the three solvents were performed using (*R*)-MeCBS at 25 °C. The results are summarised in Table 2.

Table 2
Effect of solvent on ee in reduction of **2a**–**h** at 25 °C

Product	ee (%)		
	Diethyl ether	CH_2Cl_2	DME
(*R*)-**1a**	98.0	94.5	97.0
(*R*)-**1b**	98.0	98.0	97.0
(*R*)-**1c**	91.5	78.0	96.5
(*R*)-**1d**	94.5	92.0	97.5
(*R*)-**1e**	90.0	81.5	93.5
(*R*)-**1f**	85.5	65.0	90.0
(*R*)-**1g**	[a]	74.0	89.0
(*R*)-**1h**	75.0	68.0	93.5

[a] Low solubility of substrate resulted in slow conversion.

The effect of the solvent on the enantioselectivity varied between the substrates. For the whole series, reductions in DME on average gave the highest ee-values, whilst reactions in dichloromethane gave the lowest enantioselectivity. Only minor effects of the solvent on the ee were observed in the reduction of **2a**–**b**, whereas for the reduction of **2c**–**2h** the choice of solvent was very important.

Solvent effects on enantioselectivity in similar reaction systems had previously been explained by changes in the equilibrium between the monomer and dimer species of the catalyst,[23] reduction caused by free borane,[21,24] and stabilisation of the reactive intermediates.[27,28] The solvent effect observed in this study is likely to be caused by a combination of all the above-mentioned mechanisms.

Clearly, the substrate structure has an effect on the outcome of the reaction. In all solvents, there was a decrease in ee going from **1a** to **1h**. Such effects have also been observed in similar systems.[25,26]

The enantioselectivity of (*R*)-MeCBS-catalysed asymmetric reductions has been observed to be dependant on the reaction temperature[24] and the addition time of the substrate. The effects of these two parameters were investigated in the reduction of **2a**. The reaction temperature was varied between –20 °C and +40 °C, and the substrate addition time was varied from 0 to 4 h. The results are given in Table 3.

Table 3
Effect of reaction temperature and addition time on ee in reduction of **2a**

Reaction temperature (°C)	Addition time (h)	ee (%)
40	0	92.5
40	4	93.5
10	2	98.0
10	2	98.5
−20	0	98.5
−20	4	98.5

The ee of the product, (*R*)-**1a**, depended on the reaction temperature. Lower enantioselectivity was experienced at 40 °C. The substrate addition time seemed to be less important, but a minor effect was observed at a higher reaction temperature.

Based on the above findings, all the substrates were reduced on a 1 mmol scale using (*R*)-MeCBS at −20 °C in DME. The addition of the substrates was carried out over 20 min; the results are given in Table 4.

Table 4
Asymmetric reduction of **2a**–**h** at −20 °C using (*R*)-MeCBS in DME

Product	Reaction time (min)	ee (%)	Isolated yield (%)
(R)-**1a**	30	99.5	88
(R)-**1b**	15	97.0	88
(R)-**1c**	20	96.5	84
(R)-**1d**	20	99.0	76
(R)-**1e**	20	98.5	82
(R)-**1f**	20	93.0	84
(R)-**1g**	20	91.5	74
(R)-**1h**	20	92.5	80

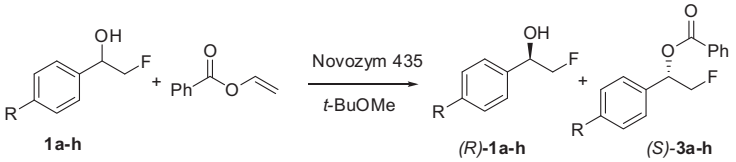
All the products were obtained in good to excellent ee, but a slight decrease in enantioselectivity was observed going from (*R*)-**1a** to (*R*)-**1h**. Comparing the reactions in DME performed at −20 °C with those at +25 °C, only minor changes in enantioselectivity were observed for most substrates. However, the enantioselectivity in the reduction of **2e** increased from 93.5% to 98.5%. This effect was not investigated, but might be due to either a temperature effect, addition time or a scale effect.

2.2. Determination of the absolute configuration

Optical rotation data had previously only been reported for (*R*)-**1c**,[10,18] and (*R*)-**1e**.[10] The absolute configuration of the remaining alcohols was determined by circular dichroism spectroscopy (CD) of the benzoates (*S*)-**3a**–**h**, (Scheme 2). The CD exciton chirality method,[33,34] had previously been used for assigning the absolute configuration of similar compounds.[35]

The stereopreference of lipase B from *Candida antarctica* is well documented.[36,37] Therefore, this lipase (Novozym 435) was used to obtain the benzoates, (*S*)-**3a**–**h**, from the racemic alcohols, *rac*-**1a**–**h**, by kinetic resolution via a 0.1 mmol scale. Vinyl benzoate was used as acyl donor and *t*-BuOMe as a solvent (Scheme 2).

The remaining substrate from the resolution had the same configuration as the alcohols, (*R*)-**1a**–**h**, obtained by the asymmetric reduction using (*R*)-MeCBS. Thus, the benzoates obtained, (*S*)-**3a**–**h**, had the opposite configuration.



Scheme 2. Kinetic resolution of racemic **1a–h** using Novozym 435 and vinyl benzoate as acyl donor.

The exciton chirality method depends on the conformation of the molecule. Therefore, an energy minimisation using Molecular Modelling Pro (MM2) was performed. The benzoates, (*S*)-**3a–h**, had similar preferred conformations, with the hydrogen atom at the stereogenic centre arranged in the same plane as the disubstituted aromatic ring, see Figure 1.

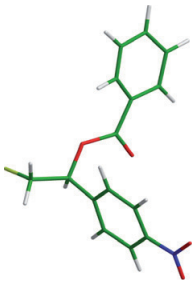


Figure 1. Favoured conformation of (*S*)-**3h**.

Table 5
Enantiomeric excess, $\Delta\varepsilon$ and λ for (*S*)-**3a–h**

Compound	R	ee (%)	$\Delta\varepsilon$	λ^a (nm)
(*S*)-**3a**	OMe	73	−5.9	233
(*S*)-**3b**	OBn	99	−14.2	234
(*S*)-**3c**	H	88	−9.0	228
(*S*)-**3d**	F	79	−7.1	228
(*S*)-**3e**	Br	94	−22.3	232
(*S*)-**3f**	CF_3	96	−6.0	227
(*S*)-**3g**	CN	90	−19.6	237
(*S*)-**3h**	NO_2	94	−9.0	265

[a] Maximum of first Cotton effect.

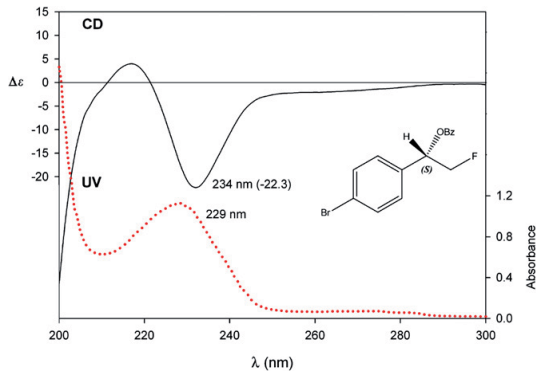


Figure 2. CD and UV spectra of (*S*)-**3e**.

The CD chirality exciton method predicts that upon looking through the centres of the two interacting dipoles, a negative sign is defined when an anticlockwise rotation brings the dipole in the front onto that in the back, and vice-versa.[38]

For the benzoates, (*S*)-**3a–h**, an anticlockwise rotation of the disubstituted phenyl ring brings it onto the benzoate dipole, thus a negative first Cotton effect was predicted. This was confirmed by CD measurements. The ee of the benzoates, (*S*)-**3a–h**, the molar extinction ($\Delta\varepsilon$) and UV absorption maximum (λ_{max}) are summarised in Table 5.

The second Cotton effect at lower wavelength was not observed because the CD spectrum is perturbed by other electronic transitions and effects caused by solvents, see Figure 2.

3. Conclusion

Eight α-fluoroacetophenones have been reduced with good to excellent enantioselectivity, using the (*R*)-MeCBS borane complex as catalyst. The enantiomeric excess of the products depended on the choice of solvent, DME being the preferred reaction medium. The enantioselectivity of the reactions was also affected by substrate structure. High enantioselectivity was obtained in the reduction of substrates having electron donating substituents, whereas a slight decrease in ee of the products were observed in reductions of substrates having electron withdrawing substituents.

Six of the prepared 2-fluoro-1-arylethanols had not previously been described. The absolute configuration of the alcohols, (*R*)-**1a–h**, was determined by CD spectroscopy using the exciton chirality method.

4. Experimental

4.1. General

The α-fluoroacetophenones were prepared as described previously.[39] The (*R*)-MeCBS borane complex was prepared according to Mathre et al.[21] starting with (*R*)-α,α-diphenyl-2-pyrolidinemethanol. Trimethylboroxine, borane dimethyl sulfide complex, vinyl benzoate and $NaBH_4$ were purchased from Aldrich. (*R*)-α,α-Diphenyl-2-pyrrolidinemethanol was a gift from Borregaard (Norway). Novozym 435 was from Novozymes A/S (Denmark). Column chromatography was performed using Silica Gel 60A from Fluka, pore size 40–63 μm. Preparative TLC plates were made by known procedures. Solvents were dried by standard procedures before use.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^1H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. ^1H and ^{13}C NMR chemical shifts are in ppm relative to TMS, whilst for ^{19}F NMR, the shift values are relative to hexafluorobenzene. Coupling constants are in Hertz. Mass spectroscopy (EI): Finnigan MAT 95 XL Mass Spectrometer (EI/70 eV). Accurate mass determination (ESI) was performed on an Agilent 6520 QTOF MS instrument equipped with a dual electrospray ion source. Samples

were injected into the MS using an Agilent 1200 series HPLC, and analysis was performed as a flow injection analysis without any chromatographic steps. All melting points are uncorrected and measured by a Büchi melting point instrument. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. CD spectra were recorded on an OLIS DSM 1000 spectrophotometer in a 1 cm cuvette, using acetonitrile as a solvent. Optical rotations were measured using sodium D line at 589 nm on a Perkin–Elmer 243 B polarimeter. The ee of the alcohols was determined by HPLC using an Agilent 1100 series system equipped with a Bruker DAD detector and a Chiracel OD column (0.46 cm × 25 cm), mobile phase: hexane/2-propanol, 98:2, flow rate 1.0 mL/min. Retention times for the enantiomers: (*S*)-**1a** 24.7 min, (*R*)-**1a** 30.0 min, (*S*)-**1b** 46.7 min, (*R*)-**1b** 49.6 min, (*S*)-**1c** 16.2 min, (*R*)-**1c** 21.4 min, (*R*)-**1d** 15.2 min, (*S*)-**1d** 16.2 min, (*R*)-**1e** 17.8 min, (*S*)-**1e** 20.4 min, (*R*)-**1f** 16.3 min, (*S*)-**1f** 18.3 min, (*R*)-**1g** 47.3 min, (*S*)-**1g** 52.7 min, (*R*)-**1h** 42.5 min, (*S*)-**1h** 47.3 min.

4.3. Screening scale (*R*)-MeCBS reductions

Under anhydrous conditions, (*R*)-MeCBS (29 mg, 0.1 mmol) was dissolved in the given solvent (0.5 mL) and added to a solution of the α-fluoroacetophenone (0.1 mmol, 0.10 M) in the same solvent. The reaction mixture was then stirred at the given temperature until full conversion as monitored by HPLC.

4.4. Preparative scale (*R*)-MeCBS reductions

The α-fluoroacetophenone (1.5 mmol) was dissolved in DME (10 mL) and cooled to −20 °C. Through an addition funnel was added a solution of (*R*)-MeCBS (437 mg, 1.5 mmol) dissolved in DME (5 mL) over 20 min. The mixture was kept at −20 °C and stirred until complete consumption of the ketone as analysed by HPLC. The reaction mixture was then quenched with MeOH (5 mL) at −20 °C and acidified with HCl (1%) at 0 °C. Water (10 mL) was added before the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was washed with water (2 × 20 mL) and dried over Na_2SO_4 before the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 100:1).

4.5. Lipase-catalysed resolution

The racemic 2-fluoro-1-arylethanols, *rac*-**1a–h**, (0.1 mmol), obtained by $NaBH_4$ reduction of the α-fluoroacetophenones, **2a–h**, were dissolved in *t*-BuOMe (3 mL). Vinyl benzoate (74 mg, 0.5 mmol) and Novozym 435 (60 mg) were added. The reaction mixture was agitated at 45 °C and monitored by HPLC. The enzyme was filtered off, and the solvent was removed under reduced pressure. The benzoate esters, (*S*)-**3a–h**, and alcohols, (*R*)-**1a–h,** were separated by preparative TLC. Degree of conversions (*c*) was determined by ^{1}H NMR spectroscopy, whilst enantiomeric excess of the substrate alcohols (ee_s) was determined as described in Section 4.2. The ee of the benzoates (ee_p) was calculated by the formula $ee_p = (ee_s/c) - ee_s$.[40]

4.6. Analytical data for (*R*)-2-fluorophenylethanols

4.6.1. (*R*)-2-Fluoro-1-(4-methoxyphenyl)ethanol (*R*)-1a

Colourless oil (224 mg, 88%), ee = 99.5%, $[\alpha]_D^{25} = -38.5$ (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.41 (br, 1H), 3.81 (s, 3H), 4.38 (ddd, *J* = 8.3, 9.5, 48.5, 1H), 4.49 (ddd, *J* = 3.4, 9.5, 46.8, 1H), 4.97 (ddd, *J* = 3.4, 8.3, 13.2, 1H), 6.89–6.93 (m, 2 H), 7.29–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 55.3, 72.5 (d, *J* = 19.8), 87.1 (d, *J* = 174.5), 114.0 (2 C), 127.6 (2 C), 130.2 (d, *J* = 8.1) and 159.7. ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −220.8 (dt, *J* = 13.4, 47.4). IR (neat, cm^{-1}): 3420, 2955, 2839, 1612, 1514, 1250, 1177 and 1089. MS (EI, *m*/*z*, %): 170 (M^+, 14), 153 (29), 137 (100), 109 (27) and 77 (37). HRMS (EI): 170.0744 (calcd 170.0743).

4.6.2. (*R*)-1-(4-(Benzyloxy)phenyl)-2-fluoroethanol (*R*)-1b

White solid (216 mg, 88%), mp 71–73 °C, ee = 97.0%, $[\alpha]_D^{25} = -19.9$ (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.39 (dd, *J* = 1.1, 2.9, 1H), 4.40 (ddd, *J* = 8.4, 9.5, 48.5, 1H), 4.48 (ddd, *J* = 3.4, 9.5, 46.8, 1H), 4.97 (m, 1H), 5.07 (s, 2H), 6.95–7.01 (m, 2H), 7.28–7.45 (m, 7H). ^{13}C NMR ($CDCl_3$) *δ*: 70.3, 72.8 (d, *J* = 19.8), 87.4 (d, *J* = 175.2), 115.3 (2C), 127.7 (2C), 127.9 (2C), 128.2, 128.8 (2C), 130.7 (d, *J* = 8.4), 137.0 and 159.1 ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −220.8 (dt, *J* = 13.4, 47.9). IR (KBr, cm^{-1}): 3427, 2948, 2860, 1612, 1512, 1248, 1170, 1078 and 1007. MS (EI, *m*/*z*, %): 246 (M^+, 3), 91 (100), 65 (11), 43 (12). HRMS (EI): 246.1056 (calcd 246.1056).

4.6.3. (*R*)-2-Fluoro-1-phenylethanol (*R*)-1c[10,18]

Colourless oil (174 mg, 84%), ee = 96.5%, $[\alpha]_D^{25} = -64.4$ (*c* 1.20, $CHCl_3$), Ref. $[\alpha]_D^{25} = -49.9$ (*c* 1.2, $CHCl_3$).[10] ^{1}H NMR ($CDCl_3$) *δ*: 2.51 (br, 1H), 4.41 (ddd, *J* = 8.3, 9.6, 48.5, 1H), 4.51 (ddd, *J* = 3.3, 9.6, 46.7, 1H), 5.01 (ddd, *J* = 3.3, 8.3, 14.0, 1H), 7.33–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) *δ*: 73.0 (d, *J* = 19.8), 87.2 (d, *J* = 174.1), 126.3 (d, *J* = 0.7, 2C), 128.5, 128.7 (2C) and 138.1 (d, *J* = 8.1). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −221.2 (dt, *J* = 13.9, 48.5). IR (neat, cm^{-1}): 3564, 3387, 2950, 1604, 1454, 1311, 1198, 1064 and 1009. MS (EI, *m*/*z*, %): 140 (M^+, 61), 123 (14), 107 (100), 105 (46), 91 (52), 79 (93) and 77 (88). HRMS (EI): 140.0639 (calcd 140.0637).

4.6.4. (*R*)-2-Fluoro-1-(4-fluorophenyl)ethanol (*R*)-1d

Colourless oil (180 mg, 76%), ee = 99.0%, $[\alpha]_D^{25} = -36.5$ (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.63 (br, 1H), 4.39 (ddd, *J* = 8.2, 9.6, 48.3, 1H), 4.48 (ddd, *J* = 3.3, 9.6, 46.7, 1H), 5.00 (ddd, *J* = 3.3, 8.3, 13.9, 1H), 7.00–7.08 (m, 2H), 7.32–7.36 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 72.3 (d, *J* = 19.6), 87.0 (d, *J* = 175.7), 115.5 (d, *J* = 21.6, 2C), 128.0 (d, *J* = 8.2, 2C), 134.7 (dd, *J* = 3.2, 11.3) and 162.7 (d, *J* = 245.3). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −114.2 (m), −221.4 (dt, *J* = 13.8, 48.2). IR (neat, cm^{-1}): 3588, 3385, 2952, 2892, 1606, 1510, 1223, 1197, 1088 and 1010. MS (EI, *m*/*z*, %): M^+ 158 (M^+, 5) 125 (72), 109 (10), 97 (52), 95 (23). HRMS (ESI): 157.0470, (calcd 157.0471 [M−H^+]).

4.6.5. (*R*)-1-(4-Bromophenyl)-2-fluoroethanol (*R*)-1e[10]

White solid (273 mg, 82%), mp 40–41 °C, ee = 98.5%. $[\alpha]_D^{25} = -32.3$ (*c* 0.90, $CHCl_3$), Ref. $[\alpha]_D^{25} = -25.9$ (*c* 0.9 $CHCl_3$).[10] ^{1}H NMR ($CDCl_3$) *δ*: 2.45 (dd, *J* = 1.1, 3.1, 1H), 4.38 (ddd, *J* = 8.2, 9.6, 48.3, 1H), 4.48 (ddd, *J* = 3.3, 9.6, 46.6, 1H), 4.97 (m, 1H), 7.27–7.30 (m, 2H), 7.45–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 72.3 (d, *J* = 20.2), 86.9 (d, *J* = 174.7), 122.4, 128.0 (2C), 131.8 (2C) and 137.1 (d, *J* = 8.3). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −221.9 (dt, *J* = 13.4, 47.4). IR (KBr, cm^{-1}): 3360, 2953, 2896, 1592, 1489, 1327, 1195, 1091 and 1008. MS (EI, *m*/*z*, %): 220/218 (M^+, 6) 187 (47), 185 (52), 78 (50), 77 (100). HRMS (EI): 217.9737 (calcd 217.9743).

4.6.6. (*R*)-2-Fluoro-1-(4-(trifluoromethyl)phenyl) ethanol (*R*)-1f

Colourless oil (265 mg, 84%), ee = 93.0%, $[\alpha]_D^{25} = -20.0$ (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.54 (d, *J* = 3.1, 1H), 4.41 (ddd *J* = 8.1, 9.6, 48.0, 1H), 4.54 (ddd, *J* = 3.3, 9.6, 46.7, 1H), 5.10 (m, 1H), 7.51–7.53 (m, 2H), 7.63–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 72.4 (d, *J* = 20.5), 86.8 (d, *J* = 174.7), 124.0 (q, *J* = 272.3), 125.6 (q, *J* = 3.9, 2C), 126.7 (d, *J* = 0.7, 2C), 130.7 (q, *J* = 32.5) and 142.1 (dq, *J* = 1.4, 7.8). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −63.2 (s, 3F), −222.4 (dt, *J* = 13.8, 47.0). IR (neat, cm^{-1}): 3581, 3386, 2954, 2895, 1621, 1418, 1327, 1166, 1068 and 1016. MS (EI, *m*/*z*, %): M^+ 208 (M^+, 2), 189 (8), 175 (100), 145 (14), 127 (88), 95 (4). HRMS (EI): 208.0503 (calcd 208.0511).

4.6.7. 4-((*R*)-2-Fluoro-1-hydroxyethyl)benzonitrile (*R*)-1g

White solid (183 mg, 74%), mp 59–61 °C, ee = 91.5%. $[\alpha]_D^{25} = -27.1$ (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 2.63 (d, *J* = 3.1, 1H), 4.40 (ddd, *J* = 8.0, 9.5, 48.0, 1H), 4.54 (ddd, *J* = 3.4, 9.5, 46.7, 1H), 5.07 (m, 1H), 7.46–7.56 (m, 2H), 7.65–7.71 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 72.2 (d, *J* = 20.3), 86.5 (d, *J* = 173.3), 112.5, 118.5, 127.0 (2C), 132.4 (2C) and 143.3 (d, *J* = 7.6). ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −222.9 (dt, *J* = 13.8, 47.0). IR (KBr, cm^{-1}): 3456, 2947, 2239, 1609, 1454, 1323, 1202, 1096, and 1009. MS (EI, *m*/*z*, %): M^+ 165 (M^+, 5), 132 (100), 104 (50), 102 (14), 77 (29). HRMS (EI): 165.0589 (calcd 165.0590).

4.6.8. (*R*)-2-Fluoro-1-(4-nitrophenyl)ethanol (*R*)-1h

White solid (223 mg, 80%), mp 97–99 °C, ee = 92.5%, $[\alpha]_D^{25} = -17.7$ (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 2.65 (br, 1H), 4.43 (ddd *J* = 7.8, 9.6, 47.9, 1H), 4.57 (ddd, *J* = 3.4, 9.6, 46.5, 1H), 5.16 (ddd, *J* = 3.4, 7.8, 14.5, 1H), 7.57–7.63 (m, 2H), 8.22–8.27 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 72.1 (d, *J* = 20.5), 86.5 (d, *J* = 175.6), 123.8 (2C), 127.2 (2C), 145.2 (d, *J* = 7.4) and 147.9. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −223.2 (dt, *J* = 14.4, 47.4). IR (KBr, cm^{-1}): 3482, 3116, 2943, 2889, 1604, 1560, 1521, 1349, 1197, 1092, and 1002. MS (EI, *m*/*z*, %): M^+ 185(M^+, 4), 152 (42), 102 (19), 83 (20). HRMS (EI): 185.0488 (calcd 185.0488).

4.7. Analytical data for the benzoates

4.7.1. (*S*)-2-Fluoro-1-(4-methoxyphenyl)ethyl benzoate (*S*)-3a

Colourless oil (11.5 mg, 43%), ee = 73%, $[\alpha]_D^{25} = -15.0$ (*c* 0.60, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -5.9$ (233 nm). ^1H NMR ($CDCl_3$) δ: 3.80 (s, 3H), 4.65 (ddd, *J* = 3.5, 10.1, 46.7, 1H), 4.75 (ddd, *J* = 7.6, 10.1, 47.8, 1H), 6.23 (ddd, *J* = 3.5, 7.6, 16.2, 1H), 6.89–6.93 (m, 2H), 7.37–7.48 (m, 4H), 7.55–7.59 (m, 1H), 8.09–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 55.3, 74.4 (d, *J* = 19.9), 84.2 (d, *J* = 179.3), 114.2 (2C), 127.6 (d, *J* = 6.8), 128.3 (2C), 128.4 (2C), 129.8 (2C), 130.0, 133.2, 160.0 and 165.7. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −221.6 (dt, *J* = 16.1, 47.0). HRMS (ESI): 297.0895 (calcd 297.0897 [M+Na^+]).

4.7.2. (*S*)-1-(4-(Benzyloxy)phenyl)-2-fluoroethyl benzoate (*S*)-3b

White solid (13.5 mg, 39%), mp 91–92 °C, ee = 99%, $[\alpha]_D^{25} = -13.9$ (*c* 1.00, $CHCl_3$) CD (acetonitrile): $\Delta\varepsilon = -14.2$ (234 nm). ^1H NMR ($CDCl_3$) δ: 4.64 (ddd, *J* = 3.5, 10.1, 46.5, 1H), 4.74 (ddd, *J* = 7.6, 10.1, 48.0, 1H), 5.05 (s, 2H), 6.23 (ddd, *J* = 3.5, 7.6, 16.2, 1H), 6.97–6.99 (m, 2H), 7.25–7.47 (m, 9H), 7.55–7.59 (m, 1H), 8.09–8.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 70.1, 74.3 (d, *J* = 20.2), 84.2 (d, *J* = 179.3), 115.1 (2C), 127.4 (2C), 127.8 (d, *J* = 6.7), 128.1, 128.3 (2C), 128.4 (2C), 128.6 (2C), 129.8 (2C), 130.0, 133.2, 136.7, 159.2 and 165.7. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −222.7 (dt, *J* = 16.1, 47.0). HRMS (ESI): 373.1207 (calcd 373.1210 [M+Na^+]).

4.7.3. (*S*)-2-Fluoro-1-phenylethyl benzoate (*S*)-3c

Colourless oil (12.0 mg, 50%), ee = 88%, $[\alpha]_D^{25} = -42.2$ (*c* 0.70, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -9.0$ (228 nm). ^1H NMR ($CDCl_3$) δ: 4.68 (ddd, *J* = 3.4, 10.1, 46.7, 1H), 4.76 (ddd, *J* = 7.3, 10.1, 47.7, 1H), 6.28 (ddd, *J* = 3.4, 7.3, 16.7, 1H), 7.33–7.48 (m, 7H), 7.56–7.60 (m, 1H), 8.11–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.7 (d, *J* = 19.8), 84.2 (d, *J* = 179.8), 126.8 (2C), 128.5 (2C), 128.8 (2C), 128.9, 129.8 (2C), 129.9, 133.3, 135.5 (d, *J* = 6.7) and 165.6. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −223.0 (dt, *J* = 16.1, 47.0). HRMS (ESI): 267.0791 (calcd 267.0792 [M+Na^+]).

4.7.4. (*S*)-2-Fluoro-1-(4-fluorophenyl)ethyl benzoate (*S*)-3d

Colourless oil (9.0 mg, 37%), ee = 79%, $[\alpha]_D^{25} = -23.3$ (*c* 0.60, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -7.1$ (228 nm). ^1H NMR ($CDCl_3$) δ: 4.67 (ddd, *J* = 3.5, 10.1, 46.7, 1H), 4.74 (ddd, *J* = 7.1, 10.1, 47.5, 1H), 6.24 (ddd, *J* = 3.5, 7.1, 16.9, 1H), 7.06–7.10 (m, 2H), 7.43–7.48 (m, 4H), 7.57–7.61 (m, 1H), 8.10–8.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (d, *J* = 20.1), 84.0 (dd, *J* = 1.1, 179.4), 115.8 (d, *J* = 21.6, 2C), 128.5 (2C), 128.8 (d, *J* = 8.5, 2C), 129.69, 129.81 (2C), 131.4 (dd, *J* = 2.8, 3.5), 133.4, 162.9 (d, *J* = 248.0) and 165.5. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −113.3 (m), −223.8 (dt, *J* = 17.2, 47.0). HRMS (ESI): 285.0696 (calcd 285.0698 [M+Na^+]).

4.7.5. (*S*)-1-(4-Bromophenyl)-2-fluoroethyl benzoate (*S*)-3e

White solid (12.0 mg, 38%), mp 52–53 °C, ee = 94%, $[\alpha]_D^{25} = -49.5$ (*c* 0.90, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -22.3$ (232 nm). ^1H NMR ($CDCl_3$) δ: 4.67 (ddd, *J* = 3.5, 10.1, 46.7, 1H), 4.73 (ddd, *J* = 6.8, 10.1, 47.5, 1H), 6.20 (ddd, *J* = 3.5, 6.8, 17.4, 1H), 7.32–7.35 (m, 2H), 7.45–7.53 (m, 4H), 7.58–7.61 (m, 1H), 8.09–8.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (d, *J* = 20.1), 83.9 (d, *J* = 179.8), 122.9, 128.5 (2C), 128.6 (2C), 129.6, 129.8 (2C), 132.0 (2C), 133.5, 134.6 (d, *J* = 6.7) and 165.5. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −224.2 (dt, *J* = 17.2, 47.0). HRMS (ESI): 344.9901 (calcd 344.9897 [M+Na^+]).

4.7.6. (*S*)-2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethyl benzoate (*S*)-3f

Colourless oil (13.5 mg, 40%), ee = 96%, $[\alpha]_D^{25} = -40.3$ (*c* 1.00, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -6.0$ (227 nm). ^1H NMR ($CDCl_3$) δ: 4.72 (ddd, *J* = 3.8, 10.1, 46.7, 1H), 4.76 (ddd, *J* = 6.3, 10.1, 47.2, 1H), 6.28 (ddd, *J* = 3.8, 6.3, 17.9, 1H), 7.46–7.50 (m, 2H), 7.55–7.67 (m, 5H), 8.11–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (d, *J* = 20.1), 83.9 (d, *J* = 179.8), 123.9 (d, *J* = 272.7), 125.8 (q, *J* = 3.9), 127.2 (d, *J* = 0.7, 2C), 128.6 (2 C), 129.4, 129.9 (2C), 131.1 (q, *J* = 32.5), 133.6 (2C), 139.5–139.6 (m) and 165.5. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −63.4 (s, 3F), −226.2 (dt, *J* = 17.2, 47.0). HRMS (ESI): 335.0662 (calcd 335.0666 [M+Na^+]).

4.7.7. (*S*)-1-(4-Cyanophenyl)-2-fluoroethyl benzoate (*S*)-3g

White solid (12.0 mg, 44%), mp 70–71 °C, ee = 90%, $[\alpha]_D^{25} = -49.5$ (*c* 0.90, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -19.6$ (237 nm). ^1H NMR ($CDCl_3$) δ: 4.72 (ddd, *J* = 3.8, 10.1, 46.7, 1H), 4.76 (ddd, *J* = 5.8, 10.1, 47.0, 1H), 6.25 (ddd, *J* = 3.8, 5.8, 18.7, 1H), 7.44–7.71 (m, 7H), 8.10–8.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 73.8 (d, *J* = 20.1), 83.6 (d, *J* = 179.8), 112.8, 118.3, 127.6 (d, *J* = 0.7, 2C), 128.62 (2C), 129.2, 129.9 (2C), 132.6 (2C), 133.7, 140.9 (d, *J* = 5.6) and 165.4. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −226.0 (dt, *J* = 18.4, 47.0). HRMS (ESI): 292.0744 ($M+Na^+$), (calcd 292.0744 [M+Na^+]).

4.7.8. (*S*)-2-Fluoro-1-(4-nitrophenyl)ethyl benzoate (*S*)-3h

White solid (12.5 mg, 43%), mp 81–82 °C, ee = 94%, $[\alpha]_D^{25} = -33.4$ (*c* 0.70, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -9.0$ (265 nm). ^1H NMR ($CDCl_3$) δ: 4.75 (ddd, *J* = 4.3, 10.1, 47.0, 1H), 4.78 (ddd, *J* = 5.6, 10.1, 47.0, 1H), 6.30 (ddd, *J* = 4.3, 5.6, 19.0, 1H), 7.47–7.52 (m, 2H), 7.60–7.66 (m, 3H), 8.11–8.14 (m, 2H), 8.24–8.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 73.6 (d, *J* = 20.5), 83.6 (d, *J* = 180.1), 124.0 (2C), 127.8 (d, *J* = 0.7, 2C), 128.7 (2C), 129.1, 129.9 (2C), 133.8, 142.8 (d, *J* = 5.3), 148.2 and 165.4. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −226.2 (dt, *J* = 19.5, 47.0). HRMS (ESI): 312.0642 (calcd 312.0643 [M+Na^+]).

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Paper IV

Fuglseth, E., Sundby, E., Hoff, B. H.

Ruthenium-catalysed asymmetric transfer hydrogenation of *para*-substituted α-fluoroacetophenones

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Short communication

Ruthenium-catalysed asymmetric transfer hydrogenation of *para*-substituted α-fluoroacetophenones

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ABSTRACT

The first examples of asymmetric transfer hydrogenation of α-fluoroacetophenones are reported. Eight *para*-substituted α-fluoroacetophenones have been reduced using four catalytic systems constructed of $[RuCl_2(p\text{-cymene})_2]_2$ or $[RuCl_2(\text{mesitylene})_2]_2$ in combinations with each of the ligands (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine ((*R*,*R*)-TsDPEN) and (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine ((*R*,*R*)-TsCYDN). All reactions were performed in both water and formic acid/triethylamine. The highest enantioselectivity was obtained using the (*R*,*R*)-TsDPEN ligand in a formic acid/triethylamine mixture, giving the (*S*)-1-aryl-2-fluoroethanols in high to moderate enantiomeric excess (97.5–84.5%). For this solvent system the presence of electron withdrawing groups in the *para* position reduced the enantioselectivity. Reactions performed in water generally gave lower enantioselectivity and reaction rate, although RuCl(mesitylene)-(*R*,*R*)-TsDPEN yielded the product alcohols with enantiomeric excess in the range of 95.5–76.5%.

1. Introduction

The importance and utilisation of optically pure secondary alcohols has been well recognised. Due to their somewhat troublesome preparation, fluorinated secondary alcohols have received considerably less attention. We have recently described routes to α-fluorinated ketones, rendering their corresponding alcohols easy accessible [1]. The potential use of such optically enriched fluorinated alcoholic building blocks is vast, and includes among others pharmaceuticals, advanced materials and agrochemicals [2–6].

Asymmetric transfer hydrogenation (ATH) using various metal complexes has emerged as an excellent alternative to established asymmetric reduction methods [7,8]. The easily available hydrogen sources, mild reaction conditions and simple experimental setup have made it an area of interest for both industrial and academic researchers [9–12]. Moreover, ATH can be performed in water [7,9,13–16], which is the ideal solvent seen from an environmental point of view, and potentially provides cost savings for commercial processes. In contrast to most transition metal catalysed reactions, asymmetric transfer hydrogenations have also been done in presence of air [16,17], without significant loss in enantioselectivity.

Acetophenones are usually the benchmark substrates for asymmetric reductions. Numerous investigations on the effects of different catalysts, metal species, solvent systems, additives, temperature and pH on the rate and selectivity of asymmetric transfer hydrogenations have been reported [7,9,10,13–21].

Sterk et al. [22] has described the ATH of trifluoromethylketones with mediocre enantioselectivity, but the ATH of monofluoroketones is an unexplored area. As part of our ongoing research, we have recently investigated chiral oxazaborolidine-catalysed borane reductions of a series of α-fluoroketones to the corresponding chiral secondary alcohols [23]. In order to develop a more robust and environmental friendly catalytic process, we have now turned our attention to ATH. Herein we wish to report an improved method for the preparation of enantioenriched 1-aryl-2-fluoroethanols using ruthenium catalysed asymmetric transfer hydrogenation.

2. Result and discussion

The α-fluoroketones **4a–e** (Scheme 1) were most conveniently prepared by fluorination of the corresponding trimethylsilyl enol ethers, **2a–e**, using Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) [1], while **4f–h** were obtained in highest yield by reacting the acetophenones, **1f–h**, with Selectfluor™ in methanol. The dimethoxyacetals, **3f–h** formed as the major products were hydrolysed using trifluoroacetic acid [1].

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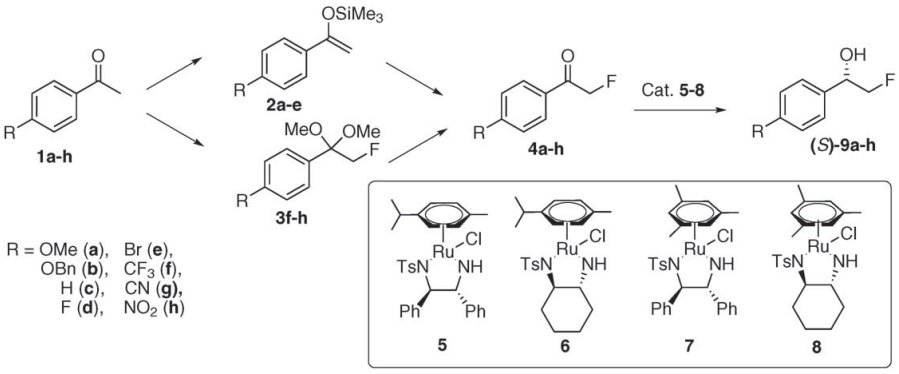

Scheme 1. Preparation and asymmetric transfer hydrogenation of the fluoroketones, **4a**–**h**, using the catalysts **5**–**8**.

The ATH of **4a**–**h** were studied using four different catalysts, **5**–**8**, which were prepared by mixing the ruthenium arene complexes, $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2(\text{mesitylene})]_2$ with (*R*,*R*)-TsDPEN and (*R*,*R*)-TsCYDN, respectively. The pre-catalyst $[RuCl_2(\text{mesitylene})]_2$ was synthesised from $RuCl_3$ and 1,3,5-trimethyl-1,4-cyclohexadiene according to literature procedures [24,25]. All reactions were performed without solvent degassing and without inert atmosphere protection [16].

Initially, **4a**–**h** were reduced with catalysts **5**–**8** in water at 40 °C using sodium formate as hydrogen donor. The reactions were monitored by HPLC for determination of conversion and enantiomeric excess. The results are summarised in Table 1. All reactions proceeded with preference of the (*S*)-enantiomer [23]. The ee of the reactions depended on both catalyst and substrate structure. The highest selectivity was obtained using catalyst **7**, giving the alcohols (*S*)-**9a**, (*S*)-**9c** and (*S*)-**9f** in ≥95% ee. The catalysts **5** and **8** gave comparable, but lower ee-values than was the case with **7**, while catalyst **6** gave only moderate enantioselectivity with ee-values ranging from 77.0 to 47.5%.

The effect of the substituents on the enantioselectivity seems complex. A general trend was that the reductions of **4c** (R = H) and **4f** (R = CF_3) gave some of the highest ee-values for all catalysts, whereas the reduction of **4g** (R = CN) and **4h** (R = NO_2) gave the lowest selectivities. Moderate enantioselectivity has also been the results in asymmetric transfer hydrogenation of 4-nitroacetophenone (**1h**) in similar catalytic systems [13,16,26].

The reaction rate was also dependant on both catalysts and substrate structures. Generally, the highest rates were observed in reductions using catalyst **5**, while catalyst **6** gave the longest reaction times. As expected, the ketones substituted with electron donating substituents tended to react slower than their more electron deficient counterparts [18]. Observed differences in conversion could also be due to the low solubility and crystalline nature of several of the α-fluoroacetophenones in water. Solubility effects might therefore overshadow electronic effects caused by the *para*-substituents.

A formic acid/triethylamine solvent mixture has previously been used in reductions of acetophenone using catalysts **5** and **7** [15,27]. The reactions yielded 1-arylethanols with high enantiomeric excess, but proceeded with a moderate reaction rate. The introduction of a fluorine atom in the α-position of the carbonyl group increases the electrophilicity at the reaction centre, and it was therefore considered worthwhile to investigate this solvent in reduction of **4a**–**h**. The reactions were performed using catalysts **5**–**8** at 40 °C, using S/C = 100, and a physical mixture of formic acid/triethylamine (5:2 mol ratio). The conversions and enantiomeric excess are summarised in Table 2.

Phase transfer limitations are less profound in the triethylamine system, since the α-fluoroacetophenones are soluble in the reaction medium. Less variance in rates was also observed within each catalytic system. The highest rates were observed in reductions using the catalysts **5** and **7**, where all starting materials were consumed within 2 h. Using catalyst **6**, the time needed to reach full conversion was increased to 24 h, whereas the reactions catalysed by **8** were terminated after 10 days, reaching only 20–66% conversion.

Reductions catalysed by **5**–**7** in formic acid/triethylamine gave overall higher selectivity than the reductions in water, and only the reduction of substrate **4f** (R = CF_3) resulted in lower ee-values. The

Table 1
Asymmetric transfer hydrogenation of **4a**–**h** using catalysts **5**–**8** in water.[a]

Substrate		Cat. 5		Cat. 6		Cat. 7		Cat. 8	
		Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. (hours)	ee (%)
4a	OMe	>99 (2)	90.0	18 (24)	67.0	>99 (5)	95.0	88 (5)[b]	87.0
4b	OBn	>99 (10)	88.0	49 (24)	74.0	71 (20)	90.0	83 (5)[b]	89.0
4c	H	>99 (2)	91.5	>99 (24)	81.5	>99 (2)	95.5	>99 (2)	90.5
4d	F	>99 (2)	87.0	>99 (24)	77.0	>99 (5)	91.0	82 (5)[b]	87.0
4e	Br	>99 (2)	87.0	>99 (24)	76.5	>99 (5)	90.5	>99 (5)	87.5
4f	CF_3	>99 (2)	91.5	>99 (24)	77.0	>99 (5)	96.0	>99 (2)	88.0
4g	CN	>99 (2)	66.0	>99 (24)	51.0	45 (20)	84.0	>99 (2)	68.5
4h	NO_2	>99 (2)	70.0	>90 (24)	47.5	99 (20)	76.5	>99 (5)	63.0

[a] A suspension of $[RuCl_2(\text{arene})]_2$ (0.001 mmol) and the ligand (0.0027 mmol) in H_2O (0.5 mL) were stirred at 40 °C for 1 h. Sodium formate (34 mg, 0.5 mmol) and the ketone (0.1 mmol) were then added and the mixture was stirred vigorously at 40 °C for the specified number of hours.
[b] Full conversion was obtained within 20 h reaction time.

Table 2
Asymmetric transfer hydrogenation of **4a–h** using catalysts **5–8** in formic acid/triethylamine.[a]

Substrate		Cat. 5		Cat. 6		Cat. 7		Cat. 8	
		Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. 10 days	ee (%)
4a	OMe	>99 (2)	95.5	>99 (24)	91.0	>99 (2)	96.0	29	44.0
4b	OBn	>99 (2)	96.5	>99 (24)	90.0	>99 (2)	97.5	28	64.0
4c	H	>99 (2)	97.0	>99 (24)	89.0	>99 (2)	97.0	30	72.0
4d	F	>99 (2)	92.0	>99 (24)	86.0	>99 (2)	93.5	24	41.0
4e	Br	>99 (2)	90.5	>99 (24)	83.5	>99 (2)	91.0	30	46.5
4f	CF_3	>99 (2)	91.0	>99 (24)	83.0	>99 (2)	90.5	20	25.0
4g	CN	>99 (2)	84.5	>99 (24)	75.5	>99 (2)	88.0	50	21.0
4h	NO_2	>99 (2)	85.0	>99 (24)	76.5	>99 (2)	84.5	66	29.0

[a] A suspension of the $[RuCl_2(arene)]_2$ (0.001 mmol) and ligand (0.0027 mmol) in CH_2Cl_2 (0.5 mL) were stirred at 20 °C for 30 min. After removal of CH_2Cl_2 by a stream of N_2, the ketone (0.1 mmol) in HCO_2H/Et_3N (5:2, 0.25 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified time.

use of catalysts **5** and **7** yielded products with higher enantiomeric excess than was the case with **6**, and the alcohols, (*S*)-**9a–h**, could be obtained with ee-values ranging from 97.5 to 84.5%. On the other hand, catalyst **8**, which performed reasonable well in water, gave only moderate to low enantioselectivity in formic acid/triethylamine.

Using catalysts **5–7** in formic acid/triethylamine, a trend regarding the effect of substituents on the enantioselectivity could be noticed. A drop in ee of the product alcohols were observed going from **4a–c** to substrates bearing more electron withdrawing substituents. Fujii et al. [27] has previously reduced a series of *para*-substituted acetophenones using (*S,S*)-**7** as catalyst in formic acid/triethylamine. At 28 °C using a catalyst/substrate ratio of 200:1, reduction of **1a** (60 h), **1c** (20 h) and **1g** (14 h) gave the corresponding alcohols in 97, 98 and 90% ee, respectively [27]. The ee of the products in our study are comparable to that obtained in reductions of the corresponding acetophenones. Substituting a methyl- with a fluoromethyl group increases the size of the substituent, and alters the electron density at the carbonyl carbon. It was noteworthy that the reduction of α-fluoroacetophenone (**4c**) was completed in less than 2 h using catalyst **5**, whereas acetophenone (**1c**) under identical conditions in our hands required 20 h to reach full conversion with 97% ee. Evidently, the introduction of one electron withdrawing fluorine increases the reaction rate significantly. Somewhat surprisingly the enantiodiscrimination process was not affected to a large extent by this substitution. The fact that the relative difference in activation energy leading to the (*R*)- and (*S*)-enantiomers is almost equal in the acetophenone and the α-fluoroacetophenone series, implies that the drop in selectivity for substrates containing electron withdrawing aromatic substituents is not solely related to the electronic content of the carbonyl carbon. This effect can rather be explained by other factors such as change in π–π interactions, solvation effects or dispersion interactions as suggested by Brandt et al. [28].

3. Conclusion

Asymmetric transfer hydrogenation of *para*-substituted α-fluoroacetophenones, **4a–h**, using the RuCl-(*p*-cymene)-(*R,R*)-TsDPEN and RuCl-(mesitylene)-(*R,R*)-TsDPEN provides the corresponding chiral 1-aryl-2-fluoroethanols, **9a–h**, in high to moderate ee. The formic acid/triethylamine system was found to give higher enantioselectivity than for reactions in water using sodium formate as hydrogen donor. Compared to the acetophenone series, the introduction of a fluorine atom in α-position to the ketone increased the reaction rates significantly without affecting enantioselectivity. ATH of α-fluoroacetophenones represent a fast, selective, robust and environmental friendly method towards enantioenriched 1-aryl-2-fluoroethanols.

4. Experimental

4.1. General experimental procedures

Solvents and reagents were used as received from the suppliers. $[RuCl_2(p\text{-cymene})]_2$, (*R,R*)-TsDPEN, (*R,R*)-TsCYDN and ruthenium(III) chloride hydrate were from Aldrich, while 1,3,5-trimethyl-1,4-cyclohxadiene was from Alfa Aesar. $[RuCl_2(mesitylene)]_2$ [24,25], and α-fluoroacetophenones [1], were prepared as described previously. Reactions were performed in an incubator shaker from Brunswic Scientific Co. Inc. NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^1H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. The ee of the alcohols were determined by HPLC using an Agilent 1100 series system equipped with a Bruker DAD detector and a Chiracel OD column (0.46 cm × 25 cm), mobile phase: hexane/2-propanol, 98:2, flow rate 1.0 mL/min [23].

4.2. Asymmetric transfer hydrogenation in water

A suspension of $[RuCl_2(arene)]_2$ (0.001 mmol) and the ligand (0.0027 mmol) in H_2O (0.5 mL) were stirred at 40 °C for 1 h. Sodium formate (34 mg, 0.5 mmol) and the α-fluoroacetophenone (0.1 mmol) was then added and the mixture was stirred vigorously at 40 °C for the specified number of hours. Samples were withdrawn from the reaction mixture, extracted with Et_2O and filtered through silica before analysis by HPLC for determination of conversion and enantiomeric excess.

4.3. Asymmetric transfer hydrogenation in formic acid/triethylamine

A suspension of the $[RuCl_2(arene)]_2$ (0.001 mmol) and ligand (0.0027 mmol) in CH_2Cl_2 (0.5 mL) were stirred at 20 °C for 30 min. After removal of CH_2Cl_2 by a stream of N_2, the ketone (0.1 mmol) in a physical mixture of HCO_2H/Et_3N (5:2 mol ratio, 0.25 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified number of hours. Samples were withdrawn from the reaction mixture and the solvent was removed under a stream of N_2. The samples were then dissolved in the HPLC-eluent, filtered through silica and analysed by HPLC for determination of conversion and enantiomeric excess.

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Paper V

Krane Thvedt, T.H., Fuglseth, E., Sundby, E., Hoff, B. H.

Enantioenriched 1-aryl-2-fluoroethylamines. Efficient lipase catalysed-resolution and limitations to the Mitsunobu inversion protocol

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Enantioenriched 1-aryl-2-fluoroethylamines. Efficient lipase-catalysed resolution and limitations to the Mitsunobu inversion protocol

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ABSTRACT

Both enantiomers of eight 1-aryl-2-fluoroethylamines have been synthesised starting with 1-aryl-2-fluoroethanones. Kinetic resolution of the amines using lipase B from *Candida antarctica* with ethyl methoxyacetate as the acyl donor gave the (*R*)-amines in 96–99% ee and the (*S*)-methoxyacetamides in >99.5% ee. The resolution was robust with respect to variation in reaction temperature, acyl donor concentration, water activity and substrate structure. Nine other lipase preparations failed to catalyse the reaction or gave a low enantioselectivity. Secondly, a Mitsunobu inversion protocol starting with enantioenriched 1-aryl-2-fluoroethanols using phthalimide as nucleophile was employed in the synthesis of the (*S*)-1-aryl-2-fluoroethylamines. Both the inversion efficiency and yield depended on the aromatic substituents. For six of the substrates, clean inversion of the stereochemistry was observed. However, racemisation and low yields were the result when electron-donating substituents were present at the aromatic ring. When substituted with a cyano or a nitro group, an unexpected fluorine elimination occurred, limiting the yield for these transformations. The absolute configuration of the 1-aryl-2-fluoroethylamines was determined using circular dichroism.

1. Introduction

1-Arylethylamines are useful building blocks for the preparation of biological active compounds.[1–4] Introduction of fluorine atoms in the α-position of amines enables tuning of the basicity of the compounds in question.[5] This can be used to modify the binding properties, increase bioavailability, reduce toxicity or to increase metabolic stability of a drug candidate. Recently, 1-arylethylamines containing fluoroalkyl groups have emerged as a new class of building blocks for medicinal use.[6–8]

Although a vast amount of research have been devoted to the preparation of enantioenriched 1-arylethylamines, only a few routes to the monofluorinated derivatives are known. One method is based on the reductive amination of α-fluoroketones with enantiopure amines.[9] A stereoselective fluoromethylation of enantioenriched *N*-(*tert*-butanesulfinyl)imines[10] and cinchona-catalysed monofluorination of *N*-Boc α-amido sulfones have also been reported.[11]

Enzyme-catalysed resolution is a well-known method for synthesising enantiopure amines.[12–14] Hydrolases are able to catalyse the amidation of primary amines using activated esters as acyl donors. A number of 1-arylethylamines have been resolved, often with a high enantiomeric ratio (*E*-value).[15,16] In the case of fluorinated analogues, a few 2,2-difluoro- and 2,2,2-trifluoro-1-arylethylamines have been resolved by hydrolysis of the corresponding chloroacetamides using the *Pseudomonas fluorescens* lipase.[17,18] The use of hydrolases to resolve compounds containing a 1,2-fluoroamine moiety has not been documented.

Another common route to enantioenriched amines is by converting enantioenriched alcohols using the Mitsunobu inversion with phthalimide or azide as nucleophiles.[19] Although various types of fluorinated reactants have been used in the Mitsunobu coupling,[20–23] the conversion of 1,2-fluorohydrins to 1,2-fluoroamines has not been investigated.

With the aim of preparing enantiopure 1-aryl-2-fluoroethylamines, we have studied the lipase-catalysed resolution of 1-aryl-2-fluoroethylamines and the Mitsunobu inversion of 1-aryl-2-fluoroethanols.

2. Results and discussion

2.1. Lipase catalysed resolution

2.1.1. Preparation of racemic starting materials. The racemic amines **2a**–**h** were prepared from the corresponding α-fluoroacetophenones **1a**–**h**. The fluoroketones **1a**–**b** were synthesised by fluorination of the corresponding trimethylsilyl enol ethers using Selectfluor,[24]

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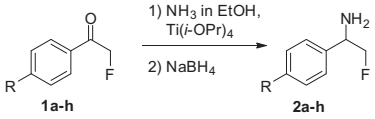
while **1c**–**h** were more conveniently prepared by a MW assisted fluorination of acetophenones.[25]

A reductive amination using ammonium acetate and $NaBH_3CN$, chosen for its simplicity, gave only mediocre conversion (33–44%). However, the use of ammonia in EtOH in the presence of titanium isopropoxide followed by sodium borohydride reduction,[26] was more successful and gave 68–92% yield (Scheme 1).



Scheme 1. Synthesis of **2a**–**h** from **1a**–**h**, R=OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**).

2.1.2. Lipase and solvent selection. Compared to their non-fluorinated counterparts, the amines **2a**–**h** have lower basicity and were expected to have altered reactivity. With the aim of identifying catalysts displaying a high activity and enantioselectivity towards these substrates, the use of 10 different lipase preparations was investigated. Being intermediate in both electronic character and size, 1-(4-bromophenyl)-2-fluoroethylamine (**2e**) was used as model substrate, and the reactions were performed in four different solvents. Ethyl methoxyacetate was used as acyl donor and the reactions were monitored for 72 h. Table 1 summarises the degree of conversion after 6 h.

Table 1
The conversion of **2e** to **3e** after kinetic resolution (6 h) catalysed by different enzymes in different solvents

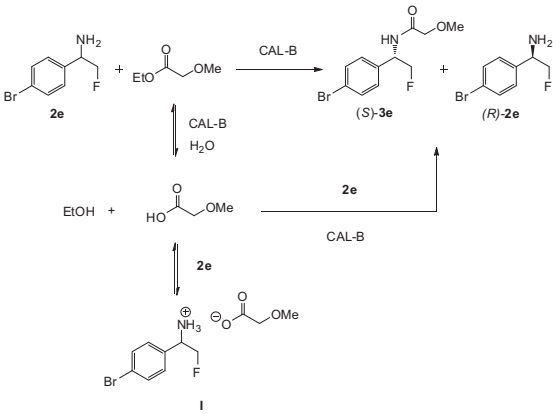
Enzyme	Conversion[b] (%)			
	THF	Toluene	Hexane	Dodecane
Seven lipase preparations[a]	0	0	0	0
Pseudomonas cepacia	2	0	0	0
Candida antarctica lipase A (Novozym 735)	0	8	14	16
Candida antarctica lipase B (Novozym 435)	23	39	50	50

[a] *Aspergillus niger*, *Aspergillus oryzae*, *Candida rugosa*, *Candida rugosa IM*, *Pseudomonas fluorescens*, *Rhizomucor miehei*, *Thermomyces lanuginosa*.
[b] The conversion was calculated by the formula conv.=ees/(eep+ees),[27] where ees and eep are the ee of the substrate and product, respectively.

Of the catalysts tested, only the two lipases from *Candida antarctica*, showed noticeable conversion within 72 h. The use of lipase B from *C. antarctica* (CAL-B) gave 50% conversion after 6 h in both hexane and dodecane, whereas 24 h were needed in THF and toluene. A high enantioselectivity (E>200) was experienced in all solvents. Using lipase A from *C. antarctica* as catalyst, a lower rate of reaction and a lower enantiomeric ratio (E=4–5) was observed. CAL-B was by far the best catalyst, and hexane was selected as solvent for further studies.

2.1.3. Reaction temperature, water activity and amount of acyl donor. The hydrolysis of ethyl methoxyacetate to produce methoxyacetic acid and ethanol was a side-reaction in the resolution. It was noticed that methoxyacetic acid and the amine **2e** formed the salt pair **I**, a process expected to reduce the reaction rate (see Scheme 2).

The reaction temperature, the concentration of acyl donor and the water activity were pinpointed as important parameters in the salt pair formation. Therefore, a two-level factorial design was performed with these three parameters as variables. The reaction temperature was varied from 20 to 60 °C, the amount of acyl donor from 1 to 3 equiv and the water activity (a_w) from ~0 to 0.33. The degree of conversion and enantioselectivity of the experiments are shown in Table 2.



Scheme 2. The enzymatic kinetic resolution and the equilibrium involving the acyl donor and water.

Table 2
Conversion and E-value after resolution of **2e** varying the reaction temperature, water activity and equivalents of acyl donor

Temp (°C)	a_w[a]	Equiv acyl donor	Conversion[b] (%)			E-value[c]
			1 h	2 h	6 h	
20	0.33	1	11	16	34	>200
20	0.33	3	13	21	42	>200
20	~0	1	14	22	37	>200
20	~0	3	19	27	42	>200
40	0.12	2	32	43	50	>200
40	0.12	2	34	45	50	>200
60	0.33	1	45	49	50	>200
60	0.33	3	43	43	49	>200
60	~0	1	44	49	50	>200
60	~0	3	41	47	49	>200

[a] Water activity (a_w) was fixed by equilibration in the presence of aqueous saturated salt solutions: $MgCl_2 \cdot 7H_2O$ (a_w=0.33), LiCl (a_w=0.12), dried over molecular sieves 4 Å (a_w=~0).
[b] The conversion was calculated by the formula conv.=ees/(eep+ees), where ees and eep are the ee of the substrate and product, respectively.[27]
[c] E-values were calculated by the method of Rakels et al. for irreversible reactions.[27]

Within the experimental constrains, the only statistically significant variable was found to be the reaction temperature (see Pareto chart in Fig. 1). A reaction temperature of 60 °C gave the highest rate, reaching 50% conversion in 2 h using 1 equiv of acyl donor. However, a temperature of 40 °C also offered acceptable

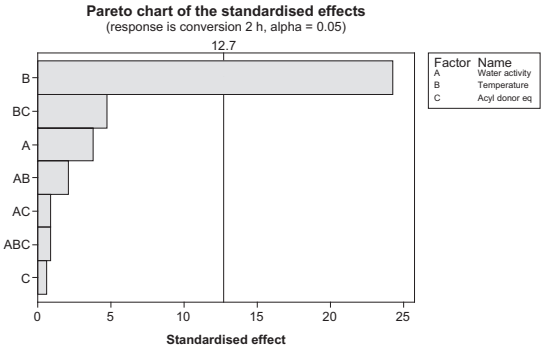


Figure 1. Pareto chart of the factorial design varying the amount of acyl donor, water activity and temperature.

reaction times at a_w=0.11 and 2 equiv of acyl donor. The enantiomeric ratio of the reactions was excellent under all conditions.

The amount of acyl donor was not a significant variable. However, at 20 °C the conversion increased when applying higher levels of acyl donor, whereas at 60 °C the highest conversion was obtained using 1 equiv of acyl donor. This observation could be accounted for by the rather complex equilibrium shown in Scheme 2. The reaction temperature is expected to have different effects on the relative rates for the amidation reaction, the non-productive hydrolysis of the acyl donor and the equilibrium between the free amine and the salt pair **I**.

The effect of changing the water activity was not significant. However, keeping a constant water activity was still considered to be important for the reproducibility of the resolutions.

It was further investigated if methoxyacetic acid could be used as acyl donor in the resolution of **2e**. Performing the resolution at 60 °C using 1 equiv of methoxyacetic acid, a 49% conversion was obtained after 6 h. This showed that the formation of **I** is reversible and that the resolution also can be performed under such conditions. Attempts to reduce the amount of acyl donor to 0.6 equiv led to an incomplete conversion after 6 h.

2.1.4. Effect of substrate structure on conversion and selectivity. Seven other 1-aryl-2-fluoroethylamines, **2a**–**d** and **2f**–**h** were then submitted to lipase-catalysed resolution using CAL-B and ethyl methoxyacetate (1 equiv) in hexane at 60 °C. The small-scale reactions of **2b**–**g** proceeded with rate comparable to that of the resolution of **1e** and with excellent enantioselectivity. A lower rate of reaction was observed for the resolution of **2a**, and the reaction stopped at 30% conversion. However, by adding fresh enzyme or diluting the reaction mixture the resolution could be driven to completion. Probably, some kind of reversible product or substrate inhibition occurs. The nitro-derivative **2h** had limited solubility in hexane and therefore reacted slowly. An increase in rate was observed when toluene was used as solvent.

Preparative kinetic resolutions were then performed on a 2.5 mmol scale. Based on results for the resolution of **2e**, a 16-fold more concentrated reaction mixture was used in the preparative resolutions. The ee of the product and substrate, conversions, enantiomeric ratio after 6 h and by completion are compiled in Table 3.

Table 3
CAL-B catalysed kinetic resolution of **2a**–**h** (2.5 mmol scale) at 60 °C using ethyl methoxyacetate (1 equiv) as acyl donor in hexane

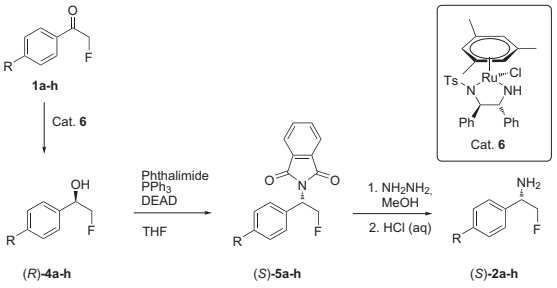
R	6 h			24 h		
	Conversion[c] (%)	**2** of ee (%)	**3** of ee (%)	Conversion[c] (%)	**2** of ee (%)	**3** of ee (%)
OMe (**a**)[a]	49.5	97.0	>99.5	49.5	97.0	>99.5
OBn (**b**)	48.0	92.5	>99.5	49.0	96.0	>99.5
H (**c**)	49.5	98.5	>99.5	50.0	>99.5	>99.5
F (**d**)	50.0	>99.5	>99.5	—	—	—
Br (**e**)	50.0	>99.5	>99.5	—	—	—
CF_3 (**f**)	50.0	>99.5	>99.5	—	—	—
CN (**g**)	47.0	87.0	>99.5	50.0	99.0	>99.5
NO_2 (**h**)[b]	—	—	—	50.0	>99.5	>99.5

[a] Hexane: 24 mL, CAL-B: 2 equiv wt.
[b] Toluene: 12 mL, CAL-B: 1 equiv wt , 48 h reaction time.
[c] The conversion was calculated by the formula conv.=ees/(eep+ees),[27] where ees and eep are the enantiomeric excess of the substrate and product, respectively.

The enantiomeric ratio was excellent in all cases (E>200) and the product (*S*)-amides **3a**–**h** could all be obtained in enantiomerically pure form. The kinetic resolution of **2d**–**f** gave full conversion and >99% ee of the amines within 6 h reaction time. The other substrates reacted slightly slower, thus, the amines **2a** and **2b** were after 24 h obtained in 97 and 96% ee, respectively. If the lower conversion is due to inhibition, low solubility of the amines or a displacement of the equilibrium towards the amine salt **I**, has not been further investigated. However, solvent tuning as demonstrated in the small-scale reaction of **2a** and **2h** is likely to bring conversion from 49 to 50% and thereby increasing the ee of the remaining substrate.

2.2. The Mitsunobu approach

The (*S*)-enantiomers of the fluoroamines **2a**–**h** were obtained from the ketones **1a**–**h** by asymmetric reduction followed by a Mitsunobu inversion protocol as depicted in Scheme 3.



Scheme 3. Synthesis of (*S*)-**2a**–**h** from **1a**–**h** using asymmetric transfer hydrogenation and Mitsunobu inversion.

2.2.1. Preparation of enantioenriched fluoroalcohols. Based on our previous findings,[28] the fluoroalcohols (*R*)-**4a**–**h** were synthesised from the corresponding α-fluoroacetophenones **1a**–**h** by asymmetric transfer hydrogenation catalysed by $[RuCl_2(mesitylene)]_2$ complexed with (1*S*,2*S*)-*N*-*p*-tosyl-1,2-diphenylethylenediamine ((*S*,*S*)-TsDPEN). The alcohols (*R*)-**4a**–**e** and (*R*)-**4g**–**h** were synthesised in a formic acid/triethylamine (5/2 mol ratio) medium, while (*R*)-**4f** was prepared using water with sodium formate as hydrogen donor. The yields and ee are summarised in Table 4. The reactions performed in formic acid/triethylamine gave the product alcohols in 61–91% yield and with good to excellent ee. However, in the reaction performed in water, the alcohol (*R*)-**3f** was isolated in a moderate 52% yield. The reason for this is somewhat unclear. ^{1}H NMR spectroscopy analysis of the distillation residue gave a spectrum with complex splitting pattern in the range of 4.2–5.3 ppm, indicating the presence of several structures containing alkyl fluoride fragments.

Table 4
Isolated yields and ee of the alcohols (*R*)-**4a**–**h**, *N*-substituted phthalimides (*S*)-**5a**–**h**, and fluoroamines (*S*)-**2a**–**h**

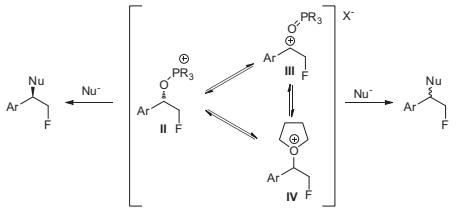
R	(*R*)-**4**		(*S*)-**5**		(*S*)-**2**	
	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)
OMe (**a**)	96.0	76	53.0	32	53.5	73
OBn (**b**)	99.5	61	60.0	37	60.0	72
H (**c**)	98.0	86	99.0	77	98.5	66
F (**d**)	93.0	79	92.5[a]	77	92.5	75
Br (**e**)	91.0	79	90.0	83	90.5	66
CF_3 (**f**)	92.5	52	92.0	78	91.5	71
CN (**g**)	87.0	85	87.5	66	87.5	75
NO_2 (**h**)	85.0	91	84.0	34	84.0	80

[a] Analysed as **2d**.

2.2.2. Mitsunobu inversion. The alcohols (*R*)-**4a**–**h** were then reacted with phthalimide in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine to yield the corresponding *N*-substituted phthalimides (*S*)-**5a**–**h**. The isolated yields and the ee of the products are shown in Table 4.

The *N*-substituted phthalimides (*S*)-**5c**–**f** were isolated in 77–83% yield and with clean inversion of the stereochemistry. Somewhat disappointingly, the reactions leading to (*S*)-**5a**–**b**, were

plagued by racemisation and poor yields. Other alcohols have been shown to partly racemise under similar conditions.[29–33] The reactions have been found to proceed via the intermediate $ROPPh_3^+$ (**II**), which is attacked by a nucleophile in an S_N2 type mechanism (Scheme 4). However, when the substrate enables stabilisation of a developing positive charge, **II** can convert to **III** and **IV**.

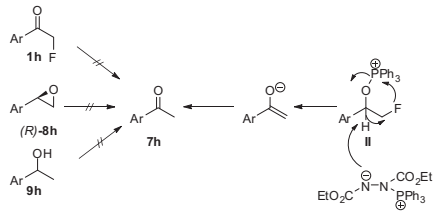


Scheme 4. Mechanistic rationale for the observed racemisation.[29]

These intermediates might react with nucleophiles via an S_N1 type mechanism to form a racemic product.[29,34] The low yields experienced indicated that other side products also might be formed via these pathways.

The alcohols (*R*)-**4g**–**h** reacted to (*S*)-**5g** and (*S*)-**5h** without racemisation, but in moderate and poor yields, respectively. The major by-product was the corresponding acetophenones **7g**–**h**. Further experiments performed on (*R*)-**4h** and racemic **4h** showed that **7h** was formed also in the absence of phthalimide. DEAD is able to oxidise alcohols to ketones,[35,36] but in this case a reaction using only DEAD failed to give **7h**. Thus, both DEAD and triphenylphosphine were required for the transformation. In an attempt to identify reaction intermediates, the reaction was run in THF-d_8 and continuously monitored by ^{1}H NMR spectroscopy. The reaction took place, but within the time scale of NMR no distinct intermediates could be detected. Having no indication of the possible mechanism, 2-fluoro-1-(4-nitrophenyl)ethanone (**1h**), (*R*)-2-(4-nitrophenyl)oxirane ((*R*)-**8h**) and 1-(4-nitrophenyl)ethanol (**9h**) were reacted with DEAD and triphenylphosphine to investigate if these compounds could be reaction intermediates. Compound **7h** was not observed in any of these experiments, excluding these possibilities.

Alcohols have been reported to undergo dehydrations, eliminations and rearrangement reactions under Mitsunobu conditions.[37–41] Phosphorus is known to have affinity for fluoride anions, and triphenylphosphine has been used as a defluorinating agent.[42,43] Based on this, and since no intermediates could be traced, we propose a concerted mechanism to **7g**–**h** via the known Mitsunobu intermediate **II** (Scheme 5). The nitro and the cyano group increase the acidity of the benzylic proton, possibly explaining why only **4g**–**h** reacted by this pathway in the presence of phthalimide.



Scheme 5. Possible explanation for the formation of the acetophenones **7g**–**h** in the Mitsunobu reaction.

To produce the target amines (*S*)-**2a**–**h**, (*S*)-**5a**–**h** were dissolved in methanol and reacted with hydrazine and hydrochloric acid. These hydrazinolysis reactions proceeded smoothly, giving the amines (*S*)-**2a**–**h** in good to moderate yields without altering the ee (Table 4).

2.3. Determination of the absolute configuration

Optical rotation data have previously only been reported for the hydrochloride salts of (*S*)-**2a** and (*S*)-**2c**.[10,11] These data were in agreement with our measurements.

The configuration of the previously unknown fluoroamines was strongly indicated by the stereoselectivity of the lipase-catalysed resolution and the Mitsunobu inversion. However, to unambiguously confirm this, the absolute configuration of the amines was determined by circular dichroism spectroscopy (CD) of the *N*-substituted phthalimides (*S*)-**5a**–**h** using the exciton chirality method.[44–46] The most stable conformation of the *N*-substituted phthalimides was predicted using semiempirical AM1 calculations. All the compounds showed the same preferred conformation, with the hydrogen attached to the stereogenic centre arranged in the same plane as the disubstituted phenyl ring (see Fig. 2A).

For (*S*)-**5a**–**h** an anticlockwise rotation of the disubstituted phenyl ring brings it onto the phthalimide dipole, thus a negative first Cotton effect was predicted. This was confirmed by CD measurements, exemplified by the CD spectrum of (*S*)-**5f** in Figure 2B. All the CD measurements are summarised in Table 5.

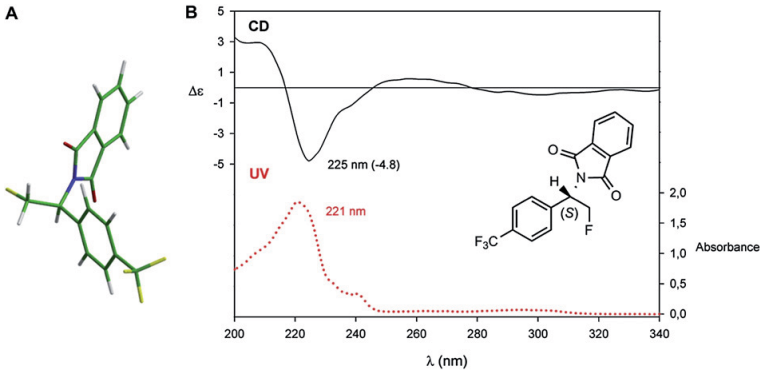


Figure 2. Favoured conformation (A) and CD and UV spectrum of (*S*)-**5f** (B).

Table 5
Enantiomeric excess, molar extinction (Δe) and absorption maximum for the first Cotton effect (λ) for (*S*)-**5a**–**h**

Compound	R	ee (%)	Δe	λ (nm)
(*S*)-**5a**	OMe	53.0	−1.3	232
(*S*)-**5b**	OBn	60.0	−3.8	234
(*S*)-**5c**	H	99.0	−3.5	223
(*S*)-**5d**	F	92.5[a]	−1.6	223
(*S*)-**5e**	Br	90.0	−3.9	230
(*S*)-**5f**	CF_3	92.0	−4.8	225
(*S*)-**5g**	CN	87.5	−2.7	237
(*S*)-**5h**	NO_2	84.0	−1.4	228

[a] Analysed as **2d**.

3. Conclusions

Starting with α-fluoroacetophenones, a lipase-catalysed resolution and a Mitsonobu inversion have been investigated for the preparation of enantioenriched 1-aryl-2-fluoroethylamines.

Using CAL-B as catalyst and ethyl methoxyacetate as acyl donor, the resolutions proceeded with high enantioselectivity and provided the product (*R*)-amines and (*S*)-amides in 96–99% and >99.5% ee, respectively. The method proved to be fairly robust with respect to the amount of acyl donor, water activity and the reaction temperature. One of the substrates (**2h**) had to be resolved in toluene due to limited solubility in hexane.

The Mitsunobu protocol gave clean inversion of the stereochemistry of the alcohols (*R*)-**4c**–**f**. The amines (*S*)-**2c**–**f** could be isolated in 90.5–98.5% ee. In the case of substrates containing electron-donating substituents, racemisation occurred. The yield decreased when both electron donating and strongly electron withdrawing substituents were present. For the latter substrates, a fluorine elimination was identified as the major side reaction.

The drawback of a kinetic resolution is the limitation of a maximum 50% yield. Therefore, despite the fact that the enzymatic resolution approach is one step shorter, the overall yields of the two routes were comparable in the case of **2c**–**g**. However, the resolution method appears more attractive since it gives the products in higher ee and involves only two simple steps from the ketone without the use of hazardous chemicals.

4. Experimental

4.1. Chemicals and equipment

The α-fluoroacetophenones, **1a**–**h**,[24,25] and $[RuCl_2(mesitylene)]_2$,[47,48] were prepared as described previously. (*R*)-2-(4-Nitrophenyl)oxirane, (*S*,*S*)-TsDPEN and phthalimide were from Aldrich. 1-(4-Nitrophenyl)ethanone, 4-acetylbenzonitrile, DEAD (40% solution in toluene) and Silica 60 were from Fluka. Triphenylphosphine was from Sigma–Aldrich.

C. antarctica lipase B (Novozym 435), *C. antarctica* lipase A (Novozym 735) and *Rhizomucor miehei* lipase (Lipozyme RM-IM) were kind gifts from Novozymes. *Pseudomonas cepacia*, *Aspergillus niger*, *Aspergillus oryzae*, *Candida rugosa*, *C. rugosa IM*, *Thermomyces lanuginosa*, *P. fluorescens* were from Aldrich. The enzymatic resolutions were performed in an Infors-HT Minitron type AY70 incubator.

4.2. Analyses

^1H and ^{13}C NMR spectra were recorded with Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz, respectively. ^{19}F NMR was performed on a Bruker Avance 500 operating at 470 MHz. For ^1H and ^{13}C NMR chemical shifts are in parts per million rel to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. HPLC was performed using an Agilent 1100 series system with a DAD detector. GC was performed using a Varian 3380. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into the MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. CD spectra were recorded on an OLIS DSM 1000 spectrophotometer in a 1 cm cell, at concentration 0.01 mg/mL in MeCN.

The ee of the amines **2a**–**h** was determined as follows: compounds **2b** and **2h** were analysed as their trifluoroacetamides by HPLC using a Daicel Chiralcel OD-H column with detection at 230 nm. Compound **2b** (trifluoroacetamide): hexane/2-propanol (85/15), flow rate 1.0 mL/min, (*S*)-**2b**: 9.2 min, (*R*)-**2a**: 13.0 min. Compound **2h** (trifluoroacetamide): hexane/2-propanol (90/10), flow rate 1.0 mL/min, (*S*)-**2h**: 12.4 min, (*R*)-**2a**: 16.8 min. Compounds **2a** and **2c**–**g** were analysed derivatised as their acetamides on GC using a CP-Chirasil-Dex CB column at 10 psi. Isothermal programs were used in each case. Compounds **2a** and **2g**: 160 °C, (*R*)-**2a**: 21.1 min, (*S*)-**2a**: 21.8 min, (*R*)-**2g**: 41.0 min, (*S*)-**2g**: 42.1 min, **2c**: 125 °C, (*R*)-**2c**: 26.5 min, (*S*)-**2c**: 28.9 min, **2d**: 135 °C, (*R*)-**2d**: 19.6 min, (*S*)-**2d**: 21.3 min, **2e**: 150 °C, (*R*)-**2e**: 38.5 min, (*S*)-**2e**: 40.9 min, **2f**: 140 °C, (*R*)-**2f**: 16.5 min, (*S*)-**2f**: 18.2 min.

The ee of the methoxyacetamides **3a**–**h** was determined as follows: compounds **3a** and **3c**–**f** were analysed on GC using a CP-Chirasil-Dex CB column at 10 psi. Isothermal programs were used in each case. Compound **3a**: 160 °C, (*R*)-**3a**: 24.8 min, (*S*)-**3a**: 25.8 min, **3c**: 125 °C, (*R*)-**3c**: 38.0 min, (*S*)-**3c**: 40.0 min, **3d**: 135 °C, (*R*)-**3d**: 26.0 min, (*S*)-**3d**: 27.1 min, **3e**: 150 °C, (*R*)-**3e**: 49.0 min, (*S*)-**3e**: 51.5 min, **3f**: 140 °C, (*R*)-**3f**: 19.5 min, (*S*)-**3f**: 20.9 min. Compound **3b** was analysed by HPLC using a Daicel Chiralcel OD-H column, eluting with hexane/2-propanol (90/10), flow rate 1.0 mL/min, detection at 230 nm: (*S*)-**3b**: 31.7 min, (*R*)-**3b**: 38.5 min. Compounds **3g**–**h**: analysed by an Astec Chirobiotic V2 column, 5 μm, 4.6×250 mm (Supelco, Pennsylvania, USA) for **3g** eluting with hexane/EtOH (concn 0.5% TFA), 91/9, flow rate: 1.0 mL/min, detection at 230 nm, (*S*)-**3g**: 47.7 min, (*R*)-**3g**: 49.2 min and for **3h** eluting with hexane/EtOH (concn 0.5% TFA), 98/2, flow rate: 3.0 mL/min, detection at 230 nm, (*R*)-**3g**: 50.1 min and (*S*)-**3h**: 53.8 min.

The ee of the alcohols (*S*)-**4a**–**h** was determined by HPLC analysis using a Daicel Chiralcel OD column (0.46 cm×25 cm) with mobile phase: hexane/2-propanol (98/2) at a flow rate of 1.0 mL/min.[49]

The ee of **5a**–**c** and **5e**–**h** was determined by HPLC using a Daicel Chiralcel OD-H column with detection at 270 nm. Compounds **5a**, **5e** and **5f**: eluent: hexane/2-propanol (90/10), flow rate 1.0 mL/min, (*S*)-**5a**: 11.2 min, (*R*)-**5a**: 12.6 min, (*R*)-**5e**: 8.9 min, (*S*)-**5e**: 10.1 min, (*R*)-**5f**: 7.5 min, (*S*)-**5f**: 8.1 min. Compound **5b**: eluent: hexane/2-propanol (99/1), flow rate: 1.0 mL/min, (*S*)-**5b**: 33.5 min, (*R*)-**5b**: 36.2 min. Compound **5c**: eluent: hexane/2-propanol (98/2), flow rate 1.0 mL/min, (*R*)-**5c**: 11.3 min, (*S*)-**5c**: 14.0 min. Compound **5g**: eluent: hexane/2-propanol (90/10), flow rate 1.2 mL/min, (*R*)-**5g**: 22.7 min, (*S*)-**5g**: 26.5 min. Compound **5h**: eluent: hexane/isopropanol (95/5), flow rate 1.0 mL/min, (*R*)-**5h**: 26.9 min, (*S*)-**5h**: 29.8 min.

4.3. General procedures

*4.3.1. Preparation of **2a**–**h**.* The following procedure is representative:

1-(4-Bromophenyl)-2-fluoroethanone (**1e**) (4.36 g, 20.1 mmol) and titanium isopropoxide (12.0 mL, 40.0 mmol) were dissolved in an ethanol/ammonia solution (2 M, 50 mL) and stirred under argon atmosphere at room temperature for 24 h. Upon full conversion as detected by ^1H NMR spectroscopy, $NaBH_4$ (1.13 g, 30.30 mmol) was

added, and the reaction mixture was stirred under argon atmosphere at room temperature for 24 h. The reaction mixture was made acidic (pH=2) using HCl (6 M), and washed with *tert*-butyl methyl ether (TBME) (3×20 mL). The mixture was made alkaline with NaOH pellets (pH=10), saturated with sodium chloride and extracted with TBME (5×30 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification using silica-gel column chromatography (EtOAc/MeOH, 4/1, R_f 0.45), gave 3.11 g (14.3 mmol, 71%) of a colourless oil.

4.3.2. Small-scale enzymatic resolution. The racemic 1-aryl-2-fluoroethylamines, **2a**–**h**, (0.04 mmol), ethyl methoxyacetate (1–4 mol equiv) and Novozym 435 (1 equiv wt) were mixed in the specified solvent (3 mL) and agitated in an incubator at 300 rpm at the specified temperature. Samples (150 μL) were withdrawn after 1, 2 and 6 h. The samples were analysed for ee of the product and remaining substrate. The water content of hexane was varied by equilibrating on the presence of saturated salt solutions: $MgCl_2 \cdot 7H_2O$ (a_w=0.33), LiCl (a_w=0.12) and dried over molecular sieves 4 Å (a_w=~0).[50]

4.3.3. Preparative scale enzymatic resolution. The racemic amines **2b**–**g** (2.5 mmol), ethyl methoxyacetate (295 mg, 2.5 mmol) and Novozym 435 (1 equiv wt) were diluted with dry hexane (12 mL) and stirred in an incubator at 300 rpm at 60 °C. When 50% conversion was reached, the reaction mixture was diluted with TBME (20 mL) and extracted with water containing acetic acid (1 M, 5×15 mL). The combined water phases were washed with TBME (2×15 mL). The organic phase was dried over Na_2SO_4, and the solvent evaporated under reduced pressure, yielding the methoxyacetamides (*S*)-**3b**–**g**, which were purified by silica-gel column chromatography (EtOAc/MeOH, 4/1). The water phase was made alkaline with NaOH (pellets), saturated with sodium chloride and extracted with TBME (5×15 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure, yielding the amines (*R*)-**2b**–**g**, which were purified by silica-gel column chromatography (EtOAc/MeOH, 4/1).

*4.3.4. Asymmetric transfer hydrogenation[28] of **1a**–**e** and **1g**–**h**.* A suspension of the $[RuCl_2(\text{mesitylene})]_2$ (23 mg, 0.04 mmol) and (*S*,*S*)-TsDPEN (44 mg, 0.12 mmol) in CH_2Cl_2 (8 mL) were stirred at 20 °C for 30 min. After removal of CH_2Cl_2, the α-fluoroacetophenone (4.0 mmol) in a mixture of HCO_2H/Et_3N (5/2 mol ratio, 10 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified number of hours before it was quenched with water (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The organic phase was then washed with brine (20 mL) and dried over Na_2SO_4 before the solvent was removed under reduced pressure. Purification is described for each individual compound.

*4.3.5. Mitsunobu inversion (S)-**5a**–**h** from (R)-**4a**–**h**.* Under an N_2-atmosphere PPh_3 (859 mg, 3.3 mmol) and phthalimide (487 mg, 3.3 mmol) were dissolved in THF (20 mL). To this mixture was added the 1-aryl-2-fluoroethanol, (*R*)-**4a**–**h**, (3.0 mmol) dissolved in THF (5 mL), followed by the DEAD solution (40% in toluene, 1.36 mL, 3.6 mmol). The mixture was stirred overnight at room temperature, before the solvent was removed under reduced pressure. The reaction mixture was then re-dissolved in CH_2Cl_2 (2 mL), K_2CO_3 (0.02 M, 10 mL) added and the mixture stirred for 1 h. The mixture was extracted with CH_2Cl_2 (3×15 mL) and the organic phase washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography.

*4.3.6. Hydrazinolysis of (S)-**5a**–**h**.* The *N*-substituted phthalimides **5a**–**h** (2.5 mmol) were dissolved in MeOH (40 mL) and N_2H_4 (1.0 M in THF, 25 mmol) was added. The mixture was stirred at room temperature until all the starting material had been consumed (TLC) (2–10 h.). Then HCl (2 M, 10 mL) was added and the reaction was stirred at room temperature overnight. Water (40 mL) was added and the mixture extracted with Et_2O (50 mL). The water phase was made alkaline with NaOH (2 M, 30 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The products, (*S*)-**1a**–**h** were purified by silica-gel column chromatography (EtOAc/MeOH, 9/1).

4.4. Racemic 1-aryl-2-fluoroethylamines (2a–h)

*4.4.1. 2-Fluoro-1-(4-methoxyphenyl)ethylamine (**2a**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-methoxyphenyl)ethanone (**1a**) (2.18 g 12.94 mmol). This gave 1.96 g (11.58 mmol, 89%) of a colourless oil. R_f (EtOAc/MeOH, 4/1) 0.47. ^{1}H NMR ($CDCl_3$) δ: 1.70 (s, 2H, $-NH_2$), 3.80 (s, 3H, $-OCH_3$), 4.22–4.53 (m, 3H, $-CHCH_2F$), 6.89 (m, 2H, $-C_6H_4-$), 7.30 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.0 (d, *J*=19.4), 55.6, 88.3 (d, *J*=174.5), 114.1 (2C), 128.0 (2C), 132.2 (d, *J*=8.5), 159.2. ^{19}F NMR ($CDCl_3$) δ: −219.15 (m). IR (neat, cm^{-1}): 3381, 3315, 2954, 2904, 2838, 1611, 1513, 1463, 1249, 1179, 1032, 995, 833. HRMS (ESI): 169.0907 (calcd 169.0903, [M+]).

*4.4.2. 1-(4-(Benzyloxy)phenyl)-2-fluoroethylamine (**2b**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 1-(4-benzyloxyphenyl)-2-fluoroethanone (**1b**) (0.76 g, 3.10 mmol). This gave 0.64 g (2.61 mmol, 84%) of a white solid, mp 42–43 °C, R_f (EtOAc/MeOH, 4/1) 0.45. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 2H, $-NH_2$), 4.22–4.54 (m, 3H, $-CHCH_2F$), 5.07 (s, 2H, CH_2Ph), 6.97 (m, 2H, $-C_6H_4-$), 7.29 (m, 2H, $-C_6H_4-$), 7.30–7.34 (m, 5H, $-C_6H_5$). ^{13}C NMR ($CDCl_3$) δ: 55.0 (d, *J*=19.0), 70.0, 88.3 (d, *J*=174.5), 115.0 (2C), 127.0, 127.4 (2C), 128.0 (2C), 128.5 (2C), 132.5 (d, *J*=8.5), 136.9, 158.5. ^{19}F NMR ($CDCl_3$) δ: −219.20 (m). IR (KBr, cm^{-1}): 3381, 3279, 3033, 2947, 2872, 1611, 1513, 1242, 1174, 1014, 839, 745, 697. HRMS (ESI): 245.1215 (calcd 245.1216, [M^+]).

*4.4.3. 2-Fluoro-1-phenylethylamine (**2c**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-phenylethanone (**1c**) (0.49 g, 3.55 mmol). This gave 0.46 g (3.28 mmol, 92%) of a colourless oil, R_f (EtOAc/MeOH, 4/1) 0.46. ^{1}H NMR ($CDCl_3$) δ: 1.72 (s, 2H, $-NH_2$), 4.28–4.57 (m, 3H, $-CHCH_2F$), 7.23 (m, 2H, Ph), 7.37 (m, 2H, Ph), 7.36 (m, 1H, Ph). ^{13}C NMR ($CDCl_3$) δ: 55.6 (d, *J*=19.4), 88.2 (d, *J*=174.1), 126.9 (2C), 127.9, 128.6 (2C), 140.2 (d, *J*=8.1). ^{19}F NMR ($CDCl_3$) δ: −219.85 (m). IR (neat, cm^{-1}): 3384, 3314, 3063, 3030, 2950, 2890, 1604, 1493, 1454, 997, 861, 760, 701. HRMS (ESI): 139.0799 (calcd 139.0797, [M^+]).

*4.4.4. 2-Fluoro-1-(4-fluorophenyl)ethylamine (**2d**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-fluorophenyl)ethanone (**1d**) (0.41 g, 2.61 mmol). This gave 0.39 g (2.48 mmol, 95%) of a colourless oil. R_f (EtOAc/MeOH, 4/1) 0.46. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 2H, $-NH_2$), 4.25–4.50 (m, 3H, $-CHCH_2F$), 7.04 (m, 2H, $-C_6H_4-$), 7.35 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.0 (d, *J*=19.4), 88.0 (dd, *J*=174.5, 1.4), 115.4 (d, *J*=21.2, 2C), 128.5 (dd, *J*=8.1, 0.7, 2C), 135.9 (dd, *J*=8.1, 2.8), 162.3 (d, *J*=246.2). ^{19}F NMR ($CDCl_3$) δ: −115.14 (m), −219.87 (m.). IR (neat, cm^{-1}): 3388, 3321, 3044, 2952, 2891, 1734, 1605, 1510, 1229, 1158, 1093, 1003, 846. HRMS (ESI): 157.0706 (calcd 157.0703, [M^+]).

*4.4.5. 1-(4-Bromophenyl)-2-fluoroethylamine (**2e**).* The synthesis is described in Section 4.3.1. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 2H, $-NH_2$), 4.22–4.52 (m, 3H, −CHCH2F), 7.27 (m, 2H, $-C_6H_4-$), 7.47 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.1 (d, *J*=19.8), 87.8 (d, *J*=174.5), 121.7, 128.6 (d, *J*=0.7, 2C), 131.7 (2C), 139.3 (d, *J*=7.8). ^{19}F NMR

($CDCl_3$) δ: −220.34 (m). IR (neat, cm^{-1}): 3383, 3330, 2950, 2890, 1590, 1488, 1406, 1073, 1004, 830. HRMS (ESI): 216.9904 (calcd 216.9902, [(^{79}Br)M^+]).

*4.4.6. 2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethylamine (**2f**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-(trifluoromethyl)phenyl)ethanone (**1f**) (0.91 g, 4.40 mmol). This gave 0.62 g (2.99 mmol, 68%) of a colourless oil, R_f (EtOAc/MeOH, 4/1) 0.49. ^{1}H NMR ($CDCl_3$) δ: 1.71 (s, 2H, $-NH_2$), 4.27–4.56 (m, 3H, $-CHCH_2F$), 7.52 (m, 2H, $-C_6H_4-$), 7.57 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.4 (d, J=19.8), 87.7 (d, J=175.2), 124.0 (q, J=272.0), 125.5 (q, J=3.8, 2C), 127.3 (d, J=0.7, 2C), 130.1 (q, J=32.5), 144.4 (dq, J=7.6, 1.3). ^{19}F NMR ($CDCl_3$) δ: −63.18 (s, 3F), −221.06 (m). IR (neat, cm^{-1}): 3392, 3330, 2954, 2895, 1621, 1420, 1326, 1160, 1120, 1068, 1017, 842, 606. HRMS (ESI): 207.0668 (calcd 207.0671, [M^+]).

*4.4.7. 4-(1-Amino-2-fluoroethyl)benzonitrile (**2g**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 1-(4-cyanophenyl)-2-fluoroethanone (**1g**) (1.03 g, 6.34 mmol). This gave 0.84 g (5.13 mmol, 81%) of a white solid, mp 48–49 °C, R_f (EtOAc/MeOH, 4/1) 0.42. ^{1}H NMR ($CDCl_3$) δ: 1.70 (s, 2H, $-NH_2$), 4.27–4.55 (m, 3H, $-CHCH_2F$), 7.53 (m, 2H, $-C_6H_4-$), 7.65 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.4 (d, J=19.8), 87.3 (d, J=175.6), 111.8, 118.6, 127.8 (d, J=0.7, 2C), 132.4 (2C), 145.8 (d, J=7.0). ^{19}F NMR ($CDCl_3$) δ: −221.61 (m). IR (KBr, cm^{-1}): 3381, 3317, 2954, 2863, 2227, 1609, 1502, 1412, 1359, 1099, 1050, 992, 832, 564. HRMS (ESI): 164.0750 (calcd 164.0750, [M^+]).

*4.4.8. 2-Fluoro-1-(4-nitrophenyl)ethylamine (**2h**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-nitrophenyl)ethanone (**1h**) (1.15 g, 6.26 mmol). This gave 0.91 g (4.95 mmol, 79%) of a white solid, mp 52–53 °C, R_f (EtOAc/MeOH, 4/1) 0.40. ^{1}H NMR ($CDCl_3$) δ: 1.72 (br s, 2H, $-NH_2$), 4.28–4.60 (m, 3H, $CHCH_2F$), 7.58–7.62 (m, 2H, $-C_6H_4-$), 8.21–8.24 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.3 (d, J=20.1), 87.3 (d, J=175.6), 123.8 (2C), 128.0 (d, J=0.7, 2C), 147.7, 147.8, (d, J=7.1). ^{19}F NMR ($CDCl_3$) δ: −221.78 (m). IR (neat, cm^{-1}): 3379, 3113, 2952, 2852, 1599, 1510, 1346, 995, 855. HRMS (ESI): 185.0726 (calcd 185.0726, [M+H^+]).

4.5. (*R*)-1-Aryl-2-fluoroethylamines ((*R*)-2a–g)

Compounds (*R*)-**2a**–**h** were obtained by lipase-catalysed resolution as described in Section 4.3.3. The NMR spectroscopic properties corresponded with that reported for the corresponding racemates.

*4.5.1. (R)-2-Fluoro-1-(4-methoxyphenyl)ethylamine ((R)-**2a**).* The resolution was performed as described in Section 4.3.3, starting with **2a** (423 mg, 2.50 mmol), but with hexane (24 mL) and Novozym 435 (846 mg). Reaction time was 24 h. This gave after silica-gel column chromatography 180 mg (1.06 mmol, 43%) of (*R*)-**2a** as a colourless oil, ee=97.0%, $[\alpha]_D^{20}$ −37.4 (*c* 0.55, $CHCl_3$).

*4.5.2. (R)-1-(4-(Benzyloxy)phenyl)-2-fluoroethylamine ((S)-**2b**).* The resolution was performed as described in Section 4.3.3, starting with **2b** (613 mg, 2.50 mmol). Reaction time was 24 h. This gave after silica-gel column chromatography 211 mg (0.86 mmol, 34%) of (*R*)-**2b** as a white solid, mp 41.5–42 °C, ee=96.0%, $[\alpha]_D^{20}$ −29.1 (*c* 0.50, $CHCl_3$).

*4.5.3. (R)-2-Fluoro-1-phenylethylamine ((R)-**2c**)*[7]. The resolution was performed as described in Section 4.3.3, starting with **2c** (348 mg, 2.50 mmol). Reaction time was 24 h. This gave after silica-gel column chromatography 126 mg (0.91 mmol, 36%) of (*R*)-**2c** as colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −40.5 (*c* 0.60, $CHCl_3$).

*4.5.4. (R)-Fluoro-1-(4-fluorophenyl)ethylamine ((R)-**2d**).* The resolution was performed as described in Section 4.3.3, starting with **2d** (393 mg, 2.49 mmol). Reaction time was 6 h. This gave after silica-gel column chromatography 169 mg (1.08 mmol, 43%) of (*R*)-**2d** as a colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −39.7 (*c* 0.71, $CHCl_3$).

*4.5.5. (R)-1-(4-Bromophenyl)-2-fluoroethylamine ((R)-**2e**).* The resolution was performed as described in Section 4.3.3, starting with **2e** (545 mg, 2.50 mmol). Reaction time was 6 h. This gave after silica-gel column chromatography 213 mg (0.98 mmol, 39%) of (*R*)-**2e** as a colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −28.5 (*c* 0.68, $CHCl_3$).

*4.5.6. (R)-2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethylamine ((R)-**2f**).* The resolution was performed as described in Section 4.3.3, starting with **2f** (518 mg, 2.50 mmol). Reaction time was 6 h. This gave after silica-gel column chromatography 195 mg (0.94 mmol, 38%) of (*R*)-**2f** as a colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −27.4 (*c* 0.61, $CHCl_3$).

*4.5.7. (R)-4-(1-Amino-2-fluoroethyl)benzonitrile ((R)-**2g**).* The resolution was performed as described in Section 4.3.3, starting with **2g** (411 mg, 2.50 mmol). Reaction time was 24 h. This gave after silica-gel column chromatography 150 mg (0.91 mmol, 37%) of (*R*)-**2g** as a white solid, mp 46.5–47.0 °C, ee=99.0%, $[\alpha]_D^{20}$ −32.0 (*c* 0.56, $CHCl_3$).

*4.5.8. (R)-2-Fluoro-1-(4-nitrophenyl)ethylamine ((R)-**2h**).* The resolution was performed as described in Section 4.3.3, starting with **2h** (460 mg, 2.50 mmol), but with toluene (12 mL) as solvent. Reaction time was 48 h. This gave after silica-gel column chromatography 200 mg (1.09 mmol, 43%) of (*R*)-**2h** as a pale yellow solid, mp 53.0–53.5 °C, ee >99.5%, $[\alpha]_D^{20}$ −20.1 (*c* 0.71, $CHCl_3$).

4.6. (*S*)-1-Aryl-2-fluoroethylamines ((*S*)-2a–h)

Compounds (*S*)-**2a**–**h** were obtained from the alcohols (*R*)-**4a**–**h** by the Mitsunobu inversion described in Sections 4.3.4–4.3.6. The NMR spectroscopic properties corresponded with that reported for the corresponding racemate.

*4.6.1. (S)-2-Fluoro-1-(4-methoxyphenyl)ethylamine ((S)-**2a**)*[10]. The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5a** (200 mg, 0.67 mmol). This gave 83 mg (0.49 mmol, 73%) of (*S*)-**2a** as a pale yellow oil, ee=53.5%, $[\alpha]_D^{20}$ +20.9 (*c* 0.54, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.37.

The hydrochloride salt of (*S*)-**2a** was obtained by treatment with HCl saturated ether (5 mL) under stirring for 20 min. The solvent was then evaporated under reduced pressure and the product isolated as a white powder, which decomposed on melting. The ^{1}H NMR data corresponded with that reported.[10] ^{1}H NMR (CD_3OD) δ: 3.82 (s, 3H, $-OCH_3$), 4.59–4.69 (m, 2H, $-CH_2F$), 4.81–8.83 (m, 1H, $-CHCH_2F$), 7.00–7.05 (m, 2H, $-C_6H_4-$), 7.38–7.43 (m, 2H, $-C_6H_4-$). $[\alpha]_D^{20}$ +17.7 (*c* 0.66, MeOH), lit.[10] +31.5 (*c* 0.66, MeOH).

*4.6.2. (S)-1-(4-(Benzyloxy)phenyl)-2-fluoroethylamine ((S)-**2b**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5b** (205 mg, 0.55 mmol). This gave 97 mg (0.40 mmol, 72%) of (*S*)-**2b** as a white solid, mp 42–43 °C, ee=60.0%, $[\alpha]_D^{20}$ +16.0 (*c* 0.52, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

*4.6.3. (S)-2-Fluoro-1-phenylethylamine ((S)-**2c**)*[9–11]. The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5c** (672 mg, 2.50 mmol). This gave 228 mg (1.64 mmol, 66%) of

(*S*)-**2c** as a colourless oil, ee=98.5%, $[\alpha]_D^{20}$ +44.0 (*c* 0.60, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

The hydrochloride salt of (*S*)-**2c** was obtained by treatment with HCl saturated ether (5 mL) under stirring for 20 min. The solvent was then evaporated under reduced pressure and the product isolated as a white powder, which decomposed on melting. The ^{1}H NMR data corresponded with that reported.[10] ^{1}H NMR (CD_3OD) δ: 4,67–4.76 (m, 2H, $-CH_2F$), 4.84 (m, 1H, $-CHCH_2F$), 7.48–7.51 (m, 5H, Ph). $[\alpha]_D^{20}$ +29.4 (*c* 0.53, MeOH), lit.[10] +29.1 (*c* 0.57, MeOH).

*4.6.4. (S)-2-Fluoro-1-(4-fluorophenyl)ethylamine ((S)-**2d**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5d** (760 mg, 2.65 mmol). This gave 311 mg (1.98 mmol, 75%) of (*S*)-**2c** as a pale yellow oil, ee=92.5%, $[\alpha]_D^{20}$ +36.4 (*c* 0.67, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.43.

*4.6.5. (S)-1-(4-Bromophenyl)-2-fluoroethylamine ((S)-**2e**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5e** (836 mg, 2.40 mmol). This gave 436 mg (2.00 mmol, 83%) of (*S*)-**2e** as a pale yellow oil, which solidified at 0 °C, ee=90.5%, $[\alpha]_D^{20}$ +27.4 (*c* 0.66, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

*4.6.6. (S)-2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethylamine ((S)-**2f**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5f** (840 mg, 2.49 mmol). This gave 366 mg (1.77 mmol, 71%) of (*S*)-**2f** as a colourless oil, ee=91.5%, $[\alpha]_D^{20}$ +25.7 (*c* 0.61, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.45.

*4.6.7. (S)-4-(1-Amino-2-fluoroethyl)benzonitrile ((S)-**2g**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5g** (609 mg, 2.07 mmol). This gave 256 mg (1.56 mmol, 75%) of (*S*)-**2g** as a solid, mp 47–49 °C, ee=87.5%, $[\alpha]_D^{20}$ +28.5 (*c* 0.54, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

*4.6.8. (S)-2-Fluoro-1-(4-nitrophenyl)ethylamine ((S)-**2h**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5h** (310 mg, 0.99 mmol). This gave 145 mg (0.79 mmol, 80%) of (*S*)-**2h** as a white solid, mp 52–53 °C, ee=84.0%, $[\alpha]_D^{20}$ +15.9 (*c* 0.69 $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.34.

4.7. (*S*)-*N*-(2-Fluoro-1-arylethyl)-2-methoxyacetamides ((*S*)-3a–h)

*4.7.1. (S)-N-(2-Fluoro-1-(4-methoxyphenyl)ethyl)-2-methoxyacetamide ((S)-**3a**).* The compound was prepared as described in Section 4.3.3. This gave 210 mg (0.87 mmol, 35%) of a white solid, mp 94–95 °C, ee >99.5%, $[\alpha]_D^{20}$ +77.1 (*c* 0.58, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.63. ^{1}H NMR ($CDCl_3$) δ: 3.43 (s, 3H, $-CH_2OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.92 (d, *J*=15.1, 1H, $-CH_2O-$), 3.95 (d, *J*=15.1, 1H, $-CH_2O-$), 4.63 (ddd, *J*=47.5, 9.5, 4.3, $-CH_2F$), 4.67 (ddd, *J*=47.5, 9.5, 4.8, $-CH_2F$), 5.27 (m, 1H, $-CHCH_2F$), 6.88–6.92 (m, 2H, $-C_6H_4-$), 7.04 (d, *J*=7.7, 1H, $-NH-$), 7.25–7.30 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 51.8 (d, *J*=19.4), 55.3, 59.1, 71.9, 84.7 (d, *J*=175.7), 114.2 (2C), 128.2 (d, *J*=1.2, 2C), 129.6 (d, *J*=3.4), 159.4, 169.1. ^{19}F NMR ($CDCl_3$) δ: −229.56 (td, *J*=47.2, 23.8). IR (neat, cm^{-1}): 3319, 1655, 1518, 1367, 1207, 1111, 1005, 833, 586. HRMS (ESI): 241.1122 (calcd 241.1114, $[M^+]$).

*4.7.2. (S)-N-(1-(4-(Benzyloxy)phenyl)-2-fluoroethyl)-2-methoxyacetamide ((S)-**3b**).* The compound was prepared as described in Section 4.3.3. This gave 246 mg (0.77 mmol, 31%) of a white solid, mp 109–110 °C, ee >99.5%, $[\alpha]_D^{20}$ +66.5 (*c* 0.53, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.66. ^{1}H NMR ($CDCl_3$) δ: 3.43 (s, 3H, $-CH_2OCH_3$), 3.92 (d, *J*=15.1, 1H, $-CH_2O-$), 3.94 (d, *J*=15.1, 1H, $-CH_2O-$), 4.63 (ddd, *J*=47.5, 9.5, 4.8, 1H, $-CH_2F$), 4.67 (ddd, *J*=47.5, 9.5, 4.3, 1H, $-CH_2F$), 5.01 (s, 2H, $-OCH_2Ph$), 5.26 (m, 1H, $-CHCH_2F$), 6.95–6.99 (m, 2H, $-C_6H_4$), 7.00 (d, *J*=7.9, 1H, $-NH$), 7.25–7.29 (m, 2H, $-C_6H_4$), 7.30–7.44 (m, 5H, $-CH_2-C_6H_5$). ^{13}C NMR ($CDCl_3$) δ: 51.8 (d, *J*=19.3), 59.1, 70.0, 71.9, 84.7 (d, *J*=175.8), 115.1 (2C), 127.4 (2C), 128.0, 128.2 (d, *J*=1.1, 2C), 128.6 (2C), 129.9 (d, *J*=3.4), 136.8, 158.6, 169.1. ^{19}F NMR ($CDCl_3$) δ: −229.60 (td, *J*=47.3, 24.0). IR (neat, cm^{-1}): 3294, 1650, 1532, 1116, 1003, 829, 542. HRMS (ESI): 317.1430 (calcd 317.1427, $[M^+]$).

*4.7.3. (S)-N-(2-Fluoro-1-phenylethyl)-2-methoxyacetamide ((S)-**3c**).* The compound was prepared as described in Section 4.3.3. This gave 170 mg (0.80 mmol, 32%) of a white solid, mp 111–112 °C, ee >99.5%, $[\alpha]_D^{20}$ +58.4 (*c* 0.46, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.62. ^{1}H NMR ($CDCl_3$) δ: 3.44 (s, 3H, $-CH_2OCH_3$), 3.94 (d, *J*=15.1, 1H, $-CH_2O-$), 3.96 (d, *J*=15.1, 1H, $-CH_2O-$), 4.66 (ddd, *J*=47.5, 9.5, 4.7, 1H, $-CH_2F$), 4.70 (ddd, *J*=47.5, 9.5, 4.3, 1H, $-CH_2F$), 5.32 (m, 1H, $-CHCH_2F$), 7.12 (d, *J*=5.1, 1H, $-NH-$), 7.29–7.41 (m, 5H, $-C_6H_5$). ^{13}C NMR ($CDCl_3$) δ: 52.3 (d, *J*=19.2), 59.2, 71.9, 84.7 (d, *J*=175.9), 126.9 (d, *J*=1.1, 2C), 128.1, 128.8 (2C), 137.5 (d, *J*=3.4), 169.2. ^{19}F NMR ($CDCl_3$) δ: −229.87 (td, *J*=47.7, 24.3). IR (neat, cm^{-1}): 3301, 1650, 1532, 1371, 1217, 1117, 1005, 847, 588. HRMS (ESI): 211.1015 (calcd 211.1009, $[M^+]$).

*4.7.4. (S)-N-(2-Fluoro-1-(4-fluorophenyl)ethyl)-2-methoxyacetamide ((S)-**3d**).* The compound was prepared as described in Section 4.3.3. Purification gave 228 mg (0.99 mmol, 40%) of a white solid, mp 79–80 °C, ee >99.5%, $[\alpha]_D^{20}$ +61.1 (*c* 0.5, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.65. ^{1}H NMR ($CDCl_3$) δ: 3.44 (s, 3H, $-CH_2OCH_3$), 3.93 (d, *J*=15.1, 1H, $-CH_2O-$), 3.95 (d, *J*=15.1, 1H, $-CH_2O-$), 4.64 (ddd, *J*=47.5, 9.5, 4.6, 1H, $-CH_2F$), 4.69 (ddd, *J*=47.5, 9.5, 4.1, 1H $-CH_2F$), 5.29 (m, , 1H, $-CHCH_2F$), 7.03–7.09 (m, 2H, $-C_6H_4-$), 7.10 (d, *J*=7.1, 1H, $-NH-$), 7.31–7.36 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 51.7 (d, *J*=19.3), 59.2, 71.8, 84.6 (d, *J*=175.9), 115.7 (d, *J*=21.6, 2C), 128.7 (dd, *J*=1.2, 8.2, 2C), 133.4 (d, *J*=3.2), 162.4 (d, *J*=246.5), 169.1. ^{19}F NMR ($CDCl_3$) δ: −230.38 (td, *J*=47.6, 25.4), −117.17 (s). IR (neat, cm^{-1}): 3308, 1656, 1511, 1217, 1112, 984, 834, 604. HRMS (ESI): 229.0917 (calcd 229.0914, $[M^+]$).

*4.7.5. (S)-N-(1-(4-Bromophenyl)-2-fluoroethyl)-2-methoxyacetamide ((S)-**3e**).* The compound was prepared as described in Section 4.4.3. Purification gave 305 mg (1.05 mmol, 42%) of a white solid, mp 111–112 °C, ee >99.5%, $[\alpha]_D^{20}$ +63.9 (*c* 0.57, $CHCl_3$). R_f (EtOAc/MeOH, 4/1) 0.66. ^{1}H NMR ($CDCl_3$) δ: 3.44 (s, 3H, $-CH_2OCH_3$), 3.93 (d, *J*=15.2, 1H, $-CH_2O-$), 3.96 (d, *J*=15.2, 1H, $-CH_2O-$), 4.64 (ddd, *J*=47.5, 9.5, 4.5, 1H, $-CH_2F$), 4.68 (ddd, *J*=47.5, 9.5, 4.3, 1H, $-CH_2F$), 5.26 (m, 1H, $-CHCH_2F$), 7.12 (d, *J*=7.5, 1H, $-NH-$), 7.21–7.25 (m, 2H, $-C_6H_4-$), 7.48–7.52 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 52.0 (d, *J*=19.1), 59.2, 71.8, 84.5 (d, *J*=176.3), 122.1, 128.7 (d, *J*=1.1, 2C), 132.0 (2C), 136.7 (d, *J*=3.2), 169.2. ^{19}F NMR ($CDCl_3$) δ: −230.60 (td, *J*=47.2, 25.8). IR (neat, cm^{-1}): 3290, 1653, 1527, 1368, 1228, 1112, 1008, 821, 594. HRMS (ESI): 289.0111 (calcd 289.0114, $[M^+]$).

*4.7.6. (S)-N-(2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethyl)-2-methoxyacetamide ((S)-**3f**).* The compound was prepared as described in Section 4.4.3. Purification gave 245 mg (0.87 mmol, 35%) of a white solid, mp 108–109 °C, ee >99.5%, $[\alpha]_D^{20}$ +47.5 (*c* 0.58, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.66. ^{1}H NMR ($CDCl_3$) δ: 3.46 (s, 3H, $-CH_2OCH_3$), 3.94 (d, *J*=15.2, 1H, $-CH_2O-$), 3.97 (d, *J*=15.2, 1H, $-CH_2O-$), 4.68 (ddd, *J*=47.5, 9.6, 4.3, 1H, $-CH_2F$), 4.73 (ddd, *J*=47.5, 9.6, 4.0, 1H, $-CH_2F$), 5.35 (m, 1H, $-CHCH_2F$), 7.21 (d, *J*=7.2, 1H, $-NH-$), 7.43–7.50 (m, 2H, $-C_6H_4-$), 7.60–7.66 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 52.1 (d, *J*=19.0), 59.2, 71.8, 84.5 (d, *J*=176.2), 123.9 (q, *J*=272.1), 125.8 (q, *J*=3.8, 2C), 127.4 (d, *J*=1.2, 2C), 130.4 (q, *J*=32.6), 141.6 (m), 169.3. ^{19}F NMR ($CDCl_3$) δ: −230.98 (td, *J*=46.4, 28.3), −65.86 (s, 3F). IR (neat, cm^{-1}): 3292, 1658, 1532, 1375, 1228, 1116, 1011, 838, 606. HRMS (ESI): 279.0895 (calcd 279.0882, $[M^+]$).

*4.7.7. (S)-N-(1-(4-Cyanophenyl)-2-fluoroethyl)-2-methoxyacetamide ((S)-**3g**).* The compound was prepared as described in Section 4.4.3. Purification gave 249 mg (1.05 mmol, 42%) of a white solid, mp 76.5–77.0 °C, ee >99.5%, $[\alpha]_D^{20}$ +82.8 (*c* 0.53, $CHCl_3$), R_f

(EtOAc/MeOH, 4/1) 0.63. ^{1}H NMR ($CDCl_3$) δ: 3.46 (s, 3H, $-CH_2OCH_3$), 3.94 (d, J=15.3, 1H, $-CH_2O-$), 3.98 (d, J=15.3, 1H, $-CH_2O-$), 4.68 (ddd, J=47.4, 9.7, 4.1, 1H, $-CH_2F$), 4.72 (ddd, J=47.4, 9.7, 3.8, 1H, $-CH_2F$), 5.34 (m, 1H, $-CHCH_2F$), 7.24 (d, J=7.7, 1H, $-NH-$), 7.46–7.50 (m, 2H, $-C_6H_4-$), 7.65–7.69 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 59.2, 71.7, 84.4 (d, J=176.4), 112.1, 118.4, 127.8 (d, J=1.1, 2C), 132.6 (2C), 143.0 (d, J=3.0), 169.3. ^{19}F NMR ($CDCl_3$) δ: −231.46 (td, J=46.4, 27.9). IR (neat, cm^{-1}): 3310, 2232, 1655, 1532, 1372, 1226, 1117, 1014, 841, 563. HRMS (ESI): 236.0963 (calcd 236.0961, $[M^+]$).

*4.7.8. (S)-N-(2-Fluoro-1-(4-nitrophenyl)ethyl)-2-methoxyacetamide ((S)-**3h**).* The compound was prepared as described in Section 4.4.3. Purification by silica-gel column chromatography (EtOAc/MeOH, 4/1) gave 217 mg (0.90 mmol, 36%) of a white solid, mp 95.0–95.5 °C, ee >99.5%, $[\alpha]_D^{20}$ +70.8 (c=0.69, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.62. ^{1}H NMR ($CDCl_3$) δ: 3.47 (s, 3H, $-CH_2OCH_3$), 3.95 (d, J=15.3, 1H, $-CH_2O-$), 3.98 (d, J=15.3, 1H, $-CH_2O-$), 4.71 (ddd, J=47.4, 9.7, 4.0, 1H, $-CH_2F$), 4.75 (ddd, J=47.4, 9.7, 4.0, 1H, $-CH_2F$), 5.39 (m, 1H, $-CHCH_2F$), 7.28 (d, J=7.2, 1H, $-NH-$), 7.52–7.56 (m, 2H, $-C_6H_4-$), 8.21–8.26 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 52.1 (d, J=19.1), 59.3, 71.8, 84.4 (d, J=176.6), 124.0 (2C), 128.0 (d, J=1.0, 2C), 145.0 (d, J=2.8), 147.7, 169.4. ^{19}F NMR ($CDCl_3$) δ: −231.62 (td, J=46.4, 28.3). IR (neat, cm^{-1}): 3273, 2970, 1650, 1516, 1348, 1110, 1012, 851, 697. HRMS (ESI): 256.0860 (calcd 256.0859, $[M^+]$).

4.8. (*R*)-1-Aryl-2-fluoroethanols ((*R*)-4a–h)

In the course of this work, calculation errors in the optical rotations data for (*R*)-**4a**–**h** in our previous study were discovered.[49] Corrected values for these data are therefore included.

*4.8.1. (R)-2-Fluoro-1-(4-methoxyphenyl)ethanol ((R)-**4a**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-(4-methoxyphenyl)ethanone (**1a**) (673 mg, 4.00 mmol). Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.47) gave 515 mg (3.03 mmol, 76%) of a colourless oil, ee=96.0%, $[\alpha]_D^{20}$ −47.1 (c 0.69, $CHCl_3$), corr. ref. ee=99.5%, $[\alpha]_D^{20}$ −55.0 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.41 (br, 1H, −O*H*), 3.81 (s, 3H, $-OCH_3$), 4.38 (ddd, J=48.5, 9.5, 8.3, 1H, $-CH_2F$), 4.49 (ddd, J=46.8, 9.5, 3.3, 1H, $-CH_2F$), 4.97 (ddd, J=13.2, 8.3, 3.3, 1H, $-CHCH_2F$), 6.87–6.91 (m, 2H, $-C_6H_4-$), 7.29–7.33 (m, 2H, $-C_6H_4-$).

*4.8.2. (R)-1-(4-(Benzyloxy)phenyl)-2-fluoroethanol ((R)-**4b**)[49].* The reaction was performed as described in Section 4.3.4 starting with 1-(4-benzyloxyphenyl)-2-fluoroethanone (**1b**) (733 mg, 3.00 mmol). Purification by silica-gel chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.26) gave 450 mg (1.83 mmol, 61%) of a white solid, mp 70–71 °C, ee=99.5%, $[\alpha]_D^{20}$ −38.3 (c 0.59, $CHCl_3$), corr. ref. ee=97.0%, $[\alpha]_D^{20}$ −33.2 (c 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.39 (dd, J=2.9, 1.1, 1H, −O*H*), 4.40 (ddd, J=48.5, 9.5, 8.3, 1H, $-CH_2F$), 4.48 (ddd, J=46.8, 9.5, 3.4, 1H, $-CH_2F$), 4.97 (m, 1H, $-CHCH_2F$), 5.09 (s, 2H, $-OCH_2Ph$), 6.95–7.01 (m, 2H, $-C_6H_4-$), 7.30–7.47 (m, 7H, Ar).

*4.8.3. (R)-2-Fluoro-1-phenylethanol ((R)-**4c**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-phenylethanone (**1c**) (553 mg, 4.00 mmol). Purification by bulb-to-bulb distillation (35–40 °C at 5.0×10^{-3} mbar) gave 480 mg (3.42 mmol, 86%) of a colourless oil, ee=98.0%, $[\alpha]_D^{20}$ −56.8 (c 1.20, $CHCl_3$), corr. ref. ee=96.5%, $[\alpha]_D^{20}$ −53.7 (c 1.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.51 (br, 1H, −O*H*), 4.40 (ddd, J=48.5, 9.5, 8.3, 1H, $-CH_2F$), 4.51 (ddd, J=46.8, 9.5, 3.3, 1H, $-CH_2F$), 5.04 (ddd, J=14.0, 8.3, 3.3, 1H, $-CHCH_2F$), 7.33–7.36 (m, 5H, $-C_6H_5$).

*4.8.4. (R)-2-Fluoro-1-(4-fluorophenyl)ethanol ((R)-**4d**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-(4-fluorophenyl)ethanone (**1d**) (752 mg, 4.82 mmol). Purification by bulb-to-bulb distillation (35–40 °C at 3.0×10^{-3} mbar) gave 603 mg (3.81 mmol, 79%) of a colourless oil, ee=93.0%, $[\alpha]_D^{20}$ −51.9 (c 0.59, $CHCl_3$), corr. ref. ee=99.0%, $[\alpha]_D^{20}$ −60.8 (c 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.63 (br, 1H, −O*H*), 4.37 (ddd, J=48.4, 9.6, 8.2, 1H, $-CH_2F$), 4.48 (ddd, J=46.7, 9.6, 3.3, 1H, $-CH_2F$), 5.03 (ddd, J=13.9, 8.2, 3.3, 1H, $-CHCH_2F$), 7.01–7.08 (m, 2H, $-C_6H_4-$), 7.32–7.36 (m, 2H, $-C_6H_4-$).

*4.8.5. (R)-1-(4-Bromophenyl)-2-fluoroethanol ((R)-**4e**)[49].* The reaction was performed as described in Section 4.3.4 starting with 1-(4-bromophenyl)-2-fluoroethanol (**1e**) (868 mg, 4.00 mmol). Purification by bulb-to-bulb distillation (60–65 °C at 1.1×10^{-2} mbar) gave 688 mg (3.14 mmol, 79%) of a white solid, mp 41–42 °C, ee=91.0%, $[\alpha]_D^{20}$ −33.4 (c 0.90, $CHCl_3$), corr. ref. ee=98.5%, $[\alpha]_D^{20}$ −35.9 (c 0.90, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.43 (dd, J=1.1, 3.1, 1H, −O*H*), 4.36 (ddd, J=48.1, 9.6, 8.2, 1H, $-CH_2F$), 4.49 (ddd, J=46.6, 9.6, 3.3, 1H, $-CH_2F$), 4.97 (m, 1H, $-CHCH_2F$), 7.28–7.30 (m, 2H, $-C_6H_4-$), 7.45–7.53 (m, 2H, $-C_6H_4-$).

*4.8.6. (R)-2-Fluoro-1-(4-(trifluoromethyl)phenyl) ethanol ((R)-**4f**)[49].* A suspension of $[RuCl_2(mesitylene)]_2$ (23 mg, 0.04 mmol) and the (*S*,*S*)-TsDPEN (44 mg, 0.12 mmol) in H_2O (20 mL) were stirred at 40 °C for 1 h. Sodium formate (1.36 g, 20.0 mmol) and 2-fluoro-1-(4-trifluoromethylphenyl)ethanone (**1f**) (825 mg, 4.0 mmol) were added and the mixture was stirred vigorously at 40 °C for 10 h before it was cooled to room temperature and extracted with CH_2Cl_2 (3×20 mL). The organic phase was then washed with brine (20 mL), filtered through a plug of silica gel and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by bulb-to-bulb distillation (40–45 °C at 1.0×10^{-2} mbar). This gave 429 mg (2.06 mmol, 52%) of a colourless oil, ee=92.5%, $[\alpha]_D^{20}$ −27.4 (c 0.69, $CHCl_3$), corr. ref. ee=93.0, $[\alpha]_D^{20}$ −28.6 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.55 (d, J=3.1, 1H, −O*H*), 4.42 (ddd J=48.0, 9.6, 8.1, 1H, $-CH_2F$), 4.55 (ddd, J=46.7, 9.6, 3.4, 1H, $-CH_2F$), 5.11 (m, 1H, $-CHCH_2F$), 7.50–7.53 (m, 2H, $-C_6H_4-$), 7.63–7.69 (m, 2H, $-C_6H_4-$).

*4.8.7. 4-((R)-2-Fluoro-1-hydroxyethyl)benzonitrile ((R)-**4g**)[49].* The reaction was performed as described in Section 4.3.4 starting with 1-(4-cyanophenyl)-2-fluoroethanone (**1g**) (653 mg, 4.00 mmol). Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99.5/0.5, R_f 0.43) gave 563 mg (3.41 mmol, 85%) of a white solid, mp 59–60 °C, ee=87.0%, $[\alpha]_D^{20}$ −35.6 (c 0.70, $CHCl_3$), corr. ref. ee=91.5%, $[\alpha]_D^{20}$ −38.7 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.62 (d, J=3.3, 1H, −O*H*), 4.40 (ddd, J=48.0, 9.5, 8.0, 1H, $-CH_2F$), 4.55 (ddd, J=46.7, 9.5, 3.4, 1H, $-CH_2F$), 5.09 (m, 1H, $-CHCH_2F$), 7.46–7.56 (m, 2H, $-C_6H_4-$), 7.65–7.71 (m, 2H, $-C_6H_4-$).

*4.8.8. (R)-2-Fluoro-1-(4-nitrophenyl)ethanol ((R)-**4h**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-(4-nitrophenyl)ethanone (**1h**) (733 mg, 4.00 mmol). Purification by silica-gel chromatography (CH_2Cl_2/MeOH, 95/5, R_f 0.52) gave 673 mg (3.63 mmol, 91%) of a white solid, mp 98–99 °C, ee=85.0%, $[\alpha]_D^{20}$ −24.7 (c 0.70, $CHCl_3$), corr. ref. ee=92.5%, $[\alpha]_D^{20}$ −25.3 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.65 (br, 1H, −O*H*), 4.42 (ddd J=47.9, 9.6, 7.8, 1H, $-CH_2F$), 4.56 (ddd, J=46.5, 9.6, 3.4, 1H, $-CH_2F$), 5.16 (ddd, J=3.4, 7.8, 14.5, 1H, $-CHCH_2F$), 7.59–7.65 (m, 2H, $-C_6H_4-$), 8.22–8.28 (m, 2H, $-C_6H_4-$).

4.9. *N*-Substituted phthalimides (*S*)-5a–h

*4.9.1. (S)-2-(2-Fluoro-1-(4-methoxyphenyl)ethyl)isoindoline-1,3-dione ((S)-**5a**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4a** (420 mg, 2.47 mmol), and reacting for 10 h prior to addition of HCl. Purification by silica-gel column chromatography eluting with CH_2Cl_2/MeOH (99.5/0.5, R_f 0.54)

followed by *i*-Pr_2O/pentane (7/3, R_f 0.28), gave 235 mg (0.79 mmol, 32%) of white solid, mp 75–76 °C, ee=53.0%, $[\alpha]_D^{20}$ −15.8 (*c* 0.50, EtOAc), CD (MeCN): $\Delta\varepsilon$=−1.3 (232 nm). ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 3H, $-OCH_3$), 4.90 (ddd, *J*=45.7, 9.6, 5.3, 1H, $-CH_2F$), 5.52 (app. dt. *J*=47.0, 9.6, 1H, $-CH_2F$), 5.63 (ddd, *J*=12.1, 9.6, 5.3, 1H, $-CHCH_2F$), 6.86–6.89 (m, 2H, $-C_6H_4OMe$), 7.43–7.47 (m, 2H, $-C_6H_4OMe$), 7.68–7.73 (m, 2H, phthal.), 7.81–7.86 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.3 (d, *J*=21.2), 55.3, 80.8 (d, *J*=175.2), 114.2 (2C), 123.4 (2C), 127.2 (d, *J*=7.8), 129.6 (2C), 131.9 (2C), 134.1 (2C), 159.8, 168.3 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.30 (td, *J*=46.9, 12.1). IR (neat, cm^{-1}): 1773, 1706, 1610, 1514, 1363, 1238, 1087, 1001. HRMS (ESI): 322.0836 (calcd 322.0850 [M+Na^+]).

*4.9.2. (S)-2-(1-(4-(Benzyloxy)phenyl)-2-fluoroethyl)isoindoline-1,3-dione ((S)-**5b**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4b** (452 mg, 1.84 mmol), and reacting for 8 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2, R_f 0.55) gave 255 mg (0.68 mmol, 37%) of a white solid, mp 82–83 °C, ee=60.0%, $[\alpha]_D^{20}$ −11.1 (*c* 0.47, EtOAc), CD (MeCN): $\Delta\varepsilon$=−3.8 (234 nm). ^{1}H NMR ($CDCl_3$) δ: 4.89 (ddd, *J*=45.7, 9.6, 5.3, 1H, $-CH_2F$), 5.04 (s, 2H, $-OCH_2Ph$), 5.52 (app. dt. *J*=47.0, 9.6, 1H, $-CH_2F$), 5.62 (ddd, *J*=12.1, 9.6, 5.3, 1H, $-CHCH_2F$), 6.92–6.96 (m, 2H, $-C_6H_4OBn$), 7.29–7.41 (m, 5H, $-CH_2C_6H_5$), 7.42–7.46 (m, 2H, $-C_6H_4OBn$), 7.68–7.73 (m, 2H, phthal.), 7.81–7.85 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.3 (d, *J*=21.5), 70.0, 80.8 (d, *J*=175.2), 115.2 (2C), 123.4 (2C), 127.4 (2C), 127.5 (d, *J*=7.8), 128.0, 128.6 (2C), 129.7 (2C), 131.8 (2C), 134.1 (2C), 136.7, 159.0, 168.2 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.29 (td, *J*=46.2, 11.9). IR (neat, cm^{-1}): 1771, 1708, 1608, 1508, 1359, 1242, 1083, 997. HRMS (ESI): 398.1148 (calcd 398.1163, [M+Na^+]).

*4.9.3. (S)-2-(2-Fluoro-1-phenylethyl)isoindoline-1,3-dione ((S)-**5c**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4c** (460 mg, 3.28 mmol), and reacting for 2 h prior to addition of HCl. Purification by silica-gel chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.73) gave 681 mg (2.53 mmol, 77%) of a white solid, mp 69–70 °C, ee=99.0%, $[\alpha]_D^{20}$ −49.0 (*c* 0.61, EtOAc), CD (MeCN): $\Delta\varepsilon$=−3.5 (223 nm). ^{1}H NMR ($CDCl_3$) δ: 4.95 (ddd, *J*=45.7, 9.1, 5.6, 1H, $-CH_2F$), 5.55 (app. dt. *J*=47.2, 9.1, 1H, $-CH_2F$), 5.69 (ddd, *J*=12.4, 9.1, 5.3, 1H, $-CHCH_2F$), 7.29–7.38 (m, 3H, $-C_6H_5$), 7.48–7.51 (m, 2H, $-C_6H_5$), 7.69–7.74 (m, 2H, phthal.), 7.82–7.87 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.8 (d, *J*=21.6), 80.8 (d, *J*=174.8), 123.4 (2C), 128.2 (2C), 128.7, 128.9 (2C), 131.8 (2C), 134.2 (2C), 135.1 (d, *J*=7.4), 168.2 (2C). ^{19}F NMR ($CDCl_3$) δ: −219.83 (td, *J*=46.2, 11.9). IR (neat, cm^{-1}): 1770, 1704, 1611, 1493, 1385, 1357, 1086, 1000. HRMS (ESI): 292.0735 (calcd 292.0744, [M+Na^+]).

*4.9.4. (S)-2-(2-Fluoro-1-(4-fluorophenyl)ethyl)isoindoline-1,3-dione ((S)-**5d**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4d** (583 mg, 3.69 mmol), and reacting for 4 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.62) gave 815 mg (2.84 mmol, 77%) of a white solid, mp 58–59 °C, ee=92.5% (analysed as **2d**), $[\alpha]_D^{20}$ −36.8 (*c* 0.73, EtOAc), CD (MeCN): $\Delta\varepsilon$=−1.6 (223 nm). ^{1}H NMR ($CDCl_3$) δ: 4.93 (ddd, *J*=45.5, 9.4, 5.8, 1H, $-CH_2F$), 5.49 (app. dt, *J*=47.0, 9.4, 1H, $-CH_2F$), 5.66 (ddd, *J*=12.1, 9.4, 5.8, 1H, $-CHCH_2F$), 7.01–7.07 (m, 2H, $-C_6H_4F$), 7.48–7.53 (m, 2H, $-C_6H_4F$), 7.70–7.75 (m, 2H, phthal.), 7.82–7.87 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.0 (d, *J*=22.3), 80.6 (d, *J*=175.6), 115.9 (d, *J*=21.6), 123.5, 130.2 (d, *J*=4.1), 131.1 (dd, *J*=4.1, 3.5), 131.7, 134.3, 162.8 (d, *J*=248.3), 168.1 (2C). ^{19}F NMR ($CDCl_3$) δ: −113.33 (s), −219.63 (td, *J*=46.2, 11.8). IR (neat, cm^{-1}): 1774, 1707, 1605, 1511, 1389, 1223, 1100, 1000. HRMS (ESI): 288.0838 (calcd 288.0831, [M+H^+]).

*4.9.5. (S)-2-(1-(4-bromophenyl)-2-fluoroethyl)isoindoline-1,3-dione ((S)-**5e**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4e** (657 mg, 3.00 mmol), and reacting for 2 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.65) gave 871 mg (2.50 mmol, 83%) of a white solid, mp 66–67 °C, ee=90.0%, $[\alpha]_D^{20}$ −19.8 (*c* 0.60, EtOAc), CD (MeCN): $\Delta\varepsilon$=−3.9 (230 nm). ^{1}H NMR ($CDCl_3$) δ: 4.95 (ddd, *J*=45.8, 9.4, 5.8, 1H, $-CH_2F$), 5.46 (app. dt, *J*=47.0, 9.4, 1H, $-CH_2F$), 5.64 (ddd, *J*=12.1, 9.4, 5.8, 1H, $-CHCH_2F$), 7.37–7.40 (m, 2H, C_6H_4Br), 7.47–7.50 (m, 2H, C_6H_4Br), 7.71–7.75 (m, 2H, phthal.), 7.82–7.87 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.1 (d, *J*=22.6), 80.5 (d, *J*=175.6), 122.9, 123.5 (2C), 129.9 (2C), 131.7 (2C), 132.1 (2C), 134.2 (d, *J*=6.7), 134.3 (2C), 168.1 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.87 (td, *J*=46.3, 11.9). IR (neat, cm^{-1}): 1770, 1708, 1591, 1491, 1385, 1355, 1077, 999. HRMS (ESI): 369.9853 (calcd 369.9849, [M+Na^+]).

*4.9.6. (S)-2-(2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethyl)isoindoline-1,3-dione ((S)-**4f**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**3f** (717 mg, 3.45 mmol), and reacting for 4 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2, R_f 0.63) gave 905 mg (2.68 mmol, 78%) of a colourless oil (solidified at 0 °C), ee=92.0%, $[\alpha]_D^{20}$ −32.4 (*c* 0.54, EtOAc), CD (MeCN): $\Delta\varepsilon$=−4.8 (225 nm). ^{1}H NMR ($CDCl_3$) δ: 5.02 (ddd, *J*=45.8, 9.4, 6.1, 1H, $-CH_2F$), 5.48 (app. dt, *J*=46.7, 9.4, 1H, $-CH_2F$), 5.74 (ddd, *J*=12.1, 9.4, 6.1, 1H, $-CHCH_2F$), 7.59–7.65 (m, 4H, $-C_6H_4CF_3$), 7.72–7.77 (m, 2H, phthal.), 7.84–7.88 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.1 (d, *J*=23.0), 80.5 (d, *J*=175.6), 123.7, 123.8 (q, *J*=272.3), 125.9 (q, *J*=3.9), 128.6, 130.9 (d, *J*=32.9), 131.7, 134.4, 139.1 (dq, *J*=6.7, 1.4), 168.0 (2C). ^{19}F NMR ($CDCl_3$) δ: −63.40 (s, 3F), −220.22 (td, *J*=46.1, 11.8). IR (neat, cm^{-1}): 1777, 1710, 1620, 1469, 1385, 1322, 1067, 1013. HRMS (ESI): 360.0617 (calcd 360.0618, [M+Na^+]).

*4.9.7. (S)-4-(1-(1,3-Dioxoisoindolin-2-yl)-2-fluoroethyl)benzonitrile ((S)-**5g**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4g** (547 mg, 3.31 mmol), and reacting for 3 h prior to addition of HCl. Purification by silica-gel column chromatography (pentane/acetone, 8/2, R_f 0.52) gave 647 mg (2.20 mmol, 66%) of a white solid, mp 89–91 °C, ee=87.5%, $[\alpha]_D^{20}$ −24.4 (*c* 0.52, EtOAc), CD (MeCN): $\Delta\varepsilon$=−2.7 (238 nm). ^{1}H NMR ($CDCl_3$) δ: 5.04 (ddd, *J*=45.7, 9.4, 6.3, 1H, $-CH_2F$), 5.40 (app. dt, *J*=46.7, 9.4, 1H, $-CH_2F$), 5.72 (ddd, *J*=12.4, 9.1, 6.3, 1H, $-CHCH_2F$), 7.61–7.68 (m, 4H, $-C_6H_4CN$), 7.73–7.78 (m, 2H, phthal.), 7.85–7.89 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.0 (d, *J*=23.3), 80.3 (d, *J*=175.9), 112.7, 118.2, 123.7 (2C), 128.9 (2C), 131.5 (2C), 132.7 (2C), 134.5 (2C), 140.3 (d, *J*=6.0), 167.9 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.36 (td, *J*=46.1, 12.2). IR (neat, cm^{-1}): 2227, 1777, 1706, 1610, 1465, 1361, 1334, 1088, 999. HRMS (ESI): 317.0694 (calcd 317.0697, [M+Na^+]).

*4.9.8. (S)-2-(2-Fluoro-1-(4-nitrophenyl)ethyl)isoindoline-1,3-dione ((S)-**5h**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4h** (648 mg, 3.50 mmol), and reacting for 3 h prior to addition of HCl. Purification by silica-gel column chromatography using CH_2Cl_2/MeOH (99.5/0.5, R_f 0.49) followed by pentane/acetone (8/2, R_f 0.50) gave 374 mg (1.19 mmol, 34%) of a white solid, mp 92–94 °C, ee=84.0%, $[\alpha]_D^{20}$ −6.5 (*c* 1.05, $CHCl_3$), CD (MeCN): $\Delta\varepsilon$=−1.4 (228 nm). ^{1}H NMR ($CDCl_3$) δ: 5.08 (ddd, *J*=45.5, 9.3, 6.3, 1H, $-CH_2F$), 5.43 (app. dt, *J*=46.5, 9.1, 1H, $-CH_2F$), 5.78 (ddd, *J*=12.4, 9.1, 6.3, 1H, $-CHCH_2F$), 7.67–7.70 (m, 2H, $-C_6H_4NO_2$), 7.74–7.79 (m, 2H, phthal.), 7.85–7.90 (m, 2H, phthal.), 8.21–8.24 (m, 2H, $-C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$) δ: 53.7 (d, *J*=23.3), 80.4 (d, *J*=176.3), 123.7 (2C), 124.1 (2C), 129.2 (2C), 131.5 (2C), 134.6 (2C), 142.2 (d, *J*=6.0), 148.0, 167.9 (2C). ^{19}F NMR ($CDCl_3$) δ: −221.22 (td,=12.1, 46.0). IR (neat, cm^{-1}): 1776, 1712, 1606, 1521, 1386, 1347, 1087, 999. HRMS (ESI): 337.0605 (calcd 337.0595, [M+Na^+]).

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Paper VI

Fuglseth, E., Otterholt, E., Høgmoen, H., Sundby, E., Charnock, C., Hoff, B. H.

Chiral derivatives of Butenafine and Terbinafine: synthesis and antifungal activity

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Chiral derivatives of Butenafine and Terbinafine: synthesis and antifungal activity

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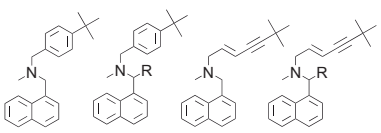
ABSTRACT

Two series of allylamines/benzylamines have been synthesised and evaluated for their antifungal activity towards *Cryptococcus neoformans*. All compounds are chiral derivatives of Butenafine and Terbinafine, having additional substituents at the carbon connected to the central nitrogen atom. In both series, the antifungal activity was strongly dependent on both the steric bulk and the electronic nature of the substituents. Compared to the parent compounds (Butenafine and Terbinafine), the activity was maintained when the hydrogen was replaced with a methyl group. Lower activity was observed for ethyl, whereas introduction of $-CH_2F$, $-CHF_2$, $-CF_3$ or –CN substituents removed all antifungal activity. Testing of (*R*)- and (*S*)-*N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine against *C. neoformans*, *Cryptococcus diffluens* and *Trichosporon cutaneum* revealed that most of the activity resides in the (*R*)-enantiomer. The (*R*)-enantiomer performed as well as, or better (lower MIC values) than Butenafine against each test strain, suggesting that antimycotics based on this compound might be an improvement of existing Butenafine-based formulations.

1. Introduction

Treatment of an increasing number of infections associated with immuno-compromised patients[1] is causing a marked increase in the number of fungal strains showing resistance to presently available antimycotic agents.[2–4] Among others, *Cryptococcosis*, caused by members of the *Cryptococcus neoformans* species, is a serious and potentially fatal fungal disease afflicting a large number of AIDS patients.[5–7] *C. neoformans* has also become the most common cause of meningitis in the developing world.[8,9] *Cryptococcus diffluens* is less commonly associated with disease, but has been frequently isolated from the skin of patients with atopic dermatitis.[10] *Trichosporon* species are usually found in soil and fresh water and are known to cause white piedra and hypersensitive pneumonia. Invasive infections due to *Trichosporon* are rare, but can be fatal to immuno-compromised patients, and have been observed with growing frequency.[11] Butenafine (**1a**) and Terbinafine (**2a**) (Fig. 1) are well established antimycotic agents used among others in topical treatment of dermatocytes invading skin and nails. Their mode of action is by inhibiting the enzyme squalene epoxidase in the ergosterol pathway responsible for converting squalene into squalene 2,3-epoxide, which is subsequently converted into lanosterol and ergosterol. Inhibition results in deficiency of the essential membrane component ergosterol and also squalene accumulation plays an essential role in the fungicidal action of these inhibitors.[12] It has also been indicated that the action of Butenafine (**1a**) can be partly due to permeabilisation of the fungal cell wall.[13] Structure–activity studies on Butenafine (**1a**) and Terbinafine (**2a**) analogues have been performed.[14–20] However, investigations of derivatives containing a stereocentre in the vicinity of the central nitrogen atom, are substantially less studied. The racemic derivatives *rac*-**1b**,[21,22] and *rac*-**2b**,[23] (Fig. 1) have previously been shown to have antifungal activity, while the usefulness of (*R*)-**2b** has been indicated by comparative molecular field analysis.[21,24]



Butenafine (**1a**) **1b-g** Terbinafine (**2a**) **2b-g**

Figure 1. The structures Butenafine (**1a**), Terbinafine (**2a**), and the studied compounds **1b–g** and **2b–g**, R=Me, Et, CH_2F, CHF_2, CF_3, CN.

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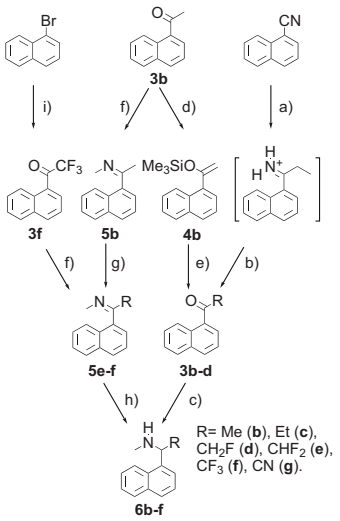
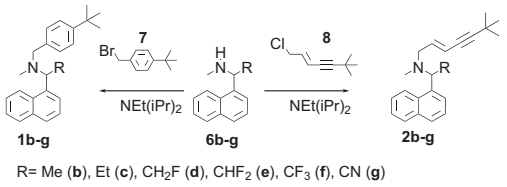
2. Results and discussion

2.1. Synthesis of potential antifungal compounds

The synthesis of the target compounds **1b**–**g** and **2b**–**g** was performed as shown in Schemes 1 and 2. Key intermediates were the secondary methyl amines **6b**–**f**. The amines, **6b**–**d**, were made from the corresponding ketones **3b**–**d** by reductive amination in methanol/acetic acid using $NaBH_3CN$ as reducing agent (53–76% yield). The moderate yields were mainly due to background reduction of the ketones giving the corresponding secondary alcohols.



Scheme 1. Synthetic methods for preparation of **6b**–**f**: (a) EtMgBr/THF; (b) H^+/H_2O;(c) NH_2Me, AcOH, $NaBH_3CN$; (d) LiHMDS, TMS–Cl; (e) F-TEDA-BF_4; (f) NH_2Me, $TiCl_4$; (g) NFSI, mol. sieve, K_2CO_3; (h) $NaBH_3CN$, AcOH; (i) ethyl trifluoroacetate; (j) $NaBH_3CN$/AcOH.



Scheme 2. Synthesis of *rac*-**1b**–**g** and *rac*-**2b**–**g**.

1-(Naphthalen-1-yl)propan-1-one (**3c**) was obtained by ethylation of 1-cyanonaphthalene followed by hydrolysis,[25] while **3d** was synthesised by fluorination of the corresponding trimethylsilyl enol ether **4b** using Selectfluor™ (F-TEDA-BF_4).[26] The preparation of α-fluoroketone **3d** was also attempted from **3c** by using F-TEDA-BF_4 in refluxing methanol.[26,27] This method gave the desired product, however two other structurally related α-fluoroketones were also formed, resulting in a troublesome purification. ^{19}F NMR spectroscopic analysis of the crude product suggested that additional ring fluorination had taken place.

The amine **6e** was most conveniently prepared by difluorination of the imine **5b** using *N*-fluorodibenzenesulfonimide (NFSI) yielding the difluoroimine **5e**. Reduction of **5e** using $NaBH_3CN$ in glacial acetic acid gave **6e** in 73% overall yield from **3b**. The use of F-TEDA-BF_4 as a fluorinating agent was also investigated in the formation of **5e**. However, this led to decomposition of the imine, yielding mainly the α,α-difluoroketone **3e**. The trifluorinated amine, **6f**, was obtained from 2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone (**3f**), which in turn was synthesised from 1-bromonaphthalene and ethyl trifluoroacetate. Treatment of **3f** with $NaBH_3CN$/methylamine in methanol did not give the desired product. However, high conversion towards **5f** was obtained when adding titanium tetrachloride to a preformed mixture of **3f** and methylamine. Reduction of the imine **5f** using $NaBH_3CN$ in glacial acetic acid yielded the amine **6f** in 63% from **3f**.

To separate a possible size effect from an electronic effect in interpretation of antifungal activity data, the cyano containing compounds **1g** and **2g** (Fig. 1) were synthesised, starting with the commercial available cyano derivative **6g**. In terms of electronic properties the cyano substituent mimics a CF_2H or CF_3 group, while it occupies a smaller space than a methyl group.[28]

The potential antifungal agents **1b**–**g** and **2b**–**g** were obtained by reacting the secondary amines **6b**–**g** with the commercially available 1-*tert*-butyl-4-(bromomethyl)benzene (**7**) and (*E*)-1-chloro-6,6-dimethylhept-2-en-4-yne (**8**), respectively. All reactions were performed in refluxing acetonitrile using *N*,*N*-diisopropylethylamine as base, see Scheme 2.

As expected, the reaction rate depended on the electronic properties of the R-group of the amine, and on the alkylating agent. Compounds **6b**–**c** reacted with **7** to full conversion within 2 h, while reactions using **6f**–**g** and **8** took several days. Isolated yields were in the range of 60–90% for **1b**–**g**, while for **2b**–**g** 40–63% were experienced. The moderate yield of **2b**–**g** can in part be explained by the presence of 4% of the *Z*-isomer of **8**, which led to a structurally related product and a consequent loss in yield during purification. Moreover, in the synthesis of **1g** and **2g**, ^1H NMR spectroscopy indicated that some hydrolysis of the nitrile group had taken place.

To evaluate the effect of stereochemistry on the antifungal activity, the (*R*)- and (*S*)-enantiomers of *N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine, (*R*)-**1b** and (*S*)-**1b**, were synthesised from (*R*)-**6b** and (*S*)-**6b** with the same procedure as outlined in Scheme 2.

2.2. Antifungal activity

The antifungal activity of compounds **1a**–**g** and **2a**–**g** was initially tested towards *C. neoformans* by the semisolid antifungal susceptibility test (SAAS).[29] The MIC values along with the calculated pK_a's for the compounds, and the steric bulk (Charton volume) of the substituents are shown in Table 1 (**2a**–**g**) and Table 2 (**1a**–**g**).

Testing of Terbinafine (**2a**) towards *C. neoformans* gave a MIC_{50} value of 0.25 μg/mL, while compound **2b** was a less efficient inhibitor (MIC_{50}: 0.5 μg/mL). Modifying the structure with an ethyl substituent (entry 3), reduced the antifungal properties further,

Table 1
Antifungal activities (MIC) of **2a**–**g** towards *C. neoformans*

Entry	Comp.	R	Calcd pK_a[a]	Rel size[b]	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)
1	**2a**	H	8.9	0	0.25	0.5
2	*rac*-**2b**	Me	9.2	0.52	0.5	1.0
3	*rac*-**2c**	Et	9.5	0.56	2–8[c]	16
4	*rac*-**2d**	CH_2F	7.6	0.62	>16	>16
5	*rac*-**2e**	CHF_2	5.8	0.68	>16	>16
6	*rac*-**2f**	CF_3	2.9	0.91	>16	>16
7	*rac*-**2g**	CN	5.1	0.40	>16	>16

[a] The pK_a values were estimated using the Marvin program suite.
[b] Charton volume is from tabulated values.[28]
[c] Trailing growth complicated assignment of MIC values.

Table 2
Antifungal activity (MIC) of **1a–g** towards *C. neoformans*

Entry	Comp.	R	Calcd pK_a[a]	Rel size[b]	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)
1	**1a**	H	9.2	0	0.125	0.25
2	*rac*-**1b**	Me	9.5	0.52	0.125	0.25
3	(*R*)-**1b**	Me	9.5	0.52	<0.031	0.031
4	(*S*)-**1b**	Me	9.5	0.52	0.5[c]	1–8[c]
5	*rac*-**1c**	Et	9.8	0.56	0.25–4[c]	8
6	*rac*-**1d**	CH_2F	7.9	0.62	>16	>16
7	*rac*-**1e**	CHF_2	6.1	0.68	>16	>16
8	*rac*-**1f**	CF_3	3.2	0.91	>16	>16
9	*rac*-**1g**	CN	5.4	0.40	>16	>16

[a] The pK_a values were estimated using the Marvin program suite.
[b] Charton volume is from tabulated values.[28]
[c] Trailing growth complicated assignment of MIC values.

whereas the compounds containing fluorines or a cyano group (entries 4–7), had no activity towards *C. neoformans* in the concentration ranges tested.

Testing of the derivatives **1a–g** (Table 2) showed that Butenafine (**1a**) was more active than Terbinafine (**2a**). Moreover, *rac*-**1b** proved to have the same activity as **1a** (MIC_{50} 0.125 μg/mL). Synthesis and antifungal activity testing of (*S*)-**1b** and (*R*)-**1b** revealed that the activity of the racemate mainly relies on the activity of the (*R*)-enantiomer (MIC_{50}<0.031 μg/mL), and it was found to be significantly more potent than Butenafine (**1a**). Compound (*S*)-**1b** also inhibited fungal growth, and the MIC values were comparable with that of **1c**. However, trailing growth typical of a fungistatic activity, complicated the analysis of the test results in both cases, making endpoint assignments more difficult. Compounds **1d–g** had no activity towards *C. neoformans* within the concentration range tested. As observed in testing of **2d**, introduction of one fluorine atom depleted the antifungal activity of the compound.

Assuming that the antifungal activity of these compounds is mainly due to inhibition of squalene epoxidase, the results suggest that both steric and electronic effects are of importance for the antifungal properties of these compounds. A drop in activity was seen going from the methyl substituted analogues, **1b** and **2b**, to inhibitors having the more bulky ethyl substituents, **1c** and **2c**. However, the cyano group occupies a smaller volume than a methyl substituent, and the activity observed for **1g** and **2g** (MIC_{50}>16), indicates that electronic effects are of equal importance. The lack of activity in testing of compounds **1d–f** and **2d–f** is therefore likely to be due to both the unfavourable size and the electron withdrawing nature of fluoro-containing substituents. As structural information of squalene epoxidases is unavailable, the effects can currently not be explained at the molecular level.

When dealing with fungistatic agents and testing fungal species for which there exist limited published data regarding antibiotic susceptibilities, it seemed pertinent to include results from alternative test regimes. To verify the main results, the MIC values of Butenafine (**1a**), (*rac*)-**1**, (*R*)-**1b** and (*S*)-**1b** were also measured using the broth microdilution method.[30] Two other fungal strains representing two other species were included in the testing (*C. diffluens* and *T. cutaneum*) to investigate the usefulness of (*R*)-**1a** as an antifungal agent. The results are summarised in Table 3. The SAAS and the broth microdilution method were in general agreement with respect to the relative activity of the compounds tested against *C. neoformans*. However, MIC values obtained using the two methods differed in some instances by more than a single doubling dilution. When (*R*)-**1b** and Butenafine (**1a**) were tested against *C. neoformans* using the broth microdilution method, MIC_{50} values of 0.125 and 0.5 μg/mL were obtained, respectively.

Although endpoints in general were easier to assign with the broth microdilution method, trailing growth complicated testing towards *C. diffluens*. However, the results suggest that (*R*)-**1b** (MIC_{50} 0.25 μg/mL) was more active than Butenafine (**1a**). All compounds tested towards *T. cutaneum* were active. Butenafine (**1a**), (*rac*)-**1b** and (*R*)-**1b** all gave a MIC_{50} value of 0.5 μg/mL. The relatively high activity of (*S*)-**1b** towards *T. cutaneum* shows that the stereochemistry of the inhibitor is less important than was the case for *C. neoformans* and *C. diffluens*. This could indicate a wider or more flexible binding pocket for the inhibitors.

3. Conclusions

Two groups of chiral amines structurally related to Butenafine (**1a**) and Terbinafine (**2a**) have been synthesised and tested as potential antifungal agents. The activity towards *C. neoformans* depended on both the steric bulk and electronic character of the substituents. Racemic *N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**1b**) was found to have the same activity as Butenafine (**1a**) towards *C. neoformans*. Assessment of antifungal activity using the SAAS method of the (*R*)- and (*S*)-enantiomers concluded that most of the activity is due to (*R*)-**1b**, giving a MIC_{50} value of <0.031 μg/mL (MIC_{50} **1a**: 0.25 μg/mL). Compounds containing electron withdrawing groups at the stereogenic centre were not active towards *C. neoformans*. Surprisingly, the insertion of one fluorine atom was sufficient to remove all antifungal activity. This could indicate that the nitrogen basicity is important for binding of the compounds to the squalene epoxidase. Antifungal testing using the broth microdilution method confirmed that (*R*)-**1b** performed as well as or better than Butenafine (**1a**) against *C. neoformans*, *C. diffluens* and *T. cutaneum*, suggesting that antimycotics based on this compound might be an improvement of existing Butenafine-based formulations.

4. Experimental

4.1. General

1-Acetonaphthone (**3b**) was purchased from Fluka. LiHMDS, Selectfluor (F-TEDA-BF_4), 1-*tert*-butyl-4-(bromomethyl)benzene, 1-naphthonitrile, 1-bromonaphthalene, (*R*)- and (*S*)-*N*-methyl-1-(naphthalen-1-yl)ethanamine ((*R*)-**6b** and (*S*)-**6b**), *N*-fluorodibenzenesulfonimide (NFSI) and trimethylsilyl chloride were from Aldrich. 2-(Methylamino)-2-(naphthalen-1-yl)acetonitrile (**6g**) was from UkrOrgSynthesis Building Blocks (Ukraine). (*E*)-1-Chloro-6,6-dimethylhept-2-en-4-yne (*trans*-**8**, 94% pure) was from Waterstone Technology. Terbinafine·HCl was from Sigma, while Butenafine·HCl was from AK Scientific Inc. Column

Table 3
Antifungal activities (MIC) of **1a**, (*rac*)-**1b**, (*R*)-**1b** and (*S*)-**1b** towards *C. neoformans*, *C. diffluens* and *T. cutaneum* by the broth microdilution method

Comp.	*C. neoformans*		*C. diffluens*		*T. cutaneum*	
	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)
1a	0.5	1.0	0.5[a]	4.0[a]	0.5	1.0
rac-**1b**	0.25	0.5	0.5[a]	2.0[a]	0.5	1.0
(*R*)-**1b**	0.125	0.25	0.25[a]	1.0[a]	0.5	1.0
(*S*)-**1b**	1.0[a]	2.0[a]	4.0[a]	>16[a]	1.0[a]	2.0[a]

[a] Trailing growth complicated assignment of MIC values.

chromatography was performed using silica gel 60A from Fluka, pore size 40–63 μm.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^{1}H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. For ^{1}H and ^{13}C NMR chemical shifts are in parts per million relative to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. MS (EI/70 eV) Finnigan MAT 95 XL, MS (ESI) Waters QTOF II and MS (CI): Waters Prospec Q. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. Optical rotations were measured using sodium D line at 589 nm on a Perkin–Elmer 243 B polarimeter. HPLC was performed using an Agilent 1100 series system equipped with a Bruker DAD detector. The enantiomeric excess of (*R*)-**1b** and (*S*)-**1b** was determined by an Astec CHIROBIOTIC V2 column, 5 μm, 4.6×250 mm (Supelco, Pennsylvania, USA) eluting with MeOH/water cont. 20 mM aq ammonium acetate, 60/40. Flow rate: 0.8 mL/min, detection at 220 nm, retention times (*S*)-**1b**: 24.2 min and (*R*)-**1b**: 28.4 min. HPLC analysis of **1b**–**g** and **2b**–**g** was performed using the same HPLC system equipped with a Symmetry C8 3.5 μm, 4.6×150 mm column. Mobile phase: water/acetonitrile 30/70 containing 0.1% diethyl amine, flow rate: 1.0 mL/min and detection at 220 nm. Retention times (min): **1b**: 37.2, **1c**: 64.6, **1d**: 34.4, **1e**: 32.3, **1f**: 37.0, **1g**: 19.0, **2b**: 23.9, **2c**: 29.5, **2d**: 17.9, **2e**: 17.0, **2f**: 27.0, **2g**: 14.5.

4.3. Microbiology

4.3.1. Fungal isolates. Cultures of two quality control strains (*C. neoformans* DSM 11959; *Trichosporon cutaneum* DSM 70698) and a strain of *Cryptococcus diffluens* isolated from drinking water were grown for 18–24 h at 35 °C on Sabouraud's dextrose agar (Oxoid, Basingstoke, UK). Well-isolated colonies were used to make the inoculum in each of the methods used for the determination of minimum inhibitory concentrations (MICs).

4.3.2. Semisolid agar antifungal susceptibility test (SAAS). The test was performed essentially as previously described.[29] Five-millilitre aliquots of semisolid heart infusion broth (Difco Laboratories, Detroit, MI) containing 0.5% agar (Bacto Agar; Difco Laboratories) at a pH of approximately 7.4 (without dextrose, buffer, or indicator) were prepared with and without an antifungal drug in 16- by 125-mm glass tubes. Analytical grade powders of Amphotericin B (Sigma–Aldrich, St. Louis, MO) and the agents to be tested were prepared as stock solutions in DMSO (Sigma–Aldrich) at 1.6 mg/mL. The concentration range tested was 0.031–16 μg/mL and was obtained by adding agent from 100-times stocks in DMSO into tubes held molten at 50 °C. A suspension equivalent to a 0.5 McFarland standard (determined photometrically) was prepared by suspending the selected yeast in sterile water. The homogeneous suspension was used for inoculation. A standard platinum loopful (~0.001 mL) of the inoculum suspension was inserted deep into each tube of medium containing a known concentration of drug, as well as a drug-free control, by a centred down–up motion to form a two dimensional inoculum. The tubes were tightly capped. A loopful of the inoculum suspension was streaked onto SAB agar to check the purity and viability of the inoculum. All cultures were incubated for 72 h at 35 °C. The growth in all tubes was compared by visual inspection with that of the drug-free control in order to determine the degree of growth inhibition. Growth was scored in the following manner: 4+, growth comparable to that of the drug-free control; 3+, growth approximately 75% that of the control; 2+, growth approximately 50% that of the control (MIC_{50}); 1+, growth 25% or less that of the control (MIC_{75}); and 0, no visible growth.

4.3.3. Broth microdilution method. Testing was performed according to the guidelines of the NCCLS document M27-A.[30] Analytical grade powders of Amphotericin B (Sigma–Aldrich, St. Louis, MO) and the agents to be tested were prepared as described above. Stock solutions were diluted with RPMI 1640 medium (with L-glutamine but without bicarbonate; Sigma–Aldrich) buffered to pH 7.0 with 0.176 M morpholinopropanesulfonic acid (MOPS, Sigma–Aldrich). The final concentration range tested was 0.031–16 μg/mL. Testing was performed in 96-well microtitration plates (Nalge Nunc International, Denmark). Yeast inocula were prepared in sterile 0.85% saline and were diluted in RPMI 1640 medium to give a final inoculum concentration in wells of 5×10^{2}–2.5×10^{3} colony forming units (CFU)/mL. The plates were lidded, and incubated at 35 °C. Endpoints were read visually at 72 h. Growth was scored as for the SAAS method.

4.4. Synthesis of intermediates

*4.4.1. 1-(Naphthalen-1-yl)propan-1-one (**3c**)*[25,31]. 1-(Naphthalen-1-yl)propan-1-one (**3c**) was prepared from 1-naphthonitrile (10.00 g, 65.28 mmol) as described by Kloetzel et al.[25] Distillation at 98–100 °C (4×10^{-3} mbar) gave 10.60 g (57.53 mmol, 88%) of a colourless oil. ^{1}H NMR spectroscopy corresponded with that reported.[31]

*4.4.2. 2-Fluoro-1-(naphthalen-1-yl)ethanone (**3d**)*[32]. Compound **3d** was synthesised from **3b** (3.43 g, 20.15 mmol) via the trimethylsilyl enol ether as described by Fuglseth et al.[26] The product was purified by silica-gel column chromatography (dichloromethane) giving an oil. A following crystallisation (EtOAc/pentane) yielded 1.10 g (5.84 mmol, 29%) of a white solid, mp 44–45 °C (lit.[33] 82–84 °C). The ^{1}H, ^{13}C and ^{19}F NMR data corresponded with that reported.[32] ^{1}H NMR ($CDCl_3$) δ: 5.60 (d, J=47.2, 2H), 7.50–7.61 (m, 2H), 7.65 (m, 1H), 7.80 (m, 1H), 7.89 (m, 1H), 8.05 (d, J=8.3, 1H), 8.71 (m, 1H).

*4.4.3. 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone (**3f**)*[34]. 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone was prepared as described by Konno et al. starting with 1-bromonaphthalene (4.15 g, 20.04 mmol).[34] Purification by silica-gel column chromatography (EtOAc/pentane, 1/20) yielded 2.99 g (13.34 mmol, 67%) of a coloured oil. ^{1}H, ^{13}C and ^{19}F NMR spectroscopy were in accordance with that reported.[34] ^{1}H NMR ($CDCl_3$) δ: 7.55–7.64 (m, 2H), 7.70 (m, 1H), 7.90–7.95 (m, 1H), 8.10–8.20 (m, 1H), 8.18–8.22 (m, 1H), 8.82 (m, 1H).

*4.4.4. N-Methyl-1-(naphthalen-1-yl)ethanamine (**6b**)*[35]. To a mixture of methylamine in MeOH (30 mL, 2 M) were added acetic acid (1.23 g, 20.48 mmol), 1-acetonaphthone (**3b**) (1.70 g, 9.99 mmol) and $NaBH_3CN$ (0.38 g, 6.05 mmol). The reaction was stirred at room temperature for 70 h. The pH was adjusted to <2 using concd HCl. After removal of MeOH the reaction mixture was diluted with water (10 mL) and the mixture was extracted using *tert*-butyl methyl ether (3×20 mL). The pH of the water phase was then adjusted to pH>10 using KOH. The water phase was saturated with NaCl and extracted with *tert*-butyl methyl ether (5×15 mL). The organic fraction was dried over Na_2SO_4, and the solvent was removed under reduced pressure. This gave a 1.40 g (7.76 mmol, 76%) of **6b** as colourless oil, which was sufficiently pure for subsequent step. ^{1}H NMR ($CDCl_3$) δ: 1.50 (d, J=6.6, 3H), 2.07 (br s, 1H), 2.42 (s, 3H), 4.53 (q, J=6.6, 1H), 7.55–7.43 (m, 3H), 7.61 (d, J=7.0, 1H), 7.75 (d, J=8.1, 1H), 7.88 (m, 1H), 8.18 (d, J=8.1, 1H). ^{13}C NMR ($CDCl_3$) δ: 23.0, 34.5, 55.4, 122.7, 122.8, 125.3, 125.7, 125.8, 127.3, 129.0, 131.4,

134.0, 141.1. HRMS (ESI): 186.1283 (calcd $C_{13}H_{16}N^+$, M+H$^+$, 186.1277). IR (neat, cm^{-1}): 3061, 2972, 1678, 1136, 800, 770, 691.

*4.4.5. N-Methyl-1-(naphthalen-1-yl)propaneamine (**6c**)*[35]. Compound **6c** was prepared as described for **6b** starting with **3c** (1.84 g, 9.99 mmol). This gave after silica-gel column chromatography (MeOH) 1.28 g (6.42 mmol, 64%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, J=7.4, 3H), 1.49 (br s, 1H), 1.88 (m, 2H), 2.34 (s, 3H), 4.34 (t, J=6.4, 1H), 7.44–7.52 (m, 3H), 7.56–7.58 (m, 1H), 7.75 (d, J=8.1, 1H), 7.86–7.88 (m, 1H), 8.24 (d, J=8.3, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.8, 30.0, 34.8, 62.0, 123.2, 123.6, 125.2, 125.6, 125.7, 127.2, 128.9, 132.1, 134.0, 139.5. HRMS (ESI): 200.1437 (calcd $C_{14}H_{18}N^+$, M+H$^+$, 200.1434). IR (neat, cm^{-1}): 2962, 1590, 1449, 1377, 1082, 775.

*4.4.6. 2-Fluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**6d**).* Compound **6d** was synthesised as described for **6b** starting with **3d** (1.00 g, 5.31 mmol) giving 0.57 g (2.80 mmol, 53%) of **6d** as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.71 (br s, 1H), 2.42 (s, 3H), 4.47 (dt, J=48.9, 9.3, 1H), 4.62 (ddd, J=47.0, 9.3, 3.4, 1H), 4.81 (m, 1H), 7.47–7.58 (m, 3H), 7.73 (d, J=7.0, 1H), 7.81 (d, J=8.3, 1H), 7.89 (m, 1H), 8.22 (d, J=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.5, 60.0 (d, J=19.0), 86.5 (d, J=175.0), 122.4, 124.91, 124.93, 125.57, 125.62, 126.3, 128.3, 129.1, 131.8, 134.0. ^{19}F NMR ($CDCl_3$) δ: −217.7 (dt, J=47.8, 14.2). IR (neat, cm^{-1}): 3060, 2948, 1589, 1144, 998, 800, 780, 691.

*4.4.7. 2,2-Difluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**6e**).*

*4.4.7.1. Compound **5b**.* Methylamine (0.90 g, 28.98 mmol) was dissolved in pentane (20 mL) and cooled to 0 °C. $TiCl_4$ (0.4 mL, 0.69 g, 3.64 mmol) was added dropwise over 5 min under rigorous stirring. 1-Acetonaphthone (**3b**) (0.83 g, 4.90 mmol) was then added in one portion and the reaction mixture was stirred for 1 h allowing the temperature to rise to ambient temperature. Diethyl ether (30 mL) was added and the suspension was filtered, followed by washing of the inorganic residue with additional ether (4×10 mL). The combined ether fractions were concentrated under reduced pressure giving 0.82 g (89%) of *N*-(1-(naphthalen-1-yl)ethylidene)methanamine (**5b**). The product was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 2.40 (q, J=1.5, 3H), 2.92 (q, J=1.5, 3H), 7.19 (dd, J=7.0, 1.3, 1H), 7.50 (m, 4H), 7.86 (m, 2H).

*4.4.7.2. Compound **5e**.* A mixture of *N*-fluorodibenzenesulfonimide (NFSI, 4.75 g, 15.06 mmol), K_2CO_3 (1.43 g, 10.35 mmol), 3 Å molecular sieve (3.00 g) and acetonitrile (30 mL) was stirred for 15 min at room temperature. Then *N*-(1-(naphthalen-1-yl)ethylidene)methanamine (**5b**) (0.64 g) in acetonitrile (20 mL) was added dropwise and the mixture was stirred at room temperature for 18 h, followed by quenching with triethylamine (2.0 mL). The resulting mixture was filtered through Celite and the Celite was washed with diethyl ether (3×15 mL). The filtrate was then washed with NaOH (0.5 M, 20 mL) and the aqueous layer was back extracted with ether (4×30 mL). The combined organic fractions were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The oily product was used in the next step without purification. ^{1}H NMR ($CDCl_3$) δ: 3.09 (t, J=2.8, 3H), 6.32 (t, J=55.6, 1H), 7.36 (d, J=7.2, 1H), 7.54 (m, 4H), 7.93 (m, 2H).

*4.4.7.3. Compound **6e**.* Crude *N*-(2,2-difluoro-1-(naphthalen-1-yl)ethylidene)methanamine (**5e**) (0.77 g, ~3.5 mmol) was dissolved in absolute MeOH (35 mL). $NaBH_3CN$ (0.35 g, 5.40 mmol) and glacial acetic acid (0.41 g, 6.90 mmol) were added and the mixture was stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the crude product was directly purified by silica-gel column chromatography (EtOAc/pentane, 1/2) yielding a colourless oil 0.56 g (2.53 mmol, 73% yield from **3c**). ^{1}H NMR ($CDCl_3$) δ: 1.75 (br s, 1H), 2.42 (s, 3H), 4.73 (td, J=10.7, 4.9, 1H), 6.00 (dt, J=56.3, 4.9, 1H), 7.55–7.50 (m, 2H), 7.57 (m, 1H), 7.77 (d, J=8.5, 1H), 7.86 (d, J=8.0, 1H), 7.91 (m, 1H), 8.24 (d, J=7.2, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.5, 62.3 (t, J=21.9), 117.2 (t, J=245.8), 122.9, 125.5, 125.7, 126.4 (2C), 128.9, 129.0, 131.6, 132.3, 134.0. ^{19}F NMR ($CDCl_3$) δ: −122.6 (dd, J=279.9, 57.4), −124.2 (ddd, J=279.9, 57.4, 11.5). HRMS (ESI): 222.1093 (calcd $C_{13}H_{14}F_2N^+$, M+H$^+$, 222.1089). IR (neat, cm^{-1}): 3353, 3053, 2972, 2851, 2795.

*4.4.8. 2,2,2-Trifluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**6f**).*

*4.4.8.1. Compound **5f**.* 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone (**3f**) (2.21 g, 9.86 mmol) and methylamine (2.60 g, 83.72 mmol) were dissolved in *n*-hexane (150 mL) and cooled to 0 °C. $TiCl_4$ (0.80 mL, 1.39 g, 7.33 mmol) in *n*-hexane (5 mL) was added dropwise under vigorous stirring. The orange suspension was slowly warmed to room temperature and stirred for 2 h. Diethyl ether (100 mL) was then added and the suspension was filtered, before the inorganic residue was washed with additional ether (3×25 mL). The solvents were removed under reduced pressure and the crude product (2.14 g, 91%) was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 3.15 (q, J=1.9, 3H), 7.39 (d, J=7.0, 1H), 7.56 (m, 4H), 7.93 (m, 1H), 7.98 (dd, J=8.3, 0.8, 1H).

*4.4.8.2. Compound **6f**.* Crude *N*-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethylidene)methanamine (**5f**) (2.14 g, 9.02 mmol) was dissolved in dry MeOH. $NaBH_3CN$ (1.01 g, 15.58 mmol) and glacial acetic acid (0.97 g, 16.10 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of satd $NaHCO_3$ (100 mL). A white precipitate was filtered off and the aqueous layer was extracted with diethyl ether (5×75 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvents evaporated under reduced pressure. The product was purified by silica-gel column chromatography (pentane/EtOAc, 9/1) yielding 1.49 g (6.23 mmol, 63% from **3f**) of **6f**. ^{1}H NMR ($CDCl_3$) δ: 1.75 (br s, 1H), 2.46 (s, 3H), 4.98 (q, J=7.2, 1H), 7.50–7.60 (m, 3H), 7.74 (d, J=7.1, 1H), 7.90 (m, 2H), 8.14 (d, J=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.8, 61.3 (q, J=29.5), 122.7, 123.3, 125.3, 125.6, 125.8, 125.9 (q, J=281.2), 126.7, 129.0, 129.5, 130.2, 134.0. ^{19}F NMR ($CDCl_3$) δ: −76.0 (d, J=6.9). HRMS (ESI): 240.0998 (calcd $C_{13}H_{13}F_3N^+$, M+H$^+$, 240.0995). IR (neat, cm^{-1}): 3353, 3053, 2972, 2867, 2802.

4.5. Potential anti-fungicidal compounds

*4.5.1. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine (**1b**).* *N*-Methyl-1-(naphthalen-1-yl)ethanamine (**6b**) (370 mg, 2.00 mmol), *N*,*N*-diisopropylethylamine (391 mg, 3.03 mmol), 1-(bromomethyl)-4-*tert*-butylbenzene (500 mg, 2.20 mmol) and acetonitrile (5 mL) were mixed and stirred at reflux under a N_2 atmosphere for 2 h. The solvent was removed at reduced pressure and dichloromethane (5 mL) was added. The dichloromethane phase was washed with water (5 mL) and the water phase was back extracted with dichloromethane (3×5 mL). The combined organic fractions were dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by silica-gel column chromatography (pentane/EtOAc, 9/1). This gave 540 mg (1.63 mmol, 82%) of colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.29 (9H, s), 1.55 (3H, d, J=6.7), 2.20 (3H, s), 3.39 (1H, d, J=13.5), 3.62 (1H, d, J=13.5), 4.38 (1H, q, J=6.7), 7.18 (2H, m), 7.28 (2H, m), 7.35–7.56 (3H, m), 7.65 (m, 1H), 7.74 (1H, d, J=8.5), 7.85 (1H, m), 8.45 (1H, d, J=7.8). ^{13}C NMR ($CDCl_3$) δ: 16.5, 34.4, 38.4, 58.7, 60.4, 124.5, 124.7, 125.0 (2C), 125.2, 125.3, 125.4, 127.4, 128.4 (2C), 128.6, 131.9, 31.4 (3C), 134.1, 137.1, 140.7, 149.5. HRMS (ESI): 332.2378 (calcd for $C_{24}H_{30}N^+$, M+H$^+$, 332.2373). IR (neat, cm^{-1}): 3045, 2948, 1516, 1249, 800 and 772.

*4.5.2. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine ((R)-**1b**).* Compound (*R*)-**1b** was synthesised as described for

1b starting with (*R*)-**6b** (370 mg, 2.00 mmol) from Aldrich, giving 403 mg (1.22 mmol, 61%) of (*R*)-**1b** as a colourless oil. ^{1}H and ^{13}C NMR were identical with that of *rac*-**1b**, ee: 99.5% (CHIROBIOTIC V2), $[\alpha]_D^{25}$ −56.1 (*c* 1.0, MeOH).

*4.5.3. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine ((S)-**1b**).* Compound (*S*)-**1b** was synthesised as described for **1b** starting with (*S*)-**6b** (370 mg, 2.00 mmol) from Aldrich, giving 467 mg (1.41 mmol, 70%) of (*R*)-**1b** as a colourless oil. ^{1}H and ^{13}C NMR spectra were identical with that of *rac*-**1b**, ee: 98.5% (CHIROBIOTIC V2), $[\alpha]_D^{25}$ 54.3 (*c* 1.0, MeOH).

*4.5.4. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)propan-1-amine (**1c**).* Compound **1c** was synthesised as described for **1b** starting with **6c** (390 mg, 1.99 mmol). Purification by silica-gel column chromatography (pentane/EtOAc, 9/1) gave 562 mg (1.63 mmol, 82%) of **1c** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 0.78 (t, *J*=7.3, 3H), 1.29 (s, 9H), 2.10 (m, 2H), 2.22 (s, 3H), 3.37 (d, *J*=13.1, 1H), 3.60 (d, *J*=13.1, 1H), 4.12 (m, 1H), 7.16–7.18 (m, 2H), 7.24–7.29 (m, 2H), 7.43–7.51 (m, 3H), 7.58 (d, *J*=6.8, 1H), 7.74 (d, *J*=8.4, 1H), 7.83–7.84 (m, 1H), 8.41 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.1, 23.5, 31.4 (3C), 34.4, 38.8, 59.0, 65.9, 124.6, 124.9 (2C), 125.0, 125.2, 125.4, 125.6, 127.4, 128.4 (2C), 128.7, 132.6, 134.2, 137.2, 137.9, 149.5. HRMS (ESI): 346.2520 (calcd $C_{25}H_{32}N^+$, M+H$^+$, 346.2529). IR (neat, cm^{-1}): 2960, 2871, 2783, 1510, 1361, 1267, 776.

*4.5.5. N-(4-tert-Butylbenzyl)-2-fluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**1d**).* *N*-(4-*tert*-Butylbenzyl)-2-fluoro-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**1d**) was prepared as described for **1b** starting with **6d** (200 mg, 0.98 mmol). The product was purified by silica-gel column chromatography using pentane/EtOAc (20/1) as eluent. This gave 294 mg (0.84 mmol, 86%) of an oil. ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 9H), 2.33 (d, *J*=1.9, 3H), 3.53 (d, *J*=13.4, 1H), 3.71 (d, *J*=13.4, 1H), 4.56 (ddd, *J*=21.0, 6.8, 3.4, 1H), 4.79 (ddd, *J*=47.8, 10.0, 3.4, 1H), 5.03 (ddd, *J*=47.6, 10.0, 6.8, 1H), 7.18–7.24 (m, 2H), 7.28–7.35 (m, 2H), 7.43–7.60 (m, 3H), 7.69 (d, *J*=7.0, 1H), 7.81 (d, *J*=8.2, 1H), 7.88 (m, 1H), 8.35 (d, *J*=8.3, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.4 (3C), 34.4, 39.2, 59.3 (d, *J*=1.8), 65.3 (d, *J*=18.7), 84.9 (d, *J*=175.6), 123.9, 125.1 (2C), 125.3, 125.6, 125.7, 126.0, 128.3 (2C), 128.4, 128.9, 131.8, 134.2, 135.1 (d, *J*=7.8), 136.5, 149.7. ^{19}F NMR ($CDCl_3$) δ: −213.3 (dt, *J*=47.0, 20.3). HRMS (ESI): 350.2284 (calcd for $C_{24}H_{29}FN^+$, M+H$^+$, 350.2279). IR (neat, cm^{-1}): 3045, 2964, 1508, 1197, 812 and 776.

*4.5.6. N-(4-tert-Butylbenzyl)-2,2-difluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**1e**).* Compound **1e** was prepared as described for **1b** starting with **6e** (448 mg, 2.02 mmol). The reaction was run for 48 h. The product was purified by silica-gel column chromatography using pentane/EtOAc (20/1) as eluent. This gave 660 mg (1.80 mmol, 90%) of an opaque oil, which solidified at 0 °C. ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 9H), 2.39 (s, 3H), 3.66 (d, *J*=13.8, 1H), 3.81 (d, *J*=13.8, 1H), 4.69 (td, *J*=12.8, 4.4, 1H), 6.69 (dt, *J*=55.3, 4.4, 1H), 7.15 (d, *J*=8.2, 2H), 7.28 (d, *J*=8.2, 2H), 7.48 (t, *J*=7.7, 1H), 7.54 (m, 2H), 7.65 (d, *J*=7.1, 1H), 7.84 (d, *J*=8.1, 1H), 7.88 (m, 1H), 8.20 (d, *J*=8.3, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.3 (3C), 34.4, 38.8, 58.8, 65.6 (t, *J*=21), 117.3 (t, *J*=247.0), 124.1, 124.8, 125.1 (2C), 125.7, 126.2, 126.5, 128.3 (2C), 128.8 (2C), 131.8, 132.5, 134.1, 136.1, 149.8. ^{19}F NMR ($CDCl_3$) δ: −120.8 (ddd, *J*=285.7, 56.2, 9.2), −123.3 (dd, *J*=285.7, 56.2). HRMS (ESI): 368.2182 (calcd $C_{24}H_{28}F_2N^+$, M+H$^+$, 368.2184). IR (neat, cm^{-1}): 3053, 2956, 2859.

*4.5.7. N-(4-tert-Butylbenzyl)-2,2,2-trifluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**1f**).* Compound **1f** was prepared as described for **1b** starting with **6f** (720 mg, 3.01 mmol) and reacting for 5 days. The product **1f** was purified by silica-gel column chromatography using pentane/EtOAc (9/1) as eluent. This gave 950 mg (2.46 mmol, 82%) of an off-white solid, mp 63–65 °C. ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 9H), 2.47 (s, 3H), 3.81 (d, *J*=13.8, 1H), 3.87 (d, *J*=13.8, 1H), 5.17 (q, *J*=8.7, 1H), 7.13(d, *J*=8.2, 2H), 7.30 (d, *J*=8.2, 2H), 7.51 (t, *J*=7.7, 1H), 7.58 (m, 2H), 7.80 (d, *J*=6.9, 1H), 7.90 (d, *J*=8.2, 1H), 7.92 (m, 1H), 8.06 (d, *J*=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.4 (3C), 34.4, 38.1, 58.0, 64.5 (q, *J*=26.1), 123.8, 124.8, 125.2 (2C), 125.8, 126.3, 126.5, 127.3 (q, *J*=290.7), 128.2 (2C), 129.0, 129.3, 129.6, 132.3, 134.1, 135.9, 150.0. ^{19}F NMR ($CDCl_3$) δ: −66.3 (s). HRMS (ESI): 386.2090 (calcd $C_{24}H_{27}F_3N^+$, M+H$^+$, 386.2090). IR (neat, cm^{-1}): 3037, 2964, 2859.

*4.5.8. 2-((4-tert-Butylbenzyl)(methyl)amino)-2-(naphthalen-1-yl)acetonitrile (**1g**).* Compound **1g** was prepared as described for **1b** starting with **6g** (191 mg, 0.97 mmol) and reacting for 4 h. The product was purified by silica-gel column chromatography using pentane/EtOAc (85/15) as eluent. This gave 250 mg (0.73 mmol, 75%) of white solid, mp 75–77 °C. ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 9H), 2.27 (s, 3H), 3.64 (d, *J*=12.9, 1H), 3.82 (d, *J*=12.9, 1H), 5.52 (s, 1H), 7.25–7.29 (m, 2H), 7.34–7.38 (m, 2H), 7.44–7.52 (m, 3H), 7.82–7.87 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 31.4 (3C), 34.6, 38.2, 59.0, 59.1, 115.3, 123.9, 124.7, 125.4 (2C), 126.2, 126.5, 127.0, 128.7, 129.0, 129.1 (2C), 130.0, 130.9, 134.0, 134.2, 150.9. HRMS (ESI): 343.2171 (calcd $C_{24}H_{27}N_2^+$, M+H$^+$, 343.2169). IR (neat, cm^{-1}): 2964, 2871, 1510, 1358, 1014, 778.

*4.5.9. (E)-N,6,6-Trimethyl-N-(1-(naphthalen-8-yl)ethyl)hept-2-en-4-yn-1-amine (**2b**).* *N*-Methyl-1-(naphthalen-1-yl)ethanamine (**6b**) (370 mg, 2.00 mmol), *N*,*N*-diisopropylethylamine (390 mg, 3.02 mmol) and *E*-1-chloro-6,6-dimethylhept-2-ene-4-yne (**8**) (340 mg, 2.17 mmol) were mixed in acetonitrile (5 mL), and refluxed under a N_2 atmosphere for 2 h. The solvent was removed at reduced pressure and dichloromethane (5 mL) was added. The dichloromethane phase was washed with water (5 mL). The water phase was back extracted with dichloromethane (3×5 mL). The combined organic fractions were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography using pentane/EtOAc (85/15) as eluent. This gave 370 mg (1.21 mmol, 61%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 1.46 (d, *J*=6.7, 3H), 2.25 (s, 3H), 2.97 (dd, *J*=14.5, 6.7, 1H), 3.16 (dd, *J*=14.5, 6.2, 1H), 4.26 (q, *J*=6.7, 1H), 5.58 (d, *J*=15.9, 1H), 6.04 (dt, *J*=15.9, 6.4, 1H), 7.37–7.52 (m, 3H), 7.56 (d, *J*=7.1, 1H), 7.73 (d, *J*=8.2, 1H), 7.83 (m, 1H), 8.38 (d, *J*=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.8, 27.9, 31.0, 38.9, 56.8, 60.3, 77.3, 98.1, 111.9, 124.2, 124.4, 125.3 (2C), 125.5, 127.4, 128.7, 131.7, 134.1, 140.1, 140.7. HRMS (ESI): 306.2212 (calcd $C_{22}H_{28}N^+$, M+H$^+$, 306.2216). IR (neat, cm^{-1}): 3053, 2964, 1443, 1192, 795 and 772.

*4.5.10. (E)-N-6,6-Trimethyl-N-(1-(naphthalen-1-yl)propyl)hept-2-en-4-yn-1-amine (**2c**).* Compound **2c** was prepared as described for **2b** starting with **6c** (400 mg, 2.01 mmol). The product **1f** was purified by silica-gel column chromatography using pentane/EtOAc (9/1) as eluent. This gave 350 mg (1.10 mmol, 55%) of an oil. ^{1}H NMR ($CDCl_3$) δ: 0.67 (t, *J*=7.3, 3H), 1.22 (s, 9H), 1.89–2.09 (m, 2H), 2.26 (s, 3H), 2.94 (ddd, *J*=1.3, 6.3, 14.7, 1H), 3.14 (ddd, *J*=1.3, 5.8, 14.7, 1H), 4.02 (br m, 1H), 5.55 (dt, *J*=1.3, 15.6, 1H), 6.02 (ddd, *J*=5.8, 6.3, 15.6, 1H), 7.40–7.50 (m, 4H), 7.74 (d, *J*=8.3, 1H), 7.83–7.85 (m, 1H), 8.39–8.40 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.8, 24.4, 27.9, 31.0 (3C), 39.3, 57.0, 66.8 (br), 77.3, 98.1, 111.9, 124.3, 125.0, 125.2, 125.5, 125.6, 127.4, 128.7, 132.5, 134.1, 137.8, 140.2. HRMS (ESI): 320.2377 (calcd $C_{23}H_{30}N^+$, M+H$^+$, 320.2373). IR (neat, cm^{-1}): 2966, 2870, 2785, 1509, 1361, 1264, 790, 776.

*4.5.11. (E)-N-(2-Fluoro-1-(naphthalen-1-yl)ethyl)-N-6,6-trimethylhept-2-en-4-yn-1-amine (**2d**).* Compound **2d** was prepared as described for **2b** starting with **6d** (163 mg, 0.80 mmol). The product **2d** was purified by silica-gel column chromatography using pentane/EtOAc (20/1) as eluent. This gave 102 mg (0.32 mmol, 41%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 2.37 (s, 3H), 3.06 (dd, *J*=14.7, 6.8, 1H), 3.22 (ddd, *J*=14.7, 5.9, 1.7, 1H), 4.46 (ddd, *J*=20.9, 6.6, 3.3, 1H), 4.67 (d, 48.0, 10.1, 3.3, 1H), 4.89 (ddd, *J*=47.5, 10.1, 6.6,

1H), 5.58 (dt, *J*=15.9, 1.5, 1H), 6.02 (ddd, *J*=15.9, 6.9, 5.9, 1H), 7.60–7.40 (m, 4H), 7.79 (d, *J*=8.3, 1H), 7.86 (m, 1H), 8.29 (d, *J*=8.2, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9 (3C), 31.0, 39.6, 57.3, 65.0 (d, *J*=20.5), 77.2, 85.1 (d, *J*=175.9), 98.3, 112.4, 123.6, 125.3, 125.6, 125.8, 126.1, 128.3, 128.9, 131.7, 134.1, 134.5 (d, *J*=7.5), 139.4. ^{19}F NMR ($CDCl_3$) δ: −212.6 (dt, *J*=47.6, 20.6). HRMS (ESI): 324.2127 (calcd $C_{22}H_{27}FN^+$, $M+H^+$, 324.2122). IR (neat, cm^{-1}): 3055, 2969, 1460, 1203, 804 and 774.

*4.5.12. (E)-N-(2,2-Difluoro-1-(naphthalen-1-yl)ethyl)-N-6,6-trimethylhept-2-en-4-yn-1-amine (**2e**).* Compound **2e** was prepared as described for **2b** starting with **6e** (370 mg, 1.67 mmol) and reacting for 6 days. The product **2e** was purified by silica-gel column chromatography using pentane/EtOAc, 40/1, then 9/1 as eluent. This gave 362 mg (1.06 mmol, 63%) of an opaque oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 2.39 (s, 3H), 3.13 (dd, *J*=14.8, 6.8, 1H), 3.27 (dd, *J*=14.8, 5.8, 1H), 4.55 (dt, *J*=12.9, 4.3, 1H), 5.56 (dt, *J*=16.0, 1.5, 1H), 5.96 (dt, *J*=16.0, 6.4, 1H), 6.30 (dt, *J*=55.1, 4.3, 1H), 7.40–7.57 (m, 4H), 7.78–7.87 (m, 2H), 8.20 (d, *J*=8.4, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 31.0 (3C), 39.3, 57.0, 65.7 (t, *J*=21.2), 77.2, 98.6, 112.7, 117.0 (t, *J*=246.9), 123.9, 124.9, 125.7, 126.3, 126.8, 128.9, 129.0, 131.6, 132.5, 134.1, 139.0. ^{19}F NMR ($CDCl_3$) δ: −120.9 (dd, *J*=285.7, 55.1), −123.3 (dd, *J*=285.7, 55.1). HRMS (ESI): 342.2042 (calcd $C_{22}H_{26}F_2N^+$, $M+H^+$, 342.2028). IR (neat, cm^{-1}): 3053, 2964, 2826.

*4.5.13. (E)-N,6,6-Trimethyl-N-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethyl)hept-2-en-4-yn-1-amine (**2f**).* Compound **2f** was prepared as described for **2b** starting with **6f** (430 mg, 1.80 mmol) and reacting for 10 days. The product **2f** was purified by silica-gel column chromatography using pentane/EtOAc 40/1, then 9/1 as eluent. This gave 286 mg (0.80 mmol, 44%) of an opaque oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 2.43 (s, 3H), 3.28 (dd, *J*=14.8, 6.2, 1H), 3.37 (dd, *J*=14.8, 6.6, 1H), 5.00 (q, *J*=8.7, 1H), 5.90 (dt, *J*=15.9, 6.2, 1H), 5.57 (dt, *J*=15.9, *J*=1.5, 1H), 7.44–7.59 (m, 3H), 7.67 (d, *J*=7.6, 1H), 7.85 (d, *J*=8.5, 1H), 7.88 (d, *J*=9.0, 1H), 8.05 (d, *J*=8.6, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 30.9, 38.3, 56.4, 64.3 (q, *J*=26.8), 77.2, 98.7, 112.6, 123.4, 124.7, 125.7, 126.3, 126.5, 127.0 (q, *J*=289.6), 129.0, 129.3, 129.4, 132.2, 134.0, 139.2. ^{19}F NMR ($CDCl_3$) δ: −67.3 (d, *J*=8.0). HRMS (ESI): 360.1936 (calcd $C_{22}H_{25}F_3N^+$, $M+H^+$, 360.1934). IR (neat, cm^{-1}): 3045, 2964, 2859.

*4.5.14. (E)-N-6,6-Trimethyl-N-(1-(naphthalen-1-yl)propyl)hept-2-en-4-yn-1-amine (**2g**).* Compound **2g** was prepared as described for **2b** starting with **6g** (200 mg, 1.02 mmol) reacting for 5 days. The product **2g** was purified by silica-gel column chromatography using pentane/EtOAc (85/15) as eluent. This gave 145 mg (0.46 mmol, 45%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.23 (s, 9H), 2.24 (s, 3H), 3.20 (ddd, *J*=13.9, 7.8, 1.0, 1H), 3.31 (ddd, *J*=13.9, 5.6, 1.8, 1H), 5.56 (s, 1H), 5.77 (dt, *J*=15.9, 1.3, 1H), 6.02 (ddd, *J*=15.9, 7.8, 5.6, 1H), 7.45–7.59 (m, 3H), 7.79 (d, *J*=7.3, 1H), 7.87–7.89 (m, 2H), 8.10 (d, *J*=8.0, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 30.9 (3C), 38.1, 56.9, 59.6, 76.7, 99.5, 114.5, 115.1, 123.8, 124.8, 126.3, 126.7, 126.9, 128.7, 128.8, 130.2, 130.8, 134.0, 137.1. HRMS (ESI): 317.2009 (calcd $C_{22}H_{25}N_2^+$, $M+H^+$, 317.2012). IR (neat, cm^{-1}): 2966, 2870, 1511, 1361, 1263, 792, 781.

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