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THÈSE

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Maria F. CESPEDES DAVILA

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New insights into the stereoselective synthesis of difluoromethylated building blocks of pharmaceutical interest

THÈSE dirigée par :

Dr Frédéric LEROUX	Directeur de Recherche CNRS, Université de Strasbourg
Dr Gilles HANQUET	Directeur de Recherche CNRS, Université de Strasbourg

RAPPORTEURS :

Pr Jean-François PAQUIN	Professeur, Université de Laval Québec
Pr Thierry LEQUEUX	Professeur, Université de Caen Normandie

MEMBRES DU JURY :

Dr Baptiste RONAN	Sanofi R&D, Small Molecule Medicinal Chemistry, Vitry-sur-Seine
Dr Armen PANOSSIAN	Chargé de Recherche CNRS, Université de Strasbourg

To my grandmother, Carmen A. Raza.

“Believe you can and you’re halfway there.”

T. Roosevelt

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Summary

Abbreviations

12-C-4: 12-crown-4 or 1,4,7,10-tetraoxacyclododecane

18-C-6: 18-crown-6 or 1,4,7,10,13,16-hexaoxacyclooctadecane

Boc: *t*-butoxy carbonyl

CFC: chlorofluorocarbons

DCM: dichloromethane

d.e.: diastereomeric excess

DET: diethyl tartrate

DIBAL-H : di-isobutyl aluminium hydride

DIPEA: *N*-ethyl-*N*-isopropylpropan-2-amine

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxyde

d.r.: diastereomeric ratio

e.e.: enantiomeric excess

e.r.: enantiomeric ratio

EFS: emergent fluorinated substituent

ESI: electrospray ionization

HFIP: Hexafluoropropan-2-ol

HMBC: heteronuclear multiple bond correlation

HMDS: hexamethyldisilazane

HPLC: high performance liquid chromatography

HRMS: high resolution mass spectroscopy

IR: infrared

HMPA: hexamethylphosphoramide

KHMDS: potassium bis(trimethylsilyl)amide

LiHMDS: lithium bis(trimethylsilyl)amide

LDA: lithium diisopropylamide

m-CPBA: *m*-chloroperoxybenzoic acid

4Å MS: molecular sieves (4Å)

MW : microwave irradiation

n.d.: non-determined

NMP: N-methyl-2-pyrrolidone

NFSI: *N*-fluorosuccinimide

NMR: nuclear magnetic resonance

PDC: pyridinium dichromate

PMHS : polymethylhydrosiloxane

PTFE: polytetrafluoroethylene

r.t.: room temperature

Selectfluor®: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

TBAF: tetra-*n*-butylammonium fluoride

TBDMSCl: *tert*-butyldimethylsilyl chloride

TBHP: *tert*-butyl hydroperoxide

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid

TFAA: trifluoroacetic anhydride

TLC: thin layer chromatography

TMAF: tetramethylammonium fluoride

TMEDA: *N*,*N*,*N*',*N*'-tetramethylethylene diamine

TMS: trimethylsilyl

TOF: time of flight spectroscopy

THF: tetrahydrofuran

Ts: *p*-Toluenesulfonyl

General considerations for the experimental sections

Unless otherwise noted, reactions were conducted in oven-dried glassware under inert atmosphere of argon with anhydrous solvents. Liquids and solutions were transferred with syringes. The solvents and reagents were dried and purified when necessary according to standard procedures. All commercial reagents were used as received. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F254 plates and analysed by UV (254 nm). Melting points (MP) were determined with a Büchi M-560 apparatus. Specific rotations $[\alpha]_D$ were determined at 20 ºC on a Anton Paar MCP 200 polarimeter. The concentration (c) is indicated in decagram per liter (dag/L). IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Perkin Elmer UATR Two spectrometer coupled to a diamond window ATR and only the more representative frequencies are reported. ^{1}H NMR (300, 400 or 500 MHz), ^{19}F NMR (376 or 471 MHz) and ^{13}C NMR (101 or 126 MHz) spectra were recorded on a Bruker Avance III HD 300, 400, and 500 MHz instruments respectively and calibrated using residual undeuterated or deuterated solvent ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm, DMSO: δH = 2.54 ppm) as an internal reference. Chemical shifts (δ) are quoted in ppm, coupling constants are quoted in Hertz (Hz); data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; m, multiplet (and their corresponding combinations); carbon multiplicities were assigned on the basis of Distorsionless Enhacement by Polarization Transfer (DEPT) experiments. ^{1}H, ^{19}F and ^{13}C signals were assigned by COSY, HSQC, and HMBC experiments. The spectra were processed with the program MestreNova (Mestrelab). High-resolution mass spectra (HRMS) were performed by the analytical facility at the University of Strasbourg (measurement accuracy ≤ 15 ppm) with a Bruker MicroTOF Spectrometer. Crude mixtures were purified by flash chromatography on silica gel 60 (230-400 mesh, 0.040-0.063 mm) purchased from Merck, which was demetalled when required by treatment with hydrochloric acid prior to its use. Automatic flash chromatographies were carried out in an Interchim puriFlash® system equipped with UV/Vis and ELSD detectors or a Teledyne Isco Combi*Flash*® Rf^{+} system equipped with UV/Vis detectors. The X-ray crystallographic structure analysis was performed by the radiocrystallographic facility at the Université de Strasbourg. The analysis was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N2 device, using Mo-Kα radiation (λ = 0.71073 Å). The X-ray crystallographic structure analysis was performed by the radiocrystallographic facility at the Université de Strasbourg. The analysis was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N2 device, using Mo-Kα radiation (λ = 0.71073 Å).

Résumé de thèse

Nouvelles voies d'accès à des composés difluorométhylés énantioenrichis d'intérêt pharmaceutique

Table des matières

A. Introduction: Le fluor, un élément essentiel

Le fluor est le 9ème élement du tableau périodique et le 13ème le plus abondant dans la croûte terrestre. L'introduction d'un atome de fluor ou d'un groupement fluoré dans une molécule permet d'améliorer remarquablement ses propriétés physico-chimiques, à savoir une plus grande stabilité métabolique et de meilleures biodisponibilité, lipophilie et perméabilité.[1–4] Une importance croissante a été accordée lors des dernières décennies à la synthèse de synthons et principes actifs fluorés, qui représentent de nos jours une grande partie des composés pharmaceutiques et agrochimiques.[5–8]

Un aperçu de cet élément depuis sa découverte jusqu'à ses nombreuses applications sera brièvement présenté dans cette partie.

1. Historique

La première mention du fluor date de 1530 par G. Agricola, qui a décrit le spath fluor (fluorure de calcium) et son utilisation pour abaisser le point de fusion de nombreux minerais et permettre leur liquéfaction.[9] Des archives historiques décrivent à leur tour l'utilisation de minéraux fluorés dans la fabrication de vases.[10,11]

Malgré ces constatations, ce ne fut que quelques siècles plus tard qu'un intérêt croissant est survenu dans l'isolement du fluor. Des scientifiques reconnus tels que A.L. de Lavoisier, L. J. Thénard et J. L. Gay-Lussac ont décrit leurs observations concernant la très haute réactivité de l'acide fluorhydrique. De nombreux chercheurs, surnommés par la suite ''les martyrs du fluor'', ont subi de graves brûlures au contact de l'acide fluorhydrique, suivies de maladies et décès dus à la toxicité des composés fluorés qu'ils étudiaient.

Sir H. Davy et E. Frémy ont tenté une nouvelle méthode d'isolement du fluor élémentaire, à savoir par électrolyse de sels fluorés. Le succès de l'isolement est cependant attribué à Henri Moissan, qui réussit à électrolyser le fluorure de potassium. L'élaboration du four à arc électrique ainsi que sa découverte dans le monde du fluor lui ont valu le prix Nobel de chimie en 1906.[12]

2. Le fluor dans la nature

Malgré le fait que le fluor soit largement présent dans la croûte terrestre, il est pratiquement absent des processus biologiques. En effet, le fluor se trouve principalement sous forme minérale, tel que pour le fluorspar, la cryolite Na_3AlF_6 ou la fluorapatite $Ca_{10}(PO_4)_6F_2$. Les métabolites présentant des atomes de fluor sont très rares. Ils se dénombrent à seulement 12 « espèces », contrairement au plus large nombre de composés naturels contenant d'autres halogènes tels que le brome ou bien l'iode.[13–15]

3. Propriétés du fluor et de la liaison C-F

Le fluor, représenté par le symbole F, a une configuration électronique $1s^2 2s^2 2p^5$ et représente le premier halogène du tableau périodique. C'est l'élément le plus électronégatif (3,98 sur l'échelle de Pauling), et a un rayon de Van der Wals de 1,47 Å. Sa masse molaire est de 18,99 $g.mol^{-1}$ et sa première énergie d'ionisation a une valeur très élevée de 402.15 $kcal.mol^{-1}$, derrière l'hélium et le néon.[16]

Le seul isotope stable existant du fluor est le ^{19}F, composé de 10 neutrons. Cet isotope présente une excellente sensibilité vis-à-vis des champs magnétiques et est très couramment utilisé en spectroscopie de Résonance Magnétique Nucléaire (RMN). L'isotope artificiel ^{18}F a été découvert en 1936 et grâce à son temps de demi-vie de 109,7 min, supérieur à celui des radionucléides les plus courants, il représente aujourd'hui un outil remarquable pour la tomographie à émission de positon (PET) en imagerie médicale.[17-20] L'introduction de composés comportant cet isotope dans le corps humain et sa détection permettent d'obtenir des informations concernant les processus biologiques dans lesquels ils sont impliqués.

D'autre part, la liaison C-F est une des plus fortes liaisons en chimie organique. Sa longueur se trouvant entre celles des liaisons C-O et C-H (**Tableau 1**). Le fluor est souvent utilisé en chimie médicinale pour remplacer un atome d'hydrogène.[16]

Tableau 1. Comparaison des longueurs et énergies de différentes liaisons en chimie organique

	C-F	C-H	C-O	C-C	C-Cl	C-Br	C-N
Longueur de liaison (Å)	1,35	1,09	1,43	1,54	1,77	1,97	1,47
Energie de liaison ($kcal.mol^{-1}$)	105	98	84	83	77	66	70

La forte électronégativité de l'atome de fluor ainsi que sa petite taille rendent la liaison C-F fortement polarisée (**Schéma 1**).

Schéma 1. Comportement dipolaire de la liaison C-F

De plus, l'introduction du fluor dans un composé organique induit des modifications électroniques dans les liaisons adjacentes. Les trois paires d'électrons non-liantes de l'atome de fluor entraînent des effets dits "push and pull" des liaisons voisines (**Schéma 2**).[21,22]

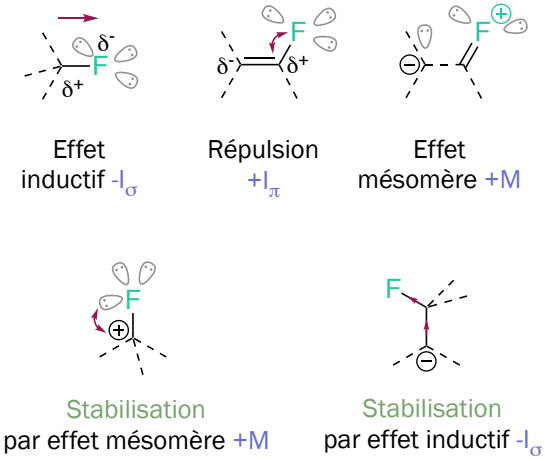


Schéma 2. Effets électroniques du fluor

Des effets mésomères donneurs +M ou inductifs donneurs $+I_x$ permettent la stabilisation des carbocations en position α et augmentent l'acidité des protons voisins. Les carbanions sont stabilisés en position β par un effet inductif attracteur $-I_x$.

4. Le fluor et ses applications

Comme nous avons pu le remarquer, les caractéristiques des liaisons fluorées ainsi que les effets induits par celles-ci dans les molécules organiques peuvent fortement influencer les propriétés des composés organiques. De ce fait, diverses utilisations industrielles de composés organofluorés connaissent de nos jours un essor considérable.[21,23]

Par le passé, les chlorofluorocarbones (CFC) ont joué un rôle majeur dans le domaine des réfrigérants, des climatisations et des aérosols. Cependant leur effet néfaste sur la couche d'ozone fait que leur utilisation est actuellement interdite.[24,25] Les composés organofluorés sont aussi présents dans l'industrie nucléaire notamment dans le processus d'enrichissement de l'uranium ^{235}U,[26,27] ainsi que dans le domaine des polymères, notamment avec la marque déposée Téflon®. De plus, des minéraux fluorés tels que le fluorure de sodium NaF, le fluorure d'étain SnF_2 ou le monofluorophosphate de sodium Na_2PO_3F inclus dans les dentifrices préviennent la formation de caries.[28–30]

Récemment, des applications dans le domaine des matériaux fluorés voient le jour. Les nanomatériaux fluorés pourraient en effet représenter une alternative aux batteries au lithium.[31,32]

Finalement, l'introduction d'un atome de fluor ou d'un groupement fluoré s'est révélé être une méthode de choix pour améliorer les propriétés de composés biologiquement actifs dans les domaines pharmaceutique ou agrochimique.[4,5,33,34]

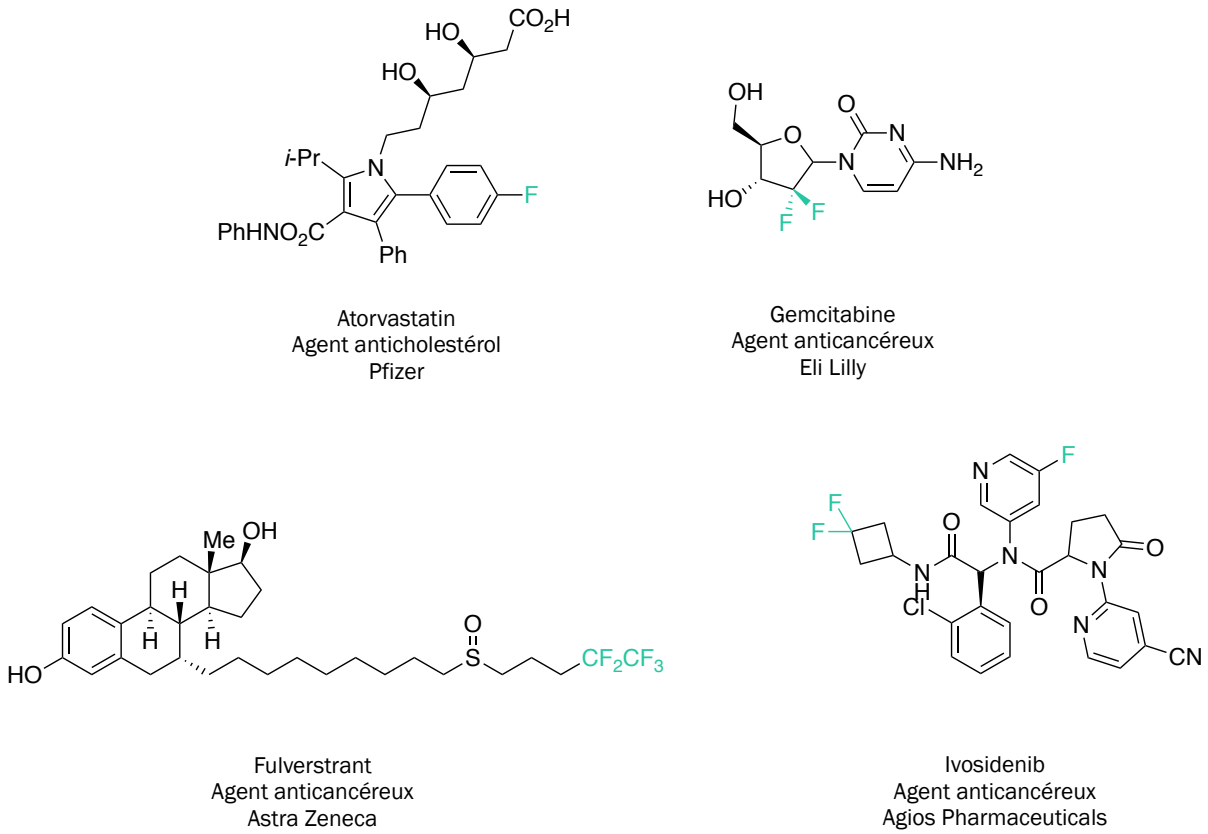
5. Contribution du fluor en chimie pharmaceutique et en agrochimie

La conception de molécules bioactives dans les domaines pharmaceutique ou agrochimique doit tenir compte d'un certain nombre de paramètres afin d'obtenir des composés avec des propriétés physico-chimiques et pharmacologiques intéressantes.[3]

L'introduction du fluor est utilisée pour moduler des paramètres tels que le pKa et la lipophilie (permettant d'améliorer la biodisponibilité), la conformation et la formation de liaisons hydrogène (influençant l'affinité du composé avec sa cible) ainsi que la stabilité métabolique pour limiter la dégradation du principe actif et avoir une bonne biodisponibilité.[22,35–40]

Compte tenu de ces améliorations qui peuvent être apportées par le fluor, et malgré son absence des composés naturels, un nombre croissant de molécules fluorées sont actuellement présentes sur le marché. Environ 20% de composés pharmaceutiques (18 sur 59 approuvés en 2018 par l'agence des produits alimentaires et médicamenteux aux Etats-Unis, FDA) et 30% des ingrédients phytosanitaires comportent du fluor.[3,6–8,41] Certains exemples sont présentés dans le **Schéma 3**.

Produits pharmaceutiques



Atorvastatin
Agent anticholestérol
Pfizer

Gemcitabine
Agent anticancéreux
Eli Lilly

Fulverstrant
Agent anticancéreux
Astra Zeneca

Ivosidenib
Agent anticancéreux
Agios Pharmaceuticals

Schéma 3. Exemples de composés pharmaceutiques fluorés sur le marché

6. Le groupement -CHF_2

En plus de ces propriétés communes aux groupements fluorés, le groupement -CHF_2 possède des propriétés spécifiques intéressantes. En effet, il a un caractère inductif attracteur important et a la capacité d'être engagé dans des liaisons hydrogène.[42–48] De plus, ce groupement permet d'obtenir des composés ayant une meilleure lipophilie afin de mieux traverser les membranes cellulaires dans l'organisme.[44,49] Finalement, il est aussi fréquemment considéré comme un bioisostère des fonctions alcool ou thiol.[40,50–54]

Lors de ce projet de thèse, nous nous sommes particulièrement intéressés à ce groupement fluoré.

7. Objectifs du projet

Les propriétés attrayantes du groupement -CHF_2 décrites précédemment ainsi que le nombre limité d'exemples de difluorométhylation énantiosélective dans la littérature nous ont amené à nous intéresser au développement de nouvelles méthodes de synthèse efficaces pour accéder à des briques moléculaires difluorométhylés potentiellement valorisables en chimie médicinale.[55–58]

La stratégie de ce projet consiste à utiliser un sulfoxyde difluorométhylé énantiopur en tant que variante chirale du difluoromethane afin d'étudier l'introduction stéréosélective du groupement difluorométhyle. Cette approche nous a permis de développer des voies d'accès à une librairie de composés qui, après désulfinylation, a donné accès à des molécules difluorométhylées de haute pureté optique.

Dans un premier temps, des études complémentaires à celles réalisées précédemment dans le groupe ont été faites concernant la synthèse du sulfoxyde difluorométhylé énantiopur et sa stabilité optique. La synthèse d'un dérivé halogéné et d'un dérivé silylé de ce sulfoxyde difluorométhylé a aussi été étudiée.

Dans un second temps, inspirés par les travaux réalisés dans le groupe pour la synthèse d'alcools difluorométhylés, nous nous sommes concentrés sur le développement d'une voie alternative de synthèse de ces composés, basée sur la réduction stéréosélective de β-cétosulfoxydes α-difluorés, ainsi que leur fonctionnalisation. Afin d'évaluer l'introduction du carbanion du sulfoxyde difluorométhylé sur une plus large gamme d'électrophiles, sa condensation a été étudiée sur des groupements carbonylés, des imines activées, des nitrones ainsi que des dérivés α,β-insaturés.

Par la suite, une sélection de composés difluorométhylés intéressants en chimie médicinale a été effectuée afin de s'intéresser à leur fonctionnalisation. Les méthodes de fonctionnalisation qui ont été étudiées consistent en des réactions de type Mitsunobu ou de substitutions nucléophiles aromatiques. Il a donc aussi été possible d'accéder à des synthons présents dans des composés biologiquement actifs par voie non-asymétrique, et la rétention de configuration lors des différentes étapes a pu être confirmée dans la voie énantiosélective.

Finalement, la rupture de la liaison C-S avec rétention de configuration du centre stéréogène créé a été étudiée afin d'accéder aux produits difluorométhylés

énantioenrichis souhaités. Différentes méthodes décrites dans la littérature sur des analogues non fluorés ont été évaluées, et notamment afin de remédier aux difficultés rencontrées avec ces méthodes sur nos composés, une nouvelle voie a été mise en place. Les différents résultats obtenus au cours de ce projet seront succinctement décrits dans ce résumé.

B. Chapitre I - Synthèse de sulfoxydes difluorométhylés énantiopurs

Les sulfoxydes énantiopurs ont été largement utilisés en synthèse asymétrique en tant qu'auxiliaires de chiralité afin d'obtenir des composés hautement énantioenrichis.[59-61]

L'utilisation de ces auxiliaires associés à un groupement fluoré émergent, tel que le -CHF_2, représente la base de ce projet afin d'obtenir des composés fluorés énantioenrichis. En effet, ce sulfoxyde difluorométhylé a été utilisé en tant qu'équivalent du groupement -CHF_2, qui, après déprotonation est additionné sur une gamme d'électrophiles (**Schéma 4**).

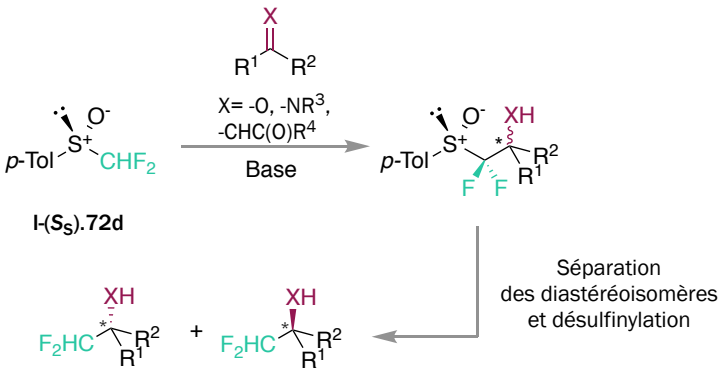


Schéma 4. Stratégie d'accès à des composés difluorométhylés énantioenrichis

1. Synthèse de sulfoxydes énantiopurs difluorométhylés

Dans un premier temps, nous nous sommes intéressés à la synthèse de ce sulfoxyde, préalablement décrit dans la littérature à 2 reprises, et ce, sans avoir été valorisée pour la synthèse de dérivés difluorométhylés énantioenrichis.[62,63]

Une méthodologie préalablement développée au sein de l'équipe utilisant une réaction de type Reformatsky ainsi que des tests complémentaires nous ont permis d'accéder au difluorométhyl *p*-tolyl sulfoxyde en versions racémique et énantiopure (**Schéma 5**).

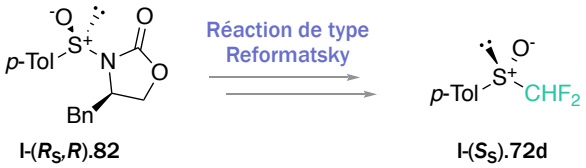


Schéma 5. Voie d'accès au *p*-tolyl sulfoxyde difluorométhylé

2. Synthèse de sulfoxydes halogénés ou silylés à partir du sulfoxyde difluoré énantiopur

Ce composé ayant été synthétisé efficacement à l'échelle multigrammes, nous avons également essayé d'accéder à des dérivés halogénés ou silylés de ce sulfoxyde difluoré. Ces composés ouvriraient la voie à d'autres réactivités, comme par exemple des substitutions nucléophiles ou des réactions de type Reformatsky dans le cas du composé halogéné. De nombreux essais nous ont finalement permis d'accéder au sulfoxyde bromodifluorométhylé. Cependant, le composé silylé n'a pas pu être synthétisé jusqu'à présent (**Schéma 6**).

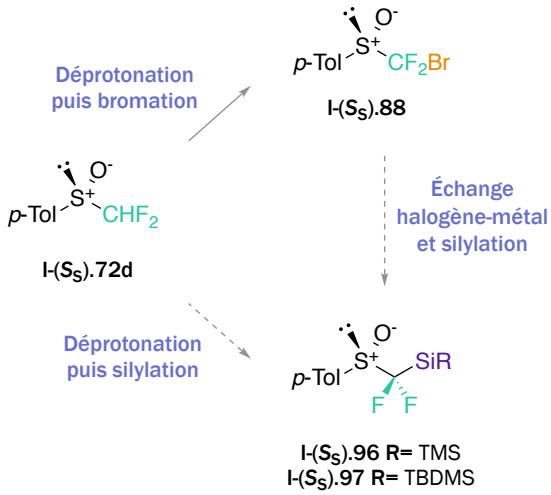


Schéma 6. Accès à des dérivés halogéné ou silylé de sulfoxydes difluorométhylés

C. Chapitre II - Accès diastéréosélectif à des composés β-difluorés grâce à l'utilisation de sulfoxydes énantiopurs en tant qu'auxiliaires chiraux

1. Accès à des β-hydroxysulfoxydes α-difluorés

Dans notre groupe de recherche, une voie d'accès à des β-hydroxysulfoxydes α-difluorés a été développée par condensation de l'anion du difluorométhyle *p*-tolyl sulfoxyde **I-(S_S).72d** sur des composés carbonylés.[64,65] Le prolongement de cette stratégie nous a permis d'obtenir des composés diastéréoenrichis (**Schéma 7**).

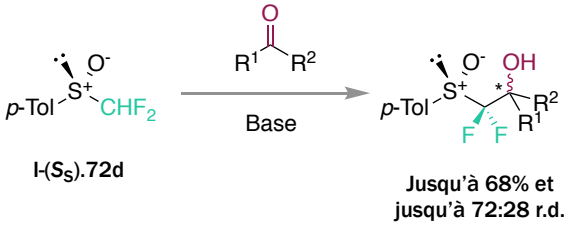
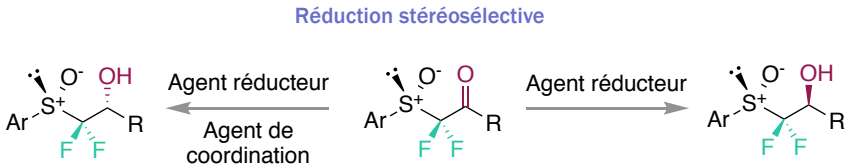


Schéma 7. Accès à des α-difluoro-β-sulfinylalcools par addition du difluorométhyl *p*-tolyl sulfoxyde sur des composés carbonylés

Certains composés sélectionnés pour l'intérêt de leurs motifs en chimie pharmaceutique ont pu être synthétisés par ce biais.

D'un autre côté, nous nous sommes intéressés à une voie d'accès alternative à ces composés, à savoir la réduction stéréosélective de β-cétosulfoxydes α-difluorés, qui donne généralement d'excellents résultats dans la littérature en série non fluorée (**Schéma 8**).[66,67]



Dans un premier temps, un β-cétosulfoxide α-difluoré a été obtenu par oxydation du β-hydroxysulfoxyde α-difluoré correspondant. Afin de développer une méthode plus efficace et générale, nous avons essayé de synthétiser ce composé par condensation de l'anion du sulfoxyde difluorométhylé sur différents électrophiles tels que des chlorures d'acyles, des esters ou encore des anhydrides carboxyliques. Cependant, dans le meilleur des cas le β-cétosulfoxyde souhaité a été obtenu avec un rendement moyen de 30%. Cette méthode n'étant donc pas très efficace, nous avons ensuite essayé de synthétiser ce composé en difluorant un β-cétosulfoxyde avec deux équivalents d'un agent de fluoration en présence de base. Différentes

bases ainsi que d'agents de fluoration électrophiles ont été testés et ont permis d'accéder au composé souhaité, mais malheureusement une fragmentation au niveau de la liaison C-C donnant le difluorométhyl *p*-tolyl sulfoxyde **II.72d** a été également observée (**Schéma 9**).

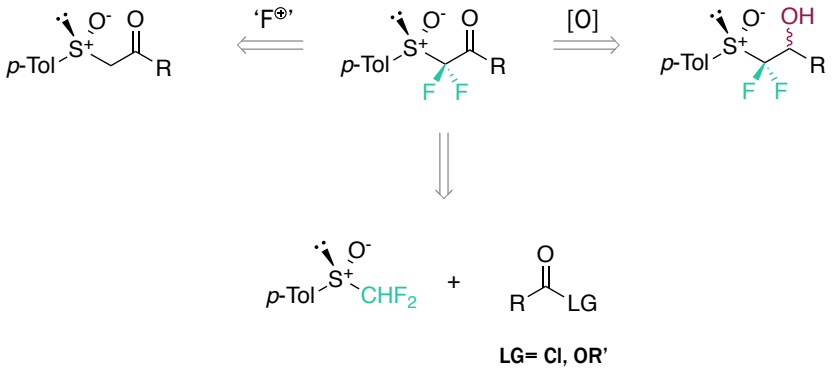


Schéma 9. Voies d'accès utilisés pour accéder à des β-cetosulfoxydes α-difluorés

Nous avons soumis ces β-cétosulfoxides α-difluorés à une réduction stéréosélective. Différents agents réducteurs ont été évalués et les meilleurs résultats ont été obtenus avec DIBAL-H. D'excellents ratios diastéreoisomériques ont été obtenus, nous permettant d'accéder à des alcools hautement énantioenrichis (**Schéma 10**).

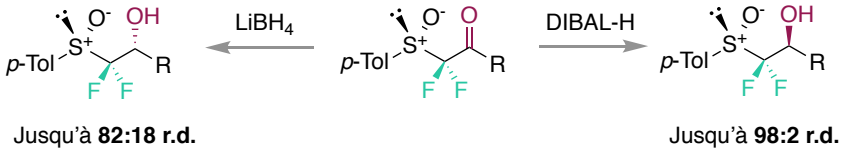


Schéma 10. Réductions stéréosélectives de β-cétosulfoxydes α-difluorés

D'autre part, nous avons souhaité comparer l'efficacité de la difluorométhylation avec notre sulfoxyde difluorométhylé sur un groupe de dérivés carbonylés plus particuliers, à savoir des aminoaldéhydes. En effet, les produits obtenus seraient des amino-alcools difluorométhylés, qui représenteraient un intérêt dans les projets de chimie pharmaceutique. La réaction a été effectuée sur certains substrats modèles, puis sur un aminoaldéhyde particulier préparé par l'équipe de chimie médicinale de Sanofi. Ceci nous a permis par la suite d'obtenir un composé cible qui pourra être utilisé prochainement dans le cadre d'un des projets de chimie médicinale (**Schéma 11**).

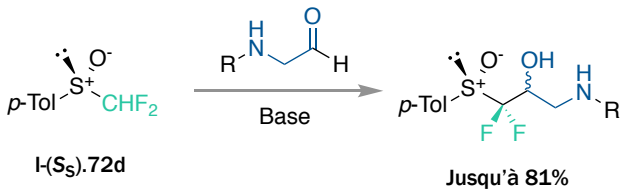


Schéma 11. Addition du *p*-tolyl sulfoxyde difluorométhylé sur des amino aldéhydes

2. Addition de l'anion du difluorométhyl *p*-tolyl sulfoxyde sur une gamme d'électrophiles

Afin de donner accès à une librairie de composés plus large, nous avons souhaité étudier l'introduction du carbanion du sulfoxyde difluorométhylé sur d'autres électrophiles que les groupements carbonylés précédemment étudiés. Pour ce faire, des substrats modèles tels que des imines activées, des nitrones ainsi que des dérivés α,β-insaturés ont été utilisés.

Dans le cas des imines, nous avons pu obtenir les composés aminés difluorés avec des rendements acceptables. De la même manière, nous avons réussi à séparer chacun des diastéréoisomères obtenus du produit issu du substrat modèle, la *N*-tosylbenzaldimine (**Schéma 12**).

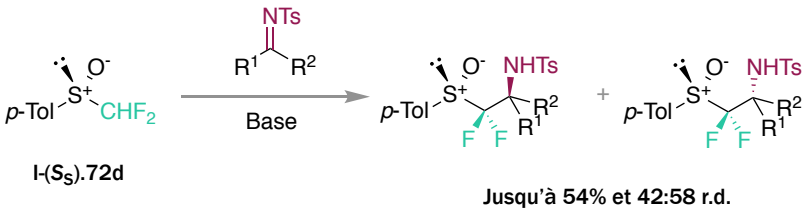


Schéma 12. Addition du *p*-tolyl sulfoxyde difluorométhylé sur des imines

Malheureusement, dans le cas des nitrones, la condensation du carbanion du sulfoxyde difluorométhylé ne nous a pas permis d'accéder aux dérivés difluorométhylés attendus.

En ce qui concerne les cétones α,β-insaturées, nous nous sommes intéressés à la réactivité du sulfoxyde difluorométhylé dans des additions nucléophiles conjuguées. Le but étant d'obtenir les dérivés d'addition 1,4, différentes conditions ont étés testées malheureusement sans succès. Les essais réalisés nous ont donné accès aux produits d'addition 1,2.

3. Utilisation du bromodifluorométhyl sulfoxyde en tant que réactif alternatif de difluorométhylation

Dans la première partie, nous avons décrit l'intérêt que nous avons porté à la synthèse de dérivés bromé et silylés du difluorométhyl *p*-tolyl sulfoxyde. Nous avons réussi à accéder en premier par déprotonation et bromation avec un réactif de bromation électrophile. Il a donc été testé en tant que réactif de difluorométhylation, afin de comparer sa réactivité à celle de l'anion du *p*-tolyl sulfoxyde difluorométhylé. Dans ce but, nous avons donc utilisé le benzaldéhyde en tant qu'électrophile. Différentes conditions de réaction de type Reformatsky ont été essayées en présence de dérivés zinciques et d'indium. Toutefois, les produits souhaités n'ont pas été obtenus et nous avons pu uniquement observer la réduction, plus ou moins importante en fonction des cas, du *p*-tolyl sulfoxyde bromodifluorométhylé en difluorométhyl *p*-tolyl sulfoxyde (**Schéma 13**). Nous n'avons donc pas poursuivi cette voie.

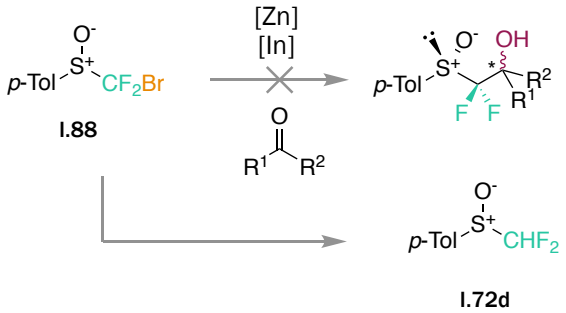


Schéma 13. Essais de réaction de type Reformatsky à partir du *p*-tolyl sulfoxyde bromodifluoré

D. Chapitre III - Fonctionnalisation de dérivés difluorométhylés préalablement obtenus

L'accès à des composés difluorométhylés optiquement purs a été étudié tout au long de ce projet. Afin de valoriser ces différents composés, nous nous sommes proposé d'étudier leur désulfinylation ainsi que leur fonctionnalisation.

1. Désulfinylation

Dans les parties précédentes, nous avons décrit l'étude qui a été effectuée lors de ce projet afin d'accéder à des composés difluorométhylés optiquement purs. Nous avons utilisé des sulfoxydes en tant qu'auxiliaires chiraux portant le groupement -CHF_2. Une fois que le groupement a été introduit sur le partenaire de réaction, il est indispensable de couper la liaison C-S avec rétention de configuration du carbone stéréogène afin d'obtenir les composés énantioenrichis souhaités. Nous avons rencontré des difficultés à effectuer cette coupure par des méthodes auparavant décrites sur les analogues non fluorés.[68–71] Il a donc été nécessaire de faire de nombreux essais de désulfinylation et nous avons finalement réussi à trouver deux méthodes efficaces qui nous ont permis d'accéder à des composés difluorométhylés énantioenrichis (**Schéma 14**).

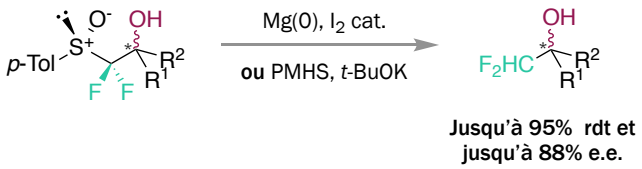


Schéma 14. Méthodes de retrait de l'auxiliaire de chiralité avec rétention de configuration

2. Réactions de type Mitsunobu

Afin d'accéder à d'autres dérivés difluorométhylés à partir de nos alcools précédemment synthétisés, nous avons étudié des réactions de type Mitsunobu. En effet, celles-ci pourraient ouvrir la voie à des dérivés aminés, portant le groupement -CHF_2, et donc très intéressants en chimie pharmaceutique. D'autre part, dans le but d'obtenir des synthons qui pourront facilement être soumis à des couplages organométalliques avec des partenaires de couplage de nos collaborateurs du groupe de chimie médicinale de Sanofi, nous avons aussi envisagé d'accéder aux dérivés difluorométhylés portant un groupement aryl substitué par une fonction ester boronique. Des expériences ont été effectués, malheureusement sans succès sur les β-hydroxysulfoxydes α-difluorés, puis sur les composés en absence de l'auxiliaire de chiralité. Dans ce deuxième cas, nous sommes parvenus à isoler le dérivé aminé et celui comportant l'ester boronique pour le substrat modèle utilisé, l'alcool α-(difluoromethyl)benzylique (**Schéma 15**).

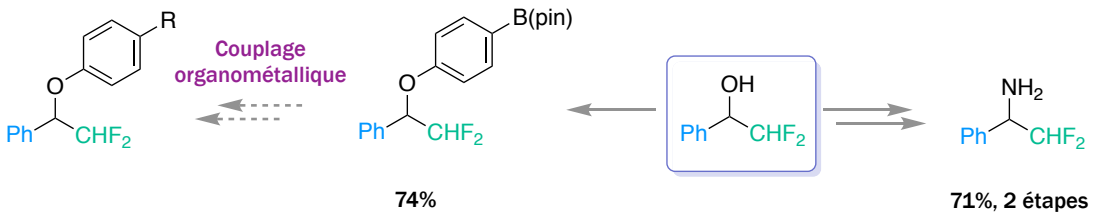


Schéma 15. Réactions de Mistunobu sur l'alcool α-(difluoromethyl)benzylique

Or, lorsque nous avons essayé d'appliquer les conditions déterminées grâce au substrat modèle sur les hétérocycles que nous souhaitions fonctionnaliser, nous n'avons pas obtenu de résultats satisfaisants. En effet, uniquement des sous-produits ou une absence totale de réactivité ont été observés (**Schéma 16**).

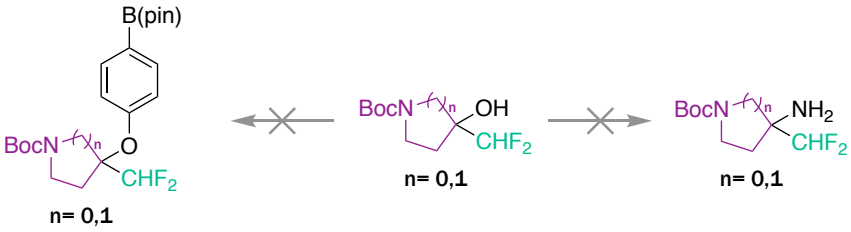


Schéma 16. Essais de réaction de Mitsunobu sur des hétérocycles azotés difluorométhylés

3. Substitutions nucléophiles aromatiques (S_NAr)

Les essais de fonctionnalisation de composés difluorés synthétisés dans les parties précédentes étant de grand intérêt dans la valorisation de notre méthodologie, nous avons décidé de continuer notre investigation cette fois ci en effectuant des substitutions nucléophiles aromatiques. En effet, cette stratégie pourrait nous donner accès à un grand nombre de dérivés (**Schéma 17**).

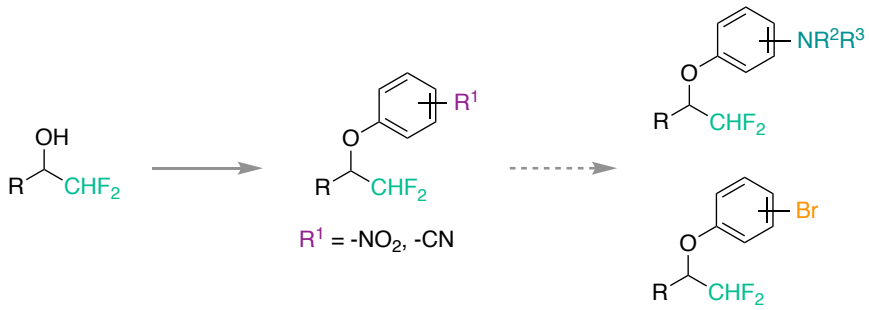


Schéma 17. Stratégie de fonctionnalisation d'alcools difluorométhylés par des substitutions nucléophiles aromatiques

Parmi ces dérivés, nous nous sommes plus particulièrement focalisés sur l'accès à des halogénoarènes, afin d'accéder à des partenaires de couplage organométallique. Une optimisation par chauffage conductif ainsi que par un chauffage aux micro-ondes de la réaction de S_NAr a été effectuée sur les alcools difluorométhylés *N*-hétérocycliques à 4, 5 et 6 chaînons. Cette optimisation ayant été effectuée à partir

des substrats racémiques dans un premier temps, nous l'avons ensuite appliquée aux analogues énantiopurs afin de confirmer la rétention de la configuration relative du centre stéréogène crée (**Schéma 18**).

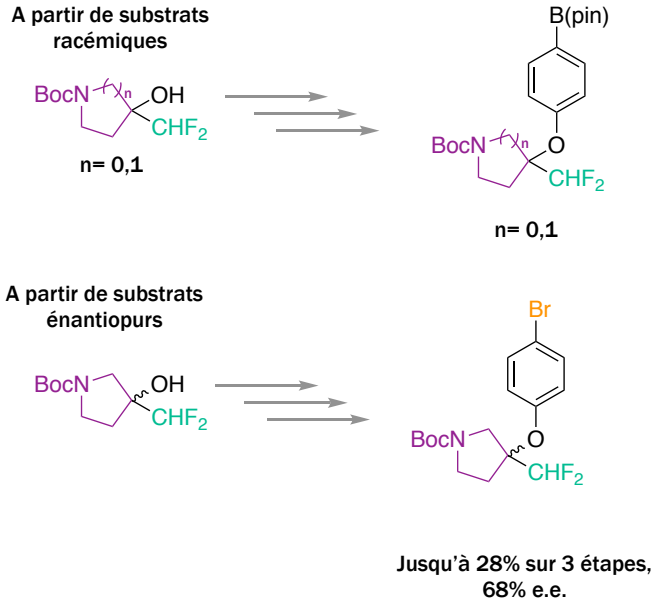


Schéma 18. Substitutions nucléophiles aromatiques sur des hétérocycles azotés difluorométhylés racémiques et énantiopurs

Ces composés seront ultérieurement couplés avec des plateformes de l'équipe de chimie médicinale, afin de fournir des composés présentés des propriétés biologiques potentielles (**Schéma 19**).

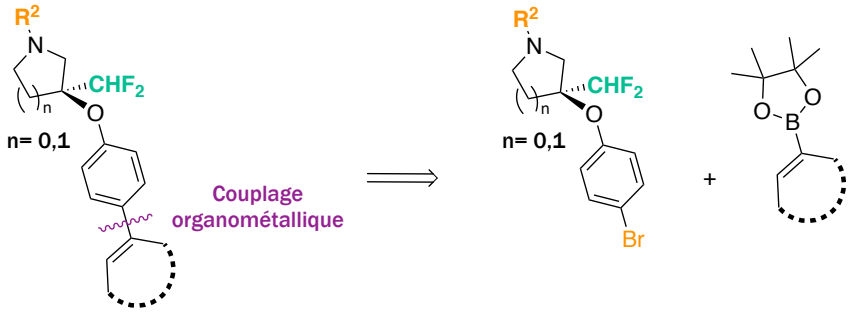


Schéma 19. Exemple d'application de dérivés difluorométhylés fonctionnalisés

E. Conclusion générale et perspectives

De nos jours, le nombre croissant de composés fluorés sur le marché pharmaceutique met en évidence l'importance de cet atome ainsi que celui des groupements fluorés émergents dans le développement de nouvelles molécules bioactives.

De nombreuses recherches sont donc consacrées au développement de méthodes efficaces permettant d'introduire ces groupements fluorés dans les composés organiques. Nous avons décidé de nous focaliser sur le groupement -CHF_2, qui présente des propriétés spécifiques supplémentaires telles qu'une capacité de donneur de liaisons hydrogène ainsi que celle d'être un bioisostère des fonctions thiol et hydroxyle. Peu de stratégies se sont focalisées jusqu'à présent sur l'introduction sélective de ce groupement, ce qui nous a amené à envisager une nouvelle voie d'accès stéréosélective à des composés difluorométhylés. Ce projet a donc consisté à utiliser un difluorométhyl sulfoxyde énantiopur en tant qu'inducteur de chiralité, qui a été condensé, après déprotonation, sur des électrophiles.

Dans un premier temps, nous avons conduit des expériences complémentaires concernant la synthèse de ce sulfoxyde difluorométhylé énantiopur, ainsi que sur la possible synthèse de composés dérivés, comportant par exemple un groupement -CF_2Br. Ensuite, nous avons souhaité évaluer la réactivité de ces sulfoxydes difluorés vis-à-vis d'un certain nombre d'électrophiles. Dans certains cas, nous avons obtenu d'excellents résultats qui nous ont permis d'accéder notamment à des β-hydroxysulfoxydes α-difluorométhylés avec de bons excès énantiomériques. De la même manière, nous avons aussi réussi à effectuer le clivage de la liaison C-S avec rétention de configuration du carbone stéréogène, nous permettant ainsi d'accéder aux composés difluorométhylés avec d'excellents excès diastéréomériques et énantiomériques. D'autre part, nous avons étudié la fonctionnalisation des composés obtenus afin de les valoriser dans le cadre de notre collaboration avec l'équipe de chimie médicinale de Sanofi. Des partenaires de couplage portant le groupement -CHF_2 ont été synthétisés et pourront être utilisés par la suite dans deux projets de drug-discovery.

Par la suite, il serait intéressant de poursuivre les études mécanistiques qui ont été en partie abordées concernant le centre soufré stéréogène du sulfoxyde difluorométhylé, pour déterminer par exemple des données théoriques telles que sa barrière de racémisation, mais aussi étudier l'acidité du proton du groupement -CHF_2. D'autre part, nous pourrions envisager d'élargir les stratégies de fonctionnalisation des différents synthons difluorométhylés obtenus par d'autres réactions complémentaires à celles qui ont été testées au cours de ce projet. Finalement, l'utilisation des sulfoxydes combinés à d'autres groupements fluorés émergents, tels que -OCF_3 ou -SCF_3, mériterait une attention particulière. En effet, ceci pourrait ouvrir le champ à des composés énantiopurs portant ces groupements fluorés émergents.

Introduction

Organofluorine chemistry in life sciences

Table of contents

A. Fluorine: an essential element in daily life

During the last decades, the emergence of fluorine chemistry has been particularly noticeable. The introduction of fluorine and fluorine-containing motifs in molecules profoundly impact their structure, reactivity and function.

In this chapter, we aim to present an overview of this element from its discovery to its applications in different fields of our daily lives, inspired by the large number of studies that have been reported over the years.

a. Discovery: brief history

The first appearance of the word "*fluores*" goes back to 1530 by Georgius Agricola, describing fluorspar ores (CaF_2) as "the element that flows" and their practical use in the extraction of metals (**Figure 0.1**).[9] Moreover, historical reports said ancient civilizations also used fluorinated minerals to make vases and cups.[10,11]

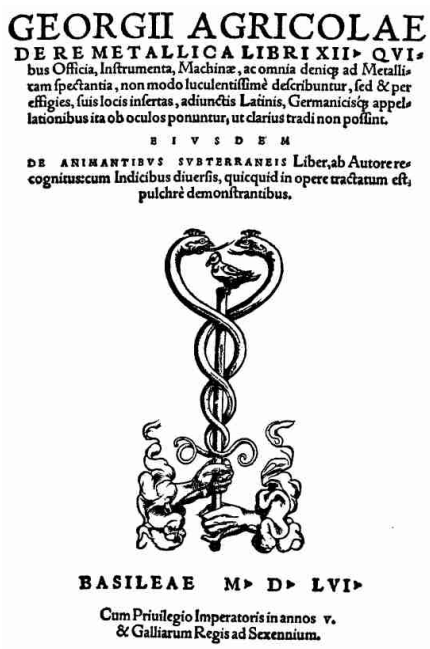

GEORGII AGRICOLAE
DE RE METALLICA LIBRI XII▸ QVI-
bus Officia, Instrumenta, Machinæ, ac omnia denique ad Metalli-
cam spectantia, non modo luculentissimè describuntur, sed & per
effigies, suis locis insertas, adiunctis Latinis, Germanicisque appel-
lationibus ita ob oculos ponuntur, ut clarius tradi non possint.
EIVSDEM
DE ANIMANTIBVS SVBTERRANEIS Liber, ab Autore re-
cognitus: cum Indicibus diuersis, quicquid in opere tractatum est,
pulchrè demonstrantibus.
BASILEAE M▸ D▸ LVI▸
Cum Priuilegio Imperatoris in annos v.
& Galliarum Regis ad Sexennium.

Figure 0.1. The first appearance of fluorine in scientific literature in *De Re Metallica Libri* by G. Agricola

Centuries later, during the XIXth century, the isolation of fluorine in its elemental form, F_2, drew the attention of different renowned scientists. A-L. de Lavoisier wrote an article summarizing previous observations regarding fluorine and hydrofluoric acid. L. J. Thénard and J. L. Gay-Lussac prepared concentrated hydrofluoric acid from fluorspar and sulfuric acid. They noticed that this acid was strongly fuming and could dissolve glass. These scientists, and also other researchers experienced impressive burns caused by contact of hydrofluoric acid with the skin, among other toxic effects. Unfortunately, severe diseases and deaths were caused in the course of fluorine isolation. As a new method to isolate fluorine, Sir H. Davy and E. Frémy tried unsuccessfully to produce it from electrolysis of fluorine salts. In 1886, Henri

Moissan finally succeeded in isolating elemental fluorine by electrolysis of liquefied, water-free hydrogen fluoride in the presence of potassium bifluoride. This discovery (together with the development of the electrical furnace) earned him the Nobel Prize in Chemistry in 1906, after a long period of exploration of this highly reactive element **(Figure 0.2)**.[12,72]

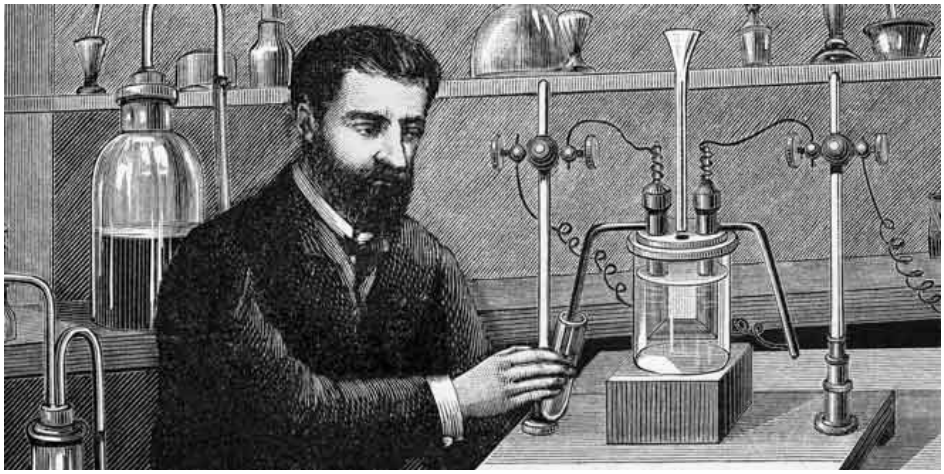


Figure 0.2. Isolation of fluorine by electrolysis performed by H. Moissan, from *Physique populaire by E. Desbeaux, 1891.*

b. Fluorine in nature

Although fluorine is commonly found in the earth's crust, it is almost completely absent from biological processes. Fluorine can be found principally under mineral form, being calcium fluoride (or fluorspar), cryolite Na_3AlF_6 or fluorapatite $Ca_{10}(PO_4)_6F_2$. Fluorinated natural products are an exception and only 12 natural metabolites containing this atom have been found in nature to date, in contrast to a large number of other halogenated natural products bearing chlorine, bromine and even iodine **(Figure 0.3)**.[13–15]

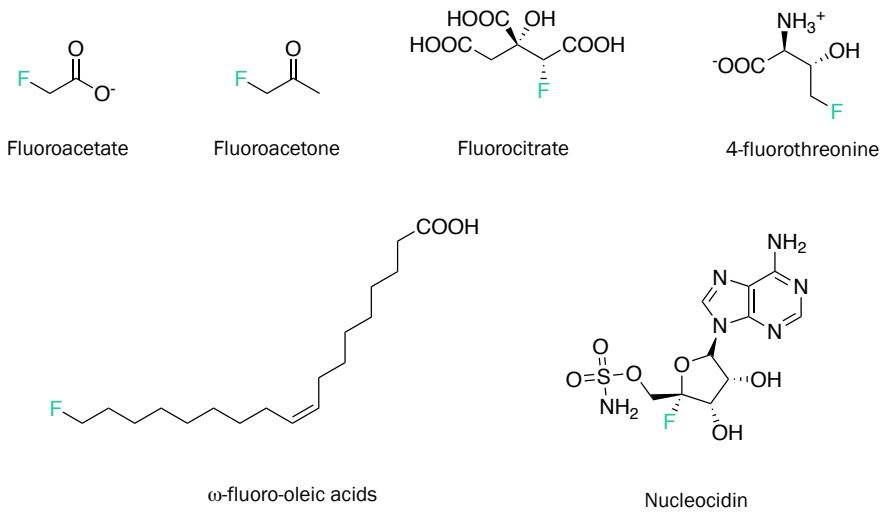


Figure 0.3. Naturally occurring fluorinated metabolites

Fluoroacetate is the most common fluorinated metabolite isolated from the Southern African plant *Dichapetalum cymosium*. This plant is able to synthesize and accumulate it, making the plant extremely toxic as this fluorinated compound is known to inhibit the Krebs cycle. Moreover, the condensation of fluoroacetyl-CoA with oxaloacetate leads to fluorocitrate, another natural metabolite.

Seed lipids of *Dichapetalum toxicarium* presented eight fatty acid derivatives of ω-fluoro-oleic acids. In 1969, the structure of nucleocidin was reported, isolated from bacterium *Streptomyces calvus*. Finally, the latest discovered metabolite is 4-fluorothreonine, extracted from *Streptomyces cattleya*.

It is noteworthy that the nature of the biological fluorination process of the few fluorinated metabolites attracted the attention of an increasing number of researchers. However, even though numerous speculative suggestions of the biosynthesis mechanism of these metabolites have been made, the details have not been elucidated yet.

c. Properties of fluorinated systems

1. Fluorine and its isotopes

Fluorine is the 9th element of the periodic table and the 13th most abundant element on Earth. It is represented by the symbol F, has a $1s^2 2s^2 2p^5$ electronic configuration and is the first halogen. It has a very high electronegativity (3.98 on Pauling the scale). This atom has a Van der Wals radius of 1.47 Å, lying between the ones of hydrogen (1.20 Å) and oxygen (1.52 Å). Its atomic weight is 18.99. The first ionization energy of fluorine is very high (402.15 kcal.mol^{-1}), just behind those of helium and neon, making this atom almost non-oxidizable.[16]

Moreover, as a consequence of its very low polarizability, the fluorine atom is less prone to intermolecular interactions, which is illustrated by the low boiling point of molecular fluorine (-188 ºC) and other fluorocarbons, when compared to other halogenated molecules, such as molecular bromine (59 ºC) or molecular iodine (184 ºC).

Regarding its isotopes, the sole stable isotope of fluorine that exists is ^{19}F, having 10 neutrons. This isotope shows an excellent sensitivity towards magnetic fields and is then largely used for NMR spectroscopy. The artificial ^{18}F isotope was discovered in 1936 and due to its longer half-life value of 109.7 min compared to the other commonly used positron-emitting radionucleides (having values between 2 and 20 min), it represents nowadays an important isotope in medical imaging.[17–20] ^{18}F is produced in a cyclotron after bombardment of ^{18}O-enriched water by high-energy protons, and immediately introduced in radiotracers prior to use. The Positron-Emission Tomography (PET) probe is then administered to patients and the radionuclide starts to decay in the body by positron emission. The emitted positron will collide with an electron in the surrounding tissue and this collision produces two γ-ray photons in exactly opposite directions that are detected by the PET scanner, which consists in a series of detectors arranged in a circular ring. It is then possible to determine the approximate location of the PET probe in the body **(Figure 0.4)**.

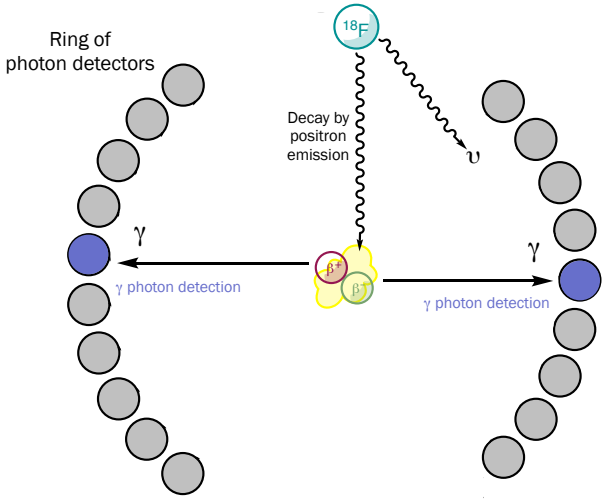


Figure 0.4. Schematic representation of the PET principle

The combination of millions of these events, called annihilations, allows to construct a PET image thanks to the PET scanner and to obtain a quantitative information of physiological and biochemical events in the body. This tool finds its application mostly in oncology to diagnose tumors, in cardiology as well as neurology to characterize early stage disorders, and in drug discovery.

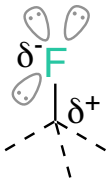
2. C-F bond properties and effects

The C-F bond is the strongest single bond in organic compounds. The bond length lies between those of C-O and C-H bonds. This is one of the reasons why fluorine is often used in medicinal chemistry to replace a hydrogen atom **(Table 0.1)**.[16]

Table 0.1. Comparison of carbon-element single bond lenghts

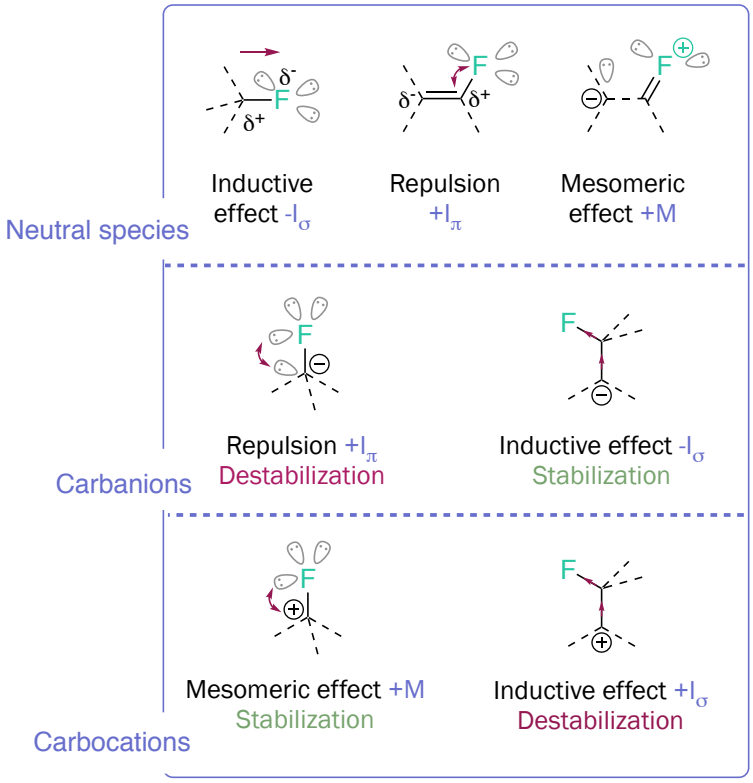
	C-F	C-H	C-O	C-C	C-Cl	C-Br	C-N
Bond lengths (Å)	1.35	1.09	1.43	1.54	1.77	1.97	1.47
Bond strength (kcal.mol^{-1})	105	98	84	83	77	66	70

The high electronegativity and the small size of fluorine highly polarize the C-F bond, inducing a large dipole moment and thus influencing greatly the conformational behaviour of organofluorine compounds by dipole-dipole interactions **(Scheme 0.1)**.



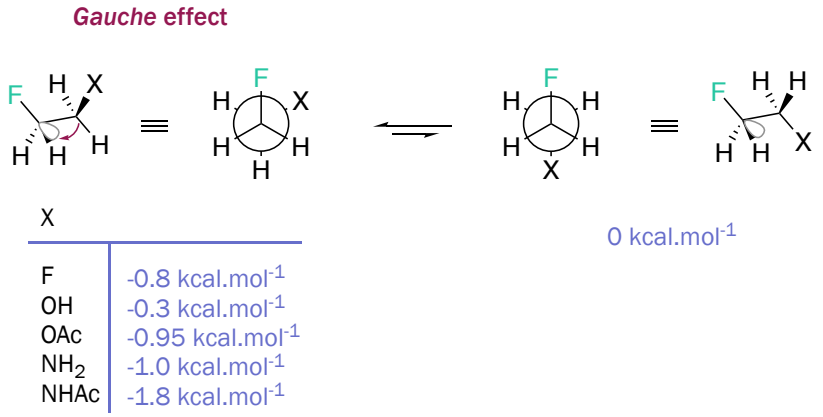
Scheme 0.1. Dipole behaviour of C-F bond

Moreover, the introduction of fluorine in a molecule leads to changes in the electronic properties of the adjacent bonds. The three non-bonding electron pairs of fluorine are responsible of electronic push and pull effects with its neighbouring systems **(Scheme 0.2)**. Fluorine lone pairs have a +Iπ and also +M effect, creating a repulsion of the π electron cloud and increasing the acidity of neighboring protons. In addition to that, these inductive and mesomeric effects stabilize carbocations generated in α–position of the fluorine atom and carbanions in β–position. Adjacent C-C single bonds are strengthened by fluorination, whereas allylic C=C double bonds are weakened.[21,22]



Scheme 0.2. Fluorine effects on the stability of neutral or charged derivatives

An additional interaction takes place when one or more vicinal fluorine atoms are located on an alkyl chain: the *gauche* effect. This phenomenon represents a preference for *gauche* conformers, being more favored than *anti* conformers, that are usually more stable. There is hyperconjugation between σ* electron-accepting orbitals of the C-F bond and the σ electron-donating orbital of a C-X vicinal bond **(Scheme 0.3)**.[73–75]



Scheme 0.3. Gauche effect observed upon fluorine introduction in a molecule

In this section, we showed that the properties of the C-F bond and the effects induced by its introduction into organic molecules can have a strong influence in properties of organofluorine derivatives. The high polarization, stability and steric interactions of the C-F bond can be assets for tuning the properties of bioactive ingredients.

B. Organofluorine chemistry: diverse applications

Often described as a "small atom with a big ego" or the "little atom that could",[76,77] fluorine has had since its discovery a big impact on our everyday lives. Several industrial fields use fluorine as an essential element.[21,23] A short summary of its major applications is presented in this section.

In the past, chlorofluorocarbons (CFC's) have played an important role as refrigerants for air-conditioning (Freon®), aerosols and extinguishing chemicals (Halon®). They were developed at the beginning of the 20th century. Unfortunately, the stability that makes these compounds so useful also allows them to reach the stratosphere and generate a detrimental interaction with the ozone layer. For these reasons, in the last decades the use of CFC's has been banned. The research for alternatives to CFC's has then been a challenge since the end of last century.[24,25]

Since the 1940's and the implementation of the Manhattan project, the nuclear industry uses fluorine for the preparation of uranium hexafluoride UF_6, needed to separate uranium isotopes and produce enriched ^{235}U.[26,27]

The addition of ppm proportions of fluorine anions to city water supplies, even if sometimes criticized, as well as NaF, SnF_2 and Na_2PO_3F included in toothpaste help in the prevention of tooth decay.[28–30]

Moreover, a major application of fluorochemicals includes solvents and high temperature resisting plastics. The most representative is Teflon® (polytetrafluoroethylene PTFE) for its non-sticking properties, and its resistance to high and low temperatures. It is encountered in frying pans, cable isolations, plumber's tape and waterproof materials.

Recently, nanofluorinated materials have caught the attention of scientists for their use in lithium batteries. These components could lead to the emergence of F-ion batteries as an alternative to Li-ion batteries.[31,32] Moreover, sulfur hexafluoride SF_6 is also used as a dielectric gas for high-power electricity transformers and hydrofluoric acid is used to etch glass, including that of light bulbs.[78]

Finally, the introduction of fluorine atom(s) in active pharmaceutical or agrochemical ingredients has become quite usual. The metabolic stability, changes in acidity and basicity, in lipophilicity and polarity made fluorine and fluorinated groups unique tools in life sciences (see following section).[4,5,33,34]

In addition to that, a new application in medicine is the previously cited (see *section A, part c*) development of radionuclides used in PET, ^{18}F being the isotope having the longest half-life among all the radionuclides currently used (^{11}C, ^{13}N, ^{15}O). The incorporation of this radiotracer allows obtaining information on physiological phenomena in the body.

C. Fluorine as an attractive element in life sciences

During the last decades, an emergence of molecules containing new fluorinated substituents has been noticed. Increasing efforts have been dedicated to the synthesis of these molecules, which are important components of agrochemicals and pharmaceuticals. This interest mainly results from the fact that incorporating fluorine can modulate different properties in biologically active compounds.[3] In this section, we will discuss these parameters.

a. Effects on the pK_a

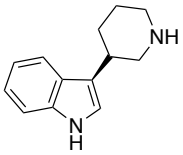
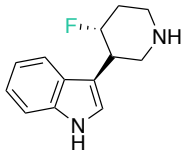
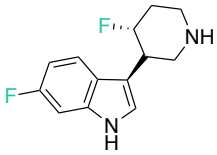
The introduction of a fluorine atom in a molecule induces unique effects on their physicochemical and biological properties. The impact on the pK_a helps to modulate the affinity for a target in the body, as well as pharmacokinetics of active pharmaceutical ingredients (API). pK_a values of acids, alcohols and amines are influenced: basicity of amine groups is reduced with the introduction of fluorine, as electron density on nitrogen is decreased, and compounds already having an acidic character become more acidic with the addition of fluorine. An overview of these effects can be found in **Table 0.2.**

Table 0.2. Effects of fluorination on the pK_a of carboxylic acids and ammoniums

Carboxylic acid	CH_3CO_2H	CH_2FCO_2H	CHF_2CO_2H	CF_3CO_2H
pK_a	4.8	2.6	1.3	0.5
Ammonium	$CH_3CH_2NH_3^+$	$CH_2FCH_2NH_3^+$	$CHF_2CH_2NH_3^+$	$CF_3CH_2NH_3^+$
pK_a	10.7	9.0	7.3	5.7

The influence of fluorine atoms in a bioactive molecule can improve, among other parameters, its bioavailability. An example of this feature was found in the development of h5-HT_{2A} receptor antagonists involved in schizophrenia.[35] A series of 3-piperidinylindole were synthesized and their bioavailability was compared in the presence of a fluorine atom in γ-position of the nitrogen of the piperidine ring **(Table 0.3)**.

Table 0.3. Example of pK_a variation in a fluorinated bioactive molecule

	Indole		
			
pK_a	10.4	8.5	-
Bioavailability F (%)	Poor	18	80

The result is an improved bioavailability in the presence of a fluorine atom, which decreases the pK_a of the compound. It is noteworthy that the second fluorine atom at the 6-position on the indole ring was not introduced to have an influence on the pK_a. However, it illustrates the beneficial modification of the properties of the molecule by the introduction of a fluorine atom (bioavailability increased from 18 to 80%).

b. Effects on lipophilicity

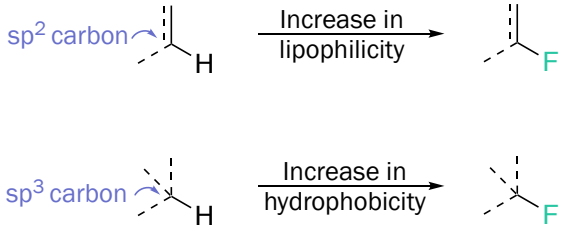
The absorption and distribution of an orally administered drug is highly dependant with the penetration of cell membranes. An important factor in this transfer is the lipophilicity of the drug candidate. In fact, the log P value for lipophilicity should be sufficient for the compound to enter the lipid core but not excessive for it not to be trapped in this lipid core and to allow the drug to be soluble in water. It is then important to have a balance between lipophilicity and hydrophilicity.

The scale ruling this factor is a logarithmic coefficient of the distribution of a molecule between water and octanol. The increasing value of this parameter is consistent with a more lipophilic compound. [36,22]

Table 0.4. Lipophilicity variations in fluoroalkylated compounds

Alcohol	CH_3CH_2OH	CF_3CH_2OH	$CH_3(CH_2)_2OH$	$CF_3(CH_2)_2OH$
Log P	-0.32	0.36	0.34	0.39
	Alkyl chain	CH_3CH_3	CH_3CHF_2	$CH_3(CH_2)_3CH_3$
	Log P	1.8	0.8	3.1

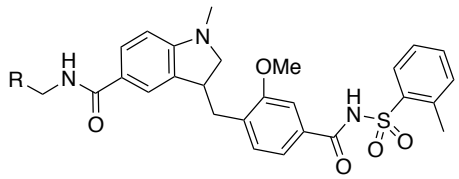
It was observed that the fluorination of aliphatic chains tends to decrease lipophilicity and increase hydrophobicity. In contrast, the introduction a fluorine atom in unsaturated compounds generally increases the lipophilicity **(Scheme 0.4)**.



Scheme 0.4. Lipophilicity changes in saturated and unsaturated derivatives

An example illustrating these effects in biologically active molecules was reported by Jacobs and Bernstein, during the synthesis of leukotriene receptors antagonists, which are involved in asthma in humans. The effect of fluorination was studied for a range of molecules by replacing alkyl chains by fluoroalkyl ones **(Table 0.5)**.[79]

Table 0.5. Example of improved lipophilicity in a fluoroalkylated molecule of pharmaceutical interest

Compound 

R	$CH_3CH_2CH(CH_3)$	$CF_3CH_2CH(CH_3)$
Log P	5.85	6.18
R	$(CH_3CH_2)_2CHCH_2$	$CF_3CH_2CH(CH_3CH_2)CH_2$
Log P	6.29	6.45

One should note that other structural modifications of the core of the molecule improved lipophilicity but also resulted in a loss of affinity for the receptor. The alternative of introducing fluorine substituents addressed this problem and allowed the authors to improve the *in vivo* potency compared to the non-fluorinated analogues. All fluorinated amides were more lipophilic than their non-fluorinated counterparts.

c. Metabolic stability

Following the uptake of a drug, the automatic response of the human body consists in eliminating the active compound or metabolizing it, prior to elimination. The

active compound is actually being considered a foreign and therefore potentially dangerous substance.

The most important group of drug-metabolizing enzymes is the Cytochrome P450 monooxygenase, found mainly in the liver. These enzymes undertake, among others, oxidation processes of bioactive molecules in order to decrease their lipophilicity and allow a more rapid clearance. A common and practical way to protect metabolically labile sites from oxidation is by blocking them with fluorine substitution, the C-F bond being strong enough not to be disrupted by the enzyme. An example of this effect is illustrated by the lead optimization of Ezetimib, a cholesterol absorption inhibitor **(Figure 0.5)**.[37]

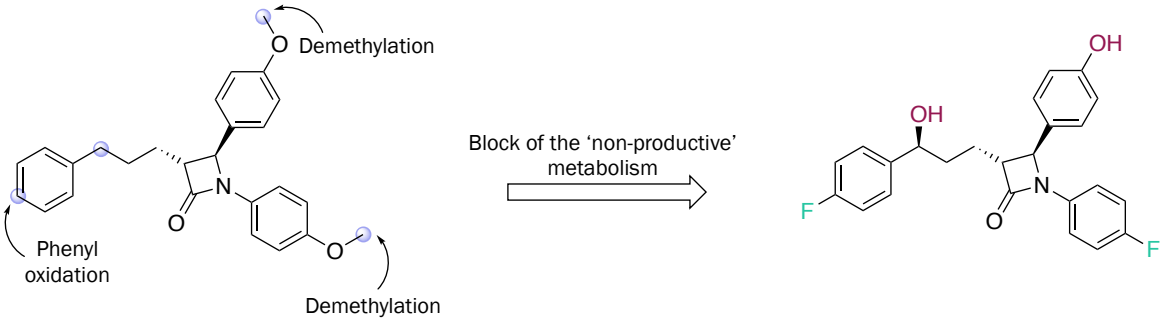


Figure 0.5. Improved metabolic stability of a drug-like compound

"Non-productive" metabolism, i.e. not leading to an enhanced activity, was blocked by the introduction of fluorine at the *p*-positions of the phenyl rings to minimize oxidation. The structural modifications finally gave a drug requiring lower doses due to higher potency and improved metabolic stability.

Moreover, the use of fluorine was also found to be beneficial in avoiding hydrolytic metabolism. Prostacyclin PGI_2 is an attractive drug candidate to treat vascular diseases. However, its acid labile enol ether moiety renders this molecule prone to hydrolysis leading to an inactive compound, 6-keto-$PGF_{1\alpha}$ **(Figure 0.6)**.[80]

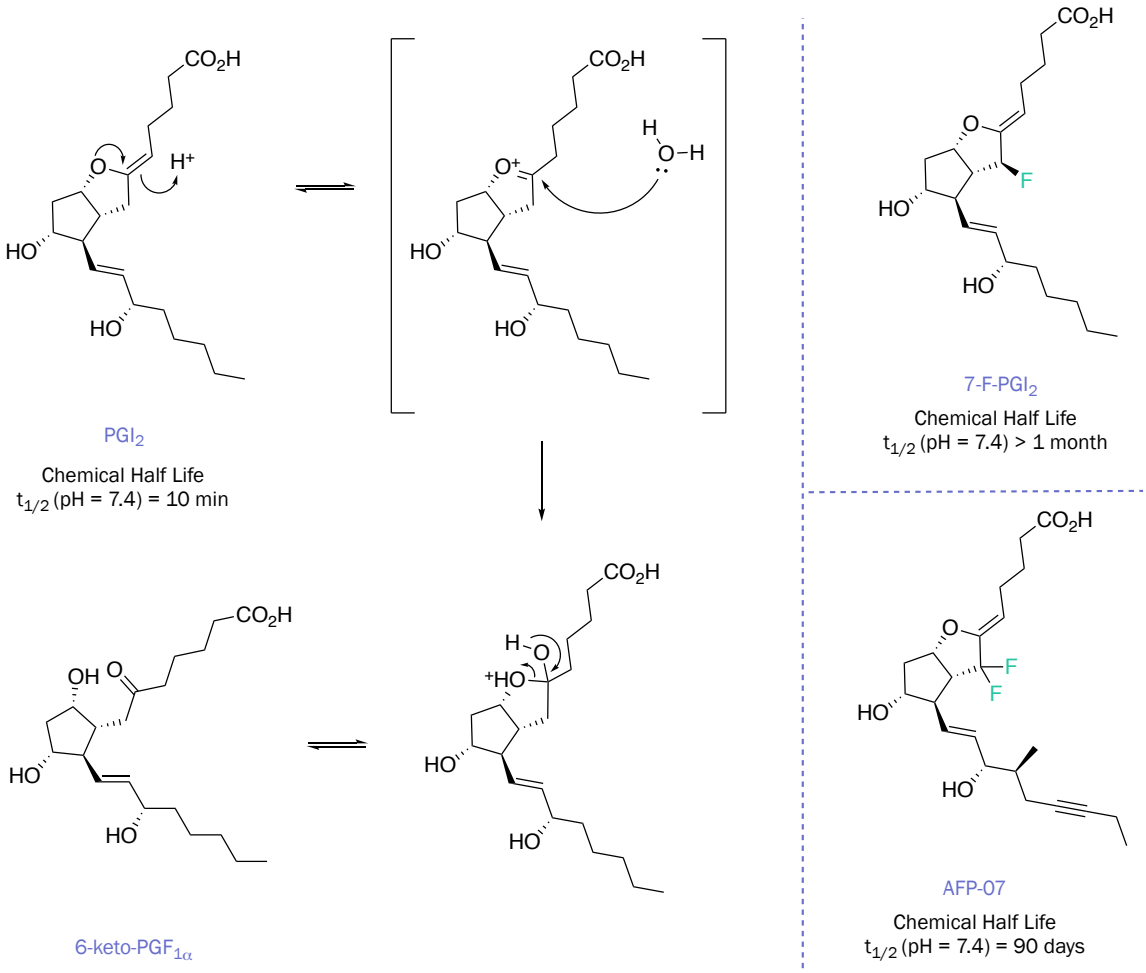


Figure 0.6. Prevention of hydrolytic metabolism by fluorination

The stability of the derivatives could be enhanced by mono- or difluorination. The rate of hydrolysis of the enol ether could be highly decreased, and as a consequence, giving a half-life value of up to 90 days instead of 10 minutes.

One last example that illustrates the role of fluorine in improving metabolic stability of drug-like compounds is the influence in *in vivo* racemization. Thalidomide is probably the most known compound expressing a harmful racemisation effect. This drug was marketed in the 1950's as a sedative used to treat morning sickness, but was withdrawn a decade later. Indeed, the two enantiomers of the drug had been found to have two different effects: the (*R*)-enantiomer is responsible for the hypnotic beneficial effects, whereas the (*S*)-enantiomer is responsible for birth defects in babies whose mothers had taken the drug.[81] This epimerization under physiological conditions due to an acidic hydrogen located on the stereogenic center could be overcome by replacement with a fluorine atom **(Figure 0.7)**.[82]

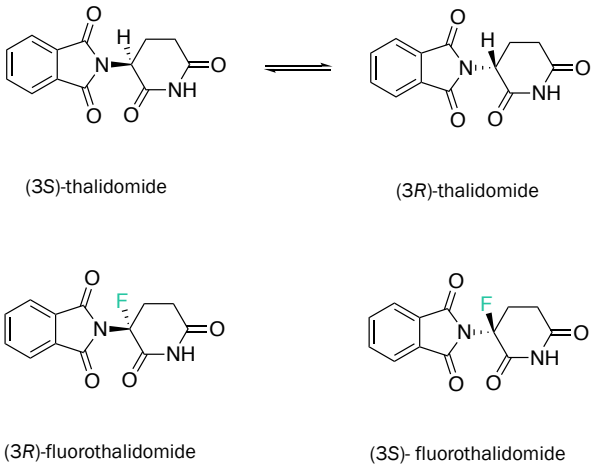


Figure 0.7. Prevention of racemization by fluorination of a stereogenic carbon center

d. Steric and electronics effects: impact on conformation

Due to their similar Van der Waals radius value, the replacement of hydrogen or hydroxyl group with fluorine only requires a minor steric demand at receptor sites. However, the introduction of larger emergent fluorinated substituents such as -CF_3, can have a higher impact on the molecule causing a significantly different spatial arrangement. Consequently, previously unfavored molecular conformations can be adopted in the newly fluorinated molecules not only due to steric effects but also to the electronegativity of fluorine atoms, the dipolar moment induced as well as the presence of lone-pairs of fluorine. It is conceivable that taking advantage of these steric and electronic effects should be interesting to have a more efficient affinity with a biological target.

A classic example of profound change in ground state conformation due to the introduction of fluorine atoms is the case of trifluoromethoxybenzene. Anisole prefers to adopt a planar conformation, whereas the –OCF_3 group of trifluoromethoxybenzene has a preference for an out of the plane conformation with a dihedral angle around 90 ºC **(Figure 0.8)**.[82]

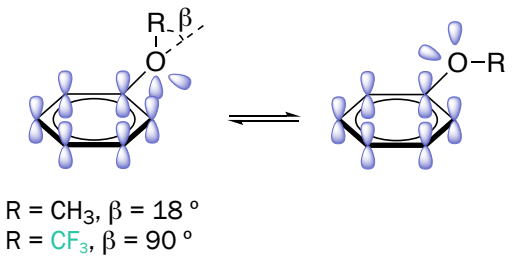
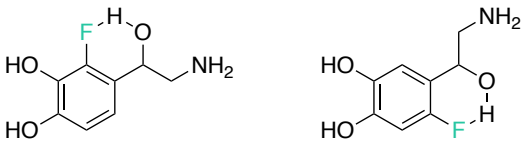


Figure 0.8. Dihedral angle variation between methoxybenzene and trifluoromethoxybenzene

Hydrogen bonds involving a fluorine atom are weak, nevertheless they can stabilize one conformation of a molecule. This was observed in the case of hydrogen bonds formed in fluoronorepinephrine, giving the two isomers different activities. The 2F-isomer is an α-adrenergic agonist, whereas the 6F-isomer is a β-adrenergic agonist **(Figure 0.9)**.[83]



2F-NE : β-adrenergic antagonist

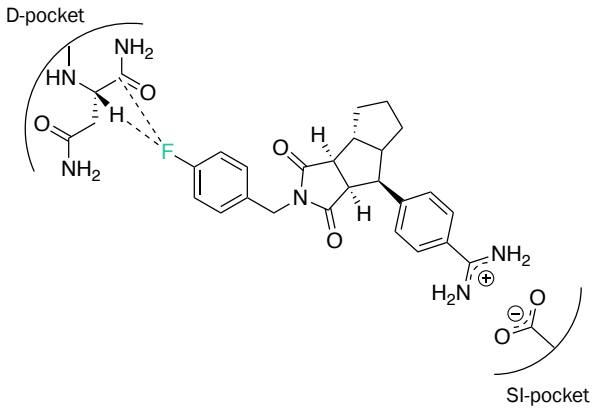
6F-NE : α-adrenergic antagonist

Figure 0.9. Hydrogen bonding observed in fluoronorepinephrine isomers

On the other hand, fluorine has the possibility to be involved in electrostatic interactions. The binding affinity of fluorinated compounds with active sites in the body can be increased thanks to such interactions. A series of thrombin inhibitors were studied, including fluorinated and chlorinated inhibitors and their inhibitory constants were found to be similar to the parent molecule. However, one of the fluorinated derivatives was more active and showed a better binding affinity. Thanks to X-Ray analysis, the authors could observe that the C–F bond came into close contact with a positively polarized carbon atom of from Asn98, due to dipolar C–F···H and C–F···C=O interactions **(Table 0.6)**.[37]

Table 0.6.Binding affinity modifications in thrombin inhibitors

Aromatic substitution	K_i [μM]
H	0.31
2-F	0.50
3-F	0.36
4-F	0.057
2,3-F_2	0.49
2,6-F_2	0.61
3,4-F_2	0.26
3,5-F_2	0.59
1,2,3,4,5-F_5	0.27
4-Cl	0.19



These examples illustrate that the presence of a fluorine substituent on a bioactive molecule may significantly influence its conformation and have important consequences in lead-optimization programs.

e. Bioisosteres

Steric and electronic properties of the fluorine atom and fluorinated groups described in the previous sections of this chapter illustrate their beneficial use to modify physico-chemical and biological properties of a molecule such as their lipophilicity, affinity with a target and metabolic stability, among others.

Bioisosteres are substitutes of another chemical function that possess similar physical or chemical properties. They are commonly used in medicinal chemistry to enhance specific biological properties of a compound without significant changes in the chemical structure.[84] Fluorine is very much used in drug-design due to its very high potential for mimicking different functional groups, i.e. for its high potential as a bioisostere. Medicinal chemists perform the replacement of chemical functions by taking into account the similarities of the fluorinated moieties and the function to be replaced. Common exchanges include hydrogens that are often replaced by a single fluorine atom, and hydroxyl or thiol functions that are replaced by a difluoromethyl group **(Figure 0.10)**.[38–40]

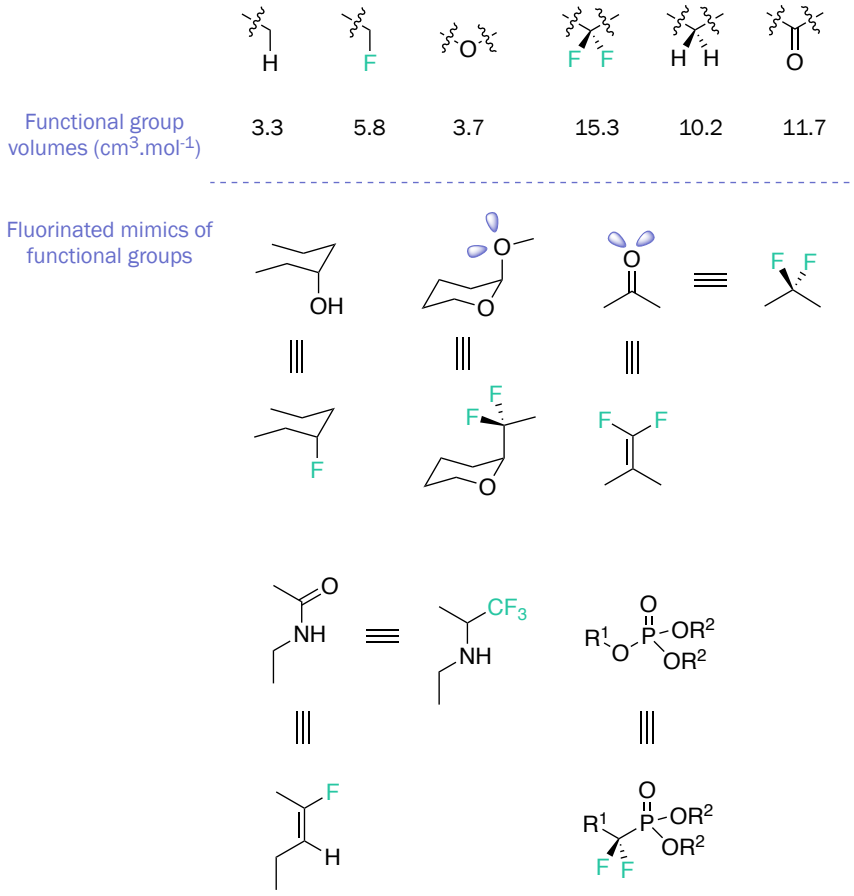


Figure 0.10. Fluorinated bioisosteres of functional groups

f. Medicinal chemistry and agrochemistry contribution

The development of new fluorination methods and reagents gave access to bioactive molecules with improved properties. Fluorine-containing molecules have become blockbusters in the pharmaceutical and agrochemical field. The synthetic methods to prepare these compounds and their properties have been the main topic of several reports.[1,3,33,40,85–88]

The number of fluorinated compounds is constantly increasing: half of the most successful drugs and almost a quarter of herbicides on the market contain at least one fluorine atom.[3,6–8,41] To illustrate the potential of fluorinated compounds in life sciences research, a few examples of marketed bioactive compounds bearing a fluorine atom or fluorinated groups are presented in **Figure 0.11**.

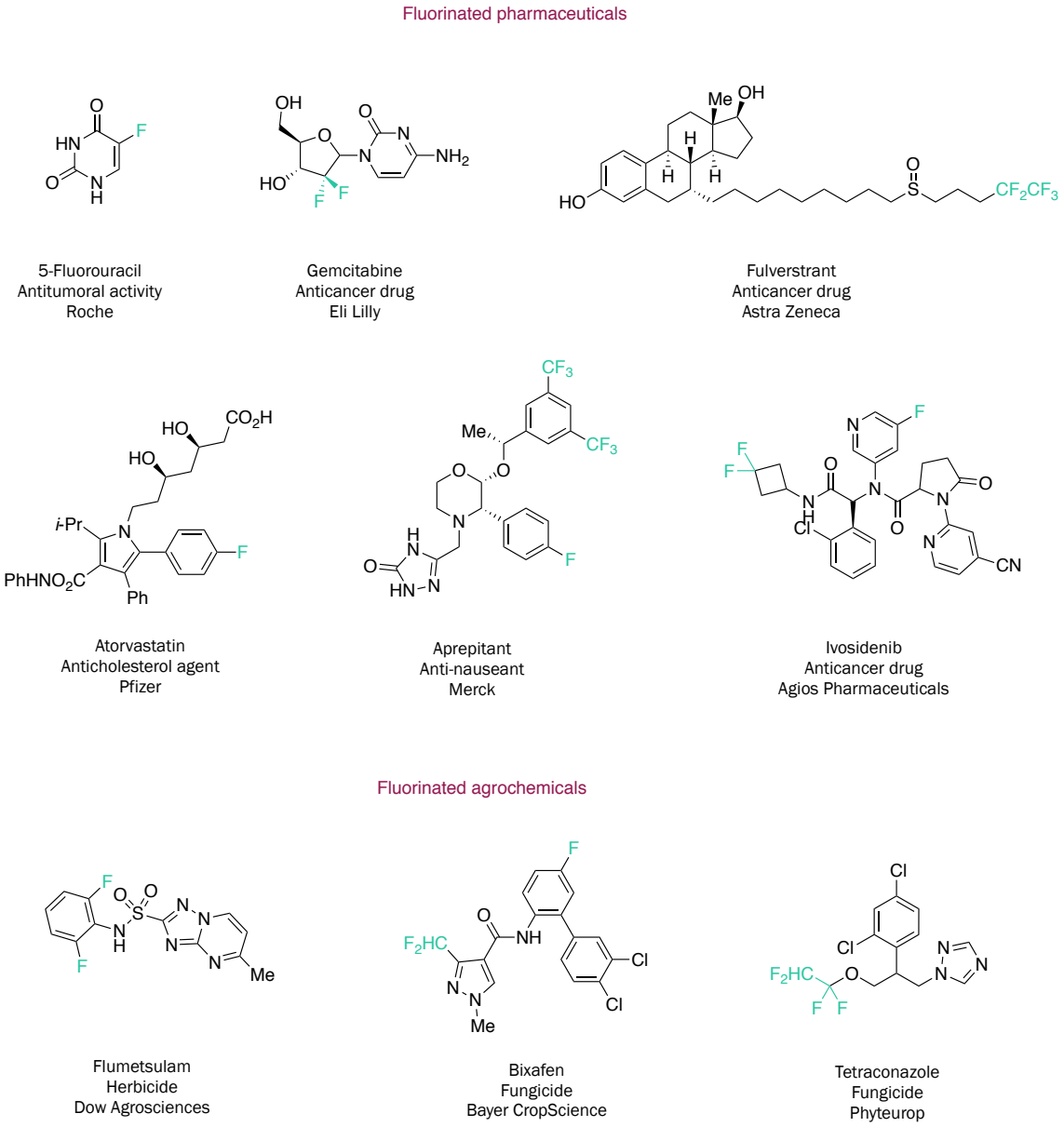


Figure 0.11. Examples of fluorinated pharmaceutical and agrochemical ingredients in the market

Fluorinated drugs currently on the market have diverse applications. These compounds are used as anticholesterol or anticancer, among others. In the agrochemical field, fluorinated molecules can be found in the three main classes of products: herbicides, fungicides and insecticides.

The large number of fluorinated drugs and agrochemicals illustrate the popularity of fluorine moieties. Nevertheless, the most represented moieties remain F and CF_3, due to the more limited number of simple synthetic strategies to introduce the other Emergent Fluorinated Substituents (EFS). It is then implied that the preparation and study of new fluorine-containing molecules is of great interest. Among these EFS, the CHF_2 group is very represented in agrochemicals in contrast to pharmaceuticals. This PhD project focused on the stereoselective introduction of this substituent. Its characteristics will be presented in the next section (*section D*).

D. The difluoromethyl group: a functional surrogate

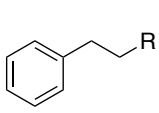
The fluorine atom or fluorinated substituents have been used for decades to modify biologically relevant properties of bioactive molecules. However, some groups, such as –CHF_2 have been less studied than –CF_3 for example. Recently, the difluoromethyl group drew the attention of organic and medicinal chemists due to its additional advantages when compared to the other fluorinated substituents. The most important physicochemical modifications induced by this group are a moderate increase in lipophilicity and its hydrogen bond donor character. Consequently, –CHF_2 is of great interest in drug discovery programs as a bioisostere of –OH or –SH functional groups.

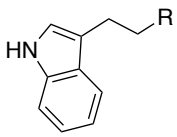
a. Lipophilicity

The difluoromethyl group induces modification in the lipophilicity of molecules. This modification is interesting as the new lipophilicity value remains moderate when compared to the one induced by a –CF_3 when replacing a methyl group.

An example illustrating the effect of difluoromethyl substitution was reported by Carreira and Müller on partially fluorinated molecules presenting aliphatic systems: *n*-propylbenzene and a series of indole derivatives.[44,49] The difluoromethylated compounds have indeed lower lipophilicity values than the analogues bearing a trifluoromethyl group **(Table 0.7)**.

Table 0.7. Lipophilicity of compounds bearing fluoroalkylated chains





R	Log P	R	Log P
CH_3	3.7	CH_3	3.3
CH_2F	3.0	CH_2F	2.8
CHF_2	3.1	CHF_2	2.9
CF_3	3.3	CF_3	3.1

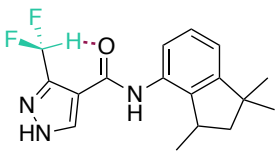
This beneficial effect of introduction of a CHF_2 group shows that it is an excellent alternative with reduced steric demand when compared to the bigger trifluoromethyl group. It would be then possible to modulate membrane permeability and oral bioavailability associated with a bioactive molecule without significant size or conformation changes.

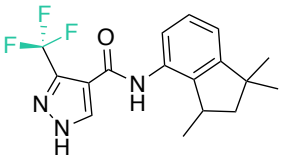
b. Hydrogen bond donor character

The hydrogen bonding interactions of the -CF_2H group were evidenced by NMR, IR and X-ray crystallography analysis as well as theoretical calculations.[42-47] The CHF_2 being a better hydrogen bond donor than its non-fluorinated analogue could be due to the increased acidity of the C–H bond due to the geminal fluorine atoms.

Intramolecular hydrogen bonds formed with a -CHF_2 group allow the stabilization of conformations that would have been different in the case of trifluoromethylated or non-fluorinated analogs. An example of these intramolecular hydrogen bonds was reported for pyrazole carboxamides, used as fungicides **(Table 0.8).**[42]

Table 0.8. Fungicide activity towards *Alternaria solani* (tomato parasite)





Dose (ppm)	Fungicide activity (%)	Dose (ppm)	Fungicide activity (%)
20	73	20	57
100	92	100	62

It is suggested that a better fungicide activity is obtained with a difluoromethyl amidopyrazole, with respect to the trifluoromethyl analogue. The stabilization of the conformation thanks to a hydrogen bond would be responsible for this improved biological activity.

The formation of intermolecular hydrogen bonds between a bioactive molecule and its target can enhance their affinity. This interaction was illustrated in the case of inhibitors of HCV/NS3 protease, in order to treat hepatitis C. The design and synthesis of these compounds was studied by Zheng and Scola.[48] The incorporation of a difluoromethyl moiety in the peptide of interest allowed the authors to obtain a higher potency of the ingredient than for the one with non-fluorinated analogues. They were able to obtain a cocrystal of the complex of the peptide and the protease, which suggested the presence of a hydrogen atom between the hydrogen bond of the CHF_2 group and the Leu135 carbonyl in the enzyme active site **(Figure 0.12).**

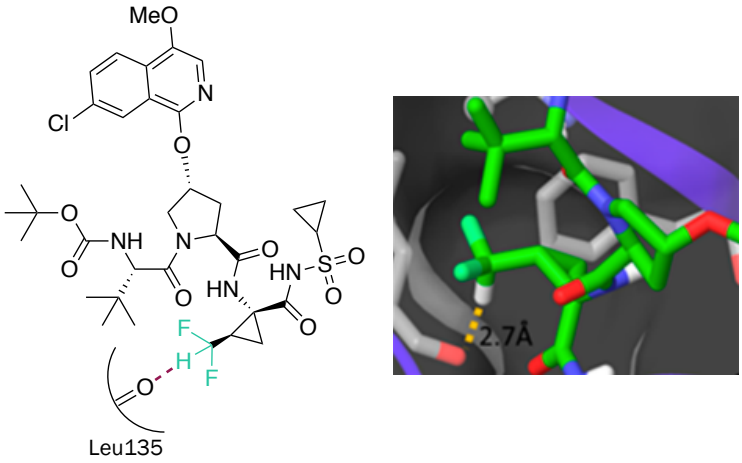


Figure 0.12. Cocrystal structure of HCV NS3 inhibitors presenting a H-bond with the protease target

The structure-activity relationship study, through analysis of the activities of -CH_3 and -CF_3 analogues indicated that the enhanced potency of the difluoromethylated peptide is due to this H-bond that cannot be formed in other cases.

c. Bioisosteres

The –CHF_2 group has been used in some cases as a bioisostere of methyl groups due to its similar molecular size.[50,51] However, it is often reported as a bioisostere of hydroxyl, thiol and amine functional groups, mostly due to their similar manner to form hydrogen bonds.[40,52,53]

In the case of the study of HCV/NS3 protease inhibitors, involved in hepatitis C, the efficient use of a difluoromethylated bioisostere was underlined. Indeed, computational studies led to the design of a difluorinated analog to replace a cysteine residue taking into account the dipolar similarity, as illustrated in **(Figure 0.13).**[52]

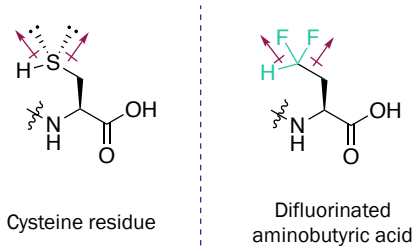


Figure 0.13. Functional mimicry between thiol and difluoromethyl groups

The application of this modification and the biological study of the obtained compound confirmed the bioisosterism between the targeted enzyme inhibitors. Furthermore, X-ray crystallographic analysis indicated that the hydrogen atom of the -CF_2H group was involved in a H-bond with the enzymatic pocket, giving the compound an improved biological activity **(Figure 0.14)**.[52,54]

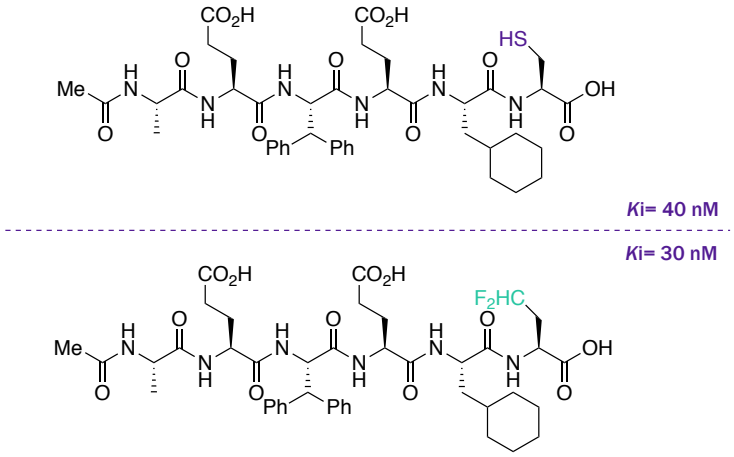


Figure 0.14. Bioisosteric replacement of a thiol group by a $-CHF_2$

E. PhD project description

The outstanding properties of the difluoromethyl group (-CHF_2) as a bioisostere of hydroxyl, thiol and amine groups, its hydrogen bond donor character and high stability, and the limited number of examples regarding enantioselective difluoromethylation that have been reported in the literature led us to develop new synthetic pathways to access chiral difluoromethylated building blocks for medicinal research.

The strategy relies on a new approach, based on the use of a difluoromethylated sulfoxide as a chiral difluoromethyl surrogate. Sulfoxides are known to be efficient chiral auxiliaries in organic synthesis. The potentially enantioselective introduction of the difluoromethyl group is based on a chirality transfer from the sulfur center of such sulfoxides.

At the beginning of this study in the group, the first challenge consisted in finding an efficient and selective pathway to synthesize the enantiopure aryl difluoromethyl sulfoxide. Indeed, only two groups had previously reported the synthesis of this kind of compounds. Their pathways presenting some drawbacks, we developed a new synthetic methodology. The stereoselective version of the aryl difluoromethyl sulfoxide synthesis was performed in the group and developed on a gram scale. The desired product was obtained with satisfying overall yields and high optical purity. Moreover, we attempted to complete the possibilities of reactivity of difluoromethyl sulfoxides by modulating the -CHF_2 pattern. In fact, we also wished to include halogenated and silylated derivatives of the difluoromethyl sulfoxide. This will be discussed in detail in the first chapter.

Once the sulfoxide was efficiently synthesized, following non-asymmetric and enantioselective pathways, we decided to explore the stereoselective introduction of the difluoromethyl group in an array of compounds in order to study the versatility of difluoromethyl sulfoxides. The condensation of the anion of the difluoromethyl sulfoxide onto carbonyl compounds was previously studied in detail by C. Batisse in the group and remained the starting point for this study. To increase the diversity of difluoromethylated structures that can be accessed using our methodology, we chose to add difluoromethyl *p*-tolyl sulfoxide **I-(S_s).72d** onto diverse electrophiles. We investigated also the use of the corresponding bromodifluoromethyl sulfoxide in Reformatsky type reactions. The results concerning these nucleophilic additions will be presented in *Chapter II*.

The obtention of highly enantioenriched compounds bearing a sulfoxide moiety as chiral auxiliary requires an efficient method to remove this auxiliary with retention of the configuration of the carbon stereocenter. This desulfinylation was achieved following two different procedures. Furthermore, the functionalization of the obtained difluoromethyl derivatives was of great interest in order to access valuable building blocks, useful for pharmaceutical research. The removal of the chiral auxiliary and the various attempts of functionalization will be presented in the third and last chapter.

Chapter I

Synthesis of difluoromethyl sulfoxides as chiral and traceless auxiliaries

Table of contents

A. Sulfoxides: generalities

Nowadays, the ability to selectively prepare enantiopure compounds has become an essential point for synthetic organic chemists. The agrochemical, food as well as pharmaceutical industries often require optically pure final products, which led to the development of a large number of synthetic methods for the preparation of enantiomerically pure compounds (EPC) during the last century.

The approaches to achieve the synthesis of EPC are numerous and were reported by Prof. Seebach in 1986, the three main methods remaining a chiral resolution of racemates, use of the pool of chiral building blocks and enantioselective transformations (**Figure I.1**).[89]

Among these methods, stereoselective synthesis remains a potent tool in the preparation of a large variety of enantiopure compounds, the asymmetric induction coming from a chiral auxiliary or catalyst.

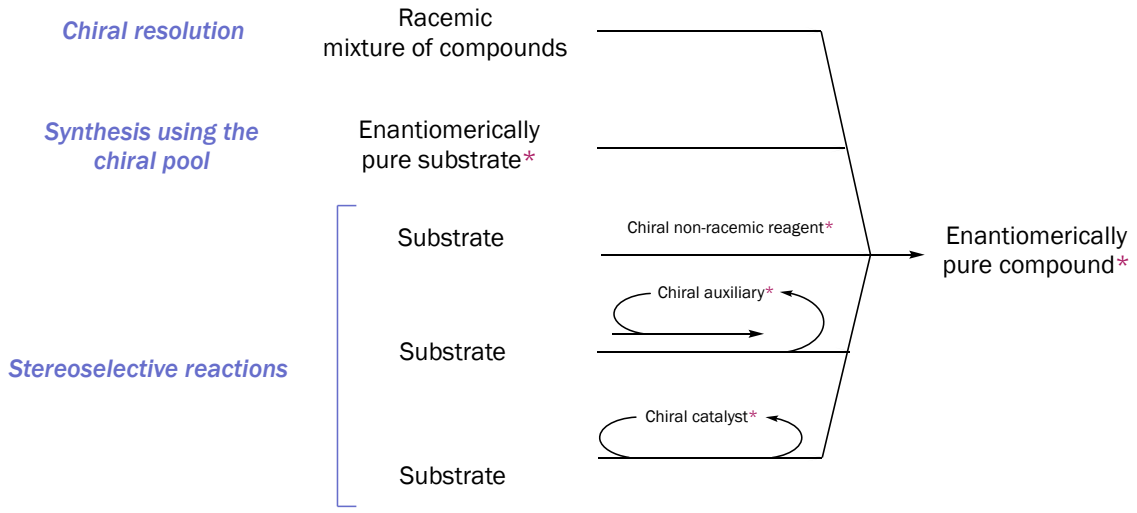


Figure I.1. General approaches to synthesize enantiomerically pure compounds

In stereoselective reactions, sulfoxides are widely used as a powerful chiral auxiliary for enantiomerically pure compound synthesis and their efficiency has been proved over the last decades. In addition to that, enantiopure sulfoxides had also been a center of interest for pharmaceutical goals due to their biological activity. Some high selling drugs containing the sulfinyl moiety became of special interest, as well as natural products having a potent biological activity (**Figure I.2)**.

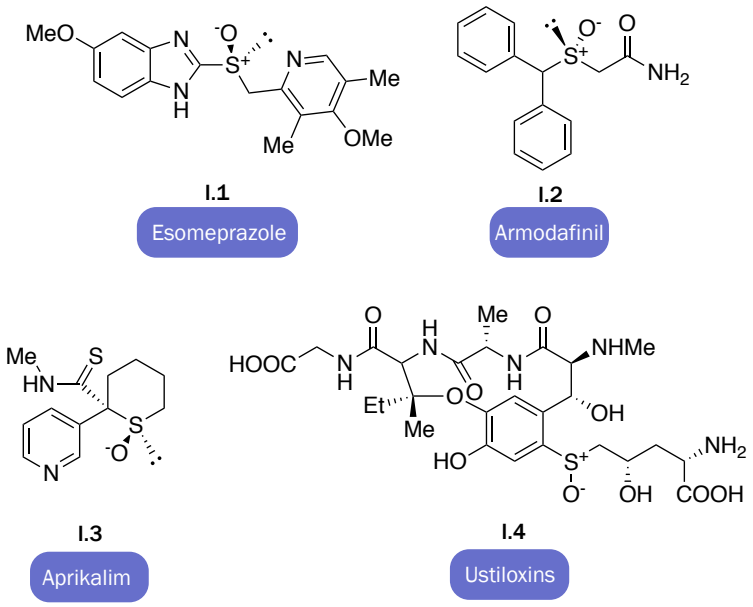


Figure I.2. Biologically active compounds bearing a sulfoxyde moiety

Esomeprazole **I.1**, the (*S*)-enantiomer of omeprazole,[90] is used to treat and relieve damages caused by excessive stomach acid in the esophagus. Modafinil **I.2** treats excessive sleepiness,[91,92] aprikalim **I.3** acts as an activator of the potassium chanel and ustiloxins **I.4** are antimitotic reagents that can be used for their anticancer or antifungal action.[93–95] These examples illustrate the broad range of attractive targets bearing an enantiopure sulfoxide, and then requiring efficient synthetic methods.

a. The sulfinyl group as chiral non racemic controller in organic synthesis

Sulfoxides are known to be highly configurationally stable and are widely used in asymmetric synthesis due to their remarkable features as chiral inductors.[60,96–98]

Their potential can be noticed in a wide range of transformations including carbon-oxygen or carbon-carbon forming reactions, 1,4-additions, cycloadditions, but they are also largely used for asymmetric catalysis.[99–102] Such an impressive ability and efficiency lies in the configuration stability and the steric and stereoelectronic differences between the substituents of the sulfur atom. The presence of a lone pair of electrons, a polarized S-O bond and two alkyl or aryl groups allows these compounds to have a stabilized conformation to control the approach of a prochiral substrate, explaining the excellent asymmetric inductions observed. Moreover, the racemization process of sulfoxides is suggested to go through a pyramidal inversion mechanism but the energy barrier values are high (**Figure I.3)**. In fact, for some derivatives the conditions to undergo racemization require temperatures of at least 200 °C.[59,103]

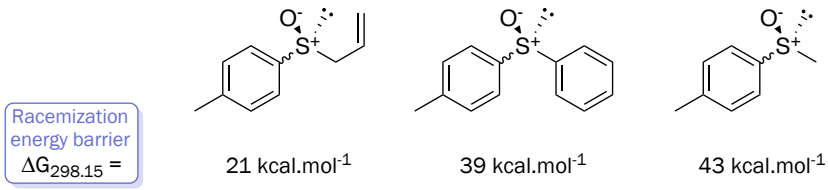


Figure I.3. Racemization barrier of enantiopure sulfoxides

The deprotonation in α-position of the sulfoxide led also to sulfinyl-stabilized carbanions, and the sulfinyl group being stereogenic, the reactions of these species with electrophiles often show good diastereoselectivities.[104]

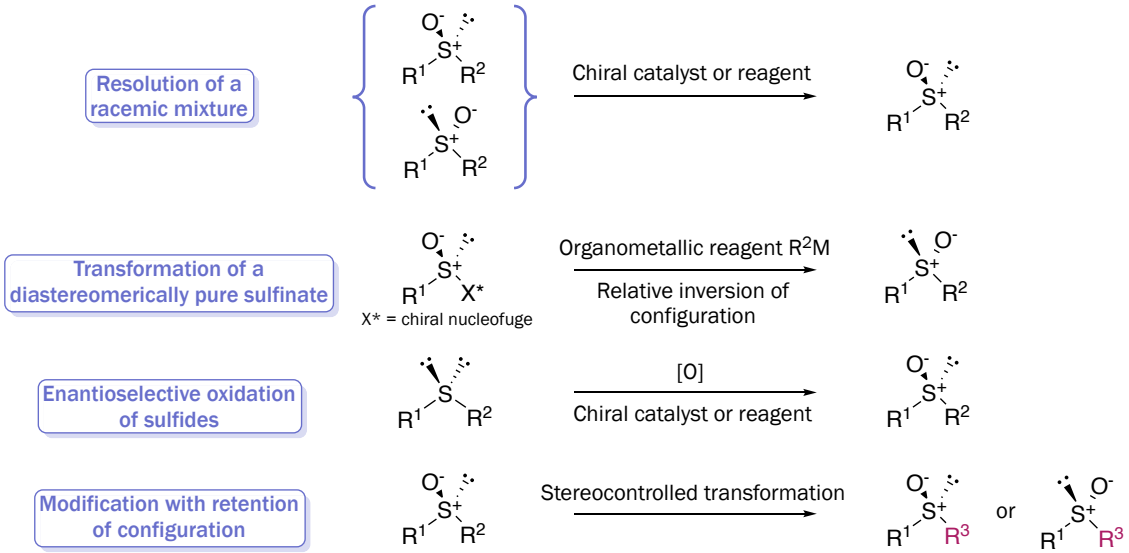
Finally, among the advantages discussed of sulfoxides as chiral inductors, we can also note the existence of several methods to access to both enantiomeric forms and their use as traceless auxiliary, as numerous methods have been described in literature for the removal of this moiety.

Due to their stability, remarkable properties and their excellent capacity to transmit chirality to other centers, optically pure sulfoxides are of huge interest for organic chemists. A large number of strategies have been developed dealing with stoichiometric stereoselective reactions or asymmetric catalyzed reactions involving enantiopure sulfoxides.

In the next part, an overview of the main routes to synthesize enantiopure sulfoxides will be listed.

b. State of the art: access to enantiopure sulfoxides

General methodologies that led to the preparation of chiral sulfoxides have been described since the last century and can be summarized in **Scheme I.1**.



Scheme I.1. General synthetic strategies leading to enantiopure sulfoxides

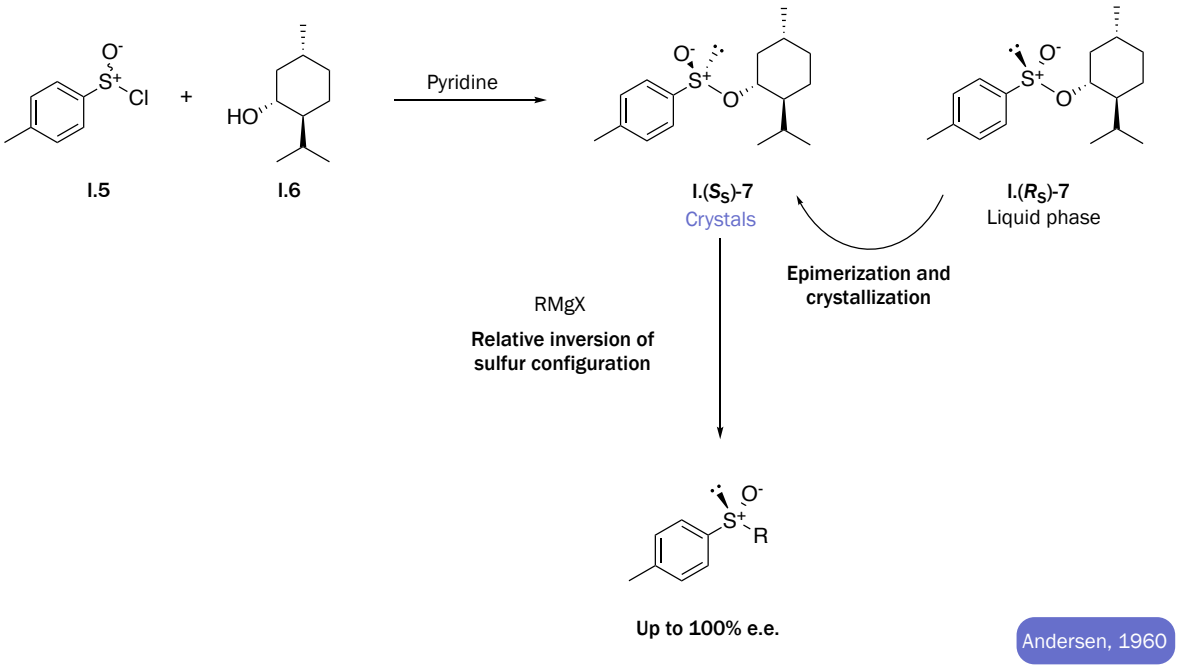
The resolution of racemic sulfinyl derivatives using chiral columns or using a chiral resolving agent remains the first method to access enantiopure sulfoxides.[60,105,106] Another readily used method is the nucleophilic substitution of non-racemic sulfinyl compounds, in order to form a new C-S bond. This is the case of the renowned Andersen's method, where a diastereomerically pure sulfinate is transformed to access sulfoxides with excellent enantiomeric excess. An alternative pathway consists in forming the S-O bond by a selective oxidation of sulfur. Prochiral sulfides are reacted with chiral oxidants or oxidants in the presence of chiral catalysts in order to reach exclusively enantiopure sulfoxides. Finally, it is also possible to directly transform chiral sulfoxides without losing the chirality at the sulfur center.

Our attention on the synthesis of high optically pure sulfoxides for this project will be focused on the asymmetric induction using a chiral auxiliary and selective oxidation involving chiral non-racemic catalysts or ligands. These pathways will be described in the next part.

1. Use of chiral non racemic sulfur precursors

i. Andersen's method

Chiral sulfinates represent the most common precursors to access enantiopure sulfoxides. In 1960, Andersen reported the synthesis of a couple of diastereomers of menthyl *p*-toluenesulfinate coming from (-)-menthol **I.6** and an *in situ* generated sulfinyl chloride **I.5** (**Scheme I.2**).[107]

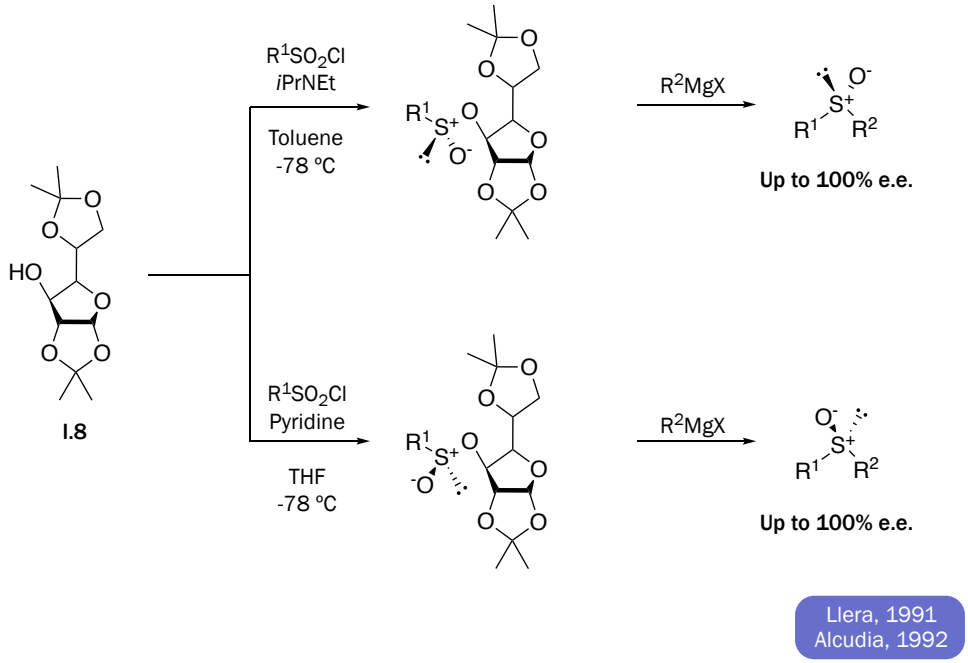


Scheme I.2. Synthesis of methyl *p*-tolyl sulfoxide using Andersen's method

The method is based on the very efficient separation of both diastereomers of (-)-menthyl *p*-toluenesulfinate **I.7**. This strategy was further studied by Solladié's group, who described the epimerization of the (R_S) diastereomer **I.(R_S)-7** in the presence of concentrated hydrochloric acid. After a series of iterative epimerizations and crystallizations, the desired diastereopure (1*R*,2*S*,5*R*)-(-)-menthyl-(*S*)-*p*-toluenesulfinate **I.(S_S)-7** can be obtained with excellent yields. The reaction of this compound with a Grignard reagent, such as methylmagnesium bromide, afforded the corresponding methyl *p*-tolyl sulfoxide with an inversion of configuration of the stereogenic sulfur.

ii. Diastereoselective synthesis of DAG-sulfinates

The use of acetone D-Glucose **I.8** was also reported as an efficient pathway to access highly optically pure sulfoxides. Llera and co-workers explored the tuning of the stereoselectivity of the reaction according to the base that is used (**Scheme I.3**). This pathway gave access to both enantiomers (R_S) and (S_S) of the corresponding sulfoxides.[108,109]



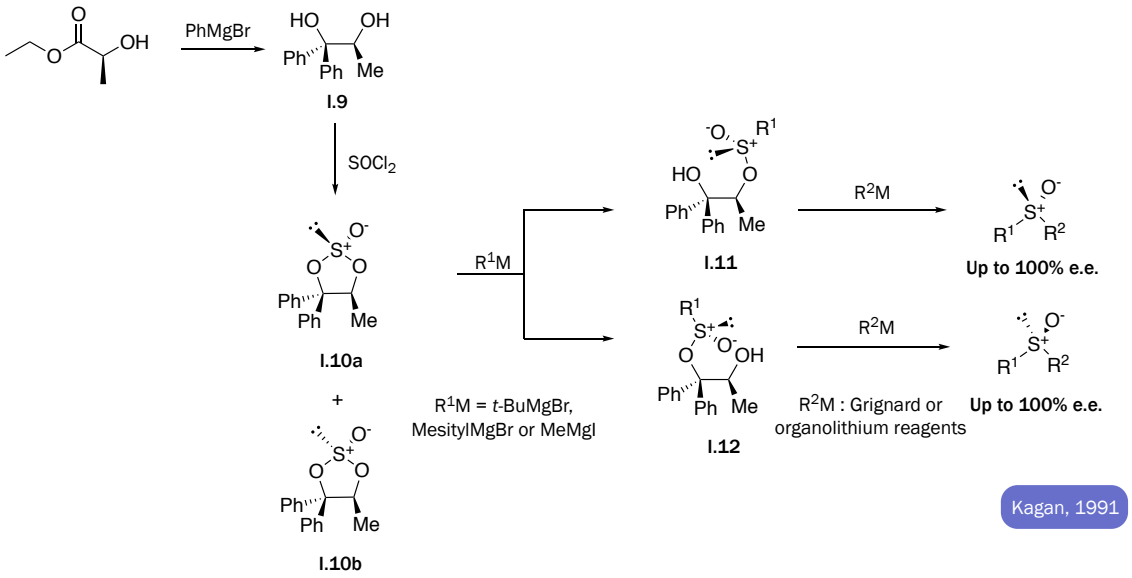
Scheme I.3. Access to enantiopure sulfoxides via D-Glucose auxiliaries

iii. Synthesis from dissymmetrical sulfites

In 1991, Kagan described the synthesis of sulfoxides from dissymmetrical sulfites bearing a stereogenic sulfur center in the presence of an organometallic reagent.[110]

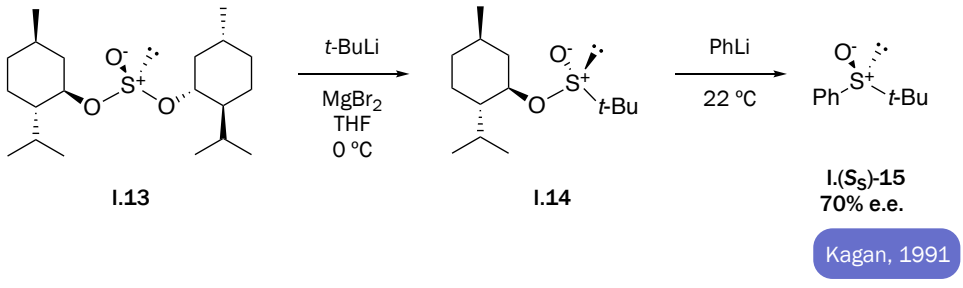
A chiral diol **I.9**, obtained from the chiral pool, was reacted with thionyl chloride in order to synthesize chiral sulfites. The ring opening using Grignard

reagents delivered chiral sulfites intermediates of both relative configurations according to the organometallic reagent used. After a second nucleophilic attack, these intermediates gave a variety of enantiopure sulfoxides with inversion of configuration at sulfur at each substitution step (**Scheme I.4**).



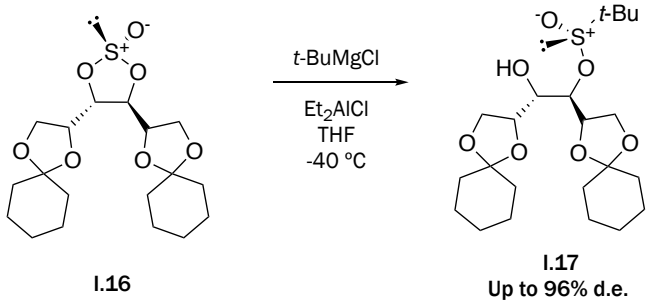
Scheme I.4. Use of disymmetrical sulfites to synthesize enantiopure sulfoxides

Moreover, C_2-symmetric sulfites derived from (-)-menthol as chiral source have also been also used by Kagan's group, and allowed the access to a bis-(-)-menthyl sulfite **I.13**. The additional attack with phenyllithium allowed the synthesis of sulfoxide **I.(S_S)-15** with an enantiomeric excess of 70% (**Scheme I.5**).



Scheme I.5. Kagan's use of menthyl sulfites to access enantiopure sulfoxides

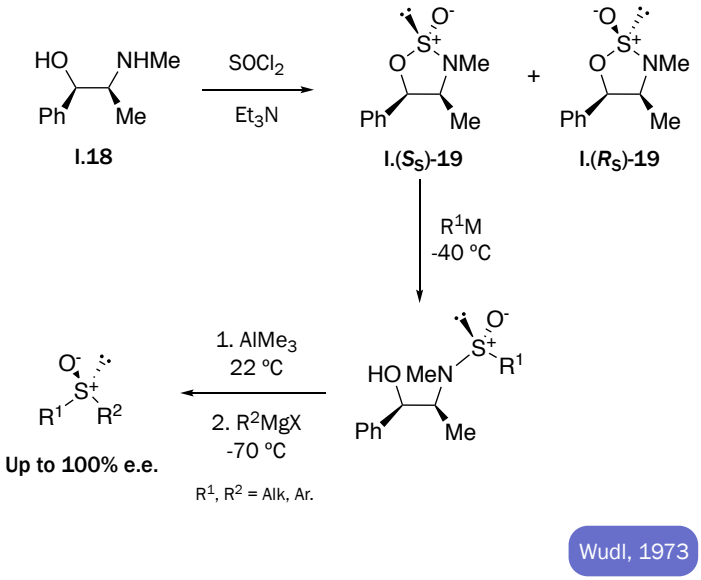
Inspired by the use of these symmetric sulfites, Vallée reported a cyclic sulfite **I.16** prepared from mannitol as a precursor for the synthesis of *tert*-butylsulfinates with an excellent diastereoselectivity (**Scheme I.6**).[95]



Scheme I.1. Mannitol cyclic sulfite precursor for the synthesis of *tert*-butylsulfinates

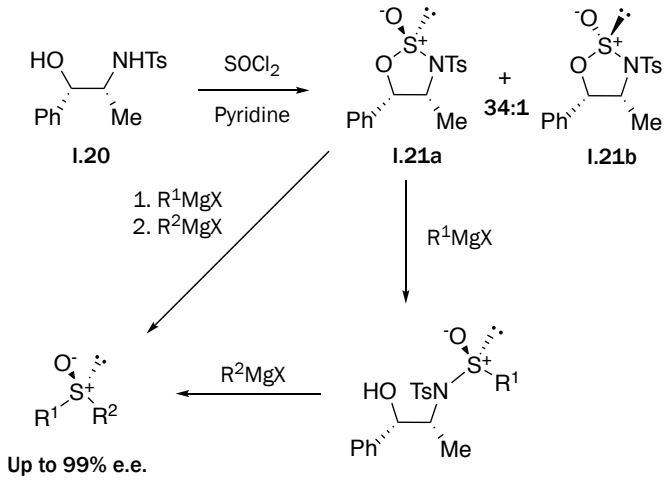
iv. Synthesis from sulfuramidite

Wudl and Lee studied the obtention of sulfoxides from cyclic sulfuramidites.[111] They used 1,2,3-oxathiazolidine-2-oxide **I.19** and were able to isolate one diastereopure isomer, that after addition of a Grignard reagent or organolithium gave regioselectively sulfinamides. The treatment with an additional organolithium or Grignard reagent in the presence of trimethyl aluminium allowed the authors to obtain a range of sulfoxides in enantiomerically pure form (**Scheme I.7**).

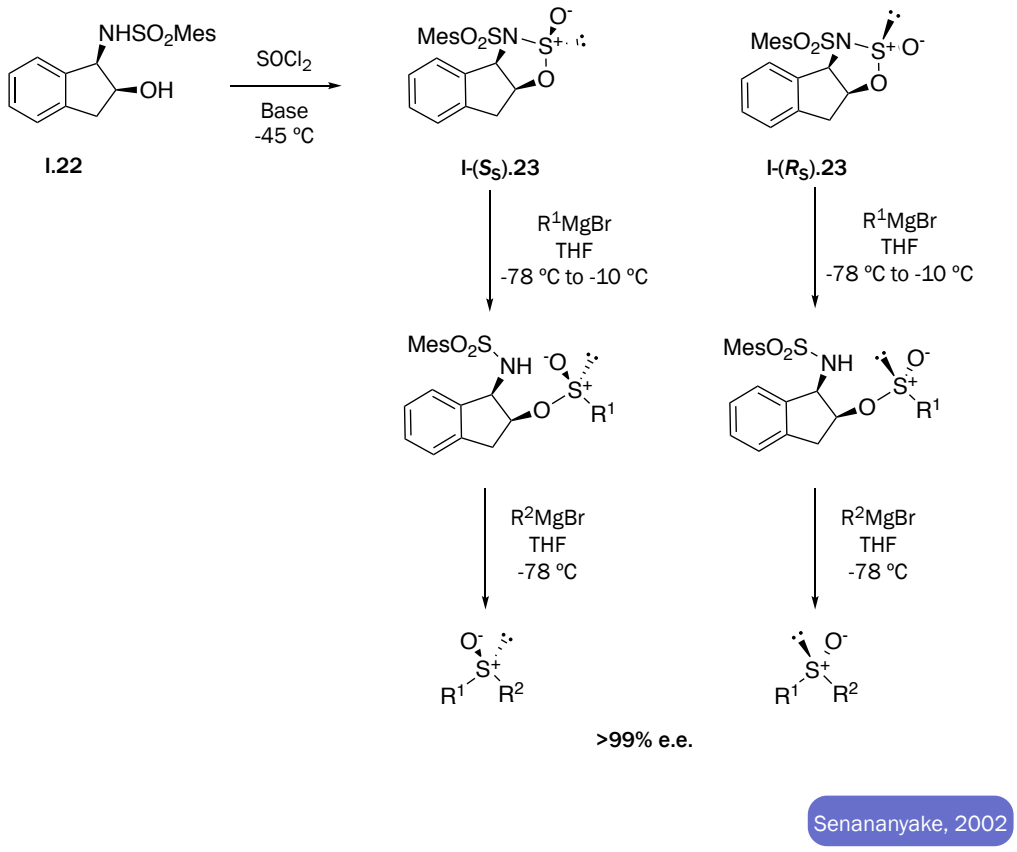


Scheme I.7. Cyclic sulfinamides mediated synthesis of enantiopure sulfoxides

Similarly, Snyder,[112] followed by Senananyake,[113,114] developed the use of *N*-tosyl oxathiazolidine-2-oxides **I.21** and **I.23** as chiral precursors of sulfoxides (**Schemes I.8** and **I.9**).



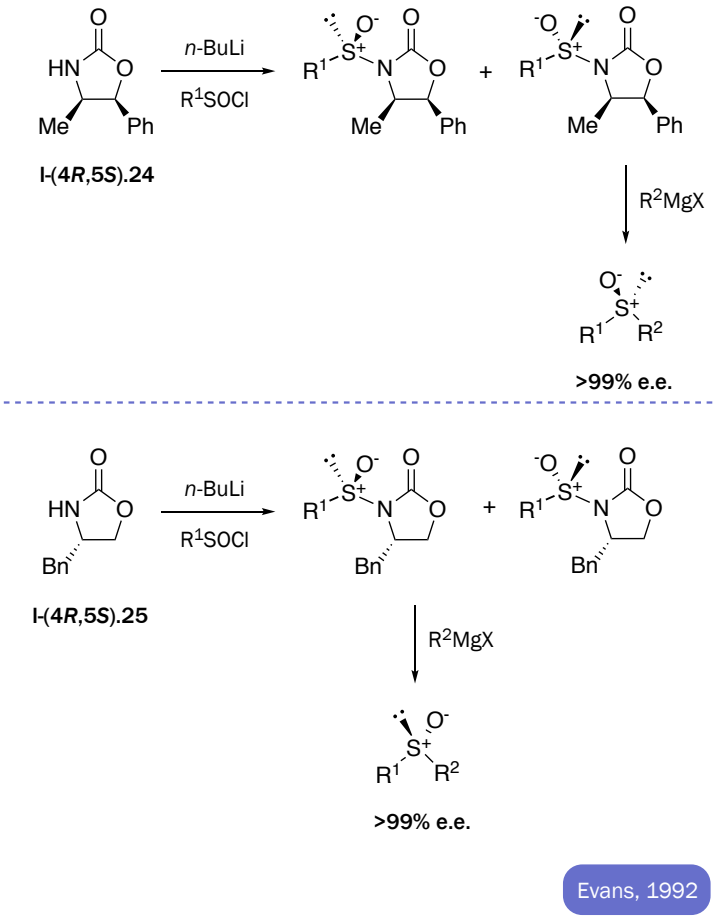
Scheme I.8. Use of an oxathiazolidine-2-oxide chiral precursor of sulfoxide by Snyder



Scheme I.9. Use of an oxathiazolidine-2-oxide chiral precursor of sulfoxides by Senananyake's group

v. Evans auxiliary

In the 1990's, Evans group focused on the use of their chiral auxiliaries, enantiopure oxazolidinones **I.24**, that after being coupled with sulfinyl chloride gave access to separable sulfinamides.[115] Moreover, the obtained sulfinyl oxazolidinones were found to be a hundred times more reactive with respect to nucleophiles than the menthyl sulfinate derivatives reported by Andersen (**Scheme I.10**).

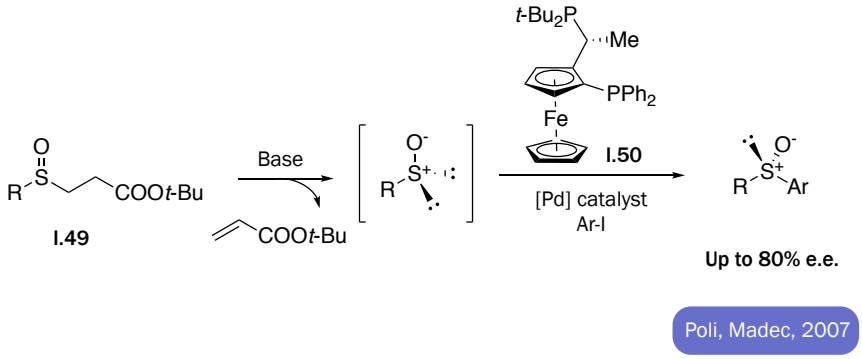


Scheme I.10. Evans auxiliary for the synthesis of enantiopure sulfoxides

These compounds remain an excellent choice of chiral sulfoxide precursors, as their reactivity towards Grignard reagents or organozinc species opens the access to a large library of derivatives. Moreover, the fact of being able to easily separate the two diastereomerically pure sulfinyl oxazolidinones allows the access to both enantiomers of the corresponding sulfoxide after nucleophilic substitution.

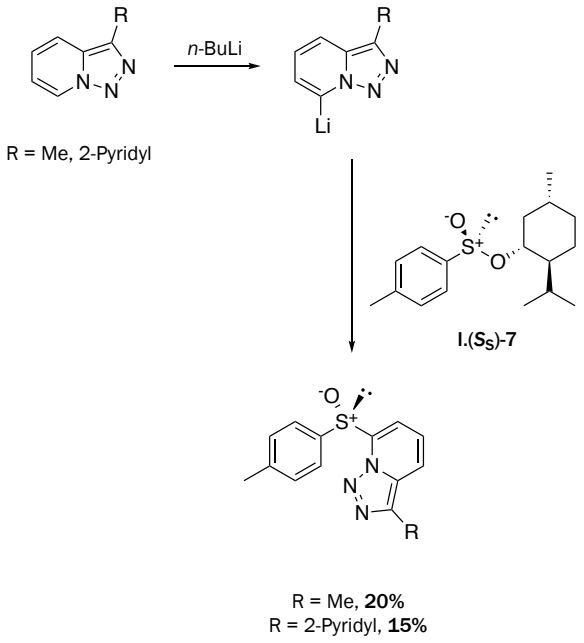
vi. Catalytic arylation of sulfenate anions

Poli, Madec and colleagues reported a new approach for the catalytic synthesis of sulfoxides.[116] Racemic sulfoxide **I.49** underwent a retro-Michael reaction under the influence of a base, which generated *in situ* its corresponding sulfenate ion. This prochiral substrate is then coupled to an aryl iodide under the influence of a Pd(0) catalyst bearing a chiral diphosphine. The authors were able to obtain the expected aryl sulfoxide with excellent yields and high enantiomeric excess up to 80% (**Scheme I.11**).



Scheme I.11. Palladium-catalyzed arylation of sulfenate anions

The access to heteroaromatic chiral sulfoxides was reported by Colobert and Leroux in 2007 (**Scheme I.12**). The first step consisted on the regioselective metalation of triazolopyridine with *n*-BuLi, followed by trapping with (*R*)-(-)-menthyl *p*-toluenesulfinate **I-(S_S)-7**. Following this pathway, the authors could access these compounds and use them as new examples of fluorescent triazolopyridines.[117,118]

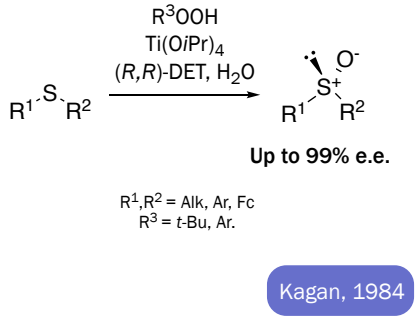


Scheme I.12. Synthesis of chiral [1,2,3]triazolo[1,5-a]pyridine *p*-tolyl sulfoxides

2. Enantioselective catalytic oxidations

i. Titanium complexes

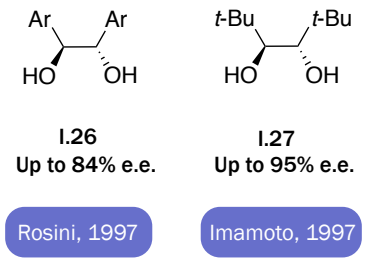
The Sharpless catalytic system, largely known for its use in asymmetric epoxidation, was a source of inspiration for Kagan, who used a modified version for the enantioselective oxidation of sulfides (**Scheme I.13**).[119]



Scheme I.13. Selective oxidation of sulfides using a modified Sharpless catalytic system

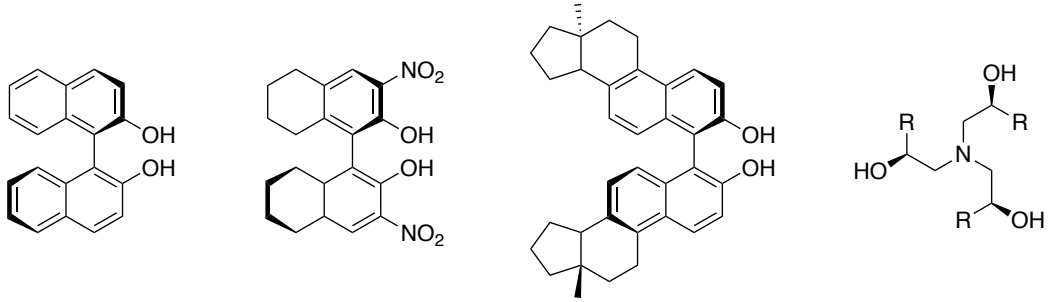
The use of titanium complexes from $Ti(OiPr)_4$ and (*R,R*)-diethyl tartrate with a hydroperoxide allowed to obtain sulfoxides with good enantiomeric excess. Their first version using stoichiometric amounts of the *in situ* formed titanium complex was further taken to a substoichiometric amount.[120,121] The optimization performed by Modena's group for this reaction allowed an improvement of the enantioselectivity by carefully choosing the hydroperoxide employed.[122] The enantiomeric excess obtained by Kagan and Modena go up to 99%.[123,124] It is noteworthy that Kagan's oxidation strategy has been applied for the industrial synthesis of biologically active compounds, such as esomeprazole commercialized by AstraZeneca.[125]

The efficiency of Kagan's method being proved, the impact due to a DET ligand replacement was studied by several groups. Indeed, a variety of C_2-symmetric 1,2-diols were used to form the titanium complexes. Rosini reported the use of a catalytic version of the reaction using 1,2-diarylethane 1,2-diols **I.26** and **I.27** which allowed the access to sulfoxides with e.e. values of up to 99%.[126,127] Complementarily, Imamoto used an analogue of this diol, this time bearing a *tert*-butyl group instead of aryl, to access enantioenriched sulfoxides (**Scheme I.14**).[128]



Scheme I.14. Use of 1,2-substituted diols for the oxidation of sulfides

The use of several titanium/chiral binaphthol complexes by Uemura, Reetz,[129] and Bolm[130] combined with a kinetic resolution led also to high enantiomeric excess values of the corresponding sulfoxides. Licini and Nugent were interested in the use of a C_3-symmetric ligand derived from triethanolamine to form a titanium catalytic complex.[131] They were able to obtain enantiomeric excess up to 85% (**Scheme I.15**).



I.28 — Up to 99% e.e. — Uemura, 1993

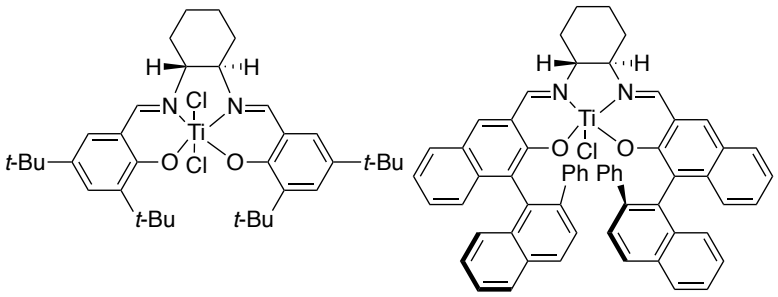
I.29 — Up to 86% e.e. — Reetz, 1997

I.30 — Up to 92% e.e. — Bolm, 1999

I.31 — Up to 85% e.e. — Licini, 1996

Scheme I.15. Chiral binaphtol and triethanolamine ligands to access enantiopure sulfoxides by selective oxidation

Katsuki explored the use of chiral salen ligands to form Salen-Ti(IV) catalysts for sulfoxidation. The use of these ligands in combination with titanium and the apropriate peroxide allowed the preparation of aryl methyl sulfoxides with e.e. values up to 99% (**Scheme I.16**).[132]



I.32 — Up to 99% e.e.

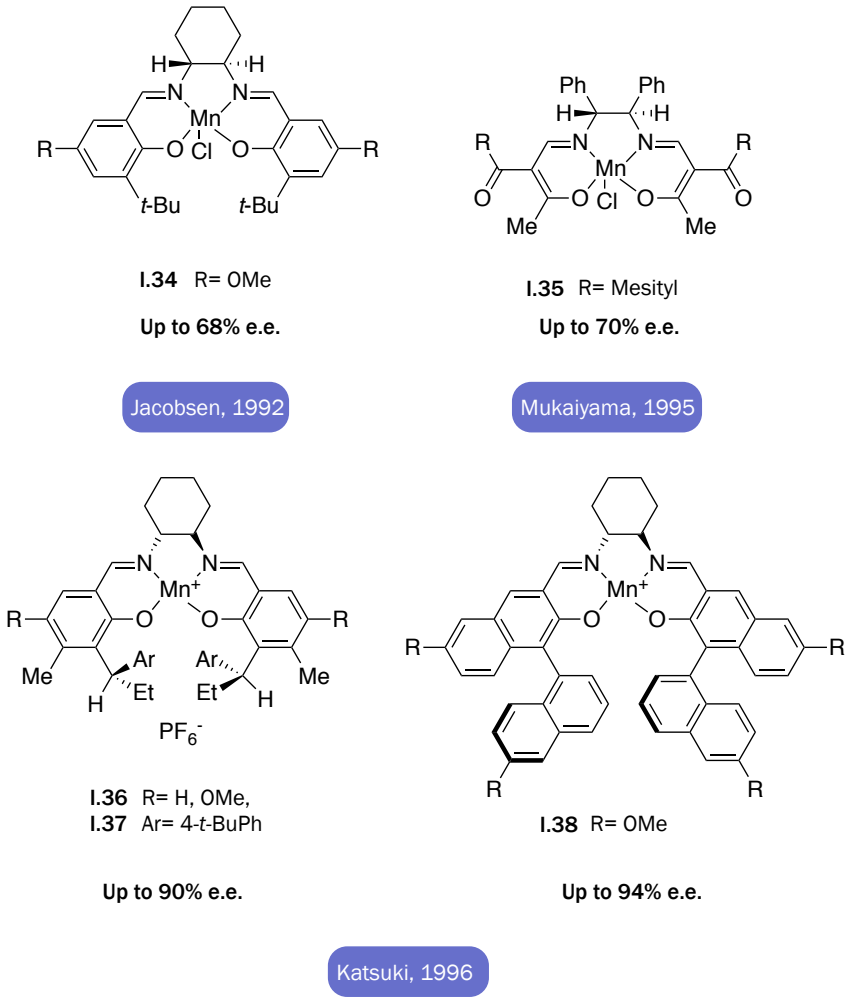
I.33 — Katsuki, 2001

Scheme I.16. Chiral salen-Ti(IV) complexes for enantioselective oxidations

ii. Manganese complexes

The use of manganese complexes for the enantioselective oxydation of sulfides was first reported by Halterman who used a manganese

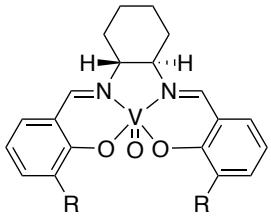
tetraphenylporphyrin catalyst.[133] The interest for these complexes kept growing and salen-manganese catalysts were developed by Jacobsen[134] and Katsuki,[135–137] giving enantiomeric excesses up to 90% using iodosobenzene as oxidant. Another example was reported by Mukaiyama using β-oxo aldiminato manganese complexes, which gave a sulfoxide in 70% e.e. (**Scheme I.17**).



Scheme I.17. Manganese complexes for enantioselective sulfoxidations

iii. Vanadium complexes

The use of Schiff bases to prepare oxo vanadium complexes and their application for the oxidation of sulfides was reported by Nakajima (**Scheme I.18**).[138]



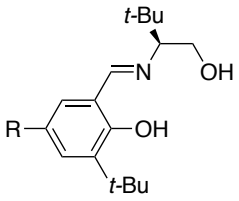
R= OMe, OEt, *t*-Bu

Up to 40% e.e.

Nakajima, 1986

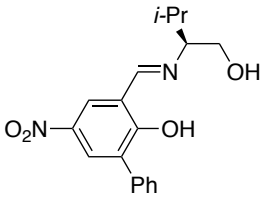
Scheme I.18. Nakajima vanadium complexes for selective oxidations

However, the enantioselectivity being moderate, an improvement was reported by Bolm's group, who prepared highly active vanadium catalyst from other Schiff bases combined to $VO(acac)_2$. The groups of Skarzewski,[139,140] Jackson, Maguire, Bolm[141] and Katsuki,[142] Berkessel, Ahn and Ellman screened several ligands, in some case tridentate ligands, in order to achieve an efficient oxidation of the sulfur with very satisfying enantiomeric excess. Some examples of these ligands are illustrated in **Scheme I.19**.



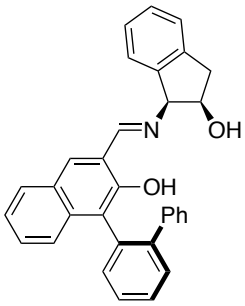
I. 39 R= NO_2
I.40 R= *t*-Bu
Up to 85% e.e.

Bolm, 1995



I.41
Up to 95% e.e.

Skarzewski, 1999

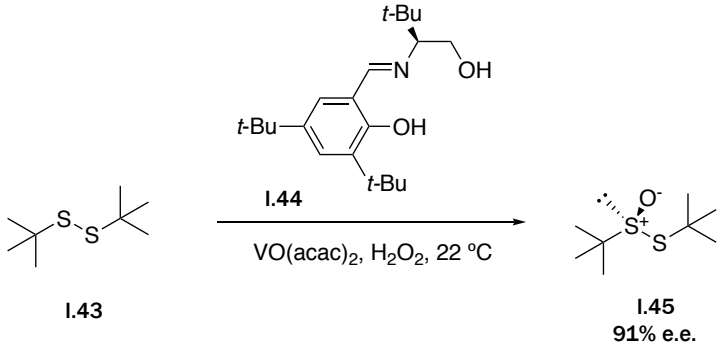


I.42
>90% e.e.

Katsuki, 2002

Scheme I.19. Tridentate ligands for enantioselective sulfur oxidation

In addition, in 1997 Ellman *et al.* used the Bolm ligand **I.44** for the monooxidation of di-*tert*-butyldisulfide **I.43** into *tert*-butyl *tert*-butanesulfinate **I.45** with an excellent enantiomeric excess of 90% (**Scheme I.20**).[143]



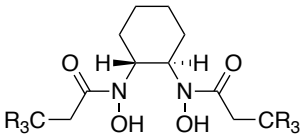
Ellmann, 1997

Scheme I.20. Ellman's example of application of vanadium-catalyzed sulfoxidation

These results prove that oxovanadium complexes are excellent catalysts in asymmetric sulfoxidations.

iv. Molybdenum complexes

Followed by the remarkable results obtained for the enantioselective sulfoxidation when using titanium or vanadium complexes, the study of molybdenum complexes was carried out by Yamamoto.[144] A chiral molybdenum complex of a bis-hydroxamic acid (**Scheme I.21**) was engaged to prepare methyl sulfoxide and methyl 1-naphthyl sulfoxide as examples, with e.e. values up to 86%. Combined to a kinetic resolution, the e.e. values obtained were even higher, opening the access to enantiopure sulfoxides using this kind of complexes.



Up to 85% e.e.

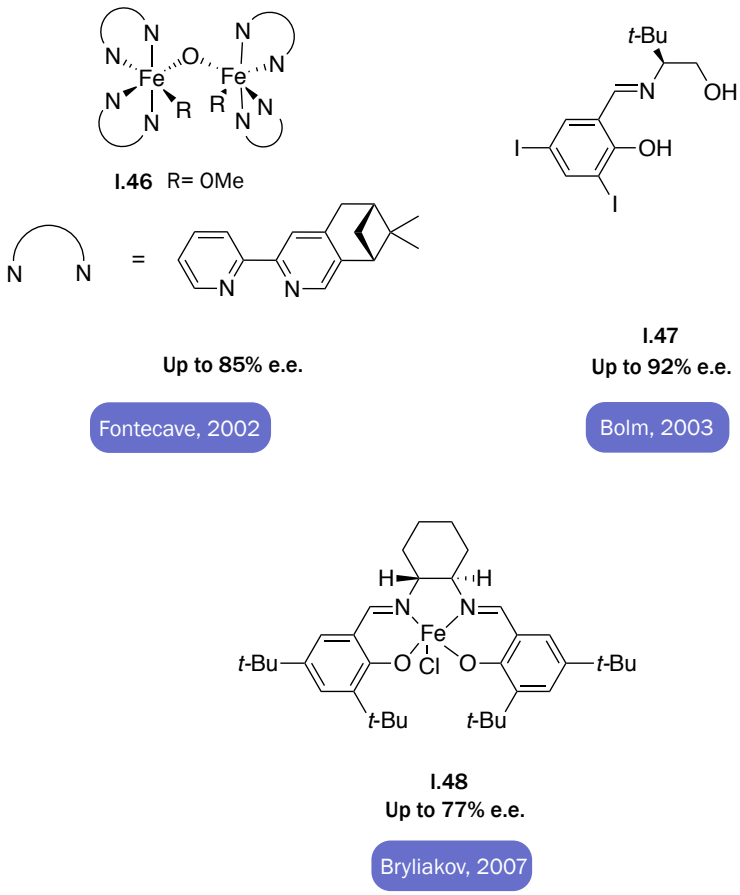
Yamamoto, 2006

Scheme I.21. Molybdenum ligand to access enantiopure sulfoxides

v. Iron complexes

Aside from the abovementioned concerning the use of organometallic complexes as catalysts of sulfoxidation, some groups focused on the use of chiral iron complexes. Groups as Fontecave's[145] and Bolm's[146-148] used respectively a binuclear iron complex **I.46** and a derivative from $Fe(acac)_3$ and a

Schiff base. The produced sulfoxides were obtained with e.e. values up to 92% (**Scheme I.22**).

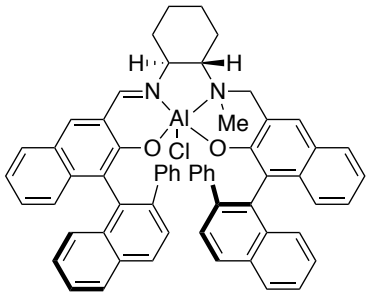


Scheme I.22. Ligands used for the iron catalyzed enantioselective oxidation of sulfides

A screening of analogues of these complexes was carried out and the mechanism of the iron-catalized oxidation of thioethers has also been reported by Bryliakov.[149]

vi. Miscellaneous

Among all the catalytic sulfoxidation methods, we have quoted a few of them in the previous sections. This illustrates the versatility of catalytic systems that can be used to synthesize high optically pure sulfoxides. The use of titanium, molybdenum, vanadium, iron or manganese complexes showed good to excellent results. In complement to these compounds, some groups reported other catalytic systems using chiral aluminum complexes, ruthenium, copper or tungsten catalysts. An example of one of these aluminum complexes has been described by Katsuki in 2007 (**Scheme I.23**). [150]



Katsuki, 2007

Scheme I.23. Aluminium chiral catalysts for sulfoxidations

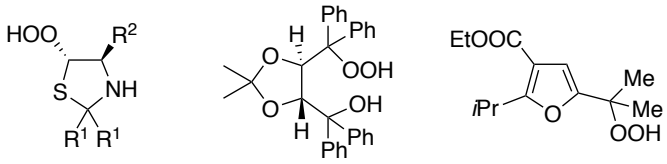
Supplementary catalytic systems, such as Shi's fructose-based dioxirane and … have also been developed, but the corresponding enantioselectivity remain inferior to the asymmetric oxygen transfer transfer catalyzed by transition metals. Furthermore, the development of biocatalysts has been of interest for some groups. The progress in biotechnologies allows the development of new biocatalytic systems and the use of enzymes or bacterias give access to a library of sulfoxides with high stereo, regio and chemoselectivity. The use of these systems will not be discussed in this manuscript. For further details, readers are invited to consult reviews dealing with this topic.[151,152]

3. Enantioselective non-catalytic oxidation of sulfides

In contrast to the catalytic systems used for the oxidation of sulfides, we can also find in literature interesting stoichiometric approaches. Three examples will be described in this section.

i. Chiral hydroperoxides

Chiral hydroperoxides proved as excellent chiral oxidants when using a titanium complex as promoter. The groups of Ando,[153] Seebach,[154] and Scettri[155] studied these compounds and were able to obtain up to 98% of enantiomeric excess (**Scheme I.24**).



I.51 | I.52

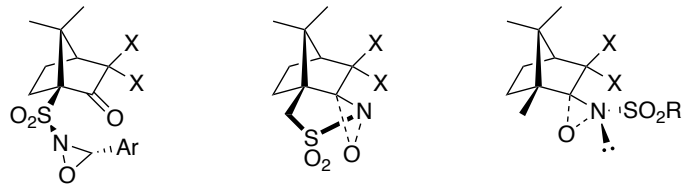
Up to 82% e.e. | Up to 86% e.e. | Up to 98% e.e.

Ando, 1986 | Seebach, 2001 | Scettri, 2002

Scheme I.24. Chiral hydroxyperoxides used to obtain enantiopure sulfoxides

ii. Chiral oxaziridines

The use of chiral *N*-sulfonyl oxaziridines by Davis was shown to be interesting for the oxidation of sulfides into enantioenriched sulfoxides. A range of reagents were prepared starting from camphor and an optimization of the substituents was performed and resulted in the obtention of sulfoxides having enantiomeric excess up to 95% (**Scheme I.25**).[156,157] A variation of two substituents of the oxaziridine was performed by Page by replacing the halogen moieties by a –OMe group to obtain a slightly better enantiomeric excess of 98%.[158]



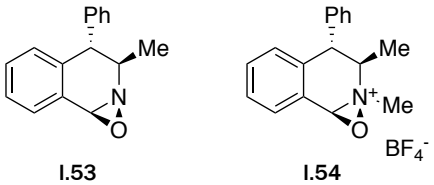
X= H, Cl | X= H, Cl, OMe | X= H, Cl

Up to 98% e.e.

Davis, 1992

Scheme I.25. *N*-sulfonyl oxaziridines for the oxidation of sulfides

A variation in the structure of oxaziridines was reported by Lusinchi, who used an oxaziridine prepared from norephedrine and its oxaziridinium salt, however the obtained enantiomeric excesses remained moderate (**Scheme I.26**).[159,160] In the presence of Brønsted acids, some oxaziridines oxidize sulfides into sulfoxides without overoxidation to sulfones, presumably through an oxaziridinium intermediate. Thus, methanesulfonic acid catalyzes the oxygen transfer from oxaziridine to an aryl methyl sulfide (with enantiomeric excess up to 44%).



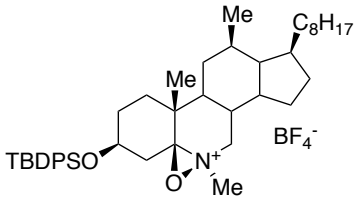
I.53 I.54

Up to 44% e.e.

Lusinchi, 1993

Scheme I.26. Lusinchi's oxaziridine and oxaziridinium salt

In 2007, Bohé reported a new oxaziridinium salt obtained from protected 6-azacholesterol, presented in **Scheme I.27**, that showed excellent enantioselectivities for the oxidation of sulfides.[161]



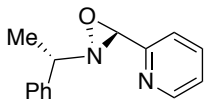
I.55

>99% e.e.

Bohé, 2007

Scheme I.27. Bohé's and oxaziridinium salt

The presence of a Brønsted or a Lewis acid gave good results concerning this oxidation of sulfides. Fontecave studied the reactivity of *N*-alkyloxaziridines activated by Lewis acids, in particular $ZnCl_2$.[162] The corresponding sulfoxides were obtained with enantiomeric excesses up to 63% (**Scheme I.28**).



I.56

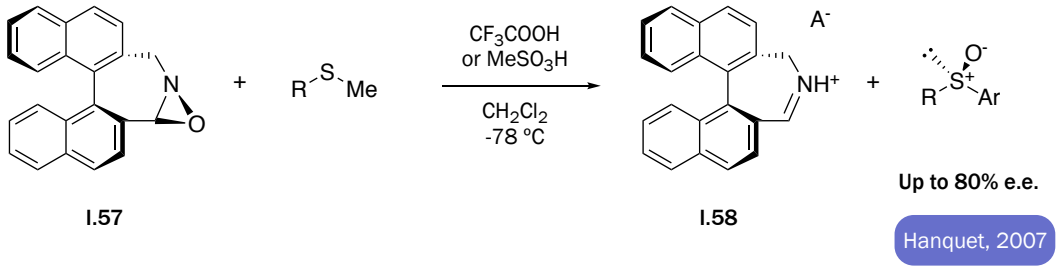
Up to 63% e.e.

Fontecave, 2007

Scheme I.28. Fontecave's N-alkyloxiaziridines

This reaction was more recently reinvestigated by Hanquet and coworkers with oxaziridines containing a binaphthyl fragment, with the best results being observed with no substituents on the binaphthyl rings. With $MeSO_3H$, the oxygen transfer was very rapid (55 min), thus producing the sulfoxide and the corresponding iminium. *Tert*-butyl methyl sulfoxide and methyl *p*-tolyl sulfoxide were formed in good yield with 60% e.e. and 47% e.e. respectively. Replacement of $MeSO_3H$ by triflic acid greatly reduced the reaction rate but improved the enantiomeric excess values (to 80% and 70%, respectively). The imine deriving from imimium ion could be recovered and recycled. It was of

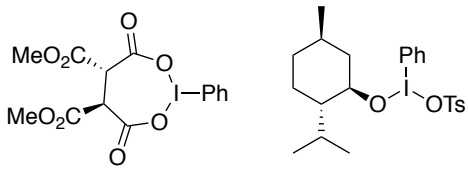
interest to note that, in the absence of acid, the employed oxaziridine may slowly oxidize *tert*-butyl methyl sulfide at room temperature, with a good enantioselectivity (70% e.e) (**Scheme I.29**).[163]



Scheme I.29. Binaphthyl-derived oxaziridines used in enantioselective oxidations

iii. Chiral hypervalent iodine reagents

As a last approach that can be used for the selective oxidation of sulfides into optically pure sulfoxides, we can find the use of chiral hypervalent iodo compounds. Remarkable examples in terms of selectivity were obtained when using derivatives from L-tartaric anhydride as **I.59** or from (-)-menthol as **I.60**, that were prepared by Imamoto's[164] and Koser's[165] groups respectively (**Scheme I.30**).



Scheme I.30. Imamoto's and Koser's hypervalent iodines

c. Removal of the chiral auxiliary: reported methods

The removal of the sulfoxide after the desired transformation remains a crucial step when these species are used as chiral auxiliaries. An efficient and traceless removal is required.

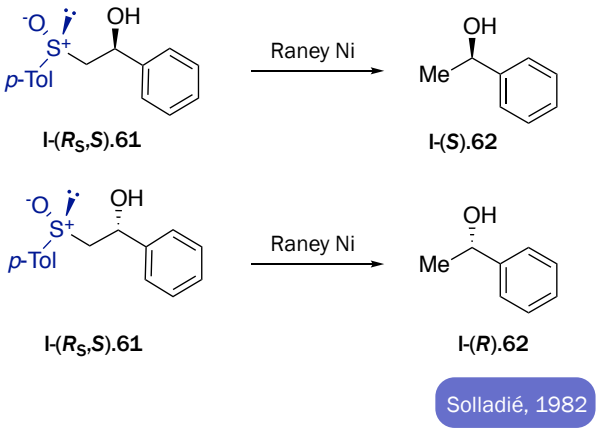
Several methods have been developed making possible to remove the sulfoxide moiety with good to excellent yields and complete retention of configuration

of stereocenters. A summary of these methods will be presented in the next section, illustrated by some examples.

1. Use of Raney nickel

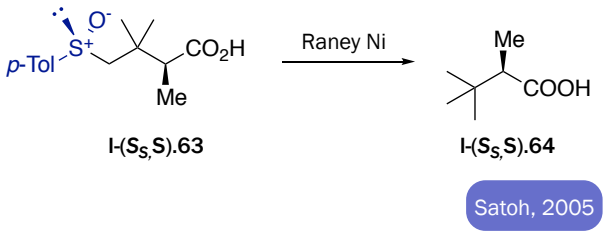
Raney nickel has been used multiple times for the C-S bond breaking cleavage, including though desulfurization, desulfinylation and desulfonylation reactions. In this paragraph, we will give a few examples of this method exclusively applied for the removal of a sulfoxide group.

Solladié reported the use of Raney nickel to perform the desulfinylation of, among others, diastereomerically pure sulfinyl alcohols. The access to both enantiomers ofthe corresponding alcohols was described with full retention of configuration at the carbon center (**Scheme I.31**).[67] Similarly, Ishibashi was able to obtain highly optically pure phenyl ethanols using this strategy.[166]



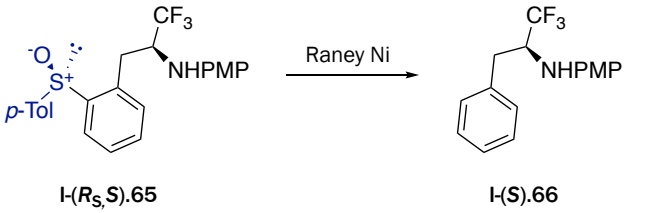
Scheme I.31.Access to enantiopure alcohols from diastereomerically pure sulfinyl alcohols

Other carboxylic acid derivatives were obtained by Satoh after the selective desulfinylation using Raney nickel (**Scheme I.32**).[167]



Scheme I.32. Desulfinylation of carboxylic acid derivatives bearing a sulfoxide

The strategy could also be applied to sulfinyl amines by Garcia Ruano's group, who obtained the corresponding substituted amines (**Scheme I.33**).[168]

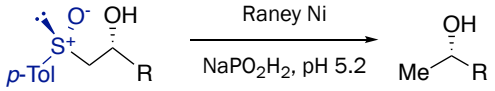


I-(R_S,*S*).65 I-(*S*).66

García Ruano 2009

Scheme I.33. Desulfinylation of enantioenriched sulfinyl amines

Even though the efficiency of Raney nickel was proved, in only a few cases a racemization of the carbon center was observed. To avoid this phenomenon, Node reported the useful addition of a sodium hypophosphite in the medium (**Scheme I.34**).[169]



Node, 1997

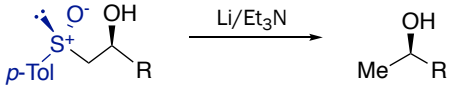
Scheme I.34. Raney nickel desulfinylation in the presence of a buffer solution

2. Organometallic reagents

Organometallic reagents were reported several times in literature as efficient exchange reagents. Organolithium or Grignard reagents undergo a sulfoxide/metal exchange that gives access to enantioenriched compounds. A short selection of examples will be described in this part.

i. Lithiated species

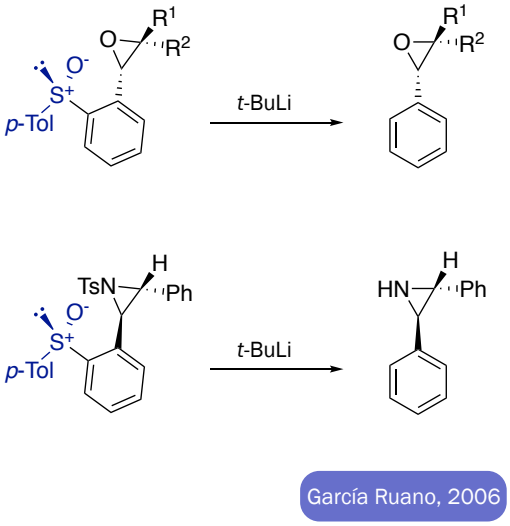
Organolithium reagents, such as *n*-BuLi or *t*-BuLi, allowed to access derivatives having identical enantiopurity after the sulfoxide/lithium exchange (**Scheme I.35**). A particular case was reported by Solladié, pointing the use of a combination of lithium in the presence of triethylamine and giving access to enantiopure alcohols from sulfinyl alcohols.[170]



Solladié, 1985

Scheme I.35. Lithium mediated desulfinylation

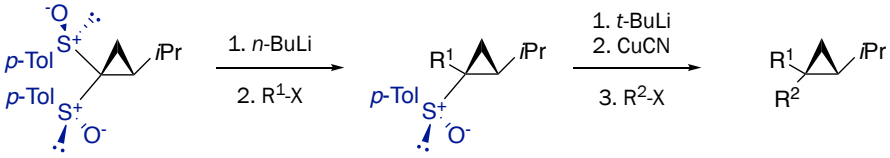
The strategy of using organometallic reagents has proved its efficiency in García Ruano's group as shown in (**Scheme I.36**).[71,171]



García Ruano, 2006

Scheme I.36. Organolithium mediated desulfinylation

Other examples of the reactivity of those reagents towards sulfoxides are given by Satoh[172]. Marek reported also the preparation of enantiomerically pure cyclopropane derivatives using two sulfoxides as auxiliaries, that are selectively exchanged and replaced by a range of electrophiles.[173] They reported the use of *n*-BuLi and *t*-BuLi to perform these two consecutive sulfoxide/lithium exchanges (**Scheme I.37**).

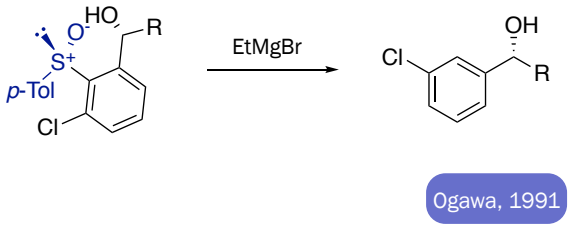


Marek, 2008

Scheme I.37. Synthesis of enantioenriched cyclopropanes using sulfoxides and organolithium desulfinylation

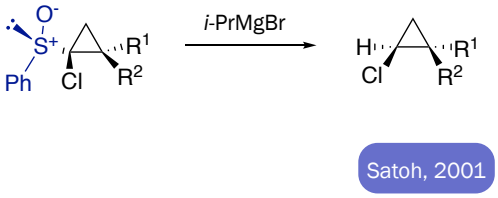
ii. Organomagnesium

Similarly to organolithiums, Grignard reagents are able to perform a sulfoxide/metal exchange. Ogawa reported in the early 1990's the access to optically pure carbinols by reaction of each sulfinylated diastereomer with Grignard reagents (**Scheme I.38**), and in some cases also with organolithium ones.[174]



Scheme I.38. Organomagnesium mediated desulfinylation

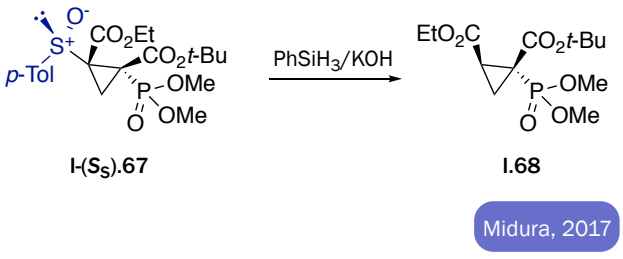
Satoh used *i*-PrMgCl to generate cyclopropylmagnesium and the corresponding derivatives from the previously synthesized cyclopropyl phenyl sulfoxides (**Scheme I.39**).[175]



Scheme I.39. Desulfinylation of cyclopropane derivatives using *i*-PrMgBr

iii. Hydrosilanes

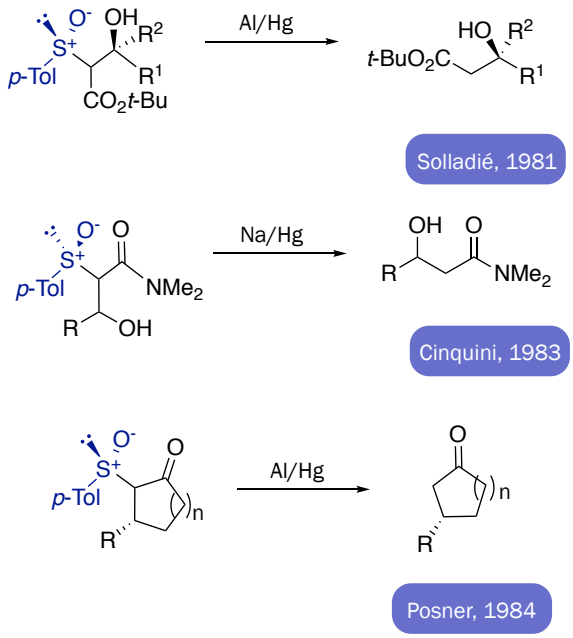
Recently, Midura reported the selective access to cyclopropanes after reacting several examples of sulfinylated derivatives with phenylsilane in the presence of a base, potassium hydroxide (**Scheme I.40**).[70] This method represents a new pathway allowing the access to optically pure derivatives.



Scheme I.40. Midura's silane mediated desulfinylation strategy

iv. Amalgams

In some cases, a sodium/mercury or aluminium/mercury amalgam was described as an efficient desulfinylation reagent as shown in **Scheme I.41**.[176-179]



Scheme I.41. Aluminium or sodium/mercury amalgam as desulfinylation reagent

However, the acute toxicity of mercury remains a limitation, especially due to the regulations in the pharmaceutical field.

B. Description of the project: use of enantiopure difluoromethyl sulfoxides

Optically active sulfoxides are well known nowadays in asymmetric synthesis for their remarkable ability as chiral inductors. The high chirality induction of this auxiliary and its configurational stability makes of them an excellent choice for a large number of transformations. As a consequence of the great interest of these compounds, several synthetic pathways to access enantiopure sulfoxides have been described in literature as it was described in part A.

As outlined in the introduction part, an increasing importance has been given to the synthesis of molecules bearing emerging fluorinated substituents due to the beneficial effects they can bring to bioactive molecules. This makes the development of new synthetic methods to introduce these moieties a center of interest for pharmaceutical research.

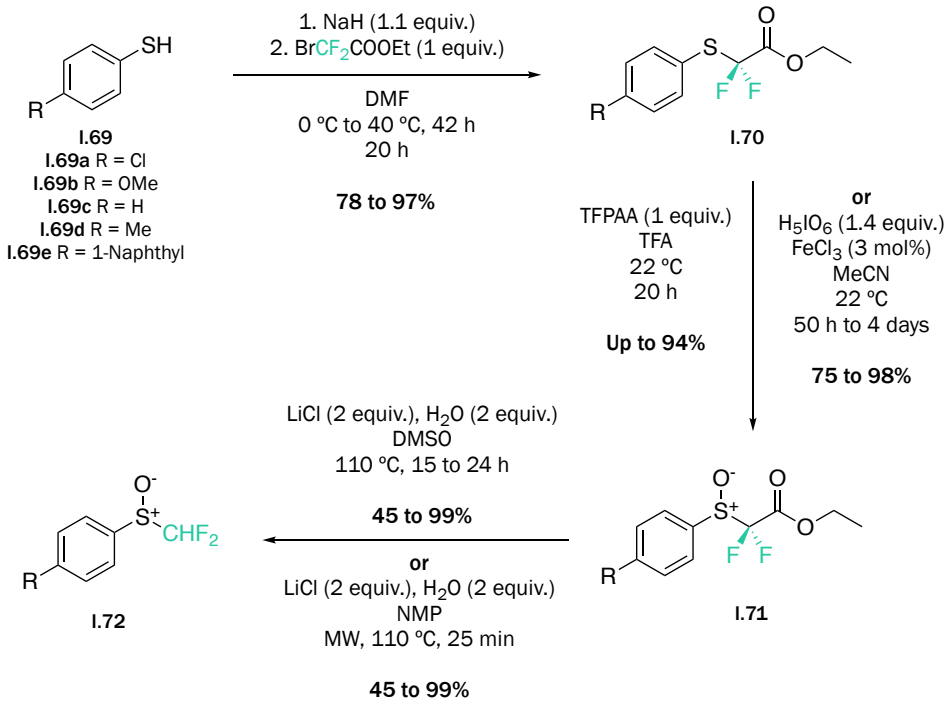
The synthetic pathways for the introduction of the –CHF_2 group being not as well established as the ones regarding single fluorine atoms or the –CF_3 group, the goal of the project was to develop a new method for its enantioselective introduction. The strategy relies on the combination of an enantiopure sulfoxide with a -CHF_2 group. In fact, taking advantage of the central-to-central chirality transfer of sulfoxide for the introduction of the difluoromethyl moiety would allow to access building blocks of high added value. Moreover, the functionalization of fluorinated carbanions with an electron-withdrawing group such as a sulfoxide will counteract the "negative fluorine effect" in order to have a stabilized nucleophilic CF_2^- species after deprotonation.

At the beginning of the project, only two strategies were reported to access enantiopure difluoromethyl sulfoxides. Even if these compounds could be synthesized by two different methods, they were not used as difluoromethylating reagents in a stereoselective fashion, and the advantage of having a chiral auxiliary was not exploited.

The preparation of an enantiopure difluoromethyl sulfoxide followed by its use as a –CHF_2 surrogate represent the starting point of this challenging project. Consequently, we studied the desulfinylation reaction, required to access enantiopure difluoromethylated compounds after introduction of the CHF_2 group bearing the chiral auxiliary. The functionalization of the whole, newly obtained difluoromethylated compounds was also included as an objective for the project, in order to provide novel fluorinated synthons for medicinal chemistry research.

C. Strategy to access racemic difluoromethyl sulfoxide

A convenient synthetic pathway was optimized in the group to access racemic aryl difluoromethyl sulfoxides.[180-182] This method was optimized to multigram scale and allowed us to obtain the corresponding compounds **I.72** for further trials (**Scheme I.42**). Racemic aryl difluoromethyl sulfoxides **I.72** have been synthesized with average overall yields around 25%.



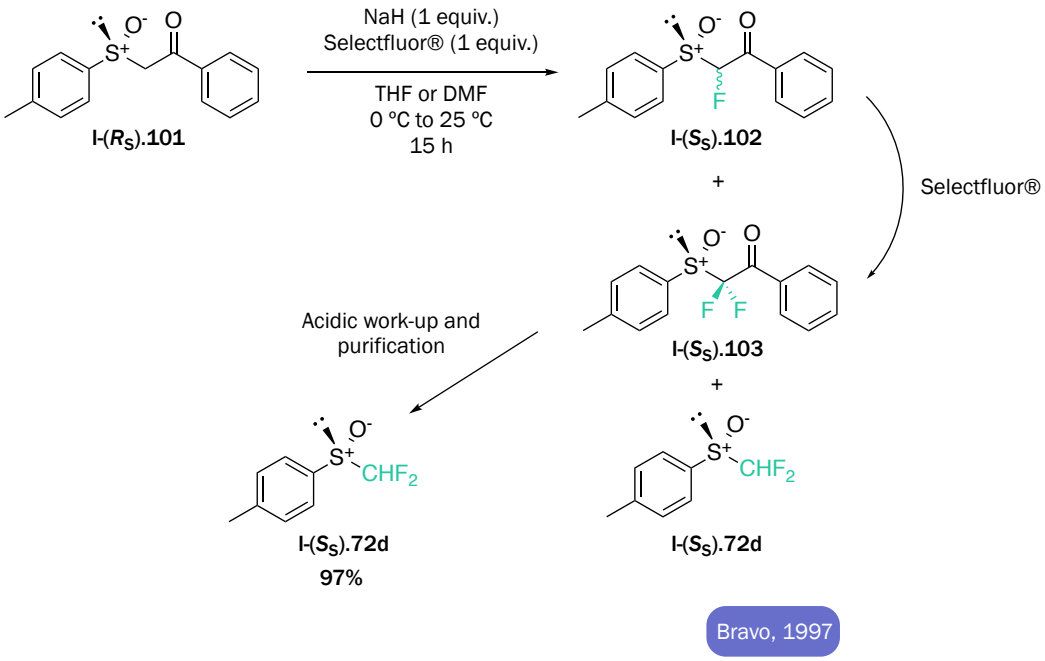
Scheme I.42. Synthesis of racemic aryl difluoromethyl sulfoxides

D. Strategy to access enantiopure difluoromethyl sulfoxides

a. State of the art

Bravo's group was the first to report the serendipitous obtention of enantiopure difluoromethyl *p*-tolyl sulfoxide. In their attempt to synthesize enantiopure α–monofluoro-β–ketosulfoxides, (S_S)-difluoromethyl *p*-tolyl sulfoxide **I-(*S*$_S$).72d** was obtained as a side-product of the reaction.[62] In fact, when using Selectfluor® with NaH to monofluorinate enantiopure β-ketosulfoxide **I-(*S*$_S$).102**, the formation of the corresponding difluorinated product was also observed as well as difluoromethyl *p*-tolyl sulfoxide **I-(*S*$_S$).72d** (**Scheme I.43**). They suspected the formation of the latter product by deacylation of the difluorinated β-ketosulfoxide **I-(*R*$_S$).103** after acidic treatment and purification by silica gel chromatography.

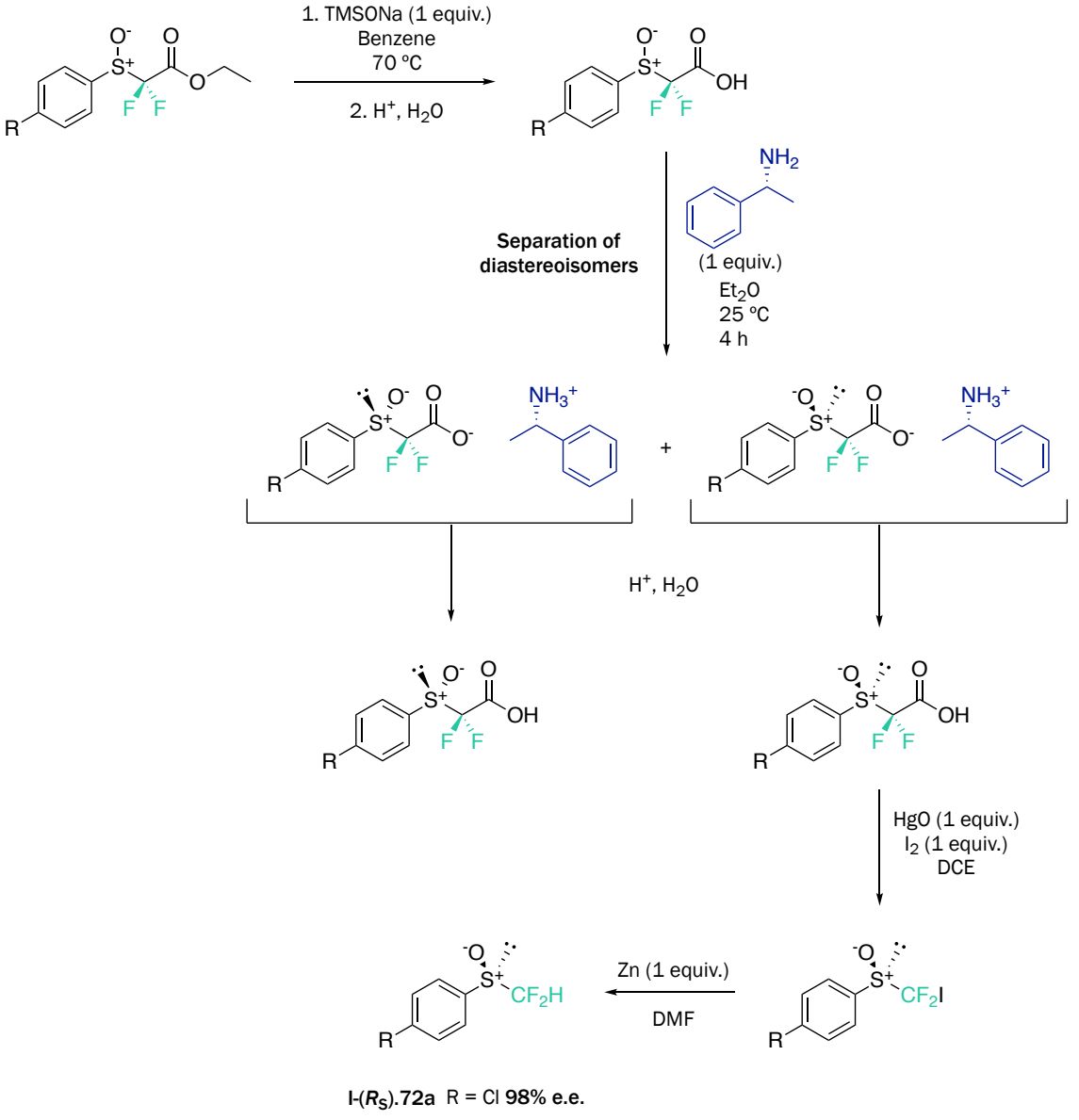
However, as we will describe in *Chapter II*, α–difluoro-β–ketosulfoxides were used in this project and are quite stable species under argon atmosphere. We generally did not observe the formation of difluoromethyl *p*-tolyl sulfoxide under the conditions described by Bravo. We suspected then that an *in situ* retro Claisen could take place in the presence of sodium hydride instead of the degradation by acidic treatment as described. To confirm this aspect, a freshly prepared α–difluoro-β–ketosulfoxide **I-(*S*$_S$).103** was reacted with two equivalents of sodium hydride in absence of Selectfluor®. We were then able to recover exclusively **I-(*S*$_S$).72d**, which comforted our hypothesis. However, the mechanism of this transformation is still unclear.



Scheme I.43. Enantiopure difluoromethyl sulfoxide obtained by Bravo's group

Bravo's strategy leading to an enantiopure difluoromethyl sulfoxide seemed interesting, but the use of Selectfluor® and ketosulfoxides is atom-economically not ideal, due to the generated waste.

Shortly after Bravo's work, Yagupolskii's group reported the access to an enantiopure aryl difluoromethyl sulfoxide. They synthesized highly enantioenriched optically active (R_S)-*p*-chlorophenyl difluoromethyl sulfoxide **I-(R_S).72a** with 98% (**Scheme I.44**).[180]



Scheme I.44. Yagupolskii's strategy to access enantiopure difluoromethyl sulfoxides

This strategy also seemed interesting to us, as the enantiomeric excess obtained were excellent (up to 98%). Unfortunately, the strategy consisted in a multi-step process, involving a chiral resolution of an arylsulfinyldifluoroacetic acid and the use of difficult-to-handle intermediates. When it was performed in our group, several problems were encountered: the very low solubility of

difluoromethyl sulfinyl carboxylic acid in organic solvents, the impossibility to separate the diastereoisomers after resolution with enantiopure phenyl ethylamine as described, and the presence of residual mercury salts after several purifications of the final compound. Another efficient method to generate highly enantioenriched aryl difluoromethyl sulfoxides was therefore developed.

b. First results within the group

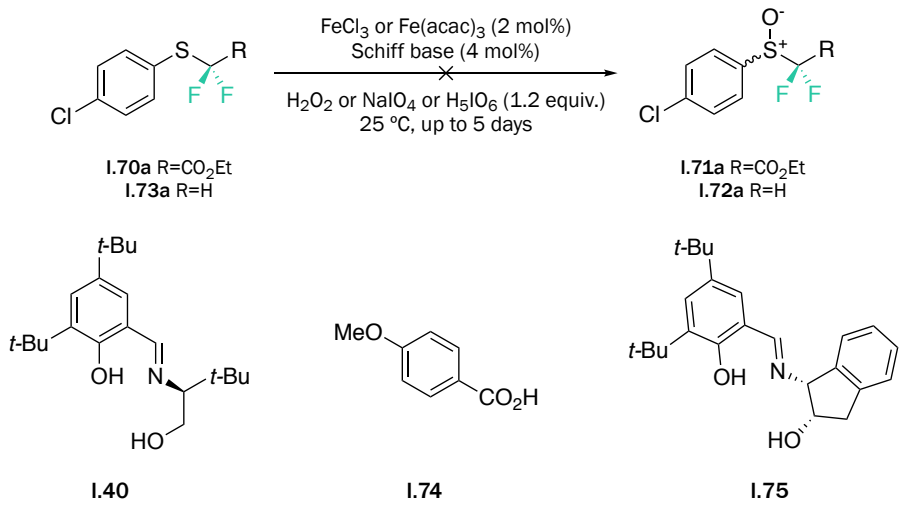
In order to develop a new and efficient synthetic pathway to access enantiopure difluoromethyl sulfoxides, the efforts were placed in the use of methods described in literature and mentioned in the previous paragraph for the synthesis of the non-fluorinated enantiopure sulfoxides. An overview of the methods that were tried within the group is going to be mentioned in this part. For a more exhaustive description of each method, readers are invited to consult our full communication describing the quest to access enantiopure difluoromethyl sulfoxides.[65]

1. Enantioselective oxidation of sulfides

Performed by Chloé Batisse, PhD.

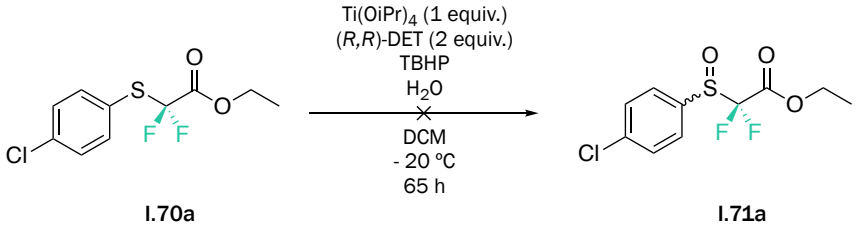
The first strategy that was chosen consisted in the selective oxidation of thioethers, which showed good results for the non-fluorinated analogues with a wide range of reagents.

Inspired by the use of iron complexes, largely described by Bolm, to access enantiopure sulfoxides, thioethers **I.70a** or **I.73a** were submitted to several oxidation conditions. The use of hydrogen peroxide, sodium periodate or periodic acid in the presence of iron acetylacetonate or iron trichloride as well as a chiral Schiff base did not afford the expected sulfoxides **I.71a** or **I.72a** (**Scheme I.45**). Even after long reaction times, up to five days, no conversion of the starting material was observed.



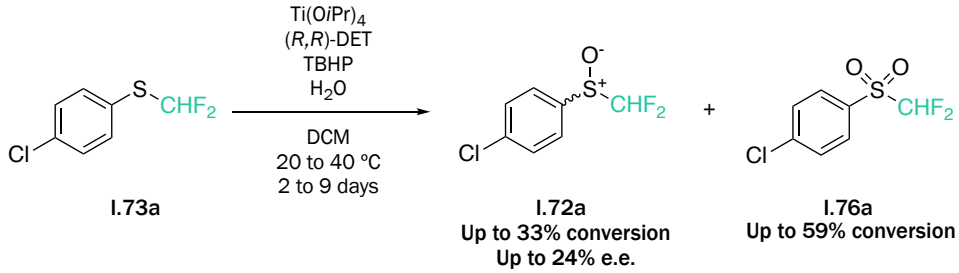
Scheme I.45. Iron catalyzed selective oxidation trials

Kagan's sulfoxidation method was performed on thioether **I.70a** in presence of (*R,R*)-diethyl tartrate. Unfortunately, the oxidation did not take place (**Scheme I.46**).



Scheme I.46. Oxidation of difluoromethyl sulfides using Kagan's conditions

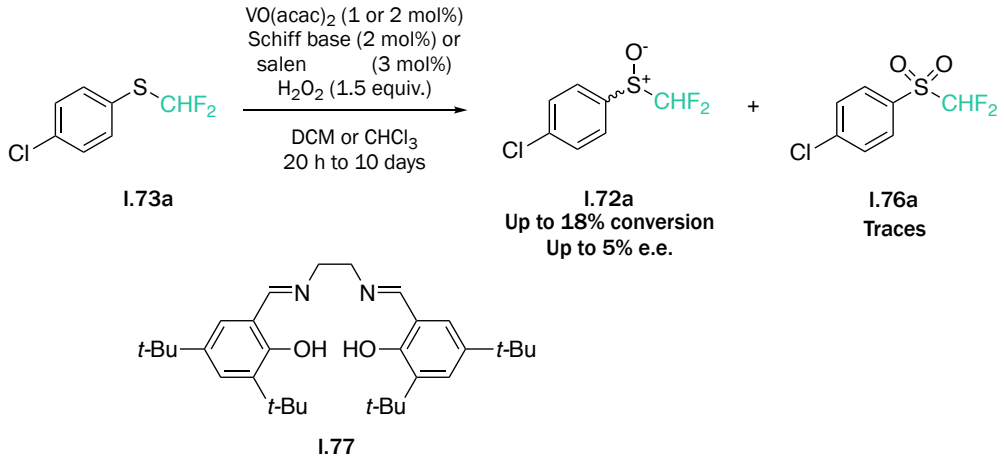
This method was used on the less electron-poor dealkoxycarbonylated thioether **I.73a** as illustrated in **Scheme I.47**.



Scheme I.47. Oxidation attempts of difluorinated thioether I.73a

With these conditions, using a slight excess of TBHP as the oxidizing reagent, it was possible to observe up to 33% conversion of **I.73a** into the corresponding sulfoxide **I.72a**. The enantiomeric excess could be determined by chiral HPLC and was found to range from 12 to 24%. However, the over oxidation of the thioether to the difluoromethylated sulfone **I.76a** could not be avoided.

Finally, inspired by Bolm's and Fujita's results, vanadium complexes were used in the presence of Schiff bases or a salen ligand **I.77** and hydrogen peroxide (**Scheme I.48**)

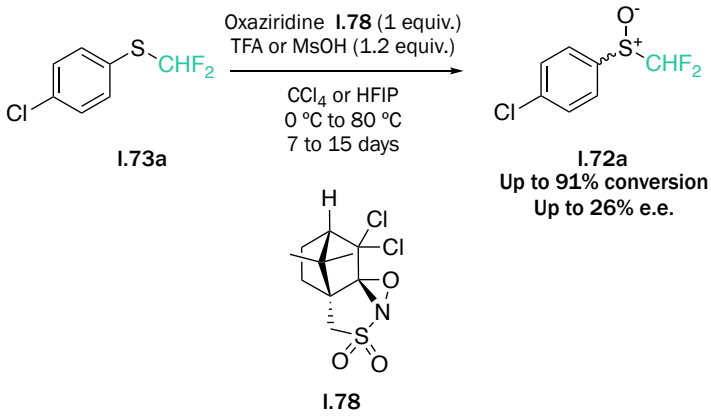


Scheme I.48. Vanadium catalyzed oxidations of a difluoromethyl thioether

Unfortunately, when Schiff bases or the salen ligand were used, only low conversions in the sulfoxide were observed. Regarding the enantiomeric excess, chiral Schiff bases afforded a very low enantiomeric excess of 5%. Due to the lack of reactivity in the presence of the achiral salen ligand, no more efforts were devoted to use a chiral one.

The catalytic sulfoxidations giving unsatisfactory results to access a highly enantioenriched difluoromethyl sulfoxide, a stoichiometric sulfoxidation using chiral oxaziridines was tried.

As Davis' work with oxaziridines only concerned the oxidation of non-fluorinated sulfides, we studied the reaction on the difluoromethylated analogues **I.73a** (**Scheme I.49**).



Scheme I.49. Use of oxaziridines for stoichiometric oxidations of difluoromethyl thioethers

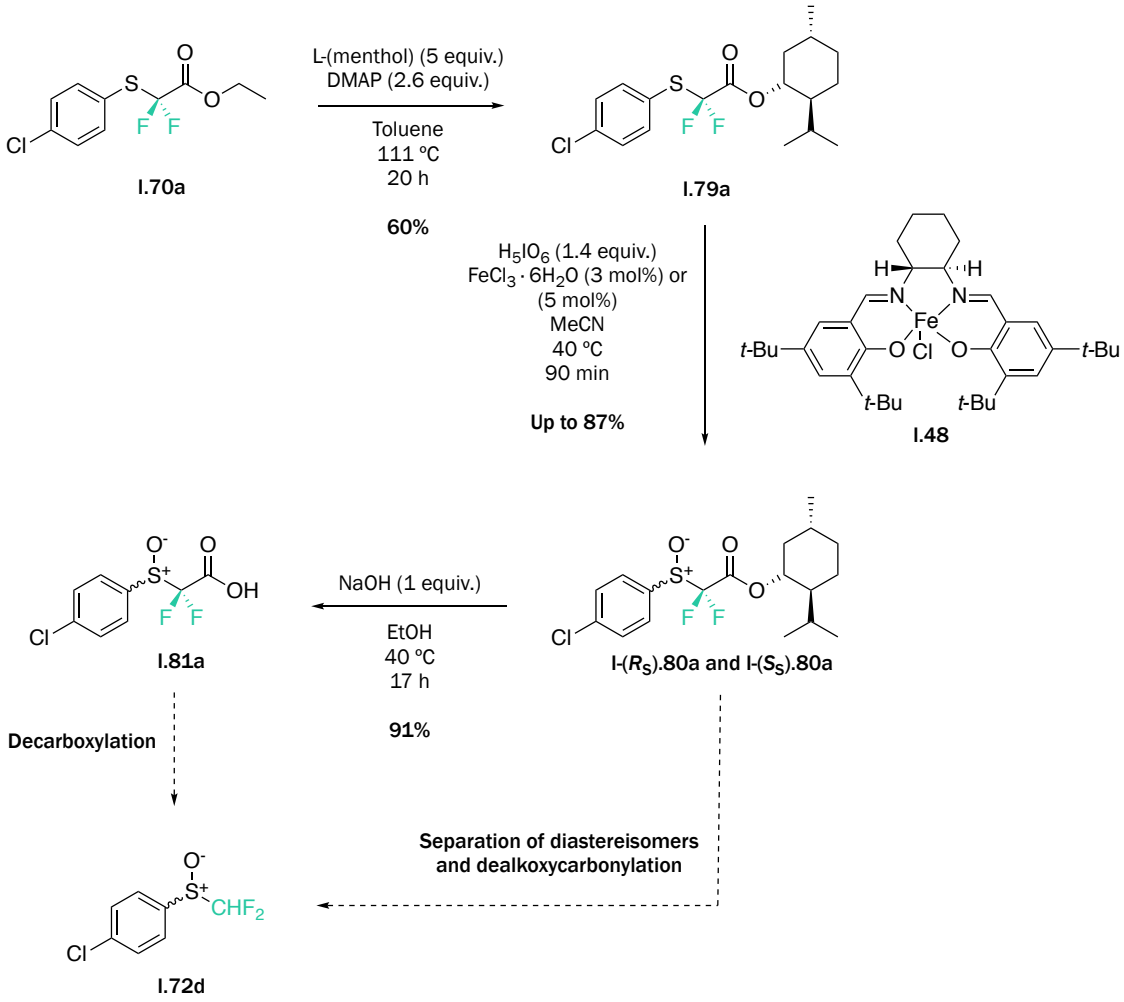
These tests required a series of optimization reactions. Starting from a minimal conversion of 5% into the expected sulfoxide **I.72a**, the change of carbon tetrachloride as the solvent to hexafluoroisopropanol and the addition of a Brønsted acid (TFA) improved the results. It was then possible to obtain *p*-chlorophenyl difluoromethyl sulfoxide **I.72a** in a 91% conversion and an enantiomeric excess of 26%, without the formation of the corresponding sulfone as an overoxidation product. Nevertheless, due to the long reaction time, up to 7 days for the best results, and to the low optical purity obtained, we decided to develop a more appropriate route and other strategies were explored for the synthesis of enantiopure difluoromethyl sulfoxides.

2. Enantioselective oxidation of (-)-menthyl (arenesulfanyl)difluoroacetate

Performed by Marco Castello, Master student.

The selective oxidation of a α-fluorinated α-sulfanyl acetate in the presence of a chiral auxiliary, (-)-menthol, was tried. The difluorinated thioether **I.79a** was prepared by a transesterification in the presence of DMAP and an excess of menthol. Once this derivative was obtained, the oxidation was performed using a combination of periodic acid and a catalytic amount of an iron complex **I.48**.

This oxidation led to a couple of diastereoisomers **I-(R_S).80a** and **I-(S_S).80a** of the desired sulfoxide. The strategy consisted then in separating the diastereoisomers before performing the decarboxylation, in order to access highly enantioenriched difluoromethyl sulfoxide **I.72d** (**Scheme I.50**).



Scheme I.50. Attempt of synthesis of an enantiopure aryl difluoromethyl sulfoxide

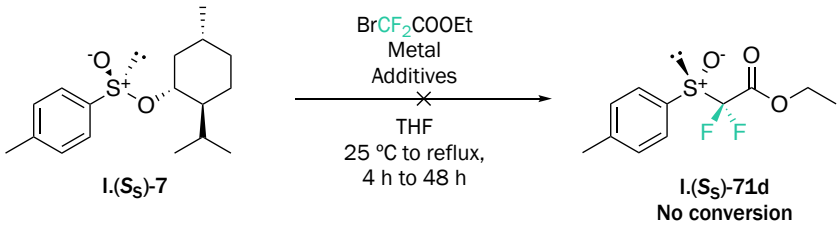
Unfortunately, neither the separation of the diastereoisomers of sulfinylacetates nor of the corresponding carboxylic acids **I.81a** were possible by classical methods such as crystallization or flash chromatography. This pathway had to be discarded.

3. Reformatsky type reactions from (1*R*,2*S*,5*R*)-(-)-Menthyl *p*-toluenesulfinate

Performed by Marco Castello, Master student.

Inspired by the literature concerning sulfoxides, the access to an enantioenriched sulfoxide was tried using sulfinates bearing a leaving group. In fact, the reaction of these species with an organometallic fluorinated

reagent *via* a Reformatsky type reaction should lead to optically pure derivatives. Several attempts were performed starting from the well-known Andersen (1*R*,2*S*,5*R*)-(-)-menthyl *p*-toluenesulfinate **I-(S_s).7** (**Scheme I.51**).

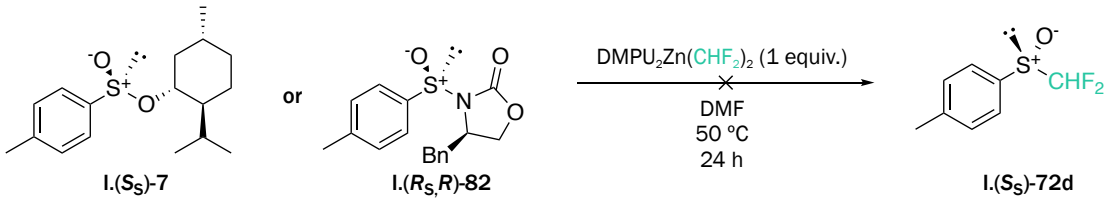


Scheme I.51. Reformatsky type reactions starting from (1*R*,2*S*,5*R*)-(-)-menthyl-*p*-toluenesulfinate

Using Reformatsky reaction conditions, an organozinc species was generated *in situ* from ethyl bromodifluoroacetate and zinc powder. Unfortunately, no conversion of the starting material **I.(S_s)-7** was observed. Moreover, some Lewis acids such as aluminium chloride, dimethylaluminium chloride or diethyl aluminium chloride were added to the medium in order to enhance the reactivity of menthyl sulfinate, without success. Wilkinson catalyst was also used in combination with diethyl zinc, this time to proceed with a Honda-Reformatsky type reaction.[183] Regrettably, these conditions were not satisfying and the desired compound could not be obtained. Finally, the use of another metal, indium, also rarely used for Reformatsky type reactions, was chosen,[184,185] but it did not show any improvement on the reaction. The use of Andersen's (1*R*,2*S*,5*R*)-(-)-menthyl *p*-toluenesulfinate **I.(S_s)-7** was then discarded for the synthesis of enantiopure difluoromethylated sulfoxides.

4. Use of a bis-difluoromethylzinc complex

Vicic[186] described the nickel catalyzed difluoromethylation of aryl iodides with a zinc complex: $DMPU_2Zn(CHF_2)_2$. Following the same idea, in 2016 Mikami described the copper catalyzed difluoromethylation reaction of allyl carbonates using $DMPU_2Zn(CHF_2)_2$ complex.[187] In collaboration with Professor Mikami's group, some attempts of synthesizing an enantiopure difluoromethyl sulfoxide were performed starting from diastereo- and enantiopure Andersen's menthyl sulfinate **I.(S_s)-7** and Evans' sulfinyl oxazolidinone **I.(R_s,*R*)-82** (**Scheme I.52**).

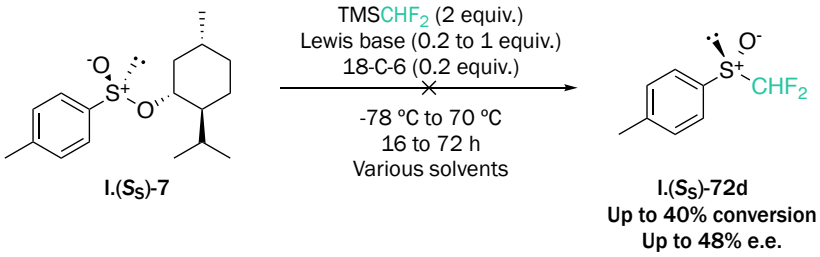


Scheme I.52. Attempts of difluoromethylation of sulfinates using a zinc complex

Unfortunately, no conversion on the desired product was observed in both cases. An optimization of this method will be necessary, by first trying other ligands than DMPU, for example TMEDA.

5. Catalyzed nucleophilic difluoromethylation

Difluoromethyltrimethylsilane is commonly used as a difluoromethylation reagent.[188–191] In this project, it was used as a nucleophile in order to prepare enantiopure difluoromethyl sulfoxides starting from menthyl sulfinate **I.(S_S)-7** in the presence of Lewis bases and crown ethers. In some attempts, the desired sulfoxide **I.(S_S)-72d** could be obtained in conversions up to 40% (**Scheme I.53**) in presence of catalytic amounts of cesium fluoride and crown ether with a moderate enantiomeric excess of 48%.



Scheme I.53. Enantioselective difluoromethylation of menthyl sulfinate using $TMSCHF_2$

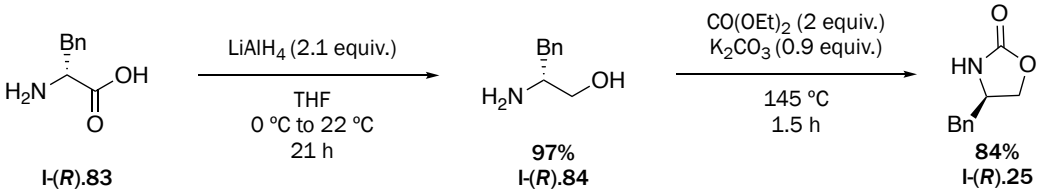
These observations led us to consider other strategies that could bring a better enantiopurity.

c. Reformatsky type reactions from sulfinyl oxazolidinones

Performed with Chloé Batisse, PhD

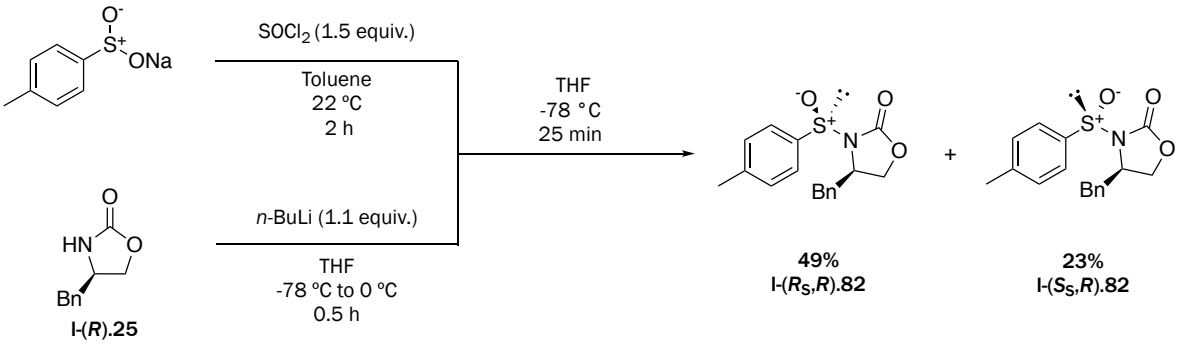
Many efforts within the group were dedicated to the synthesis of an enantiopure difluoromethyl sulfoxide without success when using classical methods described for non-fluorinated analogues. In particular, the use of sulfinates, being a usually powerful synthetic tool, to access chiral sulfoxides, proved disappointing in our case due to a lack of reactivity or selectivity. Hence, a more reactive derivative as a precursor was used: Evans' *N*-sulfinyloxazolidinones.[115]

In fact, Evans described sulfinyloxazolidinones being one hundred times more reactive than their analogues, menthyl sulfinates. The first steps consist in the synthesis of a chiral oxazolidinone following Evans protocol.[192] D-phenylalanine **I-(*R*).83** was reduced to the corresponding phenylalaninol **I-(*R*).84**. The cyclization of this enantiopure alcohol gave the (*R*)-4-benzyloxazolidin-2-one **I-(*R*).25** with a 82% yield over two steps (**Scheme I.54**).[193]



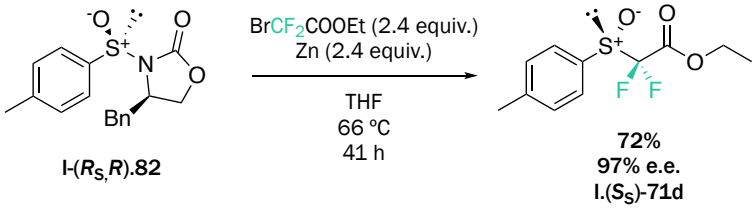
Scheme I.54. Synthesis of (*R*)-4-benzyloxazolidin-2-one

The sulfinylation step was carried out using toluenesulfinyl chloride, formed *in situ* from sodium *p*-toluene sulfinate and thionyl chloride, and the deprotonated oxazolidinone **I-(*R*).25**. The reaction gave two diastereoisomers that could be separated, as (R_S,*R*)-sulfinyloxazolidinone **I-(R_S,*R*).82** crystallizes in diethyl ether as a white solid. (S_S,*R*)-sulfinyloxazolidinone **I-(S_S,*R*).82** was obtained as a yellow oil (**Scheme I.55**).[192]



Scheme I.55. Synthesis of enantiopure *N*-sulfinyloxazolidinones

The next step, consisted in a Reformatsky type reaction on the sulfinyl oxazolidinone **I-(R_S,*R*).82**. Zinc, freshly activated with hydrochloric acid and dried under vacuum overnight, was used therefore. In many cases, this reaction afforded good yields of **I.(S_S)-71d** up to 72% and excellent enantiomeric excess up to 97% (**Scheme I.56**).



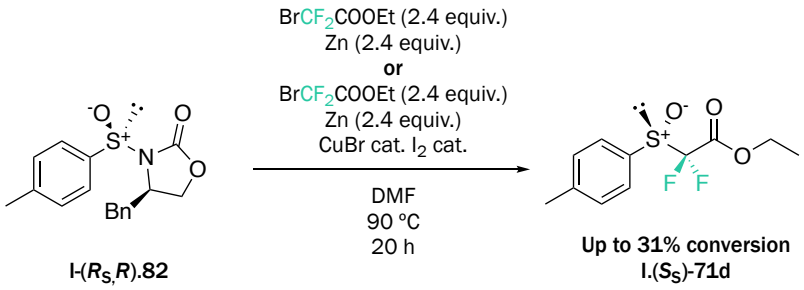
Scheme I.56. Reformatsky type reaction using zinc powder

However, some of the attempts to reproduce these results provided low conversion or a very low yield of the enantiopure ethyl 2,2-difluoro-(*p*-tolylsulfinyl)acetate **I.(S_S)-71d** despite an excellent enantiomeric excess. A complementary study of this reaction was then performed.

The use of a bromozinc-α,α-difluoroacetate was reported by B. Crousse *et al.*[192] This intermediate is previously prepared as a solution in DMF instead of THF and then used for the reaction. Following this procedure, the Reformatsky type reaction was performed but unfortunately, the conversion of the starting material did not exceed 31%. In addition to this low conversion, we also could

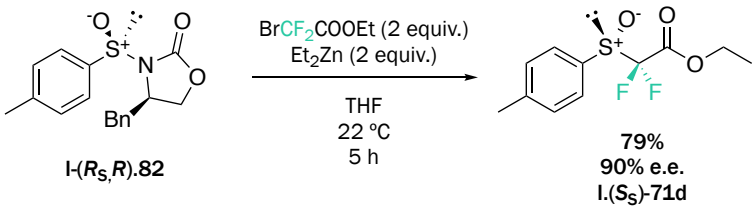
observe the presence of ethyl-2,2-difluoroacetate as a contaminant of **I.(S_s)-71d** after purification.

In 1989, Sprague and co-workers reported the use of CuBr as catalyst for the efficient reaction of an organozinc reagent to obtain 1,1-difluorinated 3-alkenephosphonates.[192] The organozinc derived from a difluorinated phosphonate in presence of a catalytic amount of copper bromide reacts with allylic halides to give difluorinated alkene phosphonates in good yields. This method was previously used by Sanofi researchers with the addition of a catalytic amount of iodine (**Scheme I.57**). Unfortunately, the conversion into **I.(S_s)-71d** observed using this strategy was lower than the one obtained using the previous conditions.



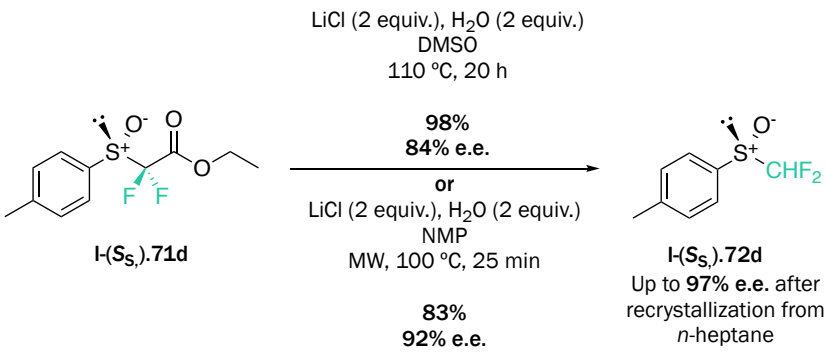
Scheme I.57. Optimization attempts of Reformatsky type reaction on *N*-sulfinyloxazolidinones

An alternative version of the Reformatsky type reaction was carried out using diethyl zinc instead of zinc metal, and bromodifluoroacetate. Under these conditions, the product was isolated with a good yield and enantiomeric excess. It is noteworthy that this reaction was also performed on a multigram scale and the enantiomeric excess obtained for all trials was between 86 and 92% (**Scheme I.58**).



Scheme I.58. Modified Reformatsky type reaction using diethylzinc

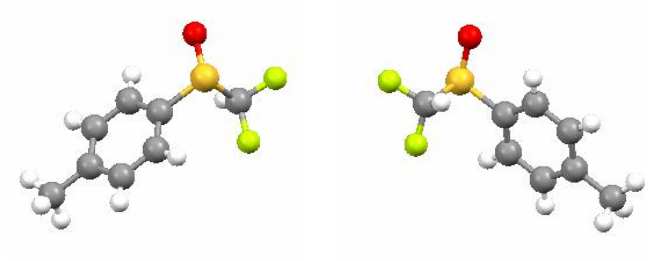
The last step of the synthesis consisted in a Krapcho dealkoxycarbonylation of **I-(S_s).71d** performed under thermal or microwave conditions that showed excellent results in terms of conversion. Microwave conditions were preferred as we could observe a small racemization due to the long heating time for the thermal conditions. The desired difluoromethyl *p*-tolyl sulfoxide **I-(S_s).72d** was obtained with a full conversion and retention of configuration at the stereogenic sulfur center from the previous step (**Scheme I.59**).



Scheme I.59. Krapcho dealkoxycarbonylation of enantiopure difluoromethyl sulfinyl acetate

A recrystallization from diethyl ether or *n*-heptane of **I-(*S*$_S$).72d** was performed, leading to an improved enantiomeric excess of up to 97%.

Difluoromethyl *p*-tolyl sulfoxide **I-(*S*$_S$).72d** provided a single crystal suitable for X-ray structure analysis. We were able to confirm the absolute configuration of the stereogenic center (**Scheme I.60**).



Scheme I.60. Crystallographic analysis of enantiopure (*S*)-difluoromethyl *p*-tolyl sulfoxide

E. Attempts to access halogenated and silylated derivatives of difluorinated aryl sulfoxides

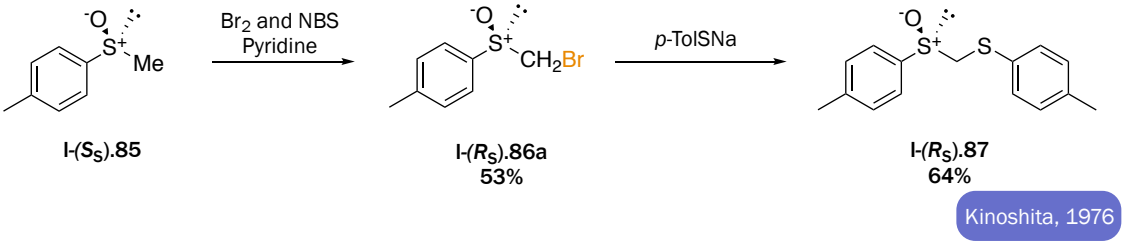
With the enantiopure difluoromethyl sulfoxide in hands, we aimed to study the synthesis of derivatives of this compound that may provide additional functionalities and increase the range of possible reactions for difluoromethylation using sulfoxides as chiral inductors.

a. Brominated derivative

1. State of the art: aryl α-bromoalkyl sulfoxides

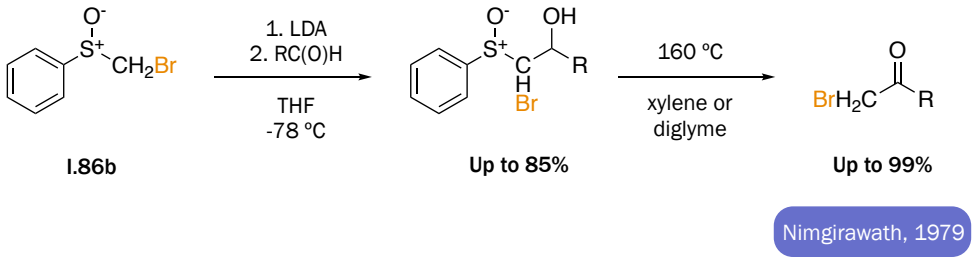
In literature, a few examples of applications of non-fluorinated bromomethyl sulfoxides have been reported.

Their preparation was described in 1976 by Kuneida, Nokami and Kinoshita starting from methyl *p*-tolyl sulfoxide **I-(S_S).85** using bromine or NBS in the presence of pyridine to access the bromomethyl derivative **I-(R_S).86a** and use it to synthesize a sulfinyl sulfide (**Scheme I.61**).[194]



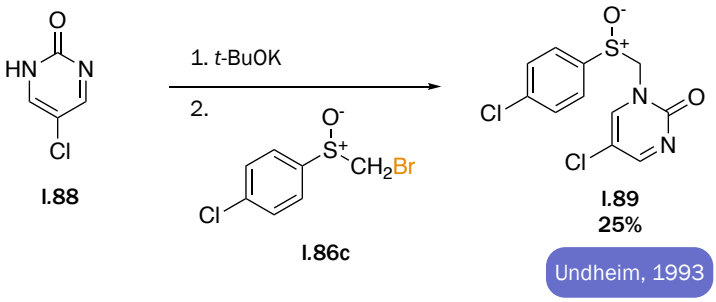
Scheme I.61. Use of bromomethyl sulfoxide to synthesize sulfinyl sulfides

By the end of the 1970's, Nimgirawath reported also one of the first applications of bromomethyl sulfoxides, namely the pyrolysis of monobrominated sulfinyl alcohols to obtain bromomethyl ketones with very good yields (**Scheme I.62**).[195]



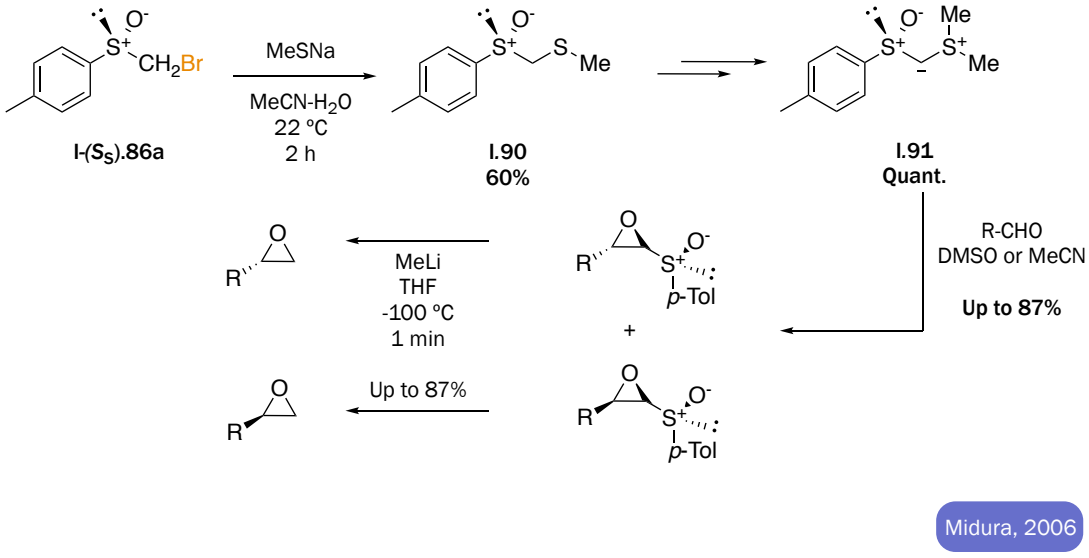
Scheme I.62. Synthesis of bromomethyl ketones from bromomethyl sulfoxides

In 1993, Undheim synthesized substituted pyrimidinones, due to their interest in their metaphase arresting effect through reversible adduct formation with thiol functions in proteins. The sulfinyl derivatives could be prepared using bromomethyl *p*-Cl phenyl sulfoxide **I.86c** in the presence of *t*-BuOK and the pyrimidinone (**Scheme I.63**). The activity of this product, as well as the one of other analogues was tested in Chang liver cells.[196]



Scheme I.63. Sulfinyl pyrimidinones of biological interest

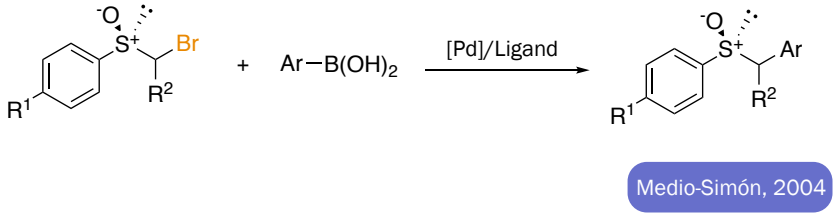
Midura reported in 2006 the use of (*S*)-bromomethyl *p*-tolyl sulfoxide **I-(S_s).86a** to access enantiopure dithioacetal monoxide **I.90** as an intermediate to access dimethylsulfonium *p*-tolylsulfinylmethylide **I.91** (**Scheme I.64**). These sulfinyl methylylides were then engaged in asymmetric epoxidation reactions, giving an good example of application of these enantiopure halogenated sulfoxides.[197]



Scheme I.64. Synthesis of enantiopure epoxides from bromomethyl sulfoxides

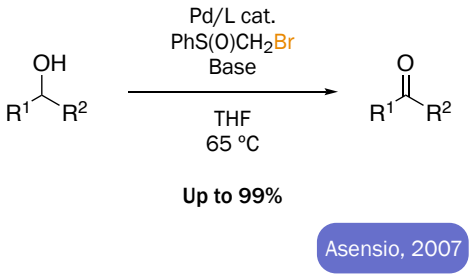
Around the same period, Asencio and Medio-Simón described the palladium-catalyzed cross-coupling reactions of racemic α-bromosulfoxides with boronic acids. In the same idea, they performed also the arylation of the corresponding enantiopure bromo sulfoxides.[198,199] They proved that the formation of the new Csp^3-Csp^2 bond occurs without racemization and with good yields with substituted aryl boronic substrates. The only exeption where less good yields

were obtained is when using heteroaromatic boronic acids (**Scheme I.65**). This case represents a good example for the preparation of chiral benzyl sulfoxides.



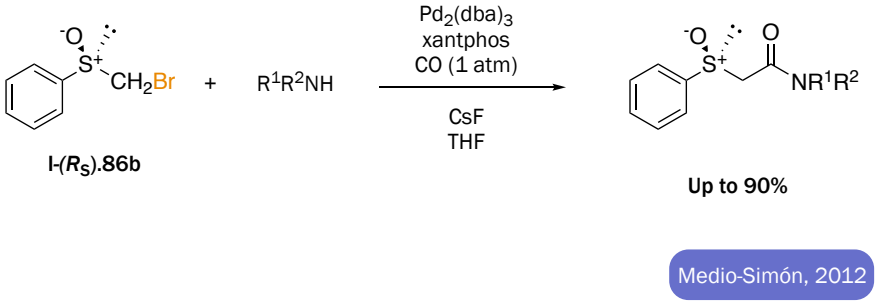
Scheme I.65. Palladium-catalyzed cross-coupling of bromomethyl sulfoxides and aryl boronic acids

In 2007, Asensio and his coworkers reported a different use of bromomethyl sulfoxide: this substrate was used as co-oxidant in the palladium-catalyzed chemoselective oxidation of allylic and benzylic alcohols (**Scheme I.66**).[200]



Scheme I.66. Chemoselective oxidation of allylic and benzylic alcohols

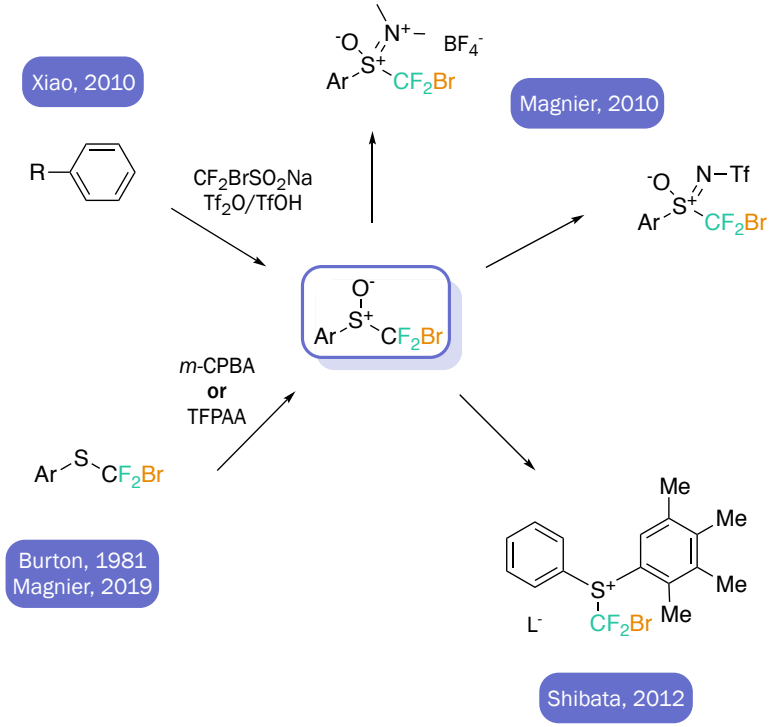
On another hand, Medio-Simón and her coworkers more recently took advantage of the electrophilicity of α-bromomethyl sulfoxides to perform nucleophilic substitution reactions, and more precisely, aminocarbonylation reactions.[201] They use palladium-catalyzed mild reaction conditions to access a wide range of products from simple starting materials and carbon monoxide (**Scheme I.67**). The reactions were performed starting from racemic bromophenyl sulfoxide, and also with the enantiopure derivative, proving after reaction a perfect retention of configuration at the sulfur center.



Scheme I.67. Aminocarbonylation reactions using bromomethyl sulfoxides

These examples showed us the potential that can come from halogenated, and more precisely brominated, sulfoxides in a wide range of transformations. The fact that they could be used as enantiopure substrates with complete retention of configuration also comforted us in the possible use of difluorinated analogues, still having sulfoxides as chiral auxiliaries.

Only a few reports describing the synthesis and the use of a racemic aryl bromodifluoromethyl sulfoxide have been found in the literature (**Scheme I.68**).



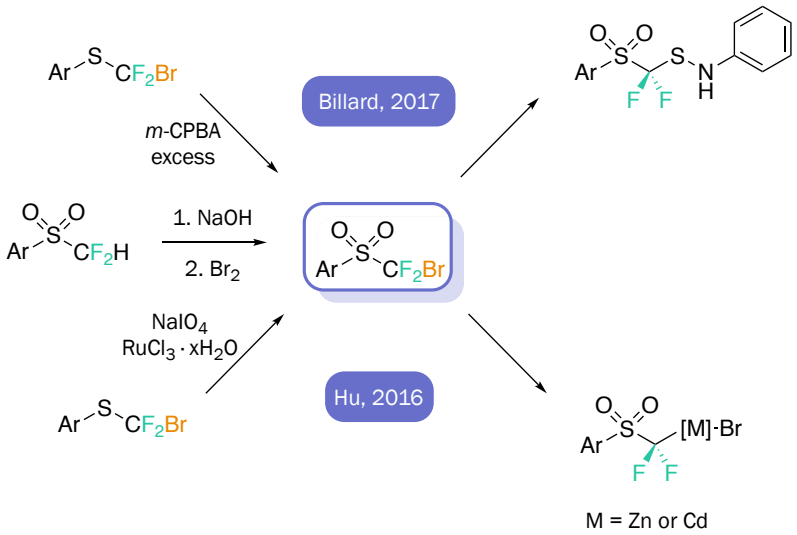
Scheme I.68. Reported synthesis and uses of racemic bromodifluoromethyl sulfoxide

Shibata reported the use of bromodifluoromethyl sulfoxides to prepare a series of unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts as electrophilic brominating reagents. These reagents proved to be effective for the electrophilic bromodifluoromethylation of acetylides.[202] In 2010, Magnier prepared sulfoximines and sulfoximinium salts from the corresponding sulfoxides to perform electrophilic fluoroalkylation reactions, and used among others a bromodifluoromethyl derivative.[203,204]

These groups using the bromodifluoromethyl sulfoxide as an intermediate for the preparation of other derivatives generally applied Burton's method.[205] They prepare first the corresponding bromodifluoromethylsulfane and after controlled oxidation using *m*-CPBA[206–208] they were able to isolate in gram-scale the desired bromodifluoromethyl *p*-tolyl sulfoxide. Recently, the selective oxidation of bromodifluoromethylsulfane has been studied using TFPAA, giving an alternative efficient procedure.[209] Xiao used sodium fluoroalkyl sulfinates and arenes in presence of triflic acid to obtain aryl bromodifluoromethyl sulfoxides.[210]

In analogy to the bromodifluoromethyl sulfinyl derivative, limited strategies are also reported to synthesize the corresponding sulfone. Hu reported the preparation of the bromodifluoromethylsulfone as intermediate to generate (phenylsulfonyl)difluoromethylcadmium or (phenylsulfonyl)difluoromethylzinc reagents for the nucleophilic difluoromethylation of aldehydes.[211]

Billard used the same intermediates as substrates in the preparation of (benzenesulfonyl)-difluoromethanesulfenamide reagents. He described the oxidation of bromodifluoromethylsulfides in the presence of three equivalents of *m*-CPBA or as an alternative, the deprotonation of aryl difluoromethyl sulfone with sodium hydroxide and bromination with dibromide (**Scheme I.69**).[212]

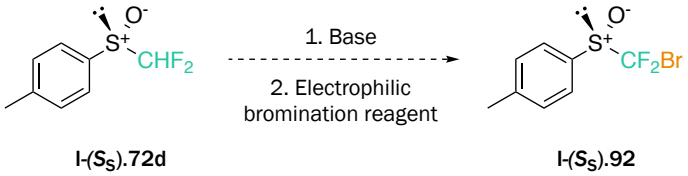


Scheme I.69. Reported synthesis and uses of bromodifluoromethyl sulfones

2. Towards the synthesis of a bromodifluoromethyl aryl sulfoxide

The different methods found in literature for the synthesis of bromodifluoromethylated sulfoxides or sulfones consisted mostly in the non-stereoselective oxidation of sulfides, and would not, accordingly, allow the synthesis of an enantioenriched bromodifluoromethyl sulfoxide.

The strategy that was chosen to access this derivative involves the bromination of enantioenriched difluoromethyl *p*-tolyl sulfoxide after deprotonation and trapping with an electrophilic bromination reagent (**Scheme I.70**).

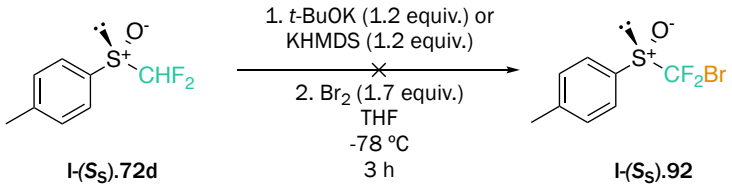


I-(S_S).72d **I-(S_S).92**

Scheme I.70. Stategy to access an enantiopure bromodifluoromethyl sulfoxide

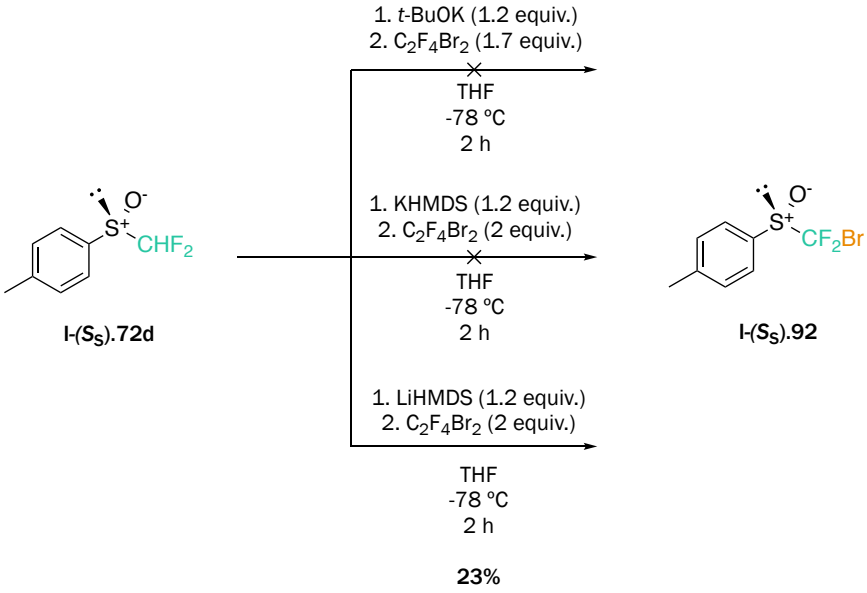
Typical reaction conditions previously described for non-fluorinated analogues or difluorinated sulfones have been selected. The choice of the bases was inspired from the ones that were commonly used to deprotonate difluoromethyl *p*-tolyl sulfoxide (detailed in *Chapter II*) like *t*-BuOK, LiHMDS or KHMDS.

The use of *t*-BuOK or KHMDS in combination with a first electrophilic bromination reagent, molecular bromine, did not give satisfying results, as only starting material **I-(S_S).72d** was recovered or side-products were observed (**Scheme I.71**).



Scheme I.71. Attempts of bromination of difluoromethyl *p*-tolyl sulfoxide using dibromide

In addition to this unsuccessful reaction, the report of Asencio[199] concerning the racemization of non-fluorinated sulfoxide upon bromination with bromine prompted us to look for an alternative bromination reagent like 1,2-dibromotetrafluoroethane (**Scheme I.72**).

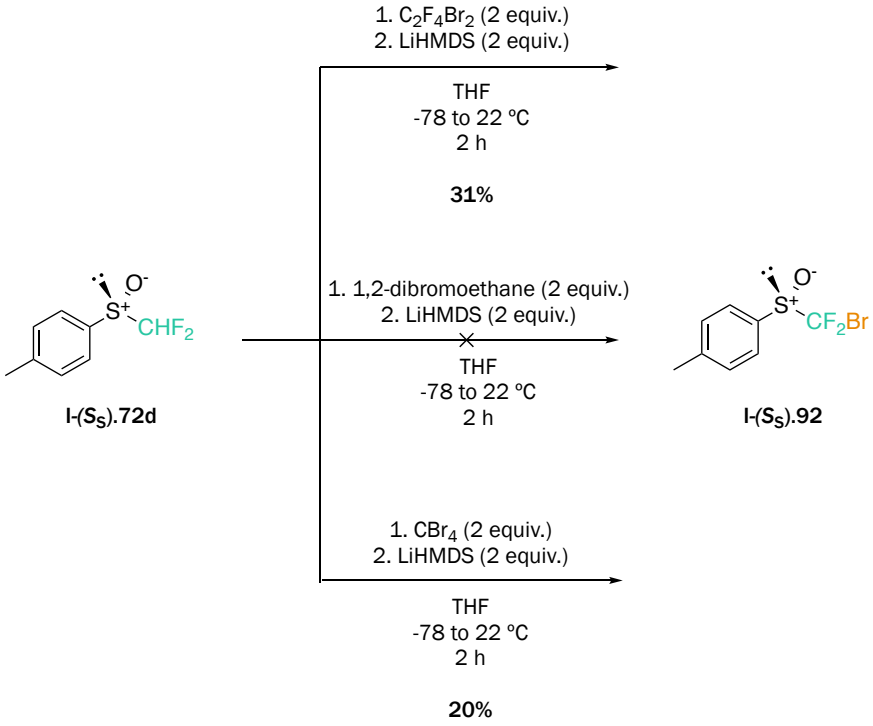


Scheme I.72. Bromination attempt using $C_2F_4Br_2$

The use of potassium *tert*-butoxide did not have any effect and the starting material was recovered. The reaction of KHMDS as a base only revealed the presence of side-products. To our delight, when deprotonating with its analogue, LiHMDS, we were able to isolate the expected product **I-(S_S).92**, with a moderate yield.

In order to optimize the yield, we tested different conditions. The mixture was allowed to reach room temperature, without any improvement. We also tried to

modify the addition order of the reagents. In fact the deprotonation followed by trapping with the brominating reagent was not found to be the best strategy. Under *in situ* trapping conditions, i.e. **I-(S_S).72d** together with $C_2F_4Br_2$ followed by the addition of the base, it was possible to improve the yield of **I-(S_S).92** up to 31%. The yield being better but remaining moderate, additional brominating reagents were tried as represented in (**Scheme I.73**).



Scheme I.73. Optimization of the bromination of difluoromethyl *p*-tolyl sulfoxide

The use of 1,2-dibromoethane, compared to its tetrafluorinated analogue, did not give the expected product. In contrast, tetrabromomethane reacted with **I-(S_S).72d** to give bromodifluoromethyl *p*-tolyl sulfoxide **I-(S_S).92** with 20% yield. As the optimum conditions were those obtained with tetrafluorodibromoethane, we kept them for further preparations of this derivative.

Further efforts were placed in the use of bromodifluoromethyl *p*-tolyl sulfoxide **I.92** as a difluoromethylation reagent. The different attempts concerning its reactivity will be described in part F of Chapter II.

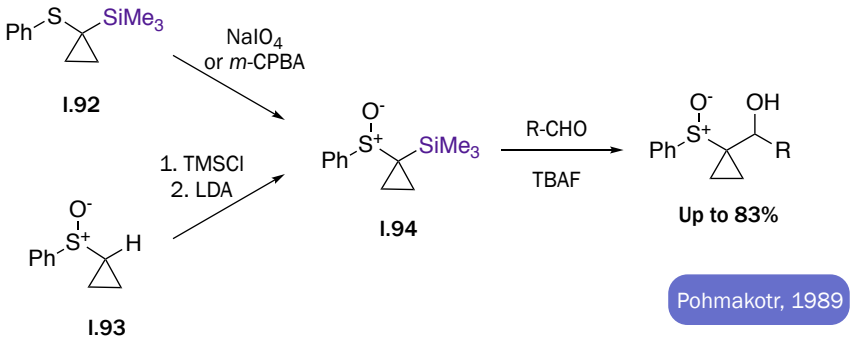
b. Silylated derivative

1. State of the art: silylated aryl sulfoxides

As a further extension of our strategy to use enantiopure difluoromethylated sulfoxides we focused on the preparation of a silylated derivative in analogy to the Ruppert-Prakash reagent $TMSCF_3$, in order to perform the introduction of the difluoromethyl surrogate under milder conditions.

The silylated derivatives of non-fluorinated sulfoxides have been described mostly as intermediates useful for Pummerer rearrangements or Peterson olefinations.

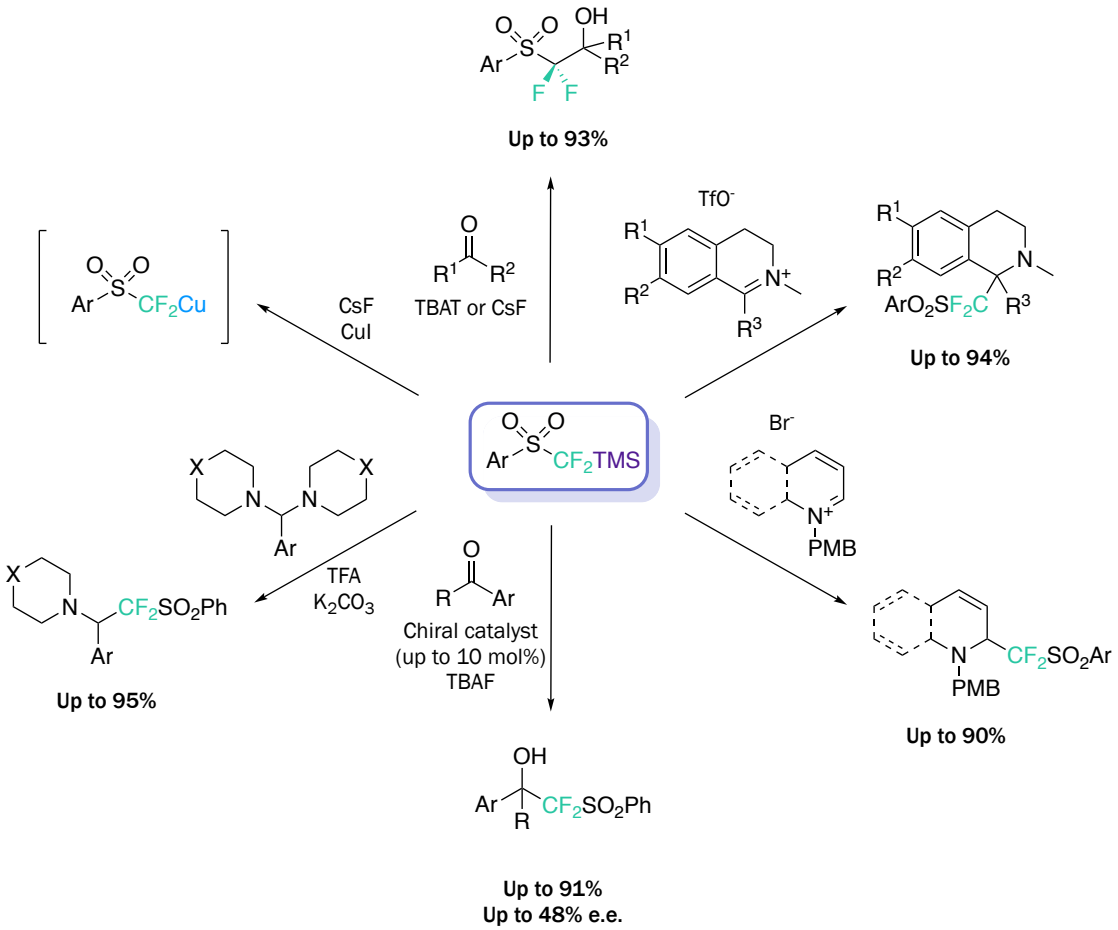
In the late 1980's, Pohmakotr used silylated sulfanyl and sulfinyl cyclopropanes **I.92** and **I.93** and performed their condensation onto aldehydes promoted by TBAF in order to access a couple of diastereoisomers of the sulfinyl alcohols (**Scheme I.74**).[213] Regarding the preparation of these derivatives, he started either from trimethylsilyl sulfide **I.92** and performed an oxidation, or deprotonated the proton in α position of the sulfoxide **I.93** in the presence of TMSCl. To the best of our knowledge, this is the only example of an α-metallation/ α-silylation sequence on alkyl aryl sulfoxides.



Scheme I.74. Pohmakotr's use of silylated sulfoxides

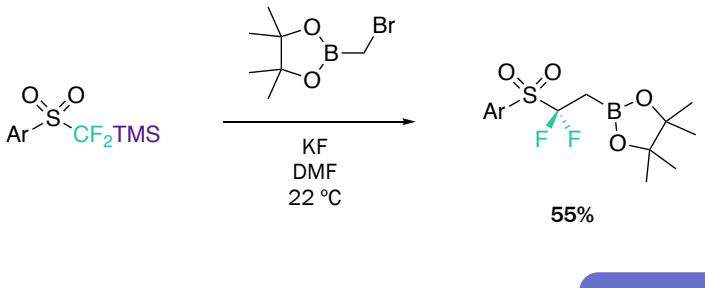
In organofluorine chemistry, many (perfluoroalkyl)trialkylsilanes have been developed over the last decades as efficient tools for different transformations. The nucleophilic activation of the silicon center allows in these reactions the transfer of the perfluoroalkyl moieties to different electrophiles.[63,214,215]

Hu reported on the use of aryl trimethylsilyldifluoromethyl sulfone derivatives in a wide range of reactions (**Scheme I.75**). He used them for example in the difluoromethylation of aminals to obtain α-difluoromethylated tertiary amines[216] and difluoromethylation of C=N bonds,[217] as well as an intermediate to form difluoromethylated organocopper reagents for the transition metal-mediated formation of a F_2C-C bond.[218] In addition, he also performed the non-asymmetric[219] and the eenantioselective[56,220] difluoromethylation of carbonyls.



Scheme I.75. Uses of difluoro(trimethylsilyl)methyl sulfones

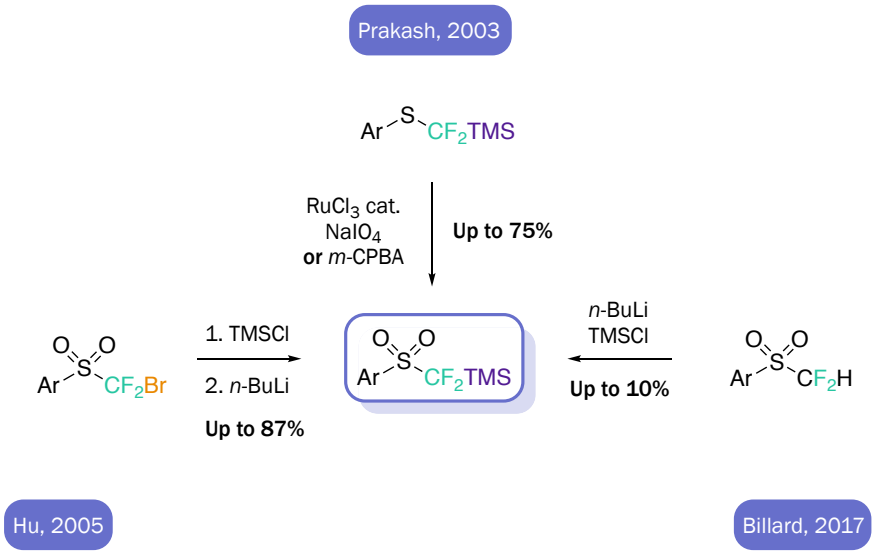
Dilman described the fluoroalkylation of bromomethaneboronic pinacol ester and fluorinated silanes, among them ((arenesulfonyl)difluoromethyl)trimethylsilanes. The resulting boronates could be used in transition metal catalyzed couplings (**Scheme I.76**).[221]



Scheme I.76. Fluoroalkylation of α-brominated pinacol boronic esters with arenesulfonyl-derived difluoromethylsilanes

Additional examples of difluoromethylation have been described with the use of fluoroalkylsilane derivatives,[222] different from sulfur derivatives, combined to a Lewis acid activator.[223,224] Confident about these studies reported in literature, we aimed to take advantage of the stability and reactivity of silanes combined to our difluoromethylated sulfoxide. This could open the access to a range of substrates, which could not be obtained by using either bromodifluoromethylated sulfoxide or α-anions of difluoromethyl sulfoxides.

It is noteworthy that so far the preparation and use of a sulfinyl-derived difluoromethylsilane have not been reported; only the analogous silylated difluoromethyl sulfones have been synthesized (**Scheme I.77**). Prakash prepared this compound by oxidizing the corresponding sulfide,[225] Hu used the brominated derivative and performed an halogen-lithium exchange in the presence of the silylated electrophiles,[219] and Billiard tried the deprotonation of aryl difluoromethyl sulfone in the presence of TMSCl.[212]



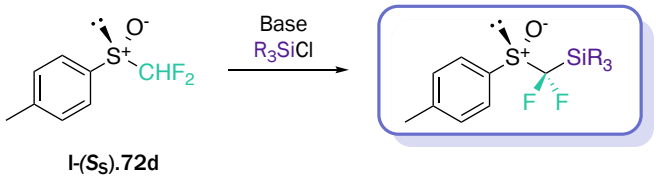
Scheme I.77. Preparation of difluoro(trimethylsilyl)methyl sulfones

2. Synthesis of aryl difluoro(trialkylsilyl)methyl sulfoxide

The access to this derivative was studied *via* a deprotonation of difluoromethyl *p*-tolyl sulfoxide and trapping the anion with TMSCl. However, we also aimed to have an alternative access as the deprotonation in presence of TMSCl only led to low yields according to Billard's report in the case of the parent sulfone.

An alternative way could also be to use as an intermediate the bromodifluoromethyl *p*-tolyl sulfoxide **I. 92** synthesized in the previous part and perform a halogen-lithium exchange, then trapping the organometallic species with the silylated electrophile as it has been reported for the sulfone analogues.

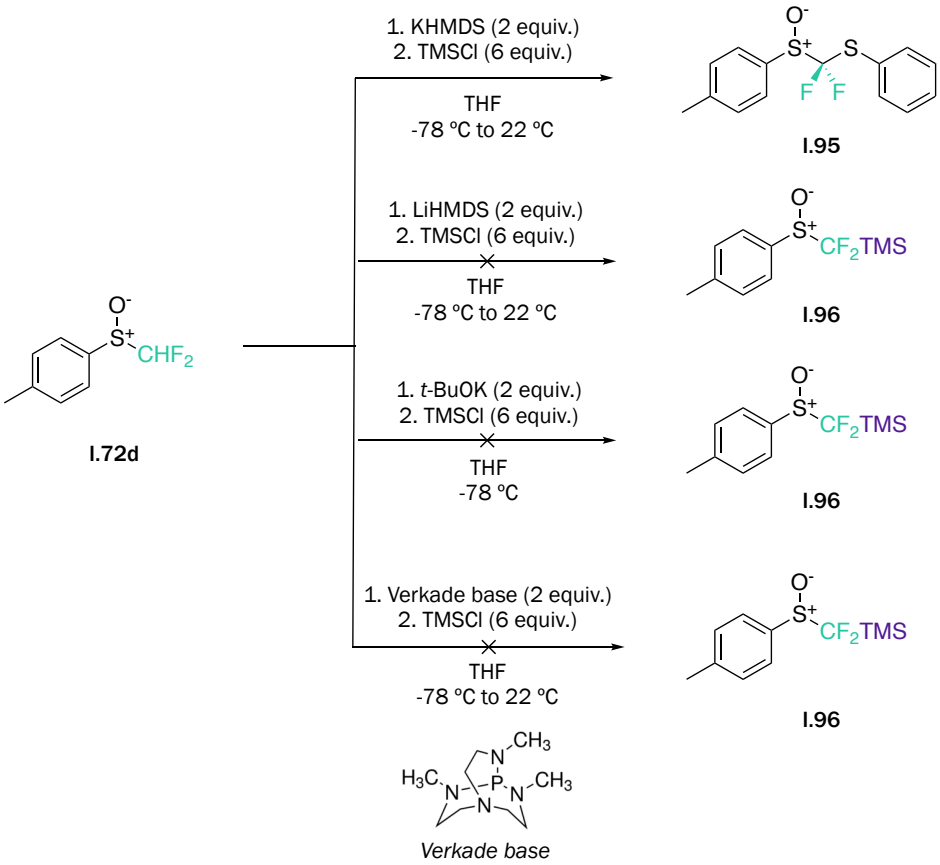
We first focused on the strategy of performing the deprotonation and trapping the anion of difluoromethyl *p*-tolyl sulfoxide by a silylated reagent, such as TMSCl or TBDMSCl (**Scheme I.78**).



I-(S_S).72d

Scheme I.78. Strategy to access aryl difluoro(trialkylsilyl)methyl sulfoxide

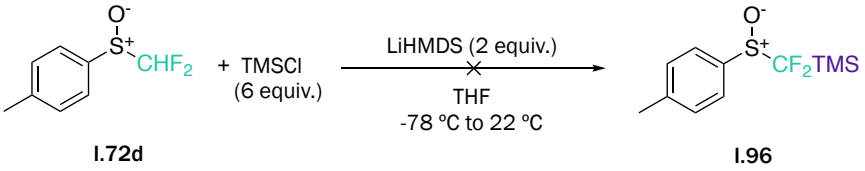
The first attempts used bases such as KHMDS, LiHMDS, *t*-BuOK but also a proazaphosphatrane (Verkade's superbase) as shown in **Scheme I.79**.



Scheme I.79. Attempts to synthesize aryl difluoro(trialkylsilyl)methyl sulfoxide

Unfortunately, at low temperature (-78 °C) and after allowing to reach room temperature for several hours, we were not able to observe any desired product. Instead, we recovered either the starting difluoromethyl *p*-tolyl sulfoxide **I.72d** or difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95** as side-product. The experiments carried out to try to understand the formation of **I.95** will be presented in the next chapter.

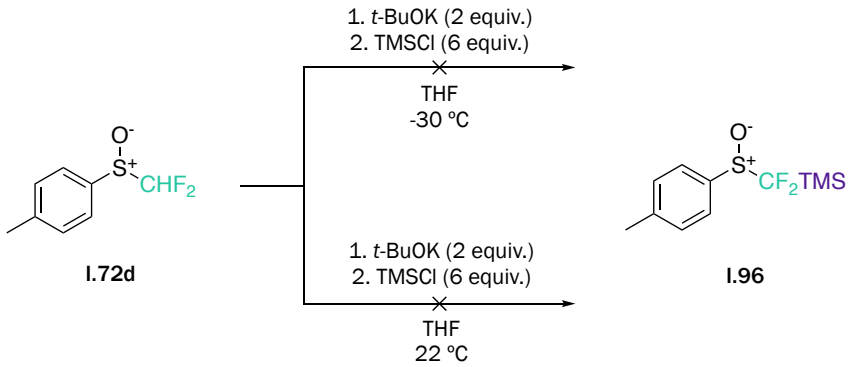
In one case, when the base was LiHMDS, we observed a small peak in fluorine NMR that could correspond to the desired silylation product **I.96**. However, due to the very small amount that was formed in the medium and probably to the instability on silica gel, we were not able to isolate even a trace of this compound after flash chromatography. This reaction was carried out again, changing the addition order, by first performing the deprotonation then the addition of the electrophile (**Scheme I.80**).



Scheme I.80. Attempt to synthesize difluoro(trialkylsilyl)methyl *p*-tolyl sulfoxide using LiHMDS

Unfortunately, the results were not much different than the ones obtained with the previous addition order. In fact, we were not able to observe any formation of the desired silylated sulfoxide **I.96**.

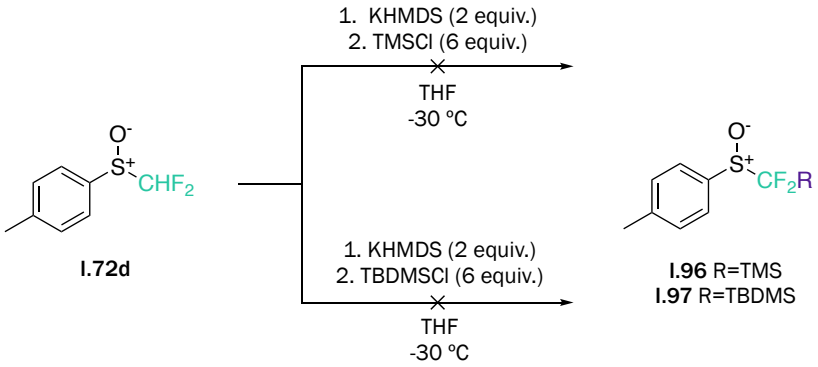
This reaction was performed at a higher temperature (-30 ºC and room temperature) using *t*-BuOK as these conditions were efficient for the deprotonation of **I.72d** (**Scheme I.81**).[65,226,227]



Scheme I.81. Use of *t*-BuOK for the synthesis of aryl difluoro(trialkylsilyl)methyl sulfoxide

Once again, we only could observe remaining starting materials as well as the formation of difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95** as a side-product at room temperature.

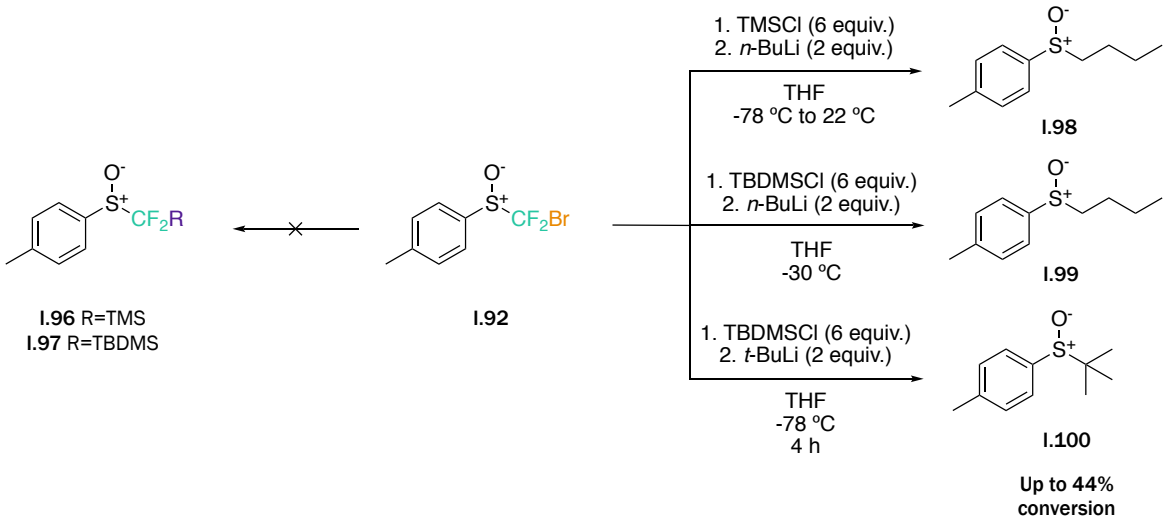
Regarding the successful conditions for the deprotonation of **I.72d** (see *Chapter II*: -30 ºC, THF, bases such as KHMDS), the same conditions were applied for the trimethylsilylation, i.e. using KHMDS as base at -30 ºC (**Scheme I.82**).



Scheme I.82. Deprotonation of difluoromethyl *p*-tolyl sulfoxide with KHMDS and addition of TMSCl

However, these attempts were once again unsuccessful.

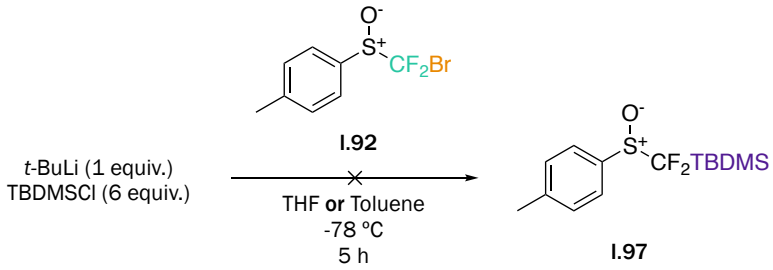
After these observations, we tried to use as an intermediate in this reaction our previously synthesized bromide **I.92** to access the silylated derivative. Indeed, as mentioned earlier, the synthesis of the difluoro(trimethylsilyl) *p*-tolyl sulfone was previously reported by Hu by performing a halogen/metal exchange with *n*-BuLi and trapping with TMSCl.[212] We used these conditions and carried out the reaction using either *n*-BuLi at -30 °C or *t*-BuLi at -78 °C (**Scheme I.83**).



Scheme I.83. Halogen-lithium exchange attempts for the silylation of difluoromethyl *p*-tolyl sulfoxide

Despite our efforts, we mostly observed the replacement of the difluorinated fragment by the alkyl chain of the lithiated species. In the case of TBDMSCl, traces of the desired sulfoxide were observed by mass spectroscopic analysis, however the signals remain too low to be taken into account.

As a last attempt to complete these studies, an *in situ* quench experiment was performed involving *t*-BuLi and TBDMSCl to perform the halogen/metal exchange and silylation on bromodifluoromethyl *p*-tolyl sulfoxide (**Scheme I.84**).



Scheme I.84. In situ quench trial to access aryl difluoro(trialkylsilyl)methyl sulfoxide

Only starting material and a small amount of non-fluorinated side-products were observed by ^{1}H NMR.

Due to the difficulties encountered to obtain and isolate the silylated derivatives **I.96** or **I.97** of difluoromethyl *p*-tolyl sulfoxide, we turned back to the bromodifluoromethyl derivative **I.92** as a reagent for difluoromethylation in Reformatsky-type reactions. These efforts will be described in Chapter II, part B.

F. Summary and conclusion

In this part our goal was to access enantiopure difluoromethyl sulfoxides and different pathways have been studied (**Scheme I.85**). Inspired by the chemistry of non-fluorinated analogues described in literature, several strategies were investigated, such as enantioselective catalytic or stoichiometric oxidations, nucleophilic substitution at a chiral sulfinyl transfer reagent, or fluorination of a functionalized sulfoxide.

The racemic difluoromethyl sulfoxide was prepared in multi-gram scale with good yields, allowing us to have a starting substrate for further optimizations.

Regarding the enantiopure difluoromethyl sulfoxide, different enantioselective oxidations of α-difluoromethyl α-sulfinylesters were not efficient as very low conversions were obtained. During the optimization, these same conditions were tried with difluoromethyl sulfides. Good conversions were obtained but enantioselectivities remained low. The more interesting method regarding selective oxidations was the one involving Davis' chiral oxaziridines. However, the maximum enantiomeric excess obtained was 26%.

We focused then on two strategies described for the fluorinated series. Bravo's method consisting in a difluorination of enantiopure β-ketosulfoxides seemed not viable to us, as in our hands α-difluoro-β-ketosulfoxides are stable and could not be converted into the desired decarbonylated compounds. Moreover, the use of Selectfluor® for electrophilic fluorination is not sufficiently attractive in terms of atom economy.

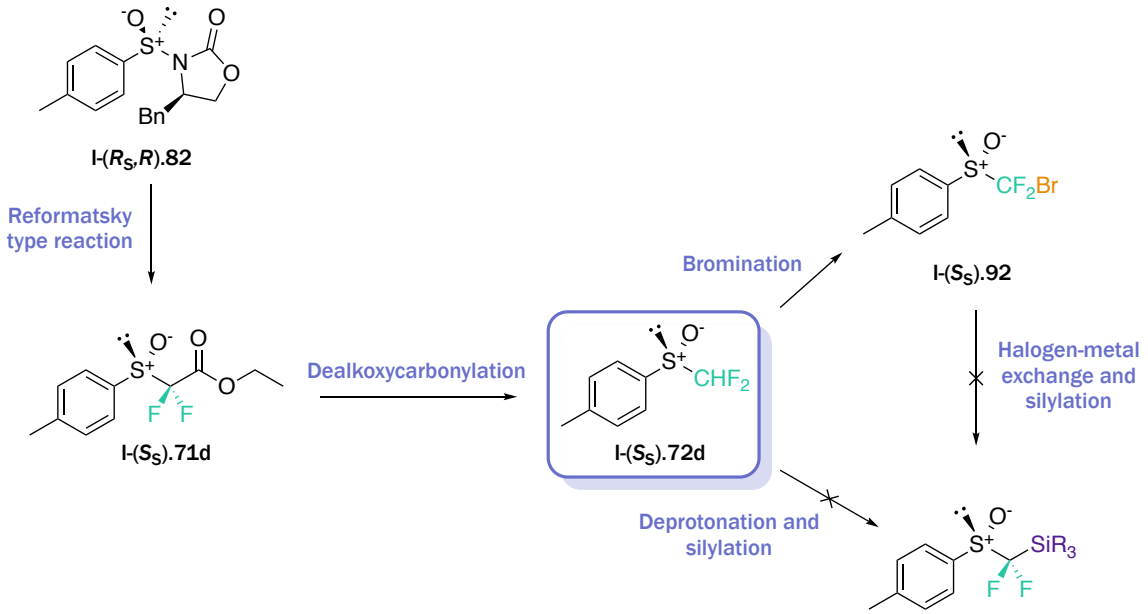
Additionally, the strategy described on the other hand by Yagupolskii, consisting in the resolution of diastereomeric ammonium α-sulfinylacetates followed by a 2-step transformation of the carboxylate, presented numerous reproducibility problems. Moreover, the toxicity of mercury salts remains a limitation.

Inspired by our expertise in asymmetric sulfoxide chemistry, we focused on Reformatsky type reactions involving chiral sulfinates or analogues as intermediates. The first attempts employed menthyl sulfinate. This reagent was found to be not reactive enough towards fluorinated organozinc reagents. To our delight, the work performed by Chloé Batisse gave us an efficient access starting from Evans sulfinyl oxazolidinones. An enantioenriched **I-(S_S).71d** was synthesized by reaction of difluorinated organozinc reagents with (R_S,*R*)-sulfinyl oxazolidinone. The use of zinc powder showing some reproducibility issues, we studied the use of other zinc systems to form *in situ* the difluoromethylzinc reagent and we were able to obtain an efficient alternative pathway using diethylzinc. After Krapcho dealkoxycarbonylation we were able to obtain a difluoromethyl *p*-tolyl sulfoxide **I-(S_S).72d** of high optical purity and confirm its relative configuration by X-ray crystallography. The corresponding difluoromethanide anion was then involved in a large number of nucleophilic additions that will be detailed in Chapter II.

Once the enantiopure difluoromethyl sulfoxide was synthesized, we aimed to explore the synthesis of further derivatives that may provide additional reactivities and increase the range of action of difluoromethylation using sulfoxides. Bromodifluoromethyl *p*-tolyl sulfoxide **I.92** as a

difluoromethylation reagent was our first target. Inspired by the conditions described for non-fluorinated sulfoxides, the bromination using electrophilic brominating reagents was studied. We were able to synthesize this compound with moderate yield after deprotonation of **I-(S_S).72d** and bromination with 1,2-dibromotetrafluoroethane.

Finally, we tried to introduce a silyl group onto the difluoromethyl sulfoxide moiety in order to prepare a "Ruppert-Prakash"-type surrogate. The preparation of a difluoro(trialkylsilyl)methyl sulfoxide was tried starting from either difluoromethyl *p*-tolyl sulfoxide **I-(S_S).72d** or bromodifluoromethyl *p*-tolyl sulfoxide **I.92**. The generation of difluoro(*p*-toluenesulfinyl)methanide by deprotonation of **I.72d** or by bromine/metal exchange on **I.92**, followed by trapping with chlorotrialkylsilanes, did not afford good results since only traces of the desired product could be observed either by fluorine NMR or mass spectroscopy. Due to these difficulties, we decided not to further investigate this route and we continued our studies using mainly difluoromethyl *p*-tolyl sulfoxide **I-(S_S).72d** as well as bromodifluoromethyl *p*-tolyl sulfoxide **I.92**.

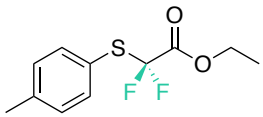


Scheme I.85. Access to enantioenriched difluoromethyl *p*-tolyl sulfoxide and its transformation into valuable bromo or silyl derivatives

G. Experimental part

Ethyl 2,2-difluoro-2-(*p*-tolylthio)acetate I.70d

A solution of *p*-toluenethiol **I.69d** (1 equiv., 20 g, 158 mmol) dissolved in anhydrous DMF (60 mL) was cannulated dropwise onto a suspension of sodium hydride (60% dispersion in mineral oil; 1.1 equiv., 7 g, 174 mmol) in anhydrous DMF (60 mL) at 0 °C under argon (caution : hydrogen evolution). Ethyl bromodifluoroacetate (1 equiv., 157 mmol, 21 mL) was then added dropwise to the previous suspension. The reacting mixture was heated at 40 °C for 20 h. The reaction was allowed to cool to 0 °C and was quenched with water. The aqueous layer was then extracted three times with 50 mL of dichloromethane. The combined organic layers were washed with large amounts of water (ca. 300 mL). The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient from 100 :0 to 95:5. Light yellow oil. 54% yield.



I.70d

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J*= 8.1 Hz, 2H), 7.20 (d, *J*= 8.4 Hz, 2H), 4.26 (q, *J*= 7.1 Hz, 2H), 2.38 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ (ppm) -82.6 (s, 2F). In agreement with previously reported data.[228]

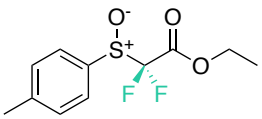
Ethyl 2,2-difluoro-2-(*p*-toluenesulfinyl)acetate I.71d

Method 1 : inspired from Kim's work[181]

Ethyl 2,2-difluoro-2-(*p*-toluenesulfanyl)acetate **I.70d** (1 equiv., 20.7 g, 84 mmol) and $FeCl_3$ (3%, 0.4 g, 2.5 mmol) were dissolved in 75 mL of acetonitrile (yellow orange solution). H_5IO_6 was added portionwise as follows : 20 min → 1.1 equiv., 21.3 g, 92.4 mmol ; 23 h → 0.2 equiv., 3.9 g, 16.8 mmol; 41 h → 0.1 equiv., 1.94 g, 8.4 mmol. At this point, 0.1 equiv. of $FeCl_3$ were also added (3%, 0.421 g, 2.52 mmol). After 102 h of reaction (full consumption of the SM), the mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with dichloromethane. The combined organic layers were washed with H_2O and brine, dried over sodium sulfate and concentrated. The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient from 100:0 to 80:20. Yellow oil. 64% yield.

Method 2 : inspired from Venier and Squires[229]

To a solution of trifluoroperoxyacetic acid (TFPAA) at 0 °C (1 equiv., prepared by mixing 1 equiv. of H_2O_2, 30% w/w in water, with 1 equiv. of trifluoroacetic acid, TFA, at 0 °C) was added dropwise sulfide **I.70d** (1 equiv.) dissolved in TFA (0.6 mol/L). The solution was warmed to 25 °C and stirred at this temperature for one day. The reaction mixture was carefully poured onto a saturated solution of NaHCO3. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient from 100:0 to 80:20. Yellow oil. 64% yield.

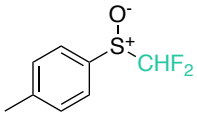


I.71d

^{1}H NMR (400 MHz, CDCl3): δ (ppm) 7.61 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J*= 8.0 Hz, 2H), 4.26 (qd, *J*= 7.2, 1.9 Hz, 2H), 2.44 (s, 3H), 1.27 (t, *J*= 7.2 Hz, 3H). **^{19}F NMR (376 MHz, CDCl3):** δ (ppm) −109.6 (d, $J_{F\text{-}F}$= 227 Hz, 1F), −111.6 (d, $^{2}J_{F\text{-}F}$= 227 Hz, 1F). In agreement with previously reported data.[228]

4-(Difluoromethanesulfinyl)toluene I.72d

To a suspension of LiCl (2 equiv., 4.41 g, 102 mmol) and ethyl 2,2-difluoro-2-(*p*-toluenesulfinyl)acetate **I.71d** (1 equiv., 14.1 g, 51.5 mmol) in 7.5 mL of DMSO was added H_2O (2 equiv., 1.86 mL, 102 mmol). The reacting mixture was heated to 110 °C for 24 hours, then poured onto cold water. The aqueous layer was saturated with NaCl and then extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with a cyclohexane : ethyl acetate gradient from 100:0 to 80:20. White solid. 73% yield.

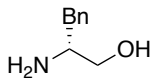


I.72d

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 7.62 (d, *J*= 8.1 Hz, 2H), 7.40 (d, *J*= 8.0 Hz, 2H), 6.01 (t, *J*= 55.5 Hz, 1H), 2.46 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** : δ (ppm) −119.4 (d, $J_{H\text{-}F}$ = 55.5 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$) :** δ (ppm) 143.9, 133.6 (t, *J*= 2.9 Hz), 130.5, 125.6, 121.1 (t, *J*= 289.4 Hz), 21.7. **IR (cm^{-1})** 2926, 1597, 1495, 1280, 1096, 1054, 813 **MP :** 60.1 ºC. **HRMS (ESI):** m/z calculated for $[C_8H_9F_2OS]^+$: 191.0337, found: 191.0340.

D-(+)-Phenylalaninol I-(*R*).84

To a slurry of $LiAlH_4$ (2.1 equiv., 2.4 M in THF, 46.4 mL, 111 mmol) in 80 mL of freshly distilled THF at 0°C was added D-phenylalanine **I-(*R*).83** (1 equiv., 8.84 g, 59.9 mmol) under an atmosphere of argon. The slurry was stirred for 1 hour at 0 °C and then heated under reflux for 20 hours. The reaction mixture was cooled to 0 °C. 140 mL of a solution of 1M NaOH was added dropwise. The slurry was filtered. The cake was washed with ethyl acetate. The combined organic fractions were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Recrystallization in ethanol. White crystals. 87% yield.



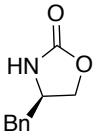
I-(*R*).84

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34-7.27 (m, 2H), 7.25-7.17 (m, 3H), 3.64 (dd, *J*= 10.5, 4.0 Hz, 1H), 3.38 (dd, *J*= 10.5, 7.2 Hz), 3.18-3.08 (m, 1H), 2.80 (dd, *J*= 13.5, 5.3 Hz, 1H), 2.53 (dd, *J*= 13.4, 8.6 Hz, 1H, *H3*), 1.90-1.50 (br s, 3H). $[\alpha]_D^{20}$= +24,08 (c=1.013, EtOH). In agreement with previously reported data.[230]

(*R*)-4-Benzyl-2-oxazolidinone I-(*R*).25

D-(+)-phenylalaninol **I-(*R*).84** (1 equiv., 6.9 g, 45.6 mmol) and dried K_2CO_3 (0.9 equiv., 5.68 g, 41.1 mmol) were put in presence of freshly distilled diethyl carbonate (2 equiv., 11.2 mL, 91.3 mmol). The slurry was heated to 145 °C (the amino alcohol liquefies at ca. 90°C) and EtOH was removed by distillation using a Vigreux column. The reacting mixture was allowed to cool to room temperature and the remaining volatiles were removed under reduced pressure. Dichloromethane was added to the resulting oil. The organic phase

was washed with water. The aqueous washings were extracted three times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified by recrystallization in cyclohexane:toluene (1:1). Orange solid. 85% yield.



I-(*R*).25

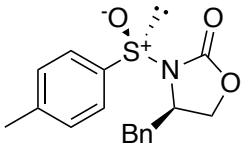
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (m, 2H), 7.31-7.27 (m, 1H), 7.21-7.16 (d, *J*= 6.7 Hz, 2H), 5.06 (br s, 1H), 4.44 (dd, *J*= 8.5, 8.0 Hz, 1H), 4.16 (dd, *J*= 8.6, 5.6 Hz, 1H), 4.13-4.05 (m, 1H), 2.98-2.77 (m, 2H). $[\alpha]_D^{20}$= +59.4 (c=1.05, $CHCl_3$). In agreement with previously reported data.[231]

(*R*)-4-Benzyl-3-((*R*)-*p*-toluenesulfinyl)oxazolidin-2-one I-(R_S,*R*).82

Preliminary synthesis of p-toluenesulfinyl chloride

A three-necked round bottomed flask equiped with a mechanical stirring system was loaded with neat $SOCl_2$ (1.42 equiv., 2.7 mL, 36.6 mmol). The flask was cooled to 0 °C with an ice-water bath. A solid funnel was fitted, and sodium *p*-toluenesulfinate (1 equiv., 4.59 g, 25.8 mmol) was added portionwise at an appropriate rate avoiding to blow back the powder by the evolving sulfur dioxide. 6 mL of toluene were added to help stirring. A viscous yellow slurry was obtained. DMF (1.77 mol%, 0.035 mL, 456 mmol) was then added. The cold bath was removed and the solution was stirred for 3 h at 22 ºC (pasty yellow solution). At this point toluene (20 mL) was added, the flask was fitted with a distillation apparatus and heated to 65-70 °C. Vaccum was applied to the mixture to distill off toluene and excess thionyl chloride (collected in a flask at -78 °C). The resulting yellow reaction mixture was used as such.

To a solution of (*R*)-4-benzyl-2-oxazolidinone **I-(*R*).25** (1 equiv., 3 g, 16.9 mmol) in 30 mL of freshly distilled THF under an atmosphere of argon at 0 °C, *n*-BuLi (1.1 equiv., 1.57 M in *n*-hexane, 111.9 mL, 18.6 mmol) was added dropwise over a 5-10 minutes period. The solution became yellow then dark orange. The resulting suspension was stirred at 0 °C for 10 min and then cooled to -78 °C. It was stirred for 10 minutes at -78 °C. The freshly prepared solution of *p*-toluenesulfinyl chloride (1.5 equiv., 4.44 g, 25.4 mmol) was then added as a slurry to the mixture of deprotonated (*R*)-benzyl-2-oxazolidinone in 20 mL of freshly distilled THF. The reaction mixture was stirred at -78°C for 30 minutes. It was quenched with a saturated solution of NH_4Cl and diluted with ethyl acetate. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed twice with a saturated solution of $NaHCO_3$ and once with brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. A NMR sample of the crude was analyzed. It revealed full conversion of (*R*)-benzyl-2-oxazolidinone with a ratio (R_S,*R*):(R_S,*S*)=67:33. The (R_S,*R*) diastereomer was crystallized from diethyl ether. White solid. 41% yield.



I-(R_S,*R*).82

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J*= 8.3 Hz, 2H), 7.48 (d, *J*= 8.0 Hz, 2H), 7,29-7.18 (m, 3H), 6.99-6.89 (m, 2H), 4.07 (dd, *J*= 9.0, 3.8 Hz, 1H), 3.97 (t, *J*= 8.3 Hz, 1H), 3.79-3.64 (m, 1H), 3.38 (dd, *J*= 13.9, 3.6 Hz, 1H), 2.90 (dd, *J*= 13.9, 10.3 Hz, 1H), 2.51 (s, 3H). $[\alpha]_D^{20}$= -133.7 (*c*= 0.7, $CHCl_3$).

IR (cm^{-1}) : 1765, 1386, 1191, 1103, 1072. In agreement with previously reported data.[115]

Ethyl (*S*)-2,2-difluoro-2-(*p*-toluenesulfinyl)acetate I-(S_S).71d

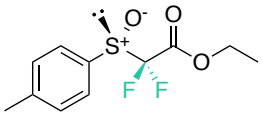
Reformatsky type reaction using zinc powder

Metallic Zn was activated with a solution of 6M HCl for approximately 1 hour. It was washed several times with water, acetone and dichloromethane. It was kept under vacuum overnight at 120 °C.

To a suspension of freshly activated Zn (2.4 equiv., 127 mg, 1.96 mmol) in 10 mL of freshly distilled THF was added one drop of ethyl bromodifluoroacetate. The mixture was refluxed. A solution of (*R*)-4-benzyl-3-((R_S)-*p*-toluenesulfinyl)-1,3-oxazolidin-2-one **I-(R_S,*R*).25** (1 equiv., 257 mg, 0.815 mmol) and ethyl bromodifluoroacetate (2.4 equiv., 0.259 mL, 1.96 mmol) in 15 mL of freshly distilled THF was then added dropwise to the previous mixture containing the (*R*)-4-benzyl-3-((R_S)-*p*-toluenesulfinyl)-1,3-oxazolidin-2-one **I-(R_S,*R*).25**. The resulting reaction mixture was stirred at 70 °C for 41 hours. $KHSO_4$ (2.6 equiv.) dissolved in 2 mL of water was added to the mixture, which was then stirred for 30 minutes and filtered through Celite®. The Celite® pad was washed carefully with diethyl ether. To the combined filtrate was added a saturated solution of NaCl and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by column chromatography with a cyclohexane:ethyl acetate gradient from 100:0 to 90:10. Yellow oil. 13% yield. 94% e.e. The enantiomeric excess of the product were determined by HPLC using a Chiracel IC column (*n*-hexane:*i*-PrOH= 80:20, flow rate 0.5 mL/min, λ = 204 nm, τ = 24.0 min and 31.6 min).

Reformatsky type reaction using diethyl zinc

A solution of (4*R*)-4-benzyl-3-((*R*)-*p*-toluenesulfinyl)-1,3-oxazolidin-2-one **I-(R_S,*R*).25** (1 equiv., 232 mg, 0.736 mmol) and ethyl bromodifluoroacetate (2 equiv., 0.194 mL, 1.47 mmol) in freshly distilled THF under nitrogen was stirred at 22 ºC. Diethylzinc (2 equiv., 1 M solution in hexane, 1.47 mL, 1.47 mmol) was added very slowly and the resulting mixture was stirred for 5 h. The reaction was quenched with a mixture of water (12 mL) and diethylether (12 mL) and stirred for 5 minutes. The heterogeneous solution was filtered through a pad of celite, which was washed with diethyl ether, and the organic layer was separated. The aqueous layer was extracted three times with diethyl ether. Organic layers were assembled, washed with brine and dried over anhydrous sodium sulfate. An NMR analysis of the crude revealed full conversion of the starting material into the desired product. The product was purified by column chromatography on silica gel with a cyclohexane :ethyl acetate gradient (100:0 to 80:20). Colorless oil. 79% yield. 90% e.e. The enantiomeric excess of the product were determined by HPLC using a Chiracel IC column (*n*-hexane:*i*-PrOH= 80:20, flow rate 0.5 mL/min, λ = 204 nm, τ = 24.0 min and 31.6 min).



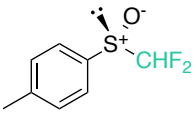
I.(S_S)-71d

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J*= 8.0 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 4.27 (qd, *J*= 7.2, 1.8 Hz, 2H), 2.45 (s, 3H), 1.28 (t, *J*= 7.2 Hz, 3H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ (ppm) -109.45 (d, $J_{F\text{-}F}$ = 227.1 Hz, 1F), -111.6 (d, $J_{H\text{-}F}$= 227.5

Hz, 1F). **^{13}C NMR (101 MHz, $CDCl_3$):** δ (ppm) 159.6, 144.3, 132.9, 130.2, 126.2, 64.3, 21.8, 14.0. $[\alpha]_D^{20}$= +111.6 (c=0.3, $CHCl_3$). **IR (cm^{-1}) :** 2154, 1761, 1304, 1161, 1132, 1095, 1068, 1013, 812. **HRMS (ESI):** m/z calculated for $[C_{11}H_{12}F_2O_3S]^+$: 263.0548, found: 263.0556.

(*S*)-4-(Difluoromethanesulfinyl)toluene I-(S_S).72d

To a suspension of LiCl (2 equiv., 45.1 mg, 1.05 mmol) and ethyl (*S*)-2,2-difluoro-2-(*p*-toluenesulfinyl)acetate **I-(S_S).71d** (1 equiv., 138 mg, 0.526 mmol) in 8.9 mL of NMP was added H_2O (2 equiv., 19 mg, 0.019 mL, 1.05 mmol). The reacting mixture was heated in the microwave reactor to 100°C for 25 minutes. The orange reaction mixture was cooled to room temperature and poured onto water. The aqueous layer was extracted four times with ethyl acetate. The combined organic layers were washed with high amounts of water to remove NMP, and with brine. They were then dried over Na_2SO_4 and concentrated under vacuum. The product was purified by column chromatography on demetalled silica gel with a cyclohexane :ethyl acetate gradient (100:0 to 80:20). White solid. 80% yield. 90% e.e. The product was recrystallized from diethyl ether and suitable crystals for a crystallographic analysis were obtained, that confirmed the (*S*) configuration of the sulfur atom. The enantiomeric excess of the product was determined by HPLC using an IC column (*n*-hexane/*i*-PrOH= 80 :20, flow rate 0.5 mL/min, λ = 206 nm).



I-(S_S).72d

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (d, *J*= 8.0 Hz, 2H), 7.40 (d, *J*= 7.9 Hz, 2H), 6.01 (t, *J*=55.5 Hz, 1H), 2.45 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ (ppm) -119.41 (d, *J*= 55.7), 1F), 2F). **IR (cm^{-1}) :** 2918, 1489, 1285, 1108, 1050, 814. **MP :** 60.1 °C. **HRMS (ESI):** m/z calculated for $[C_8H_9F_2OS]^+$: 191.0337, found: 191.0338.

To carry out the X-ray diffraction crystallography analysis, the crystals were placed in oil, and a single crystal was selected, mounted on a glass fibre and placed in a low-temperature N_2 stream. X-ray diffraction data collection was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ _= 0.71073 Å). The crystal-detector distance was 36 mm. The cell parameters were determined (Denzo software) from reflections taken from one set of 10 frames (1.0 ° steps in π angle), each at 20 s exposure. The structure was solved by Direct methods using the program SHELXS-2014. The refinement and all further calculations were carried out using SHELXL-2014. The H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H-atoms were refined anisotropically, using weighted full-matrix least-squares on F^2.

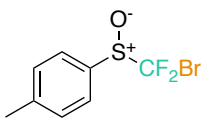
***Crystallographic data for difluoromethyl p-tolyl sulfoxide* I.(Ss)-72d**

Formule	$C_8H_8F_2OS$	Cell volume	834.253 Å^3
M (g/mol)	190.20	Z, Calculated density	4, 1.514 Mg/m^3
Temperature (K)	173 (2)	F(000)	392
Wavelength	0.71073	Crystal size	0.340 x 0.180 x 0.120 mm
Crystalline structure	Orthorhombic	Theta range for data collection	2.511 to 27.475
Space group	P 2_1 2_1 2_1		
a	4.91110 (10) Å	Z	0
b	8.9793 (2) Å	Z'	0
c	18.9180 (4) Å	Configuration	*S*
α _	90 °	Flack parameter	- 0.01 (3)
β _	90 °	R1	0.0308
γ _	90 °	wR2	0.0769

4-(Bromodifluoromethanesulfinyl)toluene I.92

To a solution of bis(trimethylsilyl)amine (2 equiv., 0.44 mL, 2,10 mmol) in THF at -78 °C was added dropwise butyllithium (2 equiv., 1,36 ml, 2,10 mmol, 1.55 M). The mixture was stirred for 40 mins at -78 °C.

In a microwave tube under argon were dissolved 4-(difluoromethanesulfinyl)toluene **I.72d** (1 equiv., 200 mg, 1.05 mmol) and 1,2-dibromo-1,1,2,2-tetrafluoroethane (1 equiv., 0.13 mL, 1.05 mmol) in 1.5 mL of THF. The freshly prepared solution of LiHMDS was added dropwise to this solution and the mixture was allowed to reach 22 °C over 2 h. A saturated solution of NH_4Cl was added to the mixture. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from 100:0 to 50:50) to provide 4-(bromodifluoromethanesulfinyl)toluene **I.92** (87 mg, 323,30 µmol, 31%) as a light yellow oil.

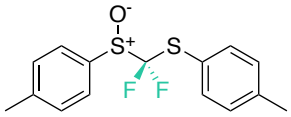


I.92

^{1}H NMR (500 MHz, $CDCl_3$) : δ (ppm) 7.68 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). **^{19}F NMR (471 MHz, $CDCl_3$)** : δ (ppm) -54.2 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 144 Hz, $\Delta\nu_{AB}$ =820 Hz, 2F). In agreement with previously reported data.[204]

Difluoro(*p*-toluenesulfanyl)methyl sulfoxide I.95

Obtained as side-product in silylation attempts. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from 100:0 to 50:50. Colorless oil.



I.95

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.65 (d, *J*= 7.9 Hz, 2H), 7.51 (d, *J*= 8.2 Hz, 2H), 7.35 (d, *J*= 7.7 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ (ppm) -78.6 (ABX system, J_{AB}= $J_{F\text{-}F}$= 190 Hz, $\Delta\nu_{AB}$=2230 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$):** δ (ppm) 143.74, 141.35, 137.10, 130.35, 129.95, 126.65, 21.78, 21.51. **HRMS (ESI):** m/z calculated for $[C_{15}H_{14}F_2KOS_2]^+$: 351.0086 found: 351.0089.

Chapter II

Use of difluoromethyl sulfoxides as chiral and traceless auxiliaries to access enantioenriched difluoromethyl derivatives

Table of contents

A. Enantioselective introduction of the difluoromethyl moiety

In the first chapter, we described the importance that has been accorded in the last decades to the introduction of Emergent Fluorinated Substituents (EFS) due to the remarkable physical, chemical and biological properties they can confer to bioactive compounds.

Among the EFS, the difluoromethyl group has received less attention when compared to the single fluorine atom or CF_3 for example. Nevertheless, its outstanding properties such as its high potential as an alcohol or thiol bioisostere due to its ability to perform H-bonding interactions makes of it a very attractive group to prepare building-blocks for life sciences.

The construction of a stereogenic center bearing a -CF_2H group has been underexplored, in contrast to the formation of F- or CF_3-containing stereogenic centers. Its interesting properties and the limited number of examples regarding enantioselective difluoromethylation led us to develop new synthetic pathways to prepare these derivatives.

An account of the reported methods found in literature for the selective introduction of -CHF_2 will be presented, followed by the description of our strategy involving enantiopure difluoromethyl sulfoxides.

a. State of the art

Several synthetic pathways have been developed by organic chemists in order to access to libraries of difluoromethylated substrates. A major challenge remains then in finding a stereoselective method allowing the introduction of the CHF_2 group in different substrates. Particularly, a restrained number of methods have been developed nowadays to access enantiopure difluoromethyl alcohols and amines. We decided then to focus on these kind of substrates.

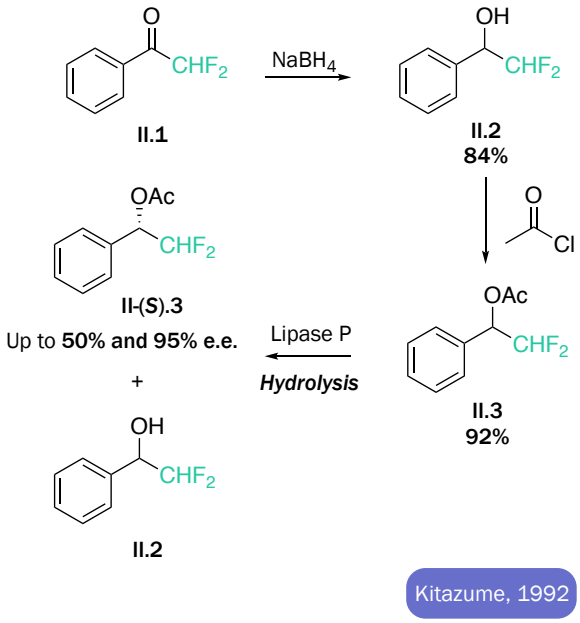
1. Asymmetric synthesis of α-difluoromethyl alcohols

i. Kinetic resolution

Biocatalysts have been used in chemical transformations as efficient reagents to obtain in a highly selective manner enantiomerically enriched compounds.

Kitazume and co-workers used lipase B in order to perform a kinetic resolution when reducing an acetylated difluoromethyl alcohol (**Scheme II.1**).[232] The acetylated racemic difluoromethyl alcohol was prepared in racemic form by reduction of a difluoroacyl derivative followed by O-acetylation using Lipase P.

The corresponding yield of the (*S*)-acetylated alcohol **II-(S).3** remains moderate but excellent enantiomeric excess was obtained using this method.

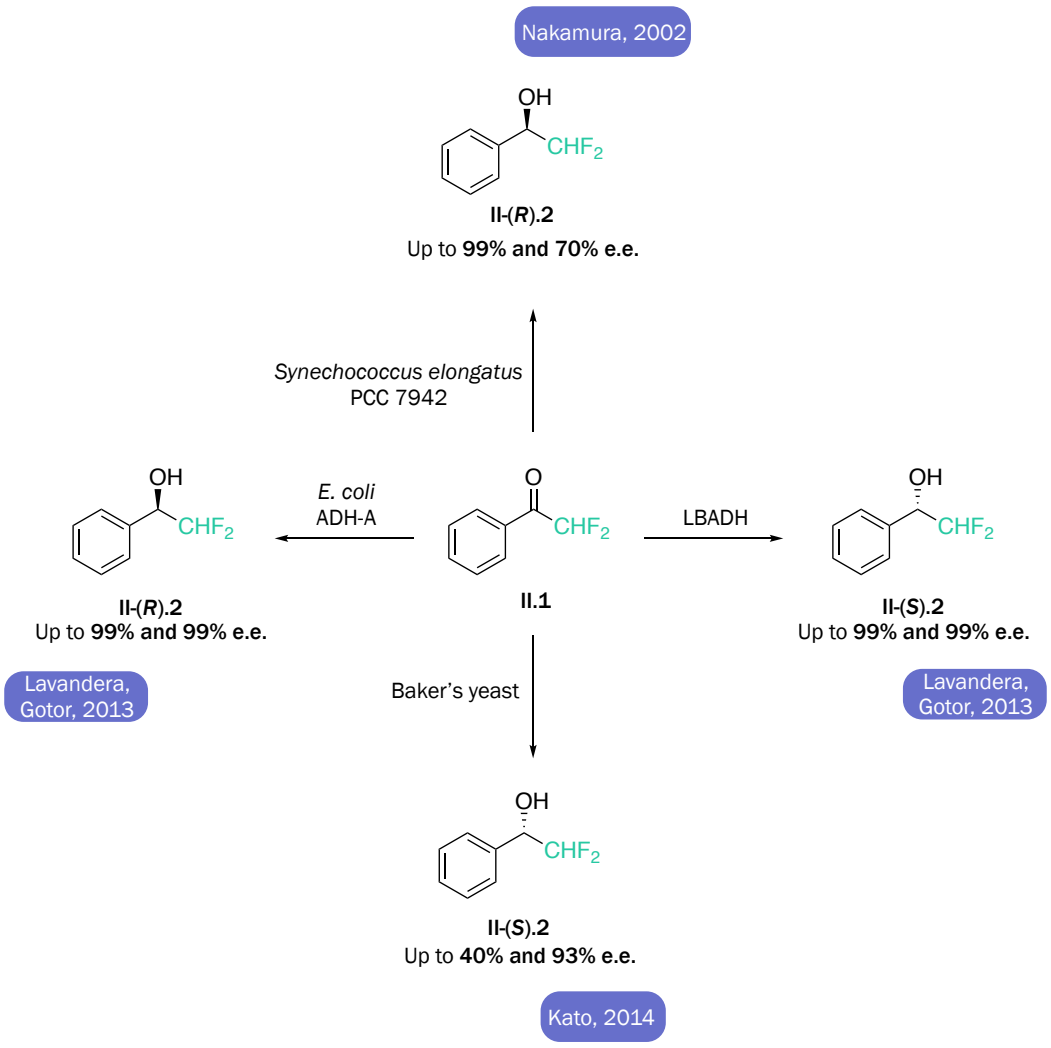


Scheme II.1. Enzymatic resolution of acetylated difluoromethyl alcohol

ii. Asymmetric reduction of ketones

Regarding the access to enantiopure difluoromethyl alcohols, the examples leading to these products by selective reduction of the corresponding acetophenones will be depicted in this paragraph.

As in the previous paragraph, some groups have used methods using biological systems giving excellent results (**Scheme II.2)**.



Scheme II.2. Biological reduction of difluoromethyl phenyl ketone

Nakamura's group used a cyanobacteria, *Synechococcus elongatus* PCC 7942, in the presence of light as a reducing agent to obtain alcohol **II-(*R*).2** with 70% enantiomeric excess.[233]

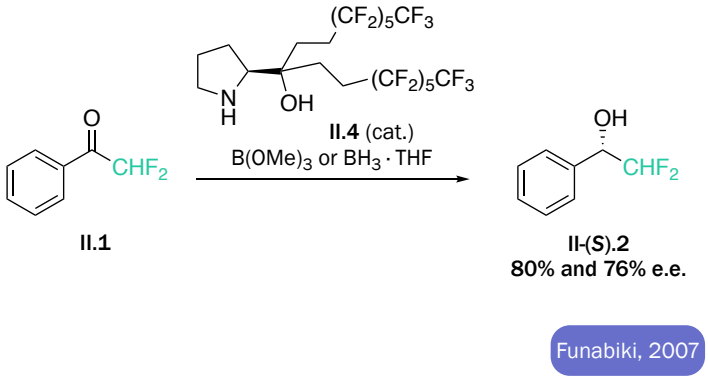
In 2013, Lavandera and Gotor performed the enzymatic reduction of difluoromethyl acetophenone using oxidoreductases. ADH contained in *E. coli* bacteria and *Lactobacillus brevis* ADH allowed the obtention of the two corresponding enantiomers of the difluoromethylated alcohols **II.2** with quantitative yield and a full selectivity.[234]

The last similar example concerning biological methods was reported in 2014 by Kato. His group used Baker's yeast (*Saccharomyces cerevisiae*) as a reducing agent to obtain enantiomerically pure fluoroalkylated alcohols. Regarding the CHF_2 case, he was able to obtain the desired product with a moderate yield and a good enantiomeric excess.[235] It is noteworthy that when this strategy was applied to other fluoroalkyl derivatives, the selectivity was found to decrease with the increasing number of fluorine atoms, revealing a potential effect of fluorine in the enantiofacial discrimination of Baker's yeast reductase according to the size of the fluorinated group.

Some examples have been described since the 1990's regarding the selective reduction of aryl difluoromethyl ketones using biological systems. These methods are efficient and easily to carry out, however their limitation remains in the fact that they are very substrate dependent.

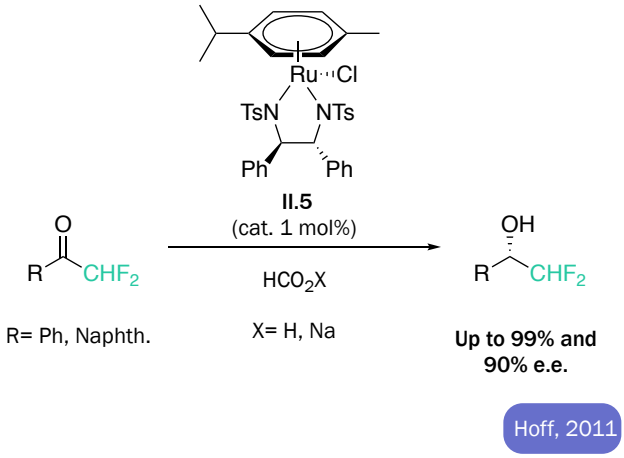
Asymmetric synthetic catalyzed transformations have been developed in order to perform the selective reduction of difluoromethyl ketones.

Funabiki reported the use of borane reducing agent, in combination to a reusable prolinol as pre-catalyst. He applied this methodology to -CH_2F and -CHF_2 bearing groups and was able to obtain very good selectivities (**Scheme II.3**).[236] Surprinsingly, no induction was observed when it was applied to -CF_3 bearing ketones.



Scheme II.3. Borane mediated reduction of difluoromethyl phenyl ketone

At the beginning of the decade, Hoff performed an Asymmetric Transfer Hydrogenation (ATR) on aromatic difluoromethyl ketones using a Noyori-type rutheniumarenediamine catalyst **II.5** (**Scheme II.4**).[237] These enantioselective reductions led to difluoromethylated derivatives with 90% e.e.

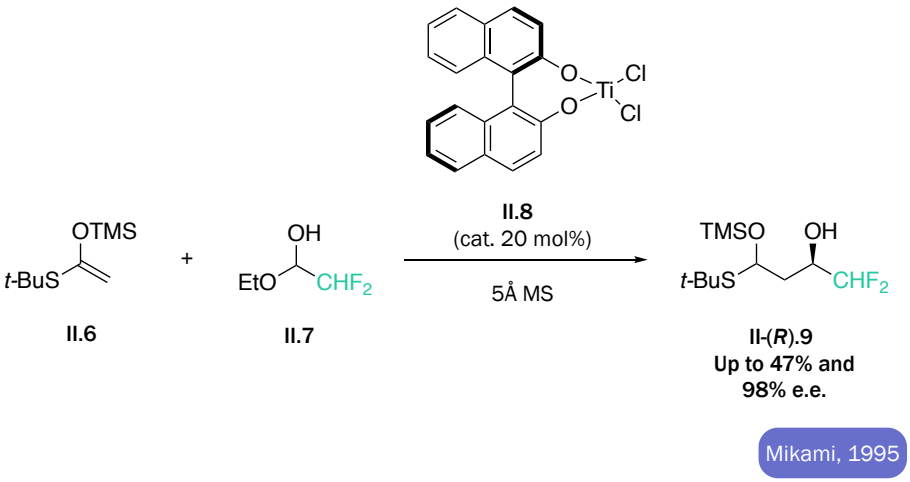


Scheme II.4. Asymmetric Transfer Hydrogenation of aromatic difluoromethyl ketones

iii. Aldol reaction

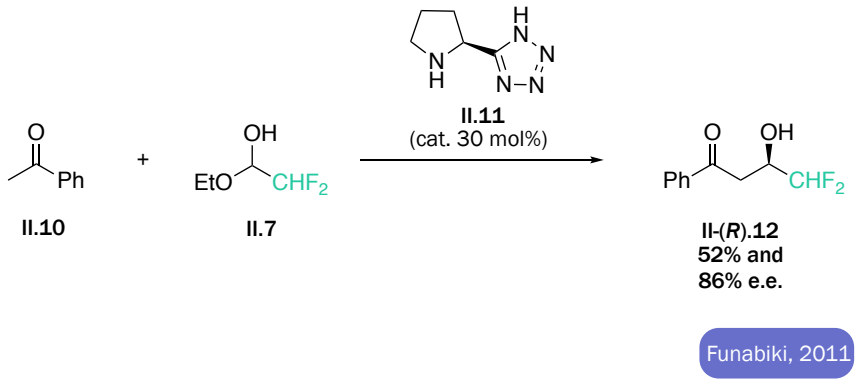
As well as some successful catalytic reductions of ketones containing the -CF_2H motif have been described, aldols reactions also have an important place among the methods to access enantiopure difluoromethyl derivatives.

In 1995, Mikami reported a Mukaiyama aldol reaction using fluorinated aldehydes or hemiacetals (**II.7**) in the case of -CHF_2 bearing substrates. The asymmetric catalytic reaction led to highly enantioenriched difluoromethylated alcohols as **II-(*R*).9** (**Scheme II.5**).[238,239]



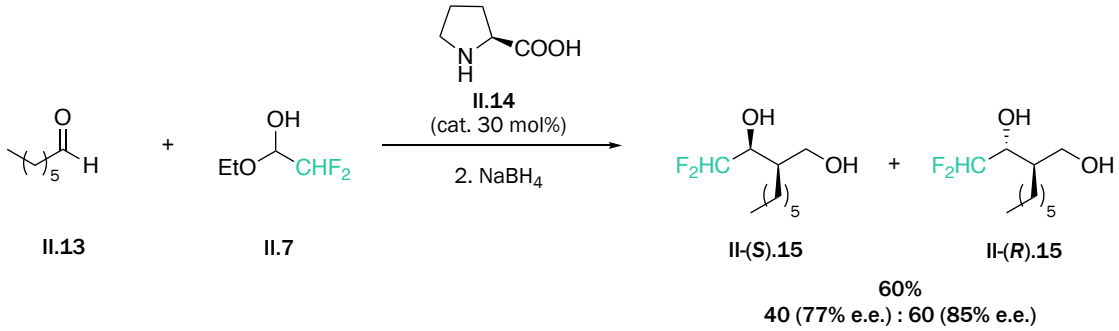
Scheme II.5. Mukaiyama aldol reaction leading to enantioenriched difluoromethylated alcohols

In the same idea, Funabiki reacted difluorinated ethyl hemiacetal with aromatic methyl ketones in the presence of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole to obtain 4,4-difluoromethyl-4-hydroxybutanones (**II-(*R*).12**) in high yields with up to 90% e.e. (**Scheme II.6**).[240]



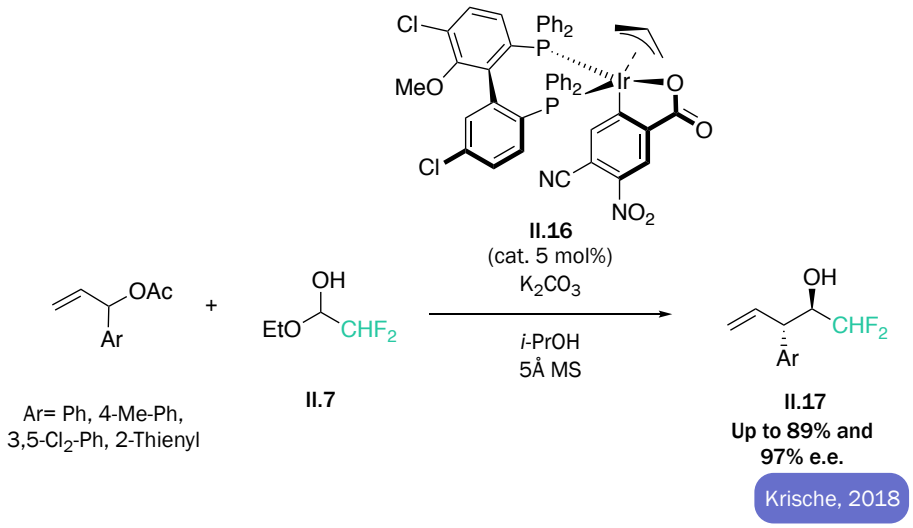
Scheme II.6. Catalytic asymmetric aldol reaction to access enantioenriched difluoromethyl alcohols

Continuing with this study, the same group reported in 2015[241] the enantioselective synthesis of 2-substituted 4,4,-difluoroacetaldehyde butane-1,3-diols (**Scheme II.7**). Various alkyl aldehydes were reacted with difluoromethyl ethyl hemiacetal **II.7** in the presence of a catalytic amount of L-proline to perform the asymmetric aldol reaction followed by a reduction with sodium borohydride giving access to the enantioenriched butane-1,3-diols **II.15** bearing a CHF_2 group with moderate to good yields and enantioselectivities.



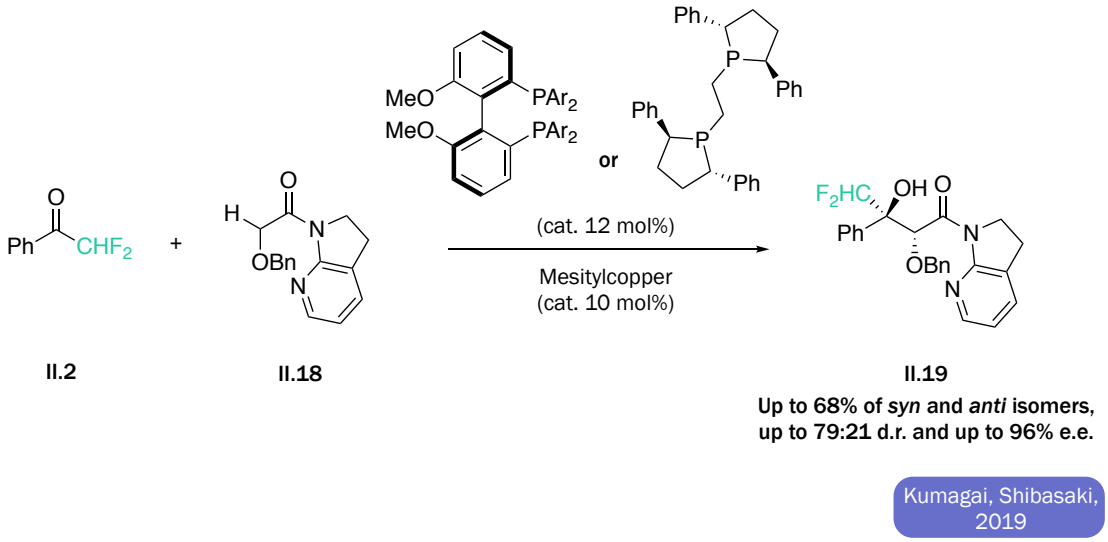
Scheme II.7. Synthesis of enantioenriched difluorinated butane-1,3-diols

More recently, the use of difluoroacetaldehyde ethyl hemiacetal was reported by Krische's group. An iridium-catalyzed *anti*-diastereo and enantioselective (α-aryl)allylation of this substrate was performed with accessible branched allylic acetate pronucleophiles (**Scheme II.8**). The enantioinduction relies on the competition between diastereomeric kinetic *vs* thermodynamic carbonyl binding modes. Some examples of -CHF_2 bearing molecules were described, among them the interesting analogues of *d*-Hyoscyamine, a FDA approved alkaloid.[242]



Scheme II.8. Iridium-catalyzed diastereo and enantioselective access to difluoromethyl-substituted alcohols

A last example that was reported for aldol catalyzed reactions giving access to access to difluoromethyl alcohols with high enantioselectivities was published by Kumagai and Shibasaki (**Scheme II.9**).[243]



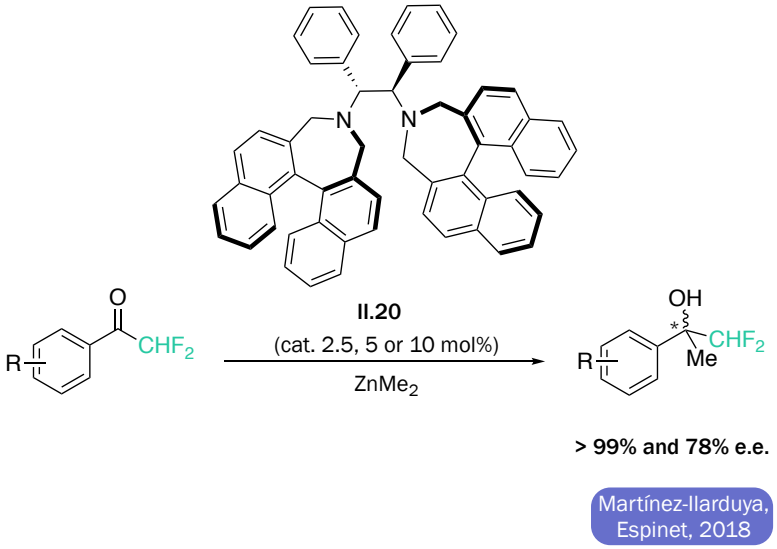
Scheme II.9. Copper-catalyzed aldol reactions for the synthesis of enantioenriched difluoromethyl alcohols bearing alkoxyamides

Difluoromethyl ketones, as well as other fluoroalkylated ketones, were reacted with alkoxyamides nucleophiles in the presence of mesytilcopper and a chiral ligand to obtain the two diastereoisomers of the corresponding alcohols. Depending on the ligand used, *syn* and *anti*-aldol adducts could be obtained with moderate yields and very good enantiomeric excess. The amide moiety of the aldol adduct can then be transformed into a variety of functional groups to give a large number of fluorinated chiral products.

iv. Catalytic asymmetric transformations of difluoromethylated ketones

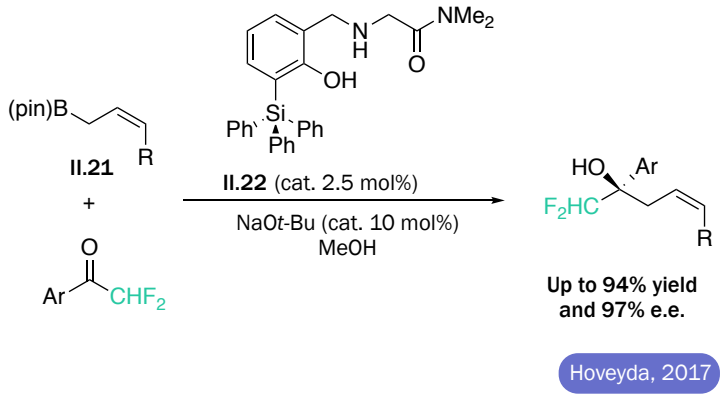
Alkylation of difluoromethyl ketones represents one of the asymmetric transformations that can be performed to access enantioenriched difluoromethyl quaternary centers.

Martinez-Ilarduya and Espinet reported an example of catalytic methylation recently, where the catalyzed addition of dimethylzinc combined to the use of a chiral diamine ligand **II.20** in a non-coordinating solvent (dichloromethane) allowed the preparation of fluorinated tertiary alcohols derived from difluorinated ketones in high yields an enantiomeric excesses up to 99%. This methodology, based on a double-cycle mechanism, could also be extended to various fluoroalkyl derivatives, such as $-CF_3$ bearing molecules (**Scheme II.10**).[244]



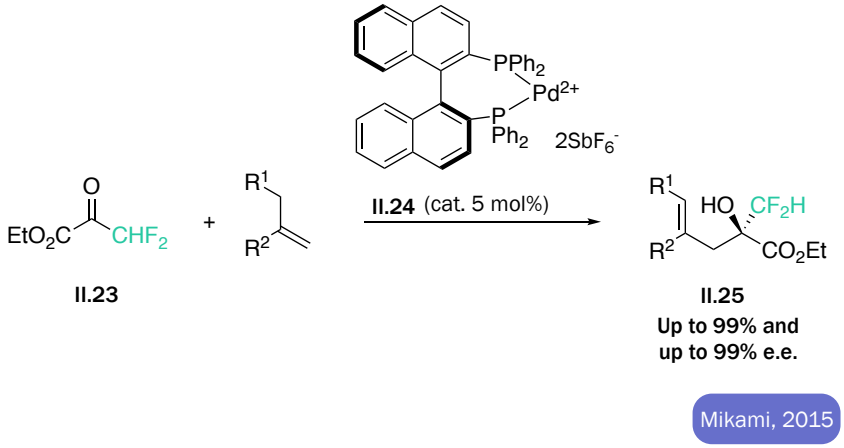
Scheme II.10. Synthesis of fluorinated tertiary alcohols in the presence of chiral diamine ligands

Regarding allylation reactions, Hoveyda was able to develop an apropriate enantioselective synthesis of fluoroalkyl-substituted *Z*-homoallylic tertiary alcohols (**Scheme II.11**).[245] Catalyst **II.22** prepared from valine aminophenol and a *Z*-γ-substituted boronic acid pinacol ester were reacted with difluoromethyl ketones in the presence of a catalytic amount of base to obtain *Z*-selective enantioenriched difluoromethyl vinyl alcohols. Some representative products were prepared in gram-scale.



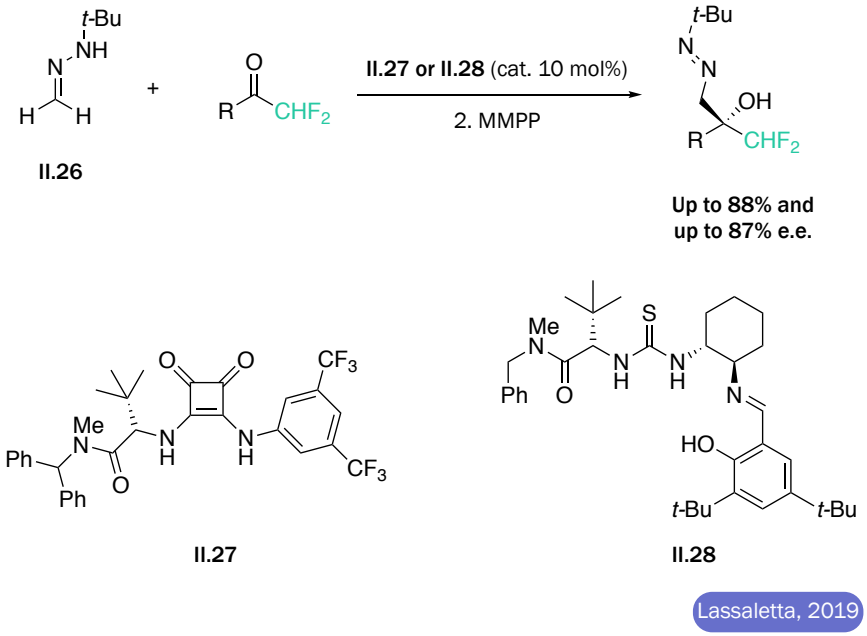
Scheme II.11. Synthesis of fluoroalkyl tertiary alcohols bearing a homoallylic substituent

Another synthetic way for accessing of enantiopure difluoromethyl-bearing alcohols has been described in 2015 by Mikami, starting from difluoropyruvate **II.23** as an electrophile to be reacted with a substituted allyl species. This catalytic asymmetric ene reaction involves a dicationic palladium complex and delivered various α-CF_2H-substituted tertiary alcohols in high yields and full enantioselectivities (**Scheme II.12**).[246]



Scheme II.12. Catalytic enantioselective ene reaction towards α-difluoromethyl alcohols

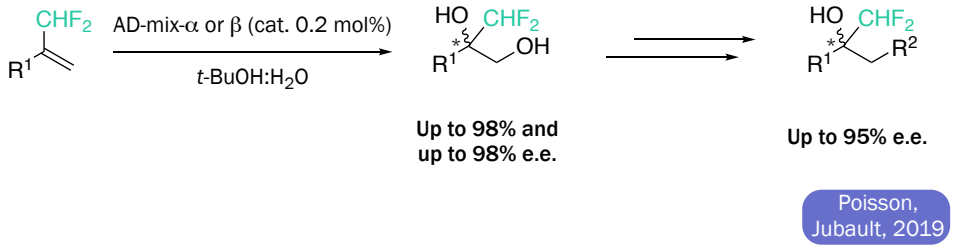
Early last year, Lassaletta's group described the use of hydrazones to be added to difluoromethyl ketones in the presence of H-bonding catalysts **II.27** or **II.28** to obtain functionalized tertiary difluoromethyl alcohols with good yields and enantioselectivities. The transformation of the hydrazone moiety represents an interesting way entry to a large number of derivatives, such as β-amino alcohols or α-hydroxy aldoximes among others, bearing a –CHF_2-substituted stereogenic carbon (**Scheme II.13**).[247]



Scheme II.13. Synthesis of enantioenriched difluoromethyl derivatives from difluoromethyl ketones and hydrazones

v. *Catalytic transformations of other difluorinated substrates*

In 2019, Poisson and Jubault developed a method to access enantiopure fluoromethylated and difluoromethylated alcohols.[248] Starting from $-CHF_2$ containing olefins applying by Sharpless asymmetric dihydroxylation reaction, they were able to obtain both enantiomers of α-difluoromethyl tertiary alcohols by using either AD-mix-α or β as the catalyst (**Scheme II.14**).



Scheme II.14. Sharpless asymmetric dihydroxylation type reaction of difluoromethyl olefins

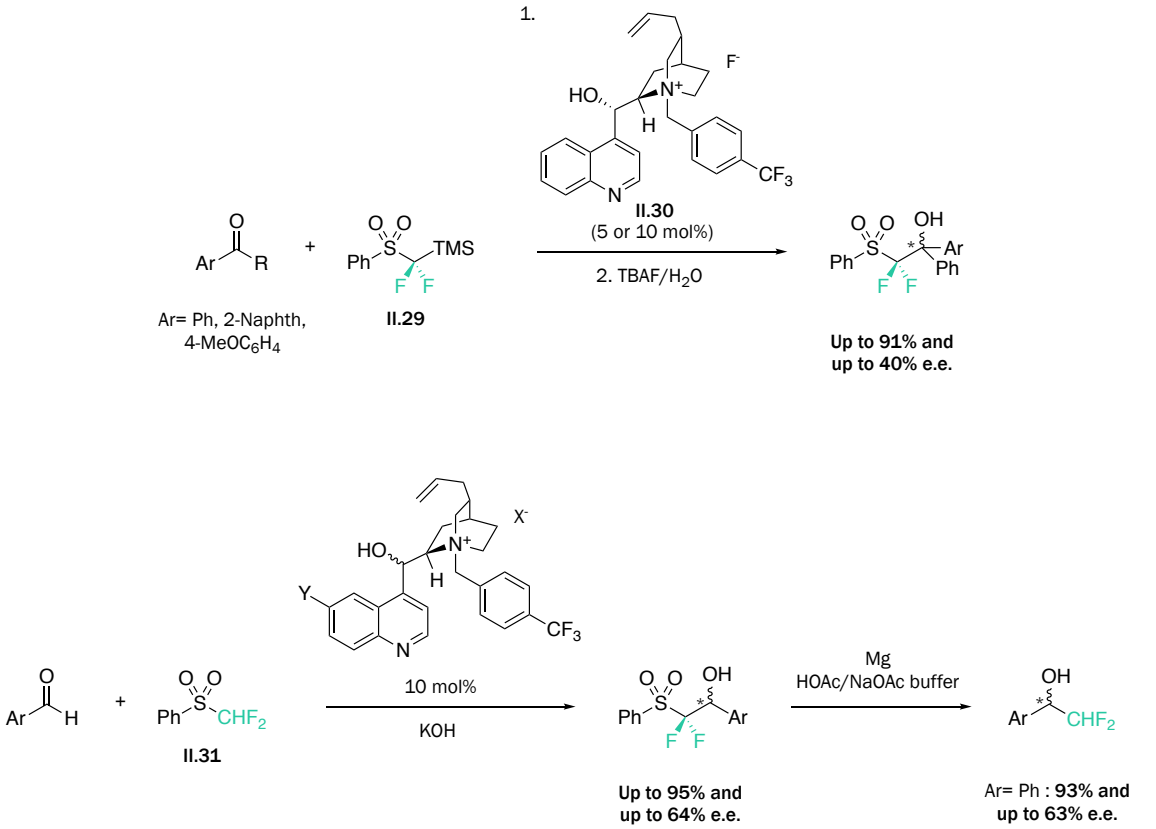
The transformation of the obtained asymmetric dihydroxylated products allowed also the synthesis of new building blocks bearing halogenated or amino groups in β–position of the enantioenriched alcohol.

vi. *Enantioselective addition of difluoromethyl nucleophiles*

As described, an alternative way of access to optically pure difluoromethyl products is the nucleophilic addition of $-CHF_2$ surrogates to electrophiles.

Some groups were interested in this pathway, being quite straightforward and allowing the synthesis of enantiomerically pure difluoromethylene derivatives. After unmasking the $-CF_2H$ group, the enantiopure difluoromethyl compounds can be obtained.

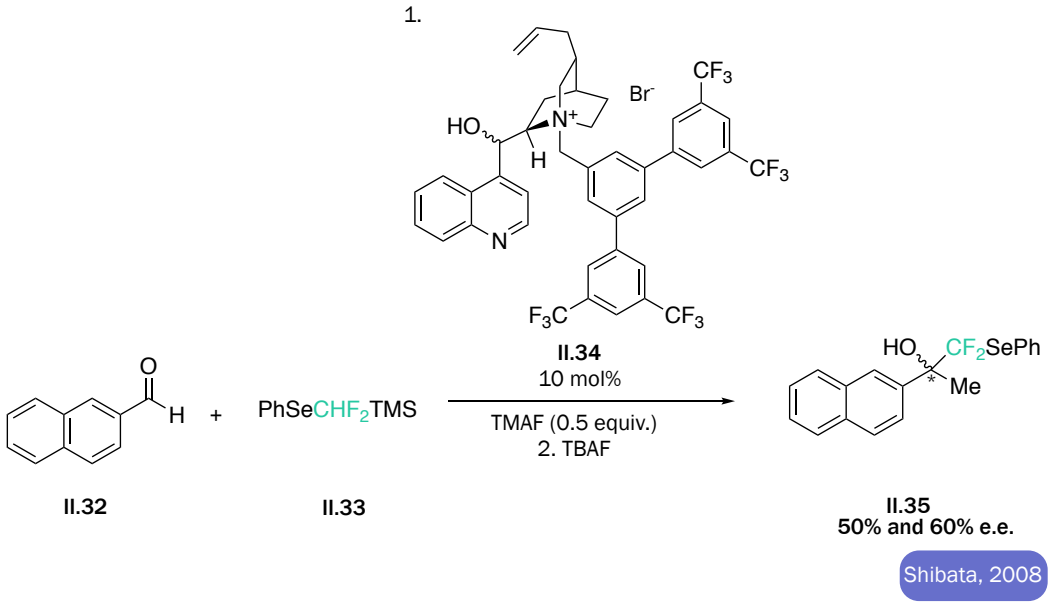
In 2008, Hu described the first enantioselective difluoromethylation of aromatic aldehydes with $PhSO_2CF_2H$ or $Me_3SiCF_2SO_2Ph$ in the presence of chiral quaternary ammonium salt (chiral cinchonium salts) as the catalyst (**Scheme II.15**).[56] Enantiomeric excesses up to 62% were obtained, but the enantioselectivity of this method remains substrate-dependent.



Hu, 2008

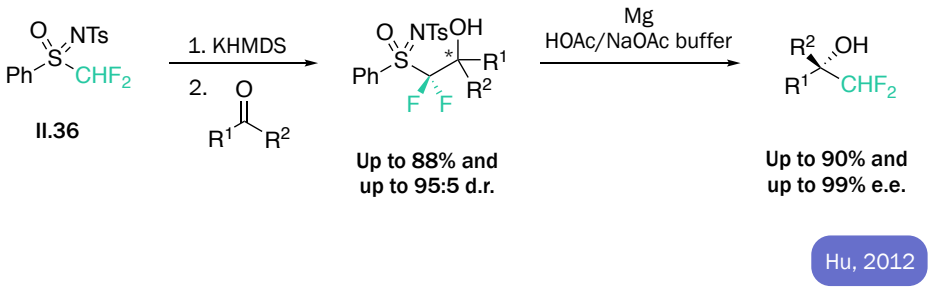
Scheme II.15. Enantioselective difluoromethylation of aromatic aldehydes in the presence of chiral cinchonium salts

In the same year, Shibata extended his enantioselective trifluoromethylation procedure this time to be applied on enantioselective difluoromethylation. The use of the combination of a chiral ammonium bromide **II.34** with TMAF using Me_3SiCF_2SePh **II.33** as a nucleophile led to the corresponding difluoroselenium alcohols with moderate yields and enantiomeric excess, slightly improved by employing more sterically hindered cinchona alkaloids (**Scheme II.16**).[55]



Scheme II.16. Enantioselective difluoromethylation of aryl aldehydes using $PhSeCHF_2TMS$ as -CHF_2 surrogate

Alternatively, Hu reported the nucleophilic difluoromethylation of aryl ketones by tuning the reactivity of difluoromethyl sulfoximines from electrophilic to nucleophilic difluoromethylating agents. The reaction was performed on diverse aldehydes and ketones to give after desulfoximination the corresponding enantiomerically enriched difluoromethyl secondary and tertiary alcohols in good yields with good diastereoselectivities (**Scheme II.17**).[57]



Scheme II.17. Difluoromethylation of aryl ketones with difluoromethyl sulfoximines

2. Asymmetric synthesis of α-difluoromethyl amines

Nitrogen and fluorine are the most common elements that can be found in medicinal and agrochemical research. Fluorinated amines, especially chiral fluorinated amines, represent a huge interest for chemists nowadays, the combined properties of the amino and fluoroalkyl groups giving these compounds important physical, chemical and biological properties as synthetic building blocks in drug-design. The fact that fluorine lowers the basicity of the amino functionality, decreases acute toxicity, and increases the metabolic

stability of a target drug makes of these compounds excellent candidates for life science applications.

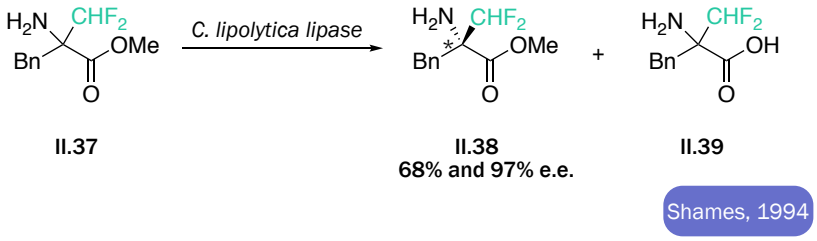
In particular, fluorinated α-amino acids are important in biology due to the enhanced properties they have such as conformational rigidity, metabolic stability, and increased lipophilicity.

Knowing these important changes that can be induced by the fluorinated substituent near the amino moiety, the study of the difluoromethylated amino derivatives was also of great interest for this project.

Some of the reported methods in litterature for the selective synthesis of α–(difluoromethyl)amines will be presented.

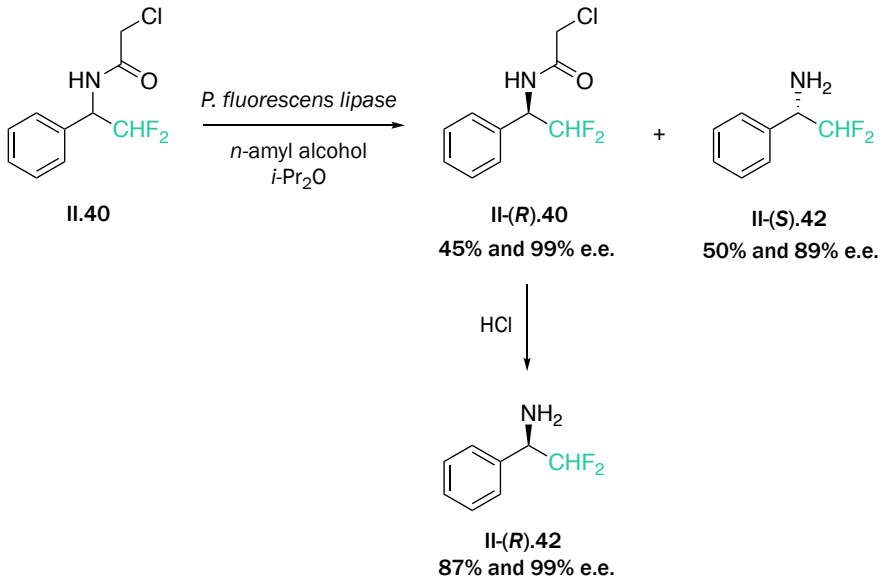
i. Biological kinetic resolutions

Hydrolases are frequently used as kinetic resolution agents in order to access enantiomerically pure compounds. In order to access optically active α-tertiary substituted α-amino acides, Shames used *Candida lipolytica* lipase, a type of serine carboxypeptidase, to perform the resolution of α-tertiary substituted carboxylic esters (**Scheme II.18**).[249] An example of enantioenriched difluoromethyl amine was reported, obtained with a very good enantiomeric excess (97%).



Scheme II.18. Kinetic resolution of α-(difluoromethyl)amine using a lipase

Another enzymatic synthetic pathway was described by Yokogawa, using *Pseudomonas fluorescens* lipase to perform the enantioselective alcoholysis of a series of chloroacetamides.[250] Among these compounds, a difluoromethylated as well as other fluoroalkyl substrates were submitted to these conditions (**Scheme II.19**).



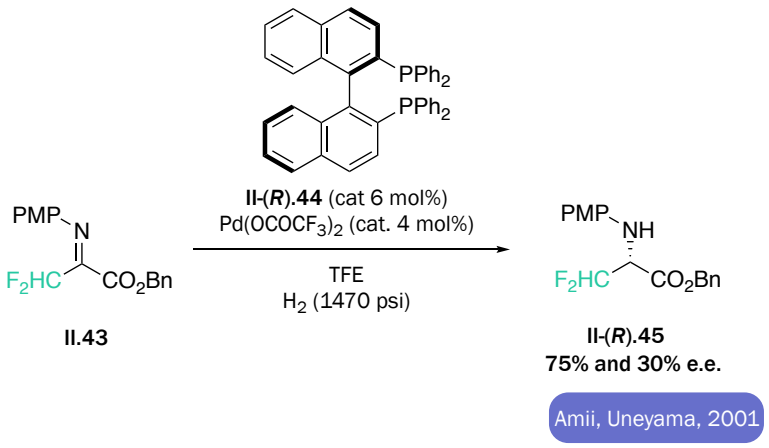
Scheme II.19. Alcoholysis of chloroacetamides to obtain enantiopure difluoromethyl amines

The enantioselectivity of the resolution performed by this lipase was very satisfying. Whereas larger fluorinated substituents favor good enantioselectivities, -CHF_2 proved superior yields when compared to larger fluoroalkyl groups. Moreover, a limitation was found in the case of large-size aromatic rings, where no reaction takes place.

ii. Catalytic enantioselective hydrogenation of imines

A commonly used transformation to access enantioenriched amines is the catalytic hydrogenation of the corresponding substituted imines, with the involvement of a chiral ligand in order to perform the hydrogenation in an enantioselective fashion.

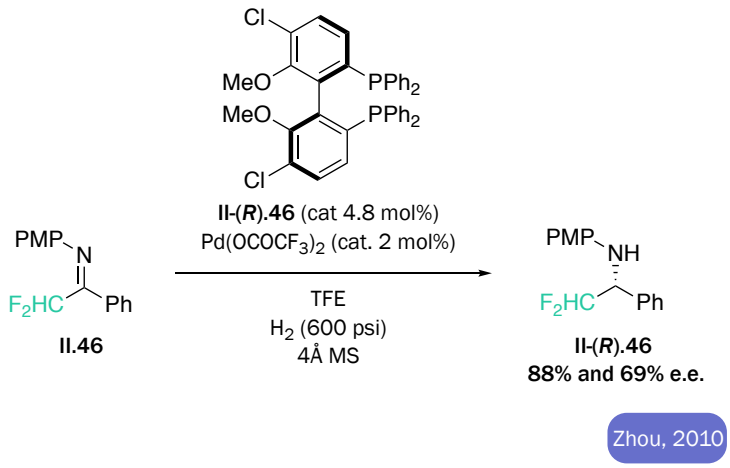
Regarding the hydrogenation of difluorinated imine derivatives, Amii reported the asymmetric hydrogenation of fluorinated iminoesters to obtain fluorinated amino esters (**Scheme II.20**).[251]



Scheme II.20. Catalytic asymmetric hydrogenation of difluoromethyl imines

The use of a Pd-catalytic system with BINAP in weakly nucleophilic and coordinating solvents such as TFE allowed this team to synthesize fluorinated amino ester and by further transformations the corresponding amino alcohols. Unfortunately, the difluoromethyl amine obtained presented a low e.e. of 30%, suspected by the authors to be due to a *E/Z* isomerisation of the starting imines.

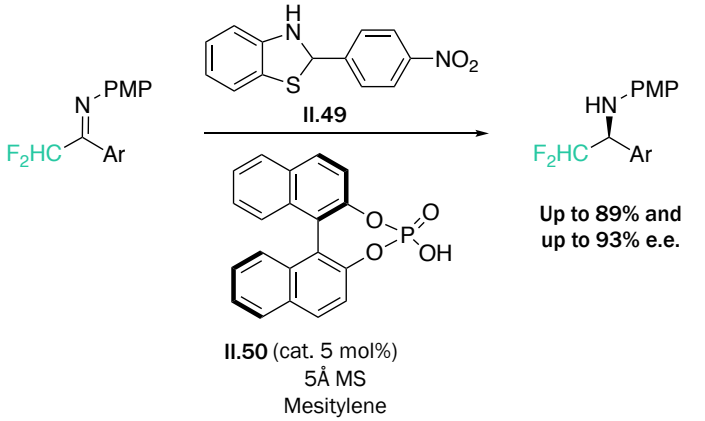
A decade later, Zhou used derivatives of BINAP and BIPHEP, as chiral ligands for the hydrogenation of fluoroalkyl *N*-protected ketimines, obtained directly from the commercially available fluoroalkylated carboxylic acids (**Scheme II.21**).[252] Highly enantioenriched perfluoroalkyl amines were obtained by this Pd-catalyzed asymmetric hydrogenation under mild conditions, and the deprotection of the *p*-methoxyphenyl group is easy performed using CAN.



Scheme II.21. Asymmetric hydrogenation of difluoromethyl imines using chiral BIPHEP as ligand

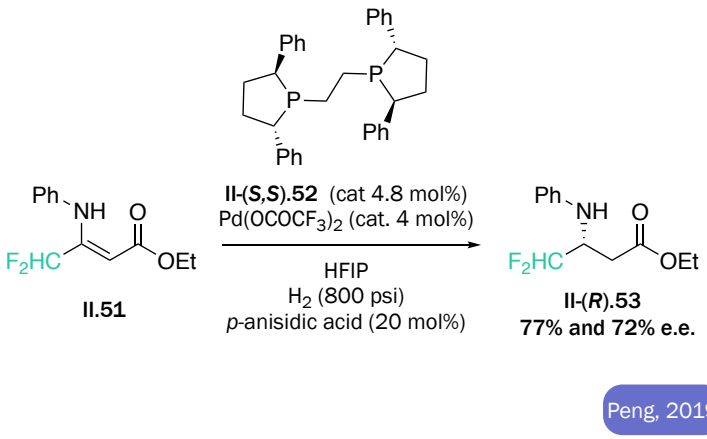
Nevertheless, as in the precedent case, the difluoromethyl derivatives presented lower enantiomeric excess than the other fluorinated groups.

Akiyama used benzothiazolines as hydrogen donor to perform the hydrogenation of ketimines.[253] The combination of these reagents with chiral phosphoric acid as catalysts led to difluoromethyl amines with excellent optical purity (**Scheme II.22**).



Scheme II.22. Hydrogenation of difluoromethyl imines using benzothiazolines

Very recently, Peng developed a new enantioselective palladium-catalyzed hydrogenation of β-aminofluoroalkyl acrylic acids to obtain chiral fluoroalkylated β-amino acids with good yields and high enantioselectivities (**Scheme II.23**).[254] The derivatives obtained could be readily transformed to the corresponding γ-amino alcohols, giving access to interesting difluoromethylated, an other fluoroalkylated, derivatives of biological interest.

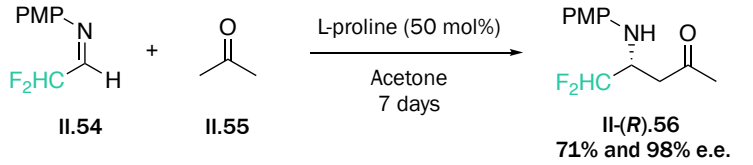


Scheme II.23. Palladium-catalyzed hydrgenation of α–fluoroalkyl amino acrylic acids

iii. Mannich reactions

By analogy with non-fluorinated β-amino acids, a general approach to access fluorinated β-amino acids is the Mannich reaction.

In 2004, Funabiki performed a Mannich reaction catalyzed with proline between polyfluoroalkylated aldimines and acetone (**Scheme II.24**).[255] The corresponding β-amino fluoroalkyl ketones were obtained in high enantioselectivities. Among these amino fluoroalkyl ketones, we can find an example of difluoromethylated amine **II-(R).56** obtained with 98% e.e.

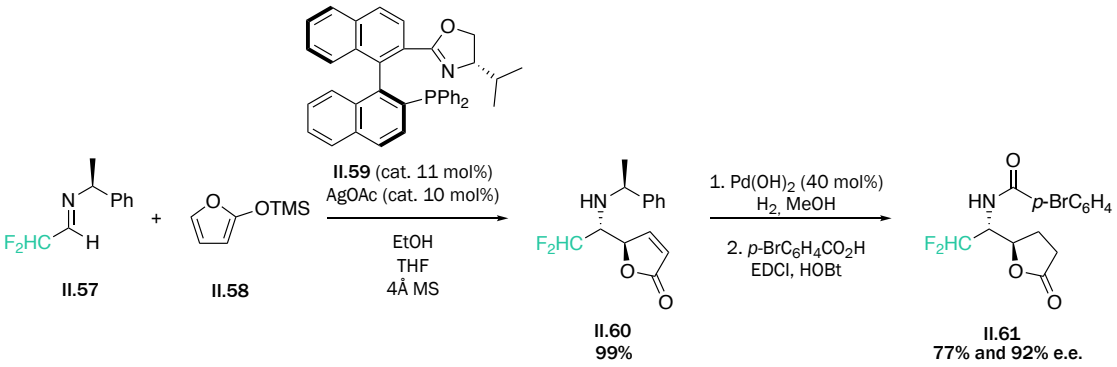


II.54 **II.55** **II-(*R*).56**
71% and 98% e.e.

Funabiki, 2004

Scheme II.24. Mannich reaction catalyzed by L-proline

A few years later, Shi reported a regio- and enantioselective Mannich reaction of fluorinated aldimines with siloxyfurans to afford chiral fluorine-containing butenolide or lactone derivatives (**Scheme II.25**).[256] The use of silver acetate in the presence of a chiral phosphine-oxazoline ligand afforded difluoromethyl amines with good yields and enantiomeric excess.



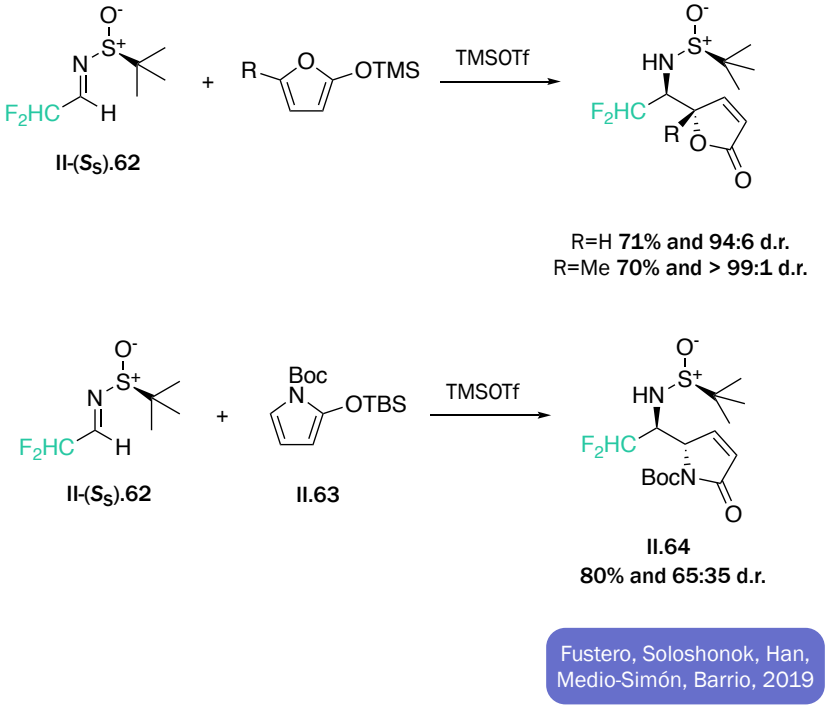
II.57 **II.58** **II.60**
99%
II.61
77% and 92% e.e.

Shi, 2011

Scheme II.25. Synthesis of chiral butenolides or lactones bearing difluoromethyl group

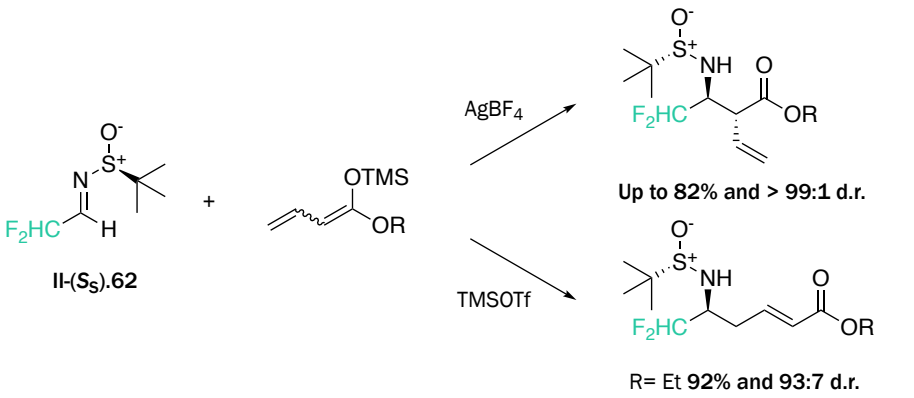
A very recent application of vinylogous Mukaiyama Mannich reactions of furan and pyrrole-derived dienoxysilanes with *N*-sulfinyl fluoroalkylimines was described by Fustero, in which amino fluoroalkyl γ-butenolides and butyrolactams were obtained in good yields and very good regio and diastereoselectivity (**Scheme II.26**).[257] Products of *anti*-configuration were obtained in all cases, as confirmed by X-ray crystallographic analysis.

Furthermore, the use of methyl substituted furane showed that an increase of the steric demand of the butenolide causes a decrease in the yields but an improvement of the asymmetric induction. The same effect was observed with the siloxy pyrrole derivatives. Moreover, the hydrogen bond interaction of the -CHF_2 group and the pyrrole is supposed to have an influence on the reaction, in favor of only one of the adducts. This synthetic pathway gave access to difluoromethyl γ-butenolides with good yield and without loss of optical purityafter deprotection of the sulfinyl moiety, leading to the corresponding hydrochloride salts.



Scheme II.26. Mannich addition of with furane and pyrrole derivatives onto *tert*-butyl sulfinylimines

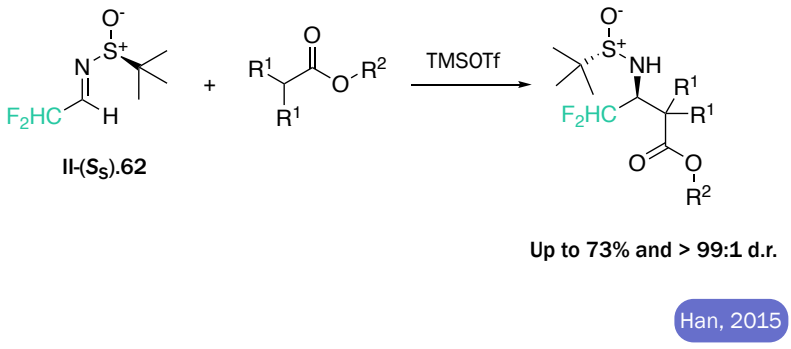
A similar transformation was performed by Qing, to access chiral α-fluoroalkyl amines by a Lewis acid-catalyzed asymmetric addition of silyl dienolates to the difluoroacetaldimines bearing a *tert*-butyl sulfinyl group at nitrogen as a chiral auxiliary (**Scheme II.27**).[258]



Scheme II.27. Addition of silyldienolates to difluoromethyl *tert*-butyl sulfinylimines

After testing Lewis acids such as AgOTf, $Sc(OTf)_3$ or $AgClO_4$ the best results were obtained with $AgBF_4$. Moreover, working a -50 ºC showed an improved regioselectivity when compared to higher temperatures. It is noteworthy that during the optimization, the authors noticed that according to the Lewis acid used, the α-addition product or the γ-product could be exclusively obtained. For instance TMSOTf as the catalyst afforded the γ-addition product with very good yield and d.r., whereas with $AgBF_4$ a series of α-addition products was obtained with up to 82% yields and up to 99:1 d.r.

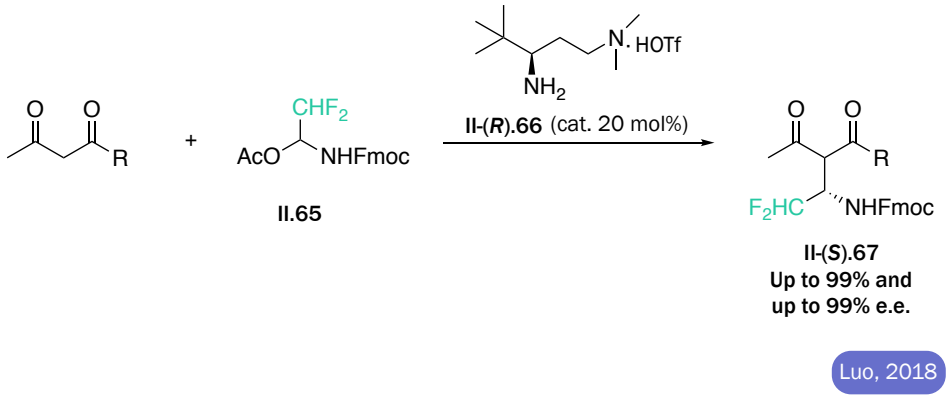
Continuing with the exploration of Mannich reactions to access difluorinated products of high optical purity, Han's group studied the use of Ellman's (*S*)-*tert*-butyl sulfinyl imines bearing -CHF_2, -$CBrF_2$ and -$CClF_2$ groups (**Scheme II.28**).[259] The addition reactions of alkyl acetate-derived enolates to these sulfinylimines led to a range of highly diastereoenriched difluoromethyl amines bearing an ester group that could be further functionalized to the corresponding carboxylic acid, alcohols and other functional groups.



Scheme II.28. Mannich reaction of difluoromethyl-bearing sulfinylimines alkyl acetates

In 2018, Luo reported an asymmetric Mannich type reaction of trifluoro-, difluoro, or trichloro-acetaldimine precursors catalyzed by a chiral primary amine. The reaction worked very efficiently and the authors described an easy purification of the compounds as they precipitated directly from the reaction solution. Pure adducts of high e.e. were obtained after filtration and washing.

The limitation of this method remains on the use of unsubstituted and unsymmetrical diketones, probably due to their easy enolization, as low diastereomeric ratios were obtained (**Scheme II.29**).[260]

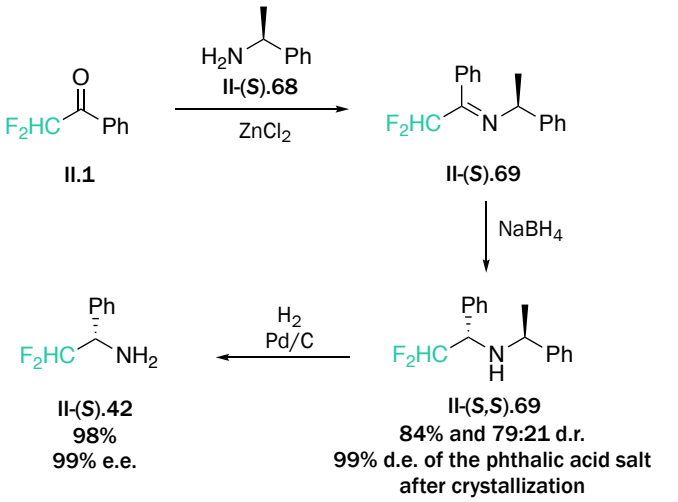


Scheme II.29. Mannich reaction of fluorinated acetaldimines

iv. Transformations of difluoromethyl imines

The synthesis of enantiopure fluoroalkyl, and particularly difluoromethyl derivatives having an amino group caught the attention of several groups, which tried to obtain these compounds from the corresponding fluorinated imines. In the previous part, Mannich reactions of these derivatives were described, however, there are a large number of other transformations of these imines that can also lead to the expected products.

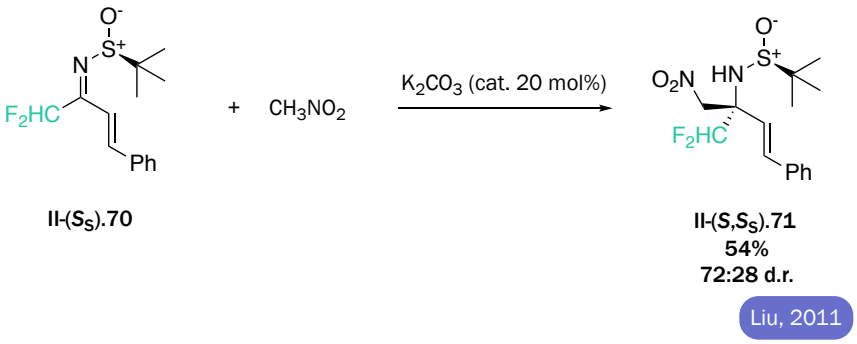
In 2005, Ishii performed the hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)amine derivatives having a difluoromethyl group at benzylic position (**Scheme II.30**).[261] The diastereomeric ratio of the latter could be improved by crystallization of the corresponding salts that also allowed them to confirm the relative configuration of the carbon centers. This group described then the regioselective hydrogenolysis under mild conditions of the benzylic derivatives to obtain the difluoromethyl amine with excellent enantiomeric excess. The authors also noticed the inversion of diastereoselectivity for the reduction of these imines: in fact, the non fluorinated analogues submitted to the same reaction conditions led to the *anti* product whereas the fluorinated compounds led to the *syn* isomer.



Scheme II.30. Hydrogenolysis of bis(α-methylbenzyl)amines bearing a -CHF_2 group

Lately, Liu developed an aza-Henry reaction of chiral fluoroalkyl α,β-unsaturated *N-tert*-butylsulfinyl ketimines in the presence of a basic catalyst.[262] Several bases such as DBU, TBD, DABCO, carbonate salts, KF or TBAF were tested but the best results were obtained with potassium carbonate. Moreover, good yields and diastereoselectivities were obtained with dichloromethane or nitromethane as solvents but due to a faster conversion rate the retained solvent was nitromethane.

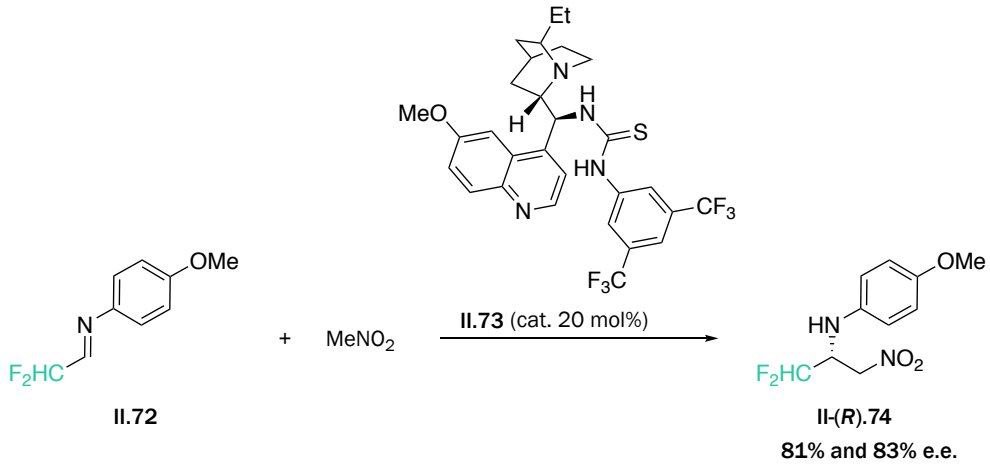
To complete their study, the authors used their optimized conditions on non-fluorinated ketimines and demonstrated the positive influence of the strong electron-withdrawing fluoroalkyl group as no reaction was observed in its absence. Moreover, the transformation of the difluoromethyl β-nitroamines to both fluoroalkylated diamines and fluoroalkylated diamino acids were also performed without losing optical purity (**Scheme II.31**).



Scheme II.31. Aza-Henry reaction of chiral α,β-unsaturated *tert*-butyl sulfinylimines

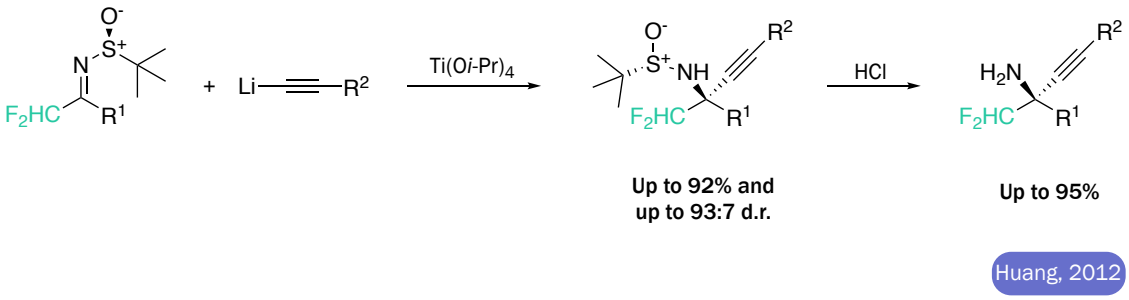
Last year, the same author performed a new asymmetric aza-Henry reaction of fluoromethylated imines catalyzed by cinchona-derived bifunctional thiourea

(**Scheme II.32**).[263] He was able to obtain difluoromethylated β-nitroamines from difluoromethylated imines and nitromethane. The use of cinchona-derived bifunctional thiourea as catalyst under mild conditions gave the corresponding products in good yields and stereoselectivities. The possible transformation of the nitroamines obtained should lead to a range of difluoromethylated compounds such as amines or saturated *N*-heterocyclic bioactive compounds.



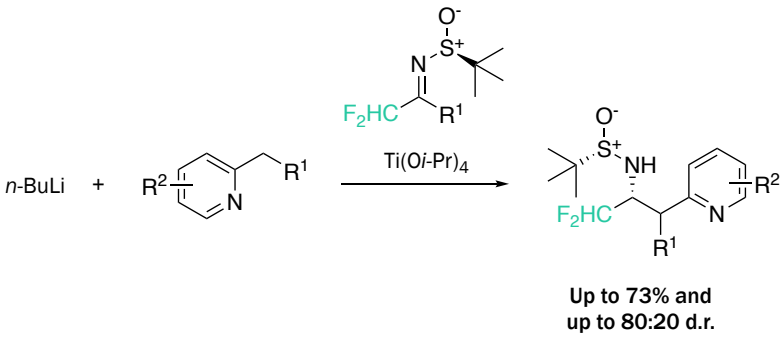
Scheme II.32. Aza-Henry reaction catalyzed by cinchona-derived bifunctional thiourea

Huang also used difluoromethylated Ellman's *tert*-butyl sulfinylimines to obtain propargyl derivatives (**Scheme II.33**).[264] The addition of lithium acetylides in the presence ot titanium isopropoxide led to α-difluoromethyl α-propargylamines with high diastereoselectivity. The *N*-tert-butyl sulfinyl group being readily cleaved under acidic conditions, the corresponding amines were obtained with excellent yields and retention of configuration at the carbon atom.



Scheme II.33. Addition of lithium acetylides to *tert*-butyl sulfinylimines

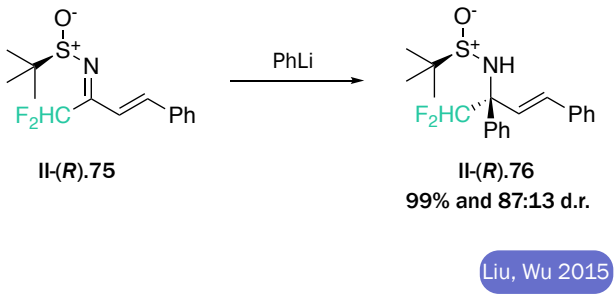
A supplementary example of the use of sulfinyl imines was described by Huang with the attack of these compounds by lithiated 2-alkylpyridines (**Scheme II.34**).[265]



Scheme II.34. Condensation of *tert*-butyl sulfinylimines and 2-alkylpyridines

Good d.r. were obtained with CHF_2 derivatives, but were better in the case of the CF_2-C derivative ones.

Li and Wu performed the addition of a range of organolithium reagents to chiral fluoroalkyl α,β-unstaturated *N-tert*-butanesufinyl ketimines (**Scheme II.35**).[266] They obtained several tertiary α-fluoroalkyl allylic amines and the corresponding amino acids after transformation.



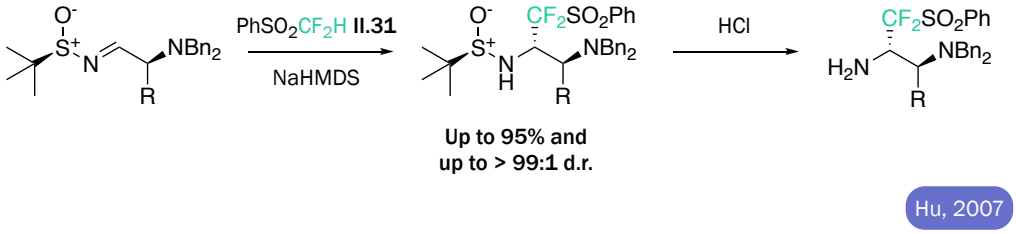
Scheme II.35. Addition of organolithium reagents to α,β-unstaturated *N*-tert-butanesufinyl ketimines

v. Addition of -CHF_2 surrogates to chiral imines

A useful pathway to access difluoromethyl amines of high optical purity is the use of nucleophilic surrogates of –CHF_2 that can be added to a range of chiral imines. *N-tert*-butyl sulfinyl imines have proved to be good substrates for nucleophilic additions of non-fluorinated carbanions, which led Hu's group to study the addition of difluoromethyl anions onto these species.

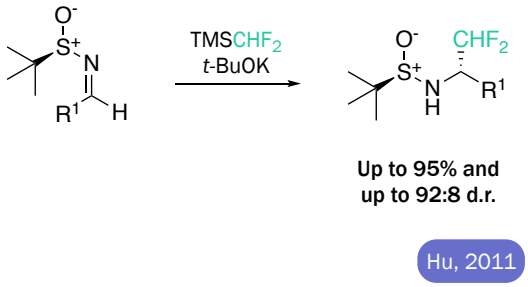
In 2007, Hu reported the addition of difluoromethyl phenyl sulfone to electrophiles, mostly carbonyls, and extended its study to imines.[267] The use of

an enantiopure *tert*-butyl sulfinyl group as chiral auxiliary allowed him to obtain a range of *N*-sulfinyl-α-(sulfonyldifluoromethyl)amines in good yields and excellent diastereomeric ratios (**Scheme II.36**).



Scheme II.36. Addition of difluoromethyl phenyl sulfone to *tert*-butyl sulfinyl imines

Some years later, the same author reported the nucleophilic addition of $TMSCHF_2$ in the presence of a base initiator to the same substrates, namely *N-tert*-butylsulfinyl imines (**Scheme II.37**).[268]



Scheme II.37. Addition of $TMSCHF_2$ to *tert*-butyl sulfinyl imines

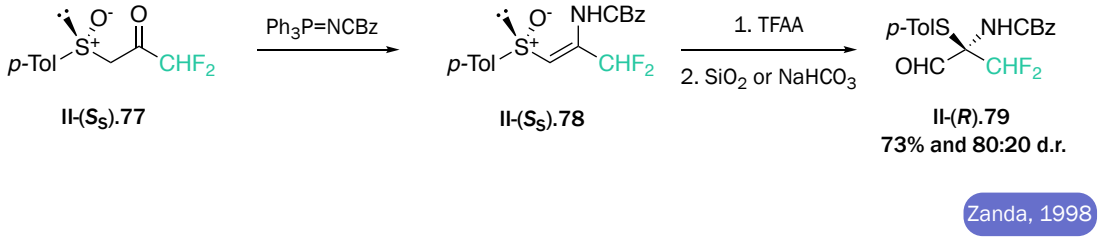
Diverse *N-tert*-butylsulfinyl imines could be efficiently difluoromethylated at low temperature (-78 ºC) giving the corresponding products in good yields and with good diastereoselectivities. However, the authors noticed a slightly lower diastereoselectivity of the reaction when compared to the $-CF_3$ analogues obtained with the Ruppert-Prakash reagent, presumably due to a minor steric hindrance of the $-CHF_2$ compared to $-CF_3$.

vi. Miscellaneous other strategies towards chiral difluoromethyl substituted amines

Two examples following other strategies have been described by Zanda and Van der Donk.

Zanda reported in the late 1990's the use of γ-difluoromethyl β-ketosulfoxides to prepare the corresponding enamines and then enantiopure difluoropyruvaldehyde *N-S*-ketals (**Scheme II.38**).[269] The reaction of an enantiopure γ-difluoromethyl β-ketosulfoxide with *N*-CBz iminotriphenylphosphorane gave α-difluoromethyl β-sulfinyl enamines that

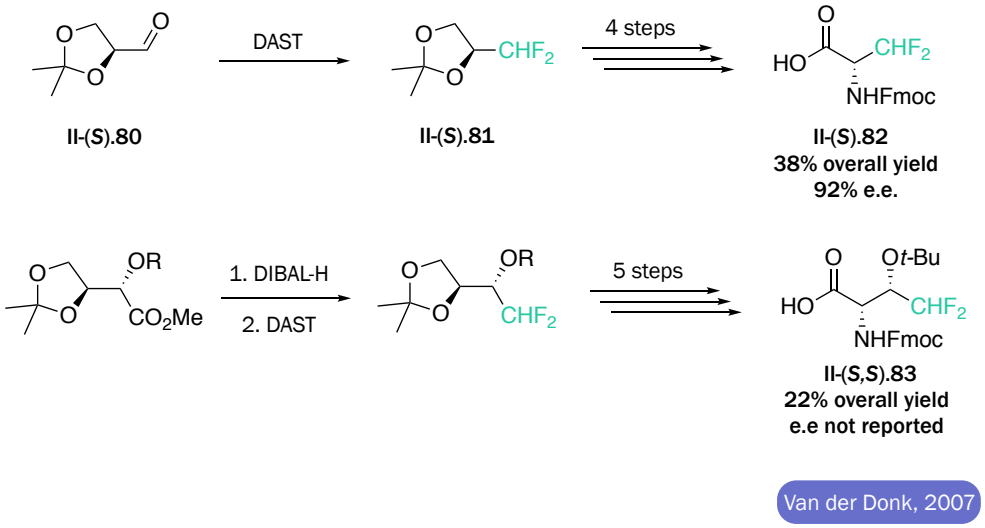
can be submitted to a Pummerer reaction and led to the expected enantiopure difluoropyruvaldehyde *N*-*S*-ketals.



Scheme II.38. Preparation of enantiopure difluoropyruvaldehyde *N*-*S*-ketals

Moreover, these compounds could be transformed by addition of Grignard reagents onto to the aldehyde group to obtain the corresponding optically enriched carbinols bearing a phenylthio group. Finally, the latter could be removed to obtain the sulfur free β-amino-γ-difluoro alcohols. This strategy is thus based on the combined stereodirecting properties of an arenesulfinyl group, a monoprotected amino group, and a fluoroalkyl group.

In the last decade, an alternative synthesis was described by Van der Donk using L-ascorbic acid as a chiral starting precursor to synthesize two difluorinated protected amino acids: β-difluoroalanine and γ-difluorothreonine (**Scheme II.39**).[270]

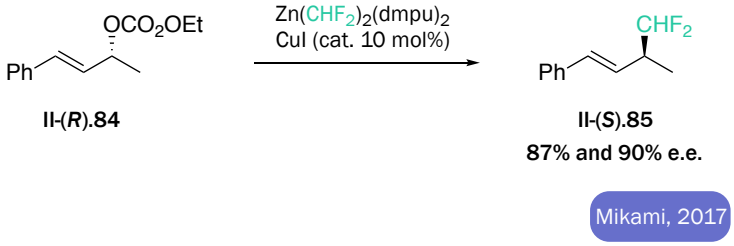


Scheme II.39. Preparation of enantiopure difluoromethyl aminoacids

The aldehydes or esters derived from L-ascorbic acid were difluorinated with diethylamino sulfurtrifluoride (DAST). After 4 or 5 synthetic steps performed on these derivatives consisting in protecting the O-R groups, then in transforming them to the corresponding azides, a final reduction step gave access to the amines without loss of stereochemical purity.

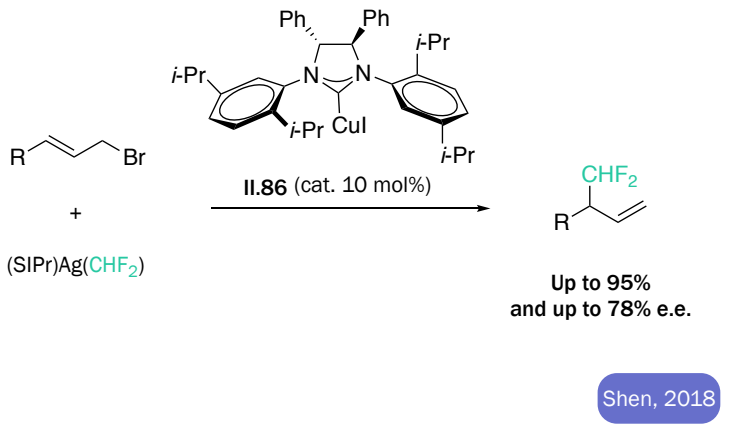
3. Selective introduction of a –CHF_2 group onto a carbon not leading to alcohol or amine derivatives

Among the large number of methods to introduce a difluoromethyl group into a carbon atom that have been intensively developed,[271–273] only a few examples deal with the formation of a CHF_2-bearing carbon stereocenter not substituted by oxygen or nitrogen. An allylic difluoromethylation with (difluoromethyl)zinc was reported three years ago by Mikami illustrating the obtention of a highly enantioenriched β-allyl difluoromethyl compound (**Scheme II.40**).[187]



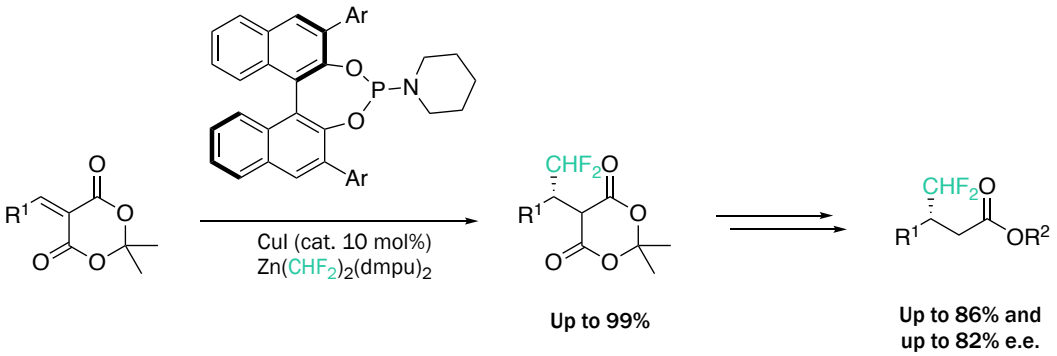
Scheme II.40. Enantioselective allylic difluoromethylation using a zinc complex

Then silver reagents were reported by Shen to afford difluoromethylated sp^3 carbon centers from derivatives of cinnamyl bromide. The use of a chiral copper complex gave the β-difluoromethylated products with good yields, β-selectivities and moderate enantiomeric ratios (**Scheme II.41**).[274]



Scheme II.41. Addition of silver difluoromethylated complexes to cinnamyl bromides

As the most recent example, last summer Mikami presented the difluoromethylation of arylidene Meldrum's acids, being Michael acceptors, with (difluoromethyl)zinc reagent catalyzed by a chiral phosphoramidite-copper complex (**Scheme II.42**).[275]



Scheme II.42. Dilfuoromethylation of arylidene Meldrum's acids with a (difluoromethyl)zinc complex

The obtained products can be easily hydrolyzed and then be transformed to the corresponding β-difluoromethyl esters and further derivatives.

b. Strategy of the project

The examples of enantioselective difluoromethylation by controlling the Csp^3 stereogenic carbons are quite limited, which highlights the need to develop efficient and selective synthetic pathways of selective introduction of the -CHF_2 groups.

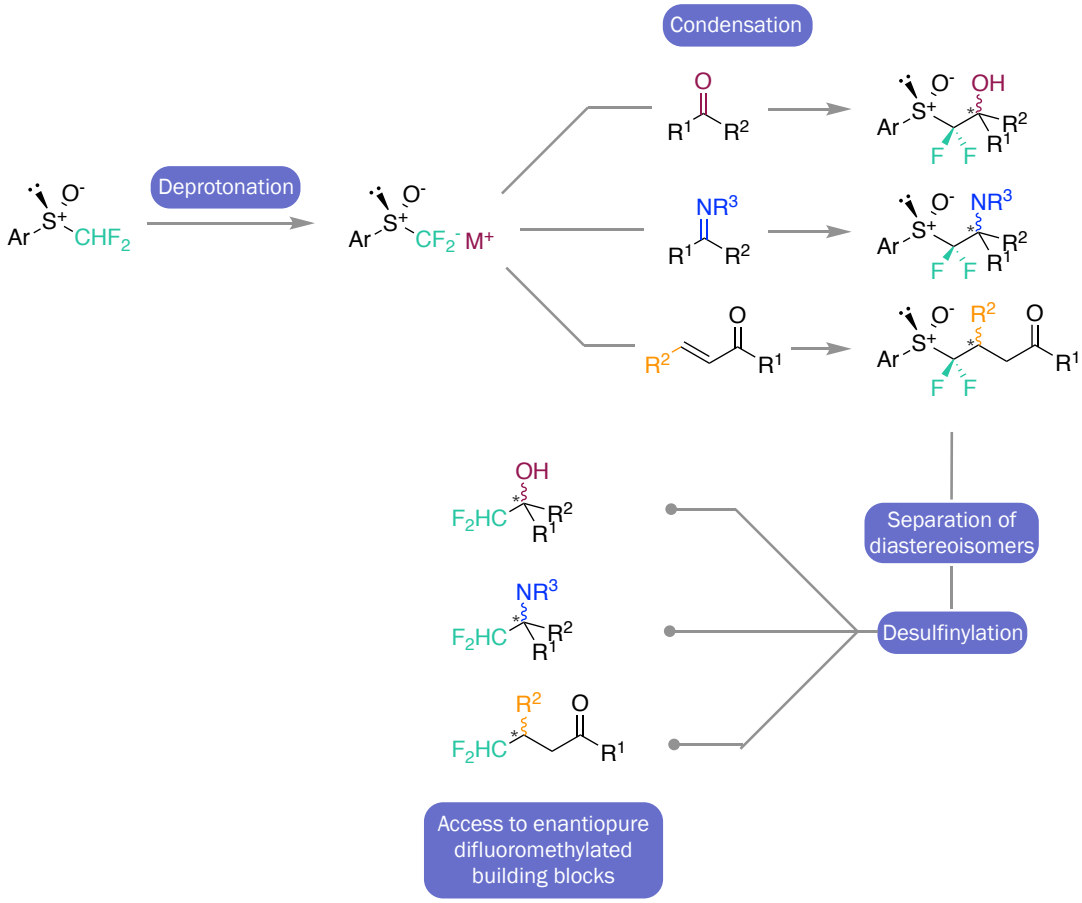
As it was described in the previous part, several methods have been devised since the 1990's to access difluoromethyl alcohols, amines or allyl species with good yields and enantiomeric excesses. Nevertheless, these strategies are quite substrate dependent. The stereoselectivity is mostly induced by the substrate itself, making these methodologies less generalizable.

The objective of this PhD project was to develop a new efficient and stereoselective strategy to introduce the difluoromethyl group in a range of electrophiles. The use of sulfoxides in asymmetric transformations has been highlighted in the second chapter, and their ability as powerful chiral inductors inspired us to develop a methodology involving enantiopure difluoromethyl sulfoxides.

As it was described in the previous chapter, a quest towards enantiopure difluoromethyl sulfoxides took place and thanks to the expertise of the group in the synthesis of enantiopure sulfoxides, we were able to access highly optically pure difluoromethyl sulfoxides.

The subsequent deprotonation of enantiopure difluoromethyl sulfoxides and reaction with electrophiles such as carbonyls, imines or α,β-unstaturated derivatives is proposed in order to obtain diastereomerically pure derivatives that after removal of the chiral auxiliary give access to optically active difluoromethyl products. The freshly created difluoromethyl-containing

fragment can then be transferred to a large number of scaffolds of pharmaceutical interest (**Scheme II.43**).



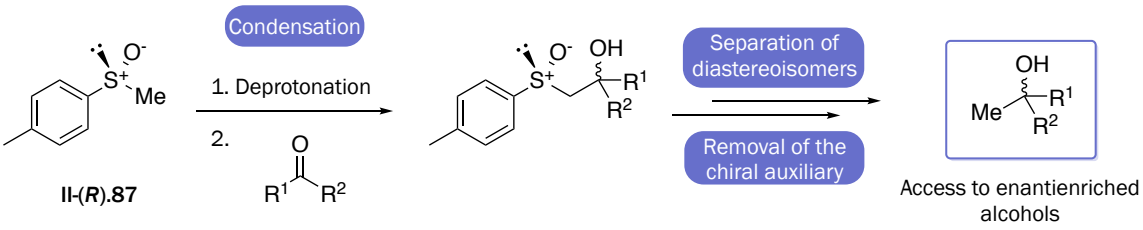
Scheme II.43. Strategy to access enantiopure difluoromethyl scaffolds of high optical purity

B. Access to difluoromethyl alcohols by means of difluoromethyl sulfoxides

a. Condensation of difluoromethyl *p*-tolyl sulfoxide on carbonyls

1. State of the art: non-fluorinated series

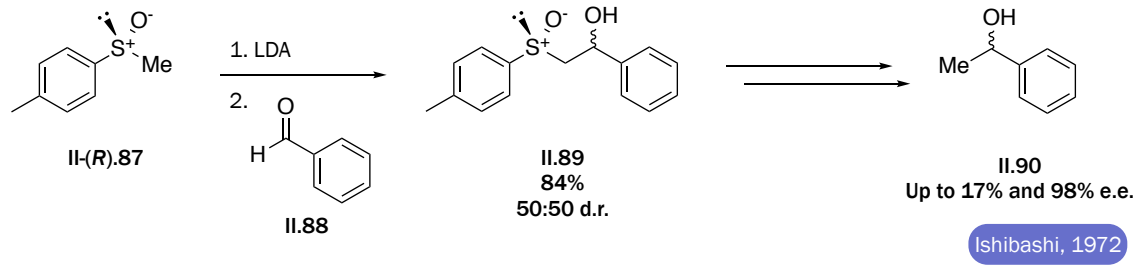
One of the numerous pathways that have been used to synthesize chiral alcohols involves enantiopure sulfoxides as chiral inductors, by carrying out the condensation of an aryl or alkyl methyl sulfoxide onto carbonyls. The obtention of either a highly diastereomerically pure sulfinyl alcohol or a separable mixture of sulfinyl alcohols allowed to obtain a library of enantiopure alcohols after removal of the chiral auxiliary (**Scheme II.44**).



Scheme II.44. Condensation of chiral sulfoxides to carbonyls to access enantioenriched alcohols

Several optimizations took place all over the years in order to have a better understanding of the parameters that impact the diastereoselectivity of the reaction, such as the substituents of the electrophiles, the substituents of the chiral auxiliary as well as the bases and additives involved. A non-exhaustive summary of these methods will be described in this section.

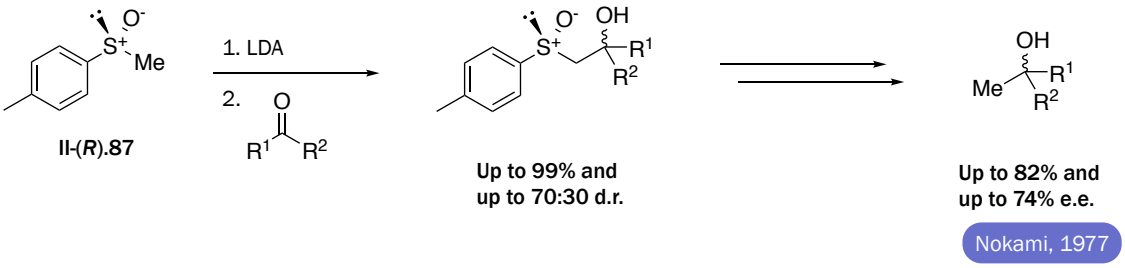
In 1972, Ishibashi reported the condensation of an α-sulfinyl carbanion onto carbonyls to obtain optically active alcohols (**Scheme II.45**).[166]



Scheme II.45. First reported condensation of methyl *p*-tolyl sulfoxide onto benzaldehyde

He used LDA to deprotonate methyl *p*-tolyl sulfoxide and by condensation onto benzaldehyde followed by separation of diastereomers and removal of

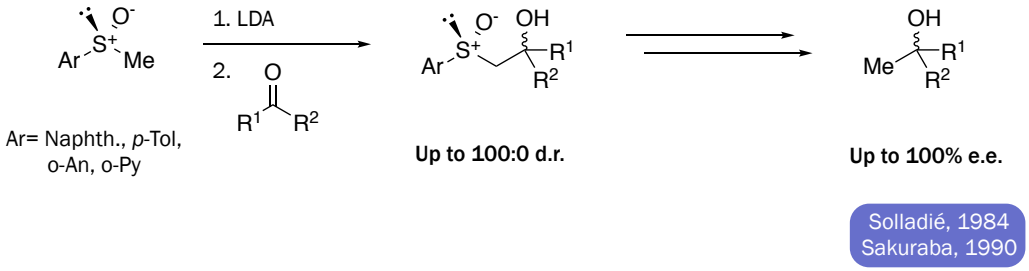
sulfoxides, 1-phenyl ethanol could be ontained with up to 98% e.e. The generalization of this reaction was studied by other groups, among them Nokami, who used different ketones as electrophiles (**Scheme II.46**).[276]



Scheme II.46. Extension of addition of methyl *p*-tolyl sulfoxide to ketones

However, no significant diastereoselectivity was noticed when using different substituents in the carbonyl. Indeed, the maximum d.r. that was obtained was of 70:30. His group succeeded to obtain enantioenriched alcohols up to 74% e.e. after separation of the diastereoisomers of sulfinyl alcohols.

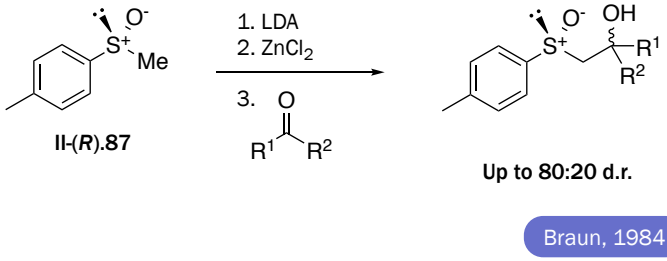
In order to optimize the diastereoselectivity of the reaction, the influence of the substituents of the chiral sulfoxide was studied independently by Solladié[277] and Sakuraba[278] groups (**Scheme II.47**). The evaluation of *p*-tolyl, *o*-anysil, *o*-pyridyl and naphtyl substituents was performed. In fact, in the presence of a supplementary coordination site to the metal (in this case lithium) of the base, better diastereoselectivities were obtained.



Scheme II.47. Condensation of a range of aryl methyl sulfoxides onto aldehydes and ketones

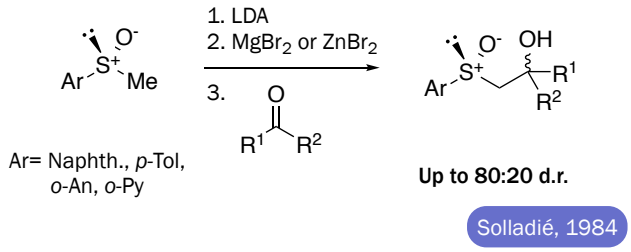
The *o*-pyridyl-bearing sulfoxide gave d.r. up to 80:20, and the naphthyl-bearing one gave a full diastereoselectivity, giving access to an optically pure alcohol after removal of the chiral auxiliary, without needing diastereomers separation.

A final parameter evaluated regards the influence of the carbanion formed. In 1984, Braun studied the influence of the counterion of sulfinylmethanide. He performed the condensation of (R_S) methyl *p*-tolyl sulfoxide deprotonated by LDA and submitted it to a transmetallation of lithium with zinc chloride to obtain the zinc reagent (**Scheme II.48**).[279]



Scheme II.48. Study of the influence of the counterions on the condensation of methyl *p*-tolyl sulfoxide onto carbonyls

In complement to these results, Solladié also studied the influence of coordination additives in this reaction (**Scheme II.49**).[277] The addition of magnesium bromide did not have an important impact, as the diastereomeric ratio was still 50:50. However, they noticed that when using zinc bromide prior to condensation reactions, they could have a slight improve of the diastereoselectivity.

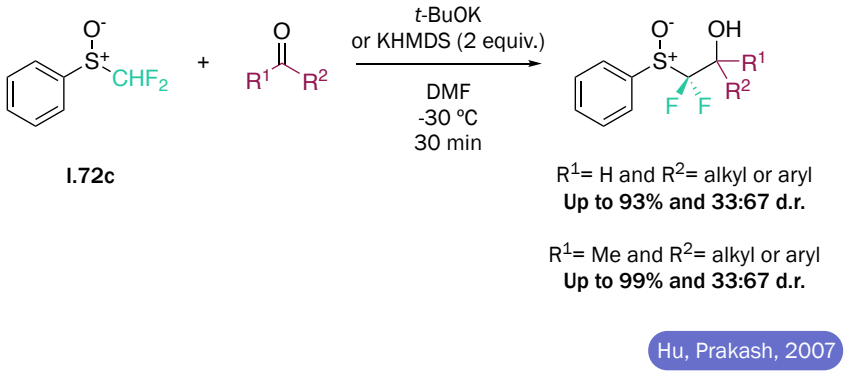


Scheme II.49. Addition of chelating agents in the condensation of methyl *p*-tolyl sulfoxide onto carbonyls

In non-fluorinated series, the condensation of sulfinyl carbanions to carbonyls showed low selectivities to obtain the corresponding sulfinyl alcohols. A separation of diastereoisomers is even though possible, in order to access after removal of the chiral auxiliary, to the enantioenriched alcohols. Several parameters can be taken into account such as the substituents of the chiral auxiliary, of the carbonyls, as well as the employed base and additives to allow better results. In view of these precedents, the group aimed to study the application of this condensation this time starting from difluoromethylated sulfoxides in order to access highly optically enriched difluoromethyl alcohols.

2. Preliminary inspiration from fluorinated series

In 2007, Hu and Prakash studied the condensation of a racemic difluoromethyl phenyl sulfoxide onto aldehydes and ketones.[226] The use of *t*-BuOK or KHMDS as the corresponding base allowed this research group to obtain a library of α-difluoro β-hydroxysulfoxides (**Scheme II.50**).

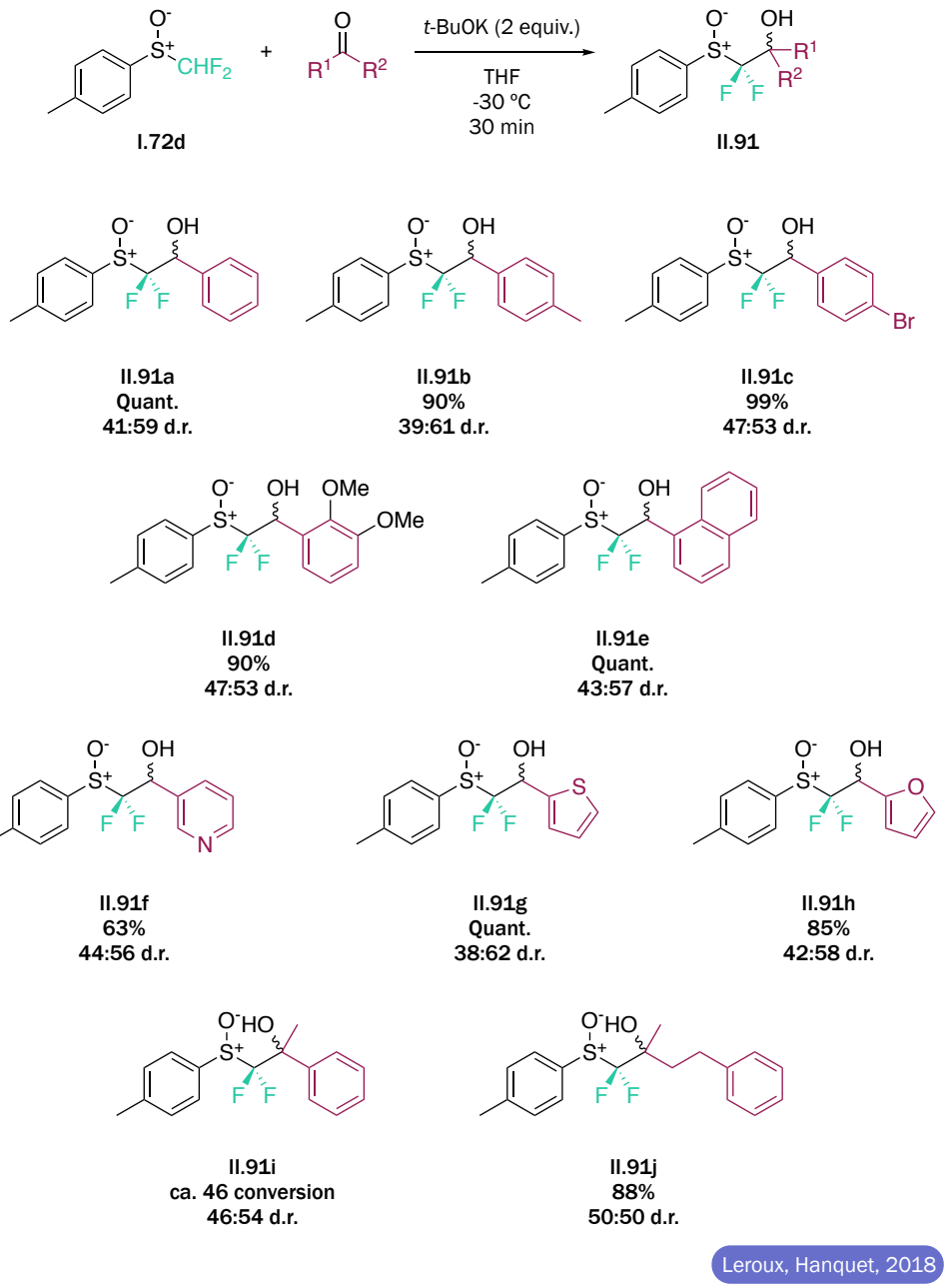


Scheme II.50. Condensation of racemic difluoromethyl phenyl sulfoxide onto carbonyls

3. Work performed in the group

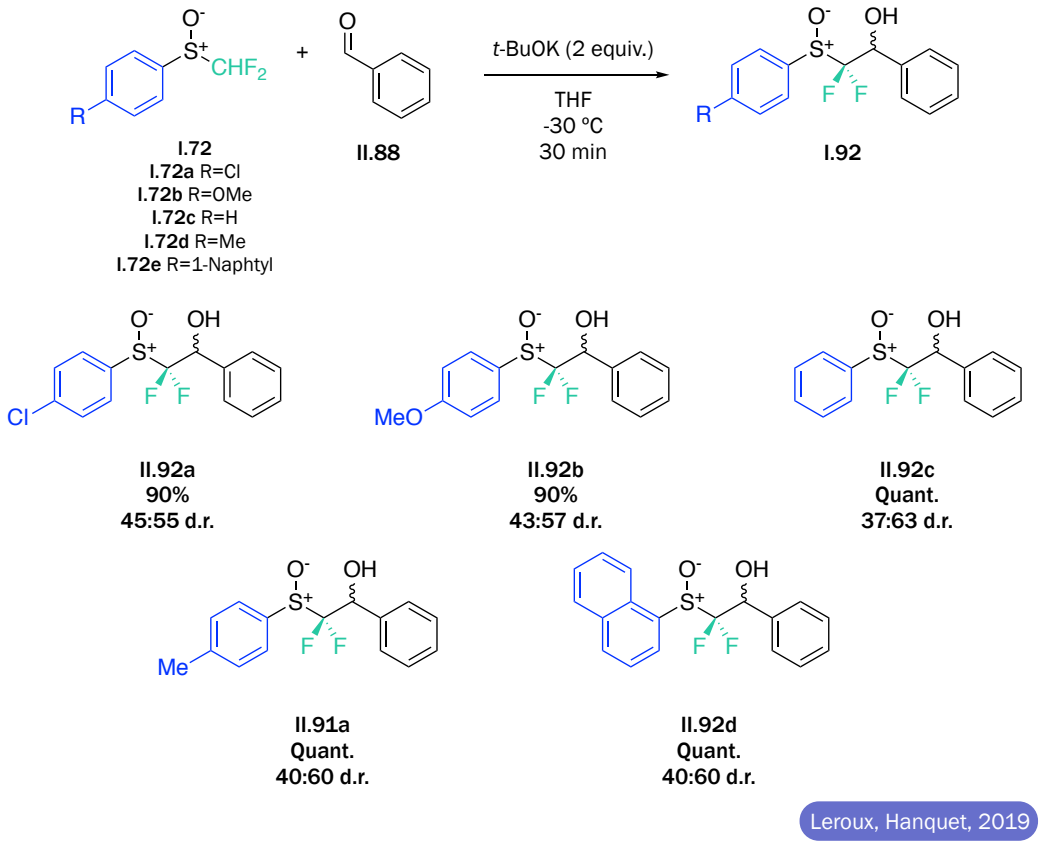
Performed by Chloé Batisse, PhD.

The starting point of our study on the condensation of difluoromethyl *p*-tolyl sulfoxide onto carbonyls was the results presented by Hu and Prakash described in the previous paragraph. In contrast to their method, it was decided to use THF in DMF as a safer an eco-friendlier solvent.[280] The desired products, as expected, were obtained in high yields (up to 99%) but with low diastereoselectivities (up to 38:62) as shown in **Scheme II.51**. A study to improve this diastereoselectivity had therefore to be carried out.



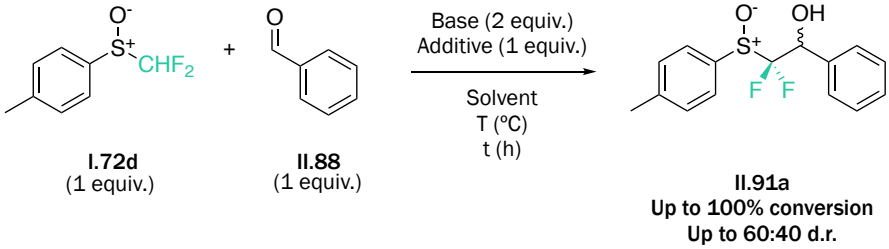
Scheme II.51. Substrate scope in addition of difluoromethyl *p*-tolyl sulfoxide to carbonyls using *t*-BuOK as base

Different aryl sulfoxide derivatives were synthesized and then tested to evaluate their influence on the diastereomeric ratios of α-difluoro-β-hydroxysulfoxides.[65] Five different sulfoxides were synthesized according to the procedure that was developed in our group and slightly better diastereomeric ratios were observed when the phenyl, *p*-tolyl and 1-naphthyl derivatives were used (respectively 37:63, 40:60 and 40:60) in comparison to the *p*-chloro and *p*-methoxy derivatives (respectively 45:55 and 43:57). Regrettably, no major improvement could be observed even by increasing the temperature (**Scheme II.52**).



Scheme II.52. Study of the influence of the aromatic substituent in aryl difluoromethyl sulfoxides in the condensation onto benzaldehyde

Then, an investigation by studying the effect of adding coordinating agents to the medium was carried out (**Scheme II.53**).

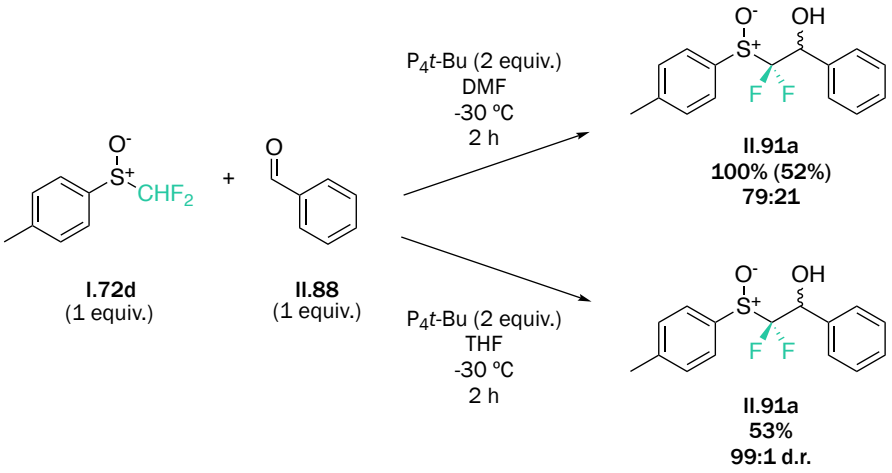


Scheme II.53. Study of the influence of chelating additives in the condensation reaction

$BF_3.OEt_2$, $Sc(OTf)_3$ were added but did not give any conversion of the starting sulfoxide into the expected product. In the presence of $TiCl_4$ or $ZnCl_2$ it was possible to get the desired α-difluoro-β-hydroxysulfoxides could be obtained but no improvement on the diastereoselectivities was observed. The use of crown ether (2,3,11,12-tetracarboxylate-substituted 18-crown-6) able to complex the potassium cation coming from the inorganic base was also tested, but the conversion was low and the diastereomeric ratio was unchanged.

The next step consisted in screening different bases in order to evaluate their impact on the diastereoselectivity of the synthesis of α-difluoro-β-hydroxysulfoxides. When using potassium *tert*-butoxide the conversion into the desired α-difluoro-β-hydroxysulfoxide was quantitative in either DMF or THF after 40 min of reaction at -30 ºC, but with low d.r. The same kind of results was observed with KHMDS, or KHMDS in presence of 18-crown-6 (18-C-6), with the unfortunate formation of side-products as well. The diastereomeric ratios obtained when using LiHMDS were similar to the ones that were usually obtained (*ca.* 6:4). By using 12-crown-4 (12-C-4) to complex the lithium cation, conversions were less interesting and the diastereomeric excesses still low. Sodium hydride was also tried and a full conversion but poor diastereoselectivity were observed.[65]

Finally, and as described in one of the publications of our group, Schwesinger's superbase, P$_4$*t*-Bu was tested and gave very good results. Total conversions of the starting sulfoxide were observed and diastereomeric excesses up to 98% were reached (**Scheme II.54**).[64]



Scheme II.54. Highly diastereoselective difluoromethylation reaction using Schwesinger's superbase

In this case, the non-coordinating counterion [P$_4$*t*-Bu/H]$^+$ was used as an attempt to increase the nucleophilicity of the anion of difluoromethyl *p*-tolyl sulfoxide **I.72d**. The attack of the sulfoxide carbanion onto the carbonyl expected to be faster, in contrast to the cases involving other cations such as Li^+, K^+ or Mg^{2+}, the carbonyl derivatives would keep a close-to-planar C-sp^2 geometry in the transition state, rather than a generally more favored C-sp^3-like tetrahedral geometry. A better chirality transfer from the sulfoxide to α-difluoro-β-sulfinyl alcohol was first expected.

A ^{19}F NMR monitoring of the conversion of sulfoxide over time was conducted with 1 and 2 equivalents of superbase (**Figure II.1**) in order to determine the quantity of superbase required and the reaction time needed to achieve full conversion.

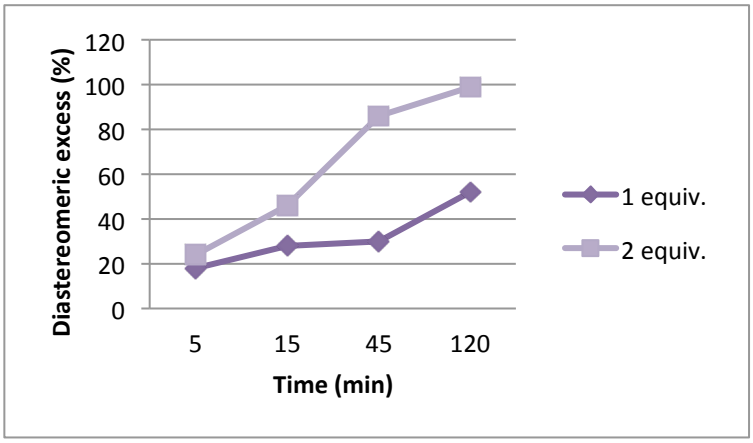
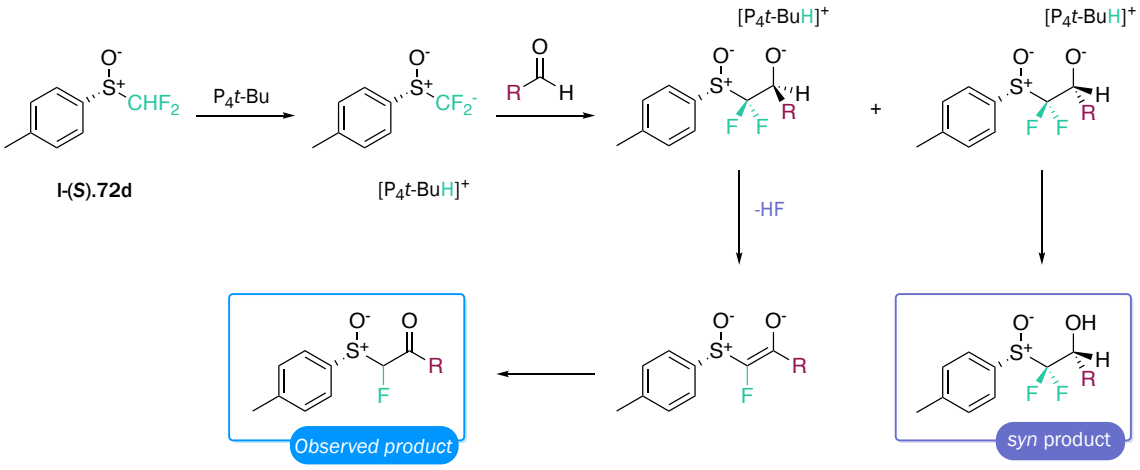


Figure II.1. Evolution of the diastereomeric ratio of the reaction over time using P_4*t*-Bu as the base

A full conversion was observed after 5 min in both cases. The diastereomeric excesses were also measured on ^{19}F NMR spectra after 5, 15, 45 and 120 min. Interestingly, the NMR spectra analyses showed increasing diastereoselectivities over time. A perfect diastereoselectivity was observed after 2 h of stirring at -30 ºC. When one equivalent was used, the diastereoselectivity was much lower after 2 h (52%).

This study implied a kinetic resolution, where one diastereoisomer of the intermediate alcoholate would preferably lead to the subsequent formal elimination of HF and formation of the corresponding α-monofluoro-β-ketosulfoxide, observed on NMR spectra of the crude mixtures (**Scheme II.55**).

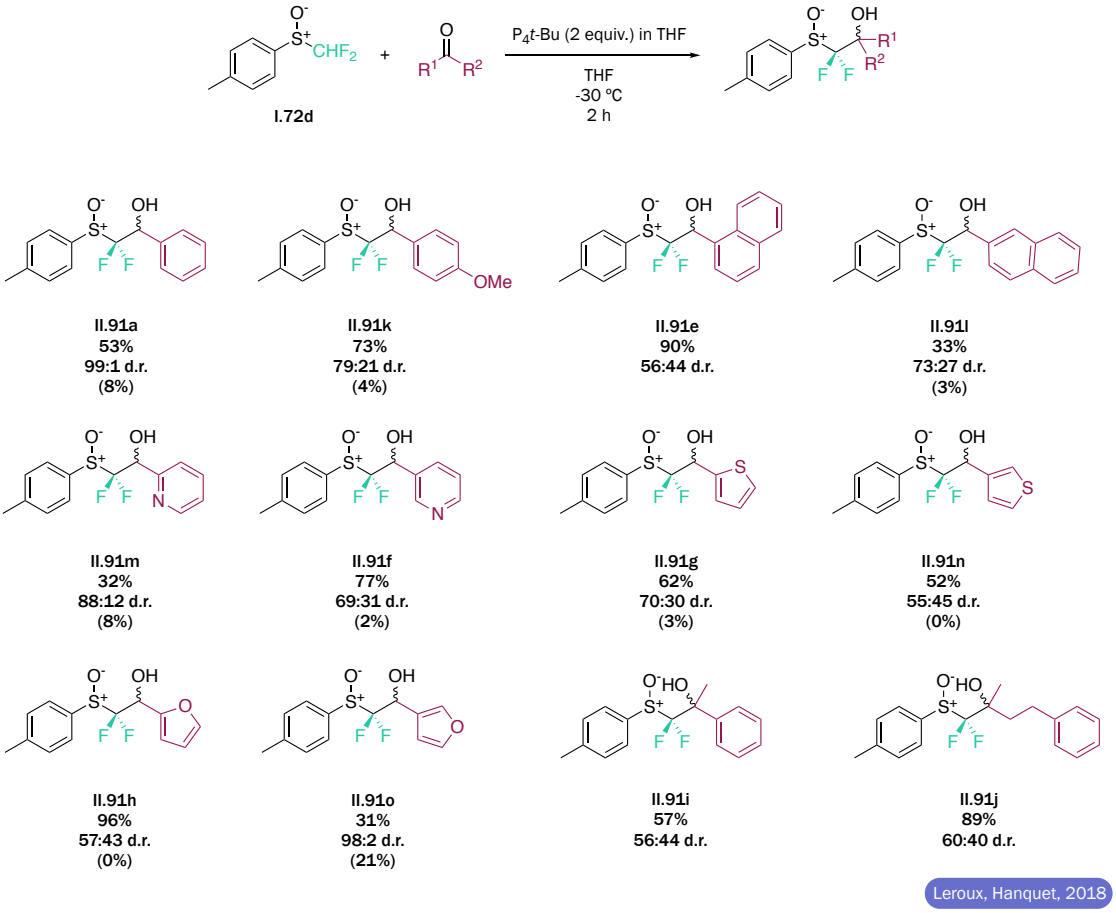


Scheme II.55. Hypothetical mechanism explaining good diastereoselectivities obtained in the condensation of difluoromethyl *p*-tolyl sulfoxide onto aldehydes

The relative *syn* configuration of the majoritary product could be determined by analogy to the X-Ray analysis obtained for the corresponding *anti* product, as detailed in *part c* of this section concerning the synthesis of α-difluoro-β-ketosulfoxides.

Such high diastereomeric ratios were not observed in the case of LiHMDS or *t*-BuOK as bases, which might be due to their lower basicity (respective pK_a values: 29.5 and *ca.* 30 in DMSO for the *t*-BuOH/*t*-BuO$^-$ couple) compared to P_4*t*-Bu (pK_a value of 30.3 in DMSO) for the C-deprotonation of the carbinol.[281,282]

A screening on different aromatic, heteroaromatic and aliphatic aldehydes and ketones was then performed using the optimised conditions. Interestingly, in some cases the diastereoselectivities obtained were very good, and in others quite low; moreover diastereoselectivities and yields were never simultaneously high (**Scheme II.56**).



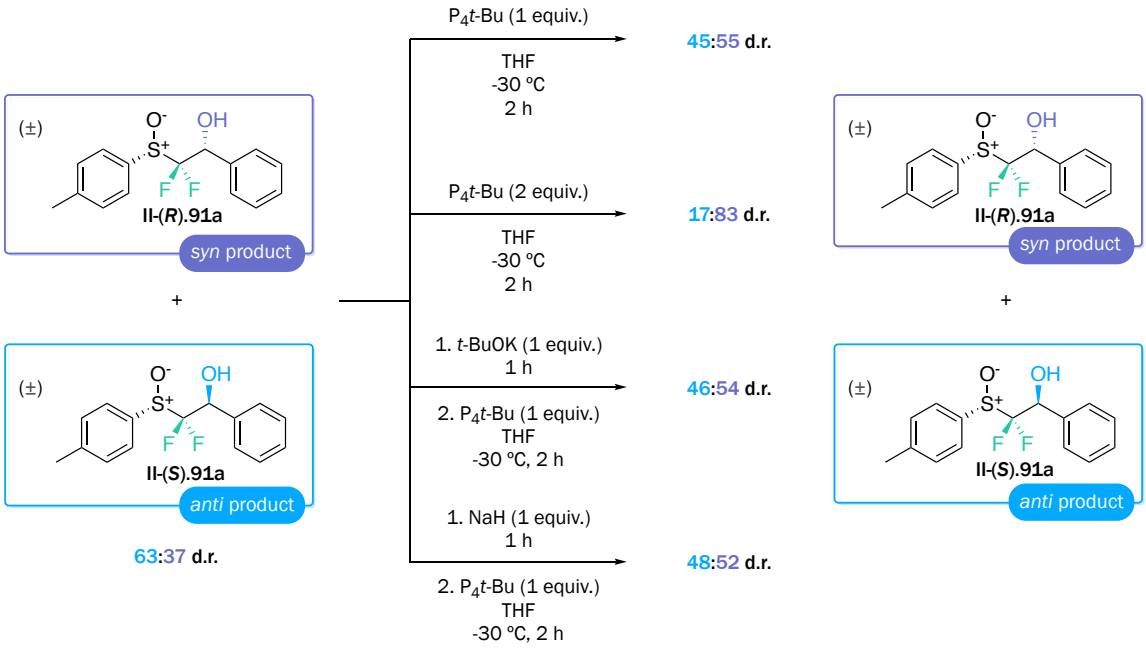
Scheme II.56. Substrate scope in the addition of difluoromethyl *p*-tolyl sulfoxide onto carbonyl compounds when using P_4*t*-Bu as the base

Moreover, the crude ^{19}F NMR spectra showed good d.r. and also revealed the presence of the corresponding α-fluoro-β-ketosulfoxides (presented in brackets). This supported the hypothesis that the obtention of better d.r. is related to the formation of these side products, combined to the fact that when ketones were used as electrophiles, diastereoselectivities were low, the generated α-difluoro-β-hydroxysulfoxides not having an hydrogen to be deprotonated. Moreover, the moderate yields associated to the good diastereoselectivities of the obtained difluoromethyl sulfinyl alcohols corroborate this assumption.

4. Complementary mechanistic investigations

In order to complement this study, we performed some experiments to investigate the effect of P_4*t*-Bu on the diastereoselectivity of the condensation of difluoromethyl *p*-tolyl sulfoxide onto carbonyls. A model α-difluoro-β-sulfinyl alcohol **II.91a**, synthesized from the addition of difluoromethyl *p*-tolyl sulfoxide to benzaldehyde after deprotonation with *t*-BuOK, was needed as starting point. This product was obtained with a diastereomeric ratio of 63:37, in favor to the *anti* product. The determination of configuration will be described later in this chapter. **II.91a** was placed under the nucleophilic addition conditions: -30 °C in THF. The series of tests consisted in adding one or two equivalents of superbase to the medium and observe the evolution of the diastereomeric ratio after two hours, time usually used for this reactions. Moreover, to define if the two equivalents of the superbase are required, the first deprotonation of the hydroxy function with one equivalent other reagents was tried: *t*-BuOK and a hydride, being NaH in this case. Indeed, the need for 2 equivalents of P_4*t*-Bu rather than just one to obtain a higher d.r. could be ascribed to a deprotonation of the benzylic proton, i.e. the one in α-position to the $-CF_2$ motif, in the intermediate sulfinyl alcoholate by the second equivalent of superbase. This proton requires a high basicity of the reagent, a criterion that might not be met by *t*-BuOK, KHMDS or other bases.

The second step to try to confirm or disprove our hypothesis would be the addition of one supplementary equivalent of phosphazene superbase, which should be basic enough for the further deprotonation of the intermediate alcoholate. The results obtained with these experiments are reported in **Scheme II.57**.



Scheme II.57. Complementary trials involving the diastereoselective evolution of α-difluoro-β-sulfinylalcohols in the presence of P_4*t*-Bu

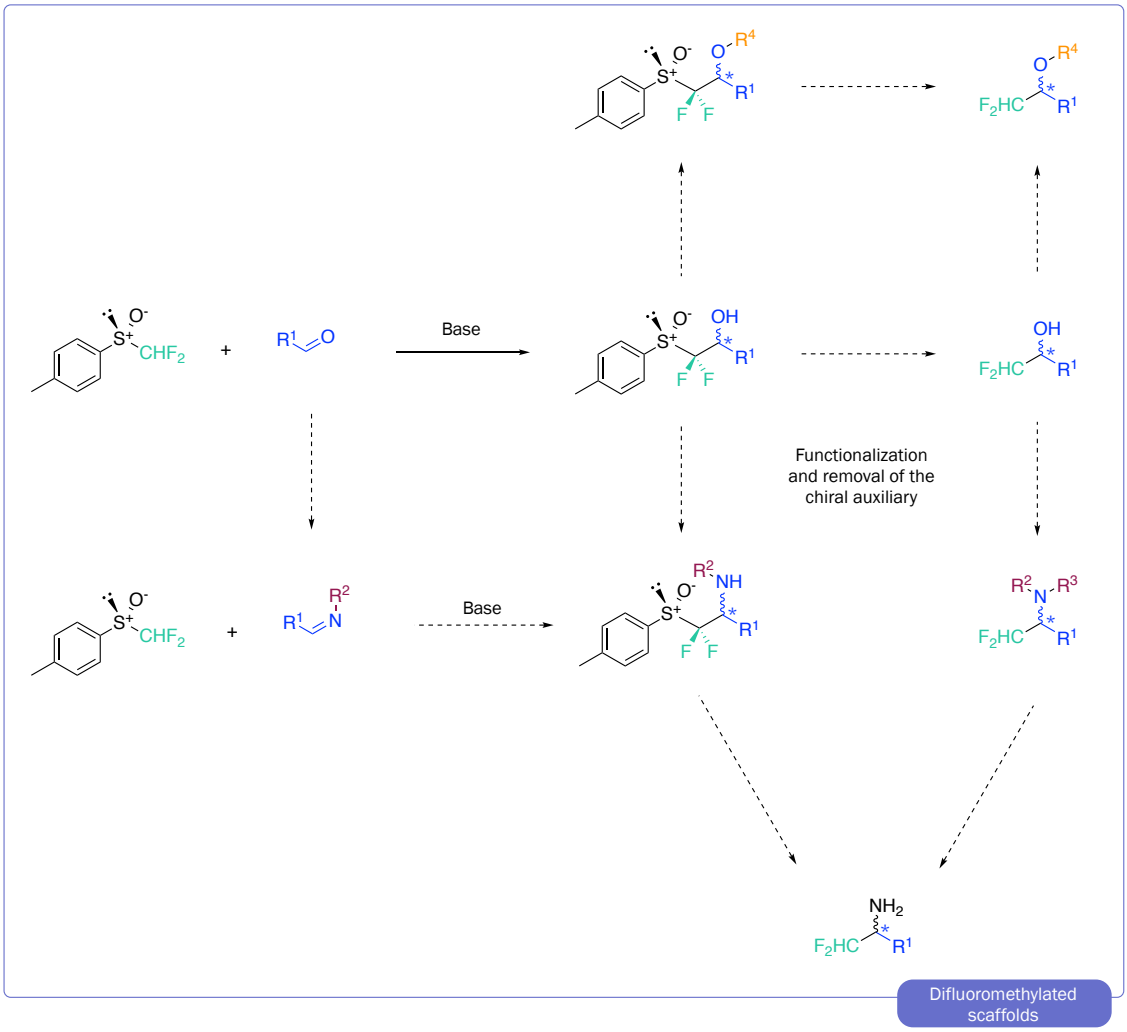
In the case of the two equivalents of P_4*t*-Bu, we can observe the kinetic resolution described in the recent article, in which only one diastereomer of the intermediate alcoholate is deprotonated, and subsequently transformed to the observed monofluorinated β-ketosulfoxide, leading to excellent diastereomeric ratios as the other diastereomer remains untouched. It is noteworthy that these observations did not occur when the base used is *t*-BuOK. Concerning the trial using only one equivalent of P_4*t*-Bu, we observe a slight inversion on the diastereomeric ratio of the α-difluoro-β-sulfinyl alcohols compared to the initial value. The same phenomenon is observed when the first equivalent of base used is *t*-BuOK or NaH. One can then also assume that the good diastereomeric ratios may come from a spontaneous elimination of fluoride from one of the two diastereomers of the alcoholate intermediate.

Altogether, these results indicate that is not yet possible to distinguish between the two mechanistic hypotheses, namely deprotonation of the alcoholate by a second equivalent of superbase *vs* the spontaneous elimination of fluoride. Both may take place concomitantly. Additionally, the nature of the cation might affect the rate of fluoride elimination. A deeper study and experiments are required to elucidate this process.

b. Towards difluoromethylated building blocks of pharmaceutical interest

1. Synthesis of selected α-difluoro-β-sulfinyl alcohols

Due to the increasing interest on fluorinated compounds for life sciences, the development of direct methods to achieve the synthesis of fluoroalkylated bulding-blocks is of great interest. Fluorinated *N*-containing molecules represent a huge interest for chemists nowadays, the combined properties of the amino and fluoroalkyl groups giving these compounds important physical, chemical and biological properties as synthetic building blocks in drug-design (**Scheme II.58**).[283,284]



Scheme II.58. Strategy to access a library of difluoromethylated scaffolds of high optical purity

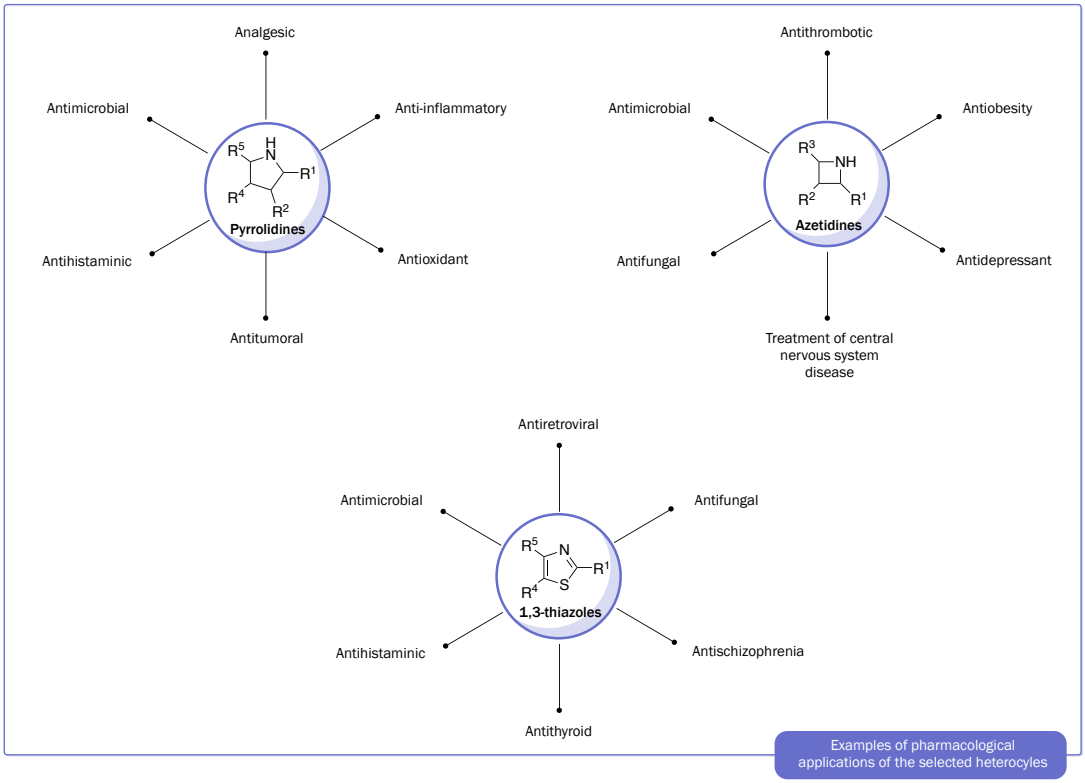
The synthesis difluoromethylated heterocycles and their precursor small molecules represent a particular interest for projets in medicinal chemistry. Selected compounds were chosen in order to functionalize them and access potential biologically active compounds building blocks for the current projects of our medicinal chemistry partners.

Azetidines are a stable four membered nitrogen-containing saturated rings. They have been used as building blocks,[285,286] ligands,[287] and they can also be found in natural products.[286] The preparation of biologically active compounds bearing azetidines with various functional groups in different positions of the ring has been widely described in litterature. These compounds showed antibacterial activity, binding to receptors and psychotropic potency.[288–290] Moreover, azetidine containing-amino acids are also very useful in the construction of short peptides.[291]

Pyrrolidines are five-membered saturated heterocycles, bearing nitrogen and four carbon atoms in the ring. This motif can be found in natural amino acids like L-proline and L-hydroxyproline, also in tobacco leaves and carrots, and in alkaloids such as hygrine.[292,293] Pyrrolidines are very reactive towards electrophiles such as aldehydes and ketones through nucleophilic additions.

We can also find these structures in asymmetric synthesis or catalysis, where they have been used as chiral building blocks, chiral ligands or organocatalysts.[294–297] Furthermore, a wide range of drugs contain a pyrrolidine-core structure, and have been used for their antitumoral, analgesic, anti-inflammatory, antimicrobial, antioxidant and antihistaminic activities.[298–300]

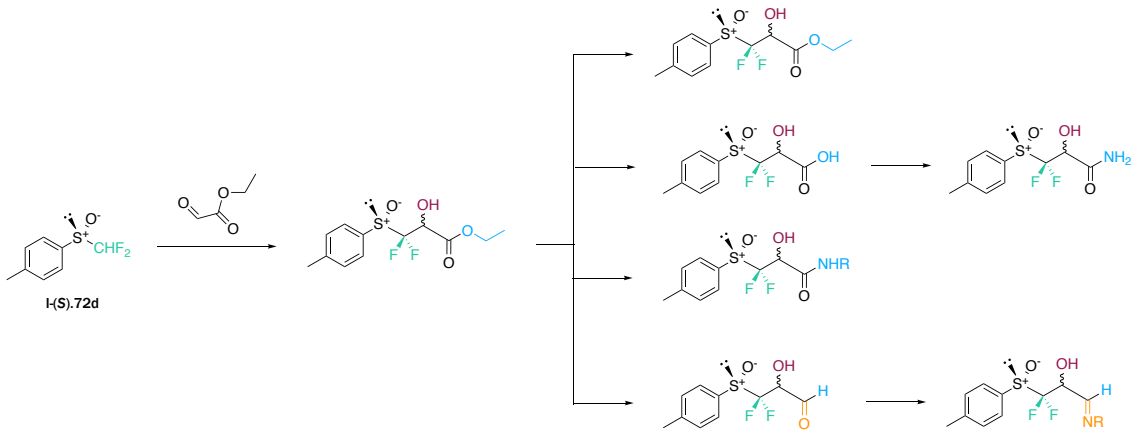
Thiazole rings are particular unsaturated 5-membered heterocycles containing one sulfur atom and one nitrogen atom. Natural products such as Vitamin B1 contain this motif and several drugs have been developed around thiazole rings. Some derivatives bearing a thiazole core present antimicrobial, antiretroviral, antifungal, antihistaminic, antischizophrenia and antithyroid activities.[301–304]



Scheme II.59. Pharmacological applications of selected heterocycles

Consequently, these 4 and 5-membered heterocycles are very attractive nowadays for therapeutic drug development. The preparation of their difluoromethylated analogues using our methodology was one of the main objectives of the project.

In addition to these heterocycles, it was of great interest to prepare difluoromethylated derivatives from ethyl glyoxalate. In fact, the corresponding difluoromethyl sulfinyl alcohols would give access to a large number of difluoromethylated derivatives after functionalization by saponification, amidation or Mitsunobu type reactions among others (**Scheme II.60**).

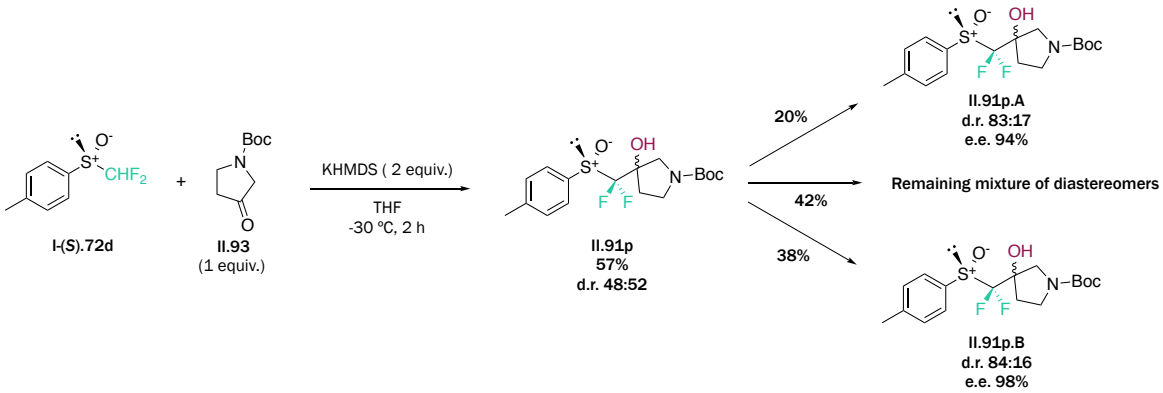


Scheme II.60. Strategy to access difluoromethylated scaffolds from difluoromethylated derivatives of ethyl glyoxalate

In order to access the target difluoromethylated heterocycles, we started from pyrrolidinone and azetidinone protected with a Boc- group in order to avoid undesired side reactions. They were prepared from the corresponding amine or used as received from chemical suppliers. In extension to the study of these 4- or 5- membered *N*-heterocycles, we also prepared the 6-membered derivatives starting from 3 and 4-piperidinones.

We applied the conditions used for the addition of difluoromethyl *p*-tolyl sulfoxide anion on carbonyl derivatives and chose the most appropriate base. We could notice that when using KHMDS, we obtained a better consumption of the starting material **I.72d**, in contrast to the use of *t*-BuOK and LiHMDS that only led to a partial or minimal conversion to the desired products **II.91**. This base was then chosen for further trials.

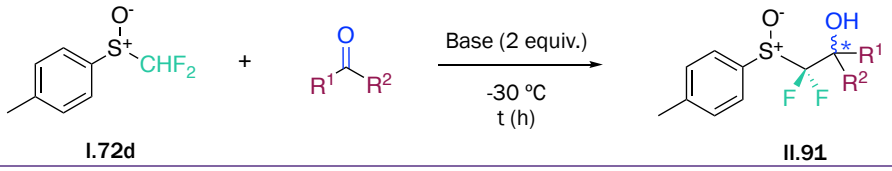
Regarding the pyrrolidine derivative, it was possible to obtain the desired compound with moderate yields and diastereomeric ratio. The access to both diastereoisomers of α-difluoro-β-sulfinyl alcohols **II.91p.A** and **II.91p.B** was possible after separation by flash chromatography (**Scheme II.61**). However, a significant amount of the mixture of diastereomers could not be separated.



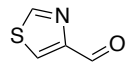
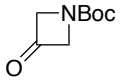
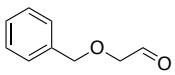
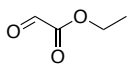
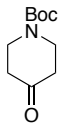
Scheme II.61. Synthesis of diastereoenriched α-difluoromethyl-β-sulfinyl alcohols bearing a pyrrolidine group

In the same manner, we were able to synthesize the thiazole, azetidine, piperidine, benzyloxy and glyoxalate bearing α-difluoromethyl-β-sulfinyl alcohols. The results are reported in **Table II.1**.

Table II.1. Results of the addition of difluoromethyl *p*-tolyl sulfoxide to a series of aldehydes and ketones



I.72d II.91

Entry	Electrophile	Base	t (h)	Product - Yield	d.r.*
1		*t*-BuOK	3	**II.91q** 29%	28:72
2		KHMDS	3	**II.91q** 47%	64:36
3		KHMDS	3	**II.91r** 69%	N.A.
4		KHMDS	3	**II.91s** 10%	42:58
5		KHMDS	4	**II.91t** 14%*	n.d.
6		KHMDS	3	**II.91u** 68%	N.A.
7		P_4*t*-Bu	3	**II.91u** 45%	N.A.
8		KHMDS	3	**II.91v** 38%	n.d.
9		P_4*t*-Bu	3	**II.91v** 32%	n.d.

*Presence of an unidentified impurity after purification

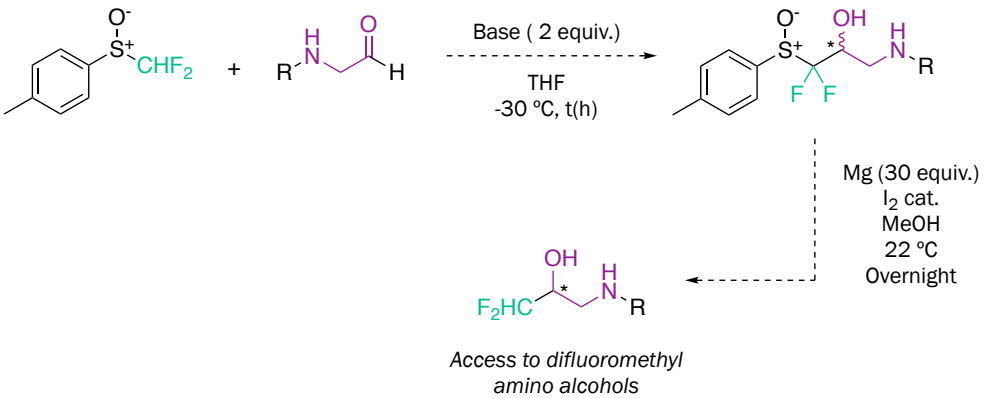
We can notice that the derivatives of benzyloxyacetaldehyde **II.91s** and ethyl glyoxalate **II.91t** (entries 4 and 5) were obtained with very poor yields, which was a drawback to continue the functionalization as planned. In fact, we noticed a limited reactivity of the difluoromethyl *p*-tolyl sulfoxide **I.72d**, as starting material was recovered, or fluorinated side-products, **I.95** among others, were present in the medium and limited the yield of the reaction.

Our attention was then focused on the 4-, 5- and 6-membered *N*-heterocycles that were obtained in moderate to satisfying yields. As we described, a majoritary amount of the two diastereomers of the pyrrolidine bearing sulfinyl alcohols could be separated. Following this idea, we wanted to separate as well the diastereomers of α-difluoro-β-sulfinyl alcohol **II.91v** bearing a piperazine in position 3. However, after performing numerous purification attempts, we were not able to separate the corresponding diastereomers for further experiences.

Due to the difficulties encountered to synthesize **II.92s** and **II.92t**, the selected range of electrophiles for their interesting motifs in medicinal chemistry was restricted to azetidine, pyrrolidine and thiazole derivatives. Their corresponding α-difluoro-β-sulfinyl alcohols were prepared and the access to the corresponding desulfinylated alcohols after removal of the chiral auxiliary as well as their funtionalizations will be described in detail in *Chapter III.*

2. Additions to amino aldehydes

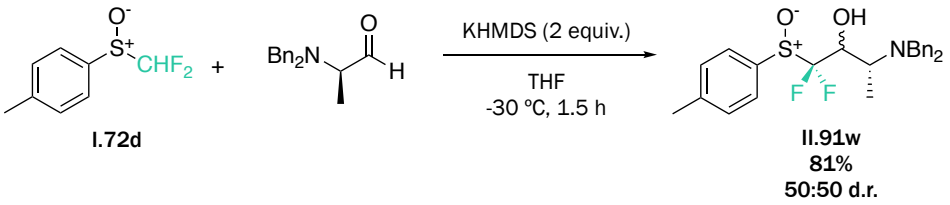
It is noteworthy that a α-difluoromethyl-β-amino alcohol functionality would be valuable for medicinal chemists as an intermediate to access amino alcohol-derived chiral fragments. So far in litterature, only the direct introduction of -CF_3 moiety has been largely reported[305–308], in contrast to the –CHF_2 group, which makes it of great interest for this project. Consequently, we explored the addition of difluoromethyl *p*-tolyl sulfoxide **I.72d** to aminoaldehydes. These substrates represent a last group of electrophiles that have not been assessed yet, in order to evaluate the efficiency of our strategy to open the access to α-difluoromethyl-β-amino alcohols (**Scheme II.62**).



Scheme II.62. Strategy to access difluoromethyl amino alcohols

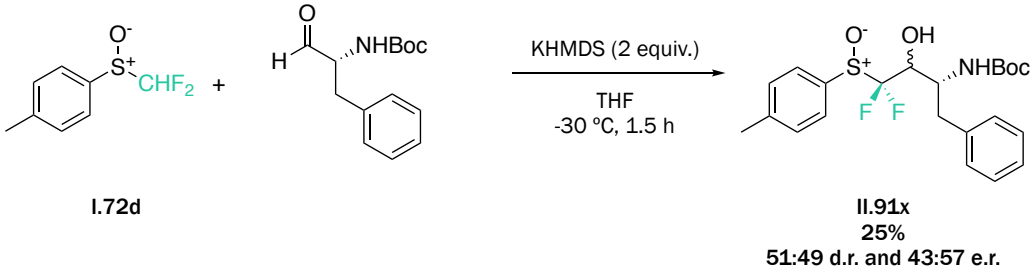
We started from commercial amino aldehydes and one synthesized by the Sanofi medicinal chemistry team.

Chiral *N,N*-dibenzyl-L-alaninal has been used in litterature as a model to introduce $-CF_3$ motif.[307,308] We tried then the introduction of $-CHF_2$ by condensation of racemic **I.72d**. To our delight, we were able to obtain the expected compound with a good yield (**Scheme II.63**).



Scheme II.63. Introduction of the difluoromethyl moiety onto *N,N*-dibenzyl-L-alaninal

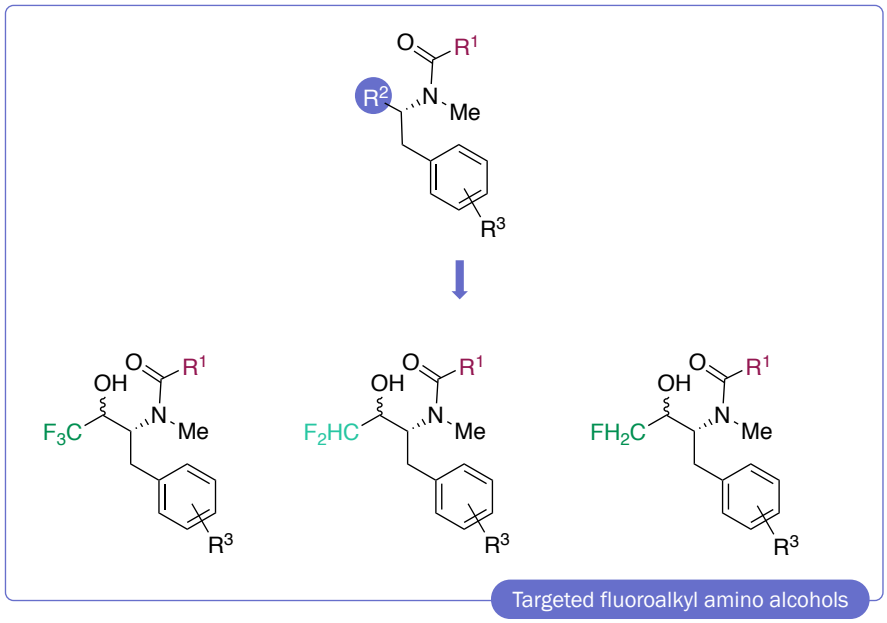
The extension to the protected *N*-Boc-D-phenylalaninal led to the corresponding difluoromethyl sulfinyl alcohol with a moderate yield of 25% (**Scheme II.64**), probably due to the undesired deprotonation in α-position of the amine function.



Scheme II.64. Synthesis of difluoromethylated derivative of *N*-Boc-D-phenylalaninol

With these two encouraging results in hand, we tested an amino aldehyde prepared in the medicinal team group. In fact, special attention was given to the synthesis of fluorinated alcohols in the course of identification of small molecules as covalent inhibitors in a drug-discovery project.

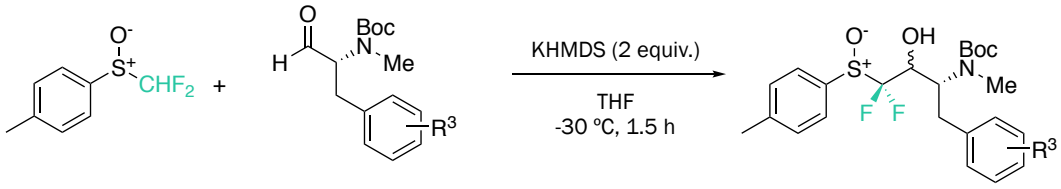
Currently, the medicinal chemistry team is working on the optimization of the structure of a pre-candidate in a core structure presented in **Scheme II.65**. The side-chain represented by –R is being replaced by a range of functional groups. Among them, a side-chain of alcohols bearing substituents such as $-CHF_2$, $-CF_3$ or $-CH_2F$ would give an overview of the possible beneficial effects of emergent fluorinated substituents.



Scheme II.65. Fluorinated amino alcohols of interest for a medicinal chemistry project

The monofluorinated and the trifluoromethylated derivatives were successfully prepared using commercially available fluorination and trifluoromethylation reagents and performing a chiral separation. Regarding the derivative bearing the -CHF_2 group, it was not yet possible to obtain it using $TMSCHF_2$. We decided then to apply our sulfoxide-based methodology to perform the synthesis of the final compound.

The successful synthesis of the difluoromethylated sulfinyl alcohol from *N*-Boc-D-phenylalaninal was encouraging for this application. The condensation of difluoromethyl *p*-tolyl sulfoxide was then performed on the suitable aldehyde (**Scheme II.66**).



I.72d **II.91y** **17%** **49:51 d.r.**

Scheme II.66. Synthesis of a difluoromethyl amino alcohol from a functionalized phenylalaninal derivative

The desired compound was obtained with a low yield of 17%. It would be worth to perform further optimization of these reaction conditions, but due to the PhD deadlines this was not performed yet and the product was used as obtained for further functionalization steps. The desulfinylation of the product as well as it coupling to the other partner (R^1) will be presented in *Chapter III.*

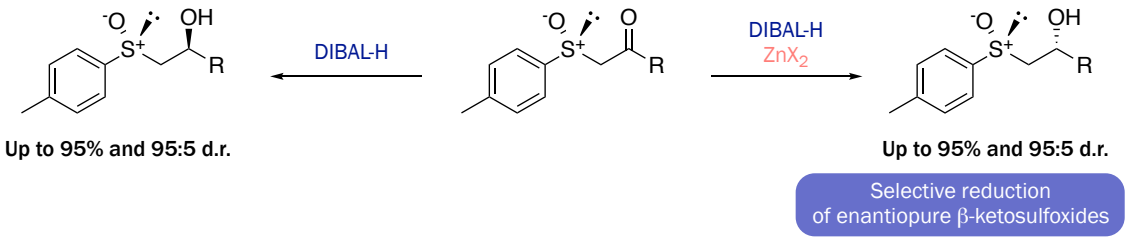
c. Access to α-difluoromethyl-β–sulfinyl alcohols *via* α-difluoro-β-ketosulfoxides

1. State of the art: non-fluorinated series

The synthesis of non-fluorinated β-ketosulfoxides has been developed independently by Russell in 1963[309] and Corey in 1964,[310] by reacting methylsulfinyl carbanion with a range of esters to obtain β-ketosulfoxides. Russell performed Pummerer rearrangements on these products and Corey used this new synthesis as a new way of access to ketones after removal of the sulfoxide.

A decade later, Cinquini studied a new transformation of enantiopure β-ketosulfoxides, namely their stereoselective reduction by metal hydrides.[66] The use of $NaBH_4$, $LiAlH_4$ and other lithium aluminium derivatives allowed them to obtain d.r. of the corresponding sulfinyl alcohols up to 83:17.

The synthesis of β-ketosulfoxides starting from (*R*)-methyl *p*-tolyl sulfoxide and their selective reduction was further largely studied by Solladié to access both diastereomers of the corresponding sulfinyl alcohol (**Scheme II.67**).[170,311–313] The authors noticed that the stereoselectivity of the reductions is controlled by the choice of hydrides and coordinating agents involved in the reduction of β-ketosulfoxides.



Scheme II.67. Selective reductions of enantiopure β-ketosulfoxides reported by Solladié

A non-chelated model in the absence of halogenated zinc agents and a chelated model rationalized this selectivity when they are involved in the reaction. When DIBAL-H is employed, the aluminium atom is chelated by sulfur and carbonyl oxygens to give two possible transition states **I** and **II**. However, the transition state **II** having the *p*-tolyl group in pseudo-axial position is not favored due to the high steric hindrance and 1,3-diaxial interactions. The hydride is then transferred and the reduction occurs in the conformation **I** to give the *anti* product (**Figure II.2**).

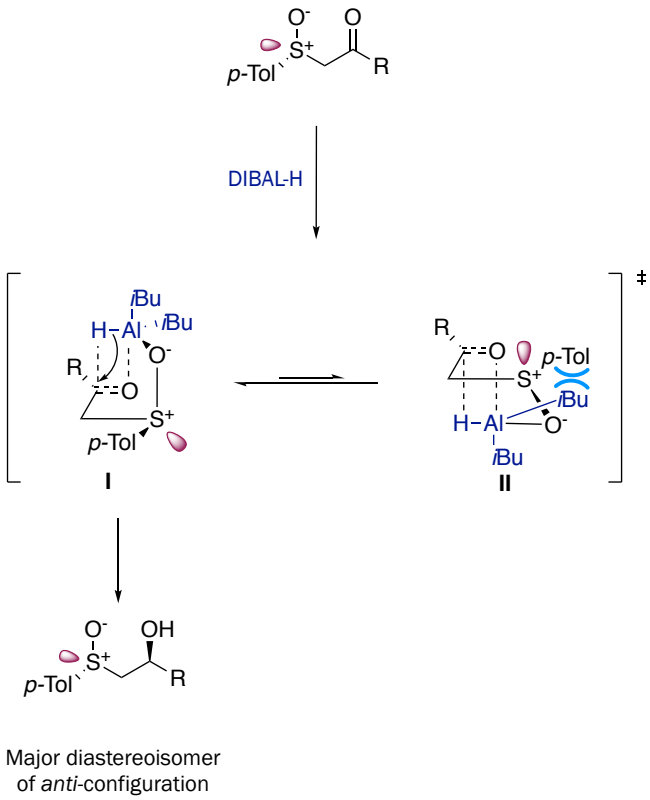


Figure II.2. Non-chelated model of diastereoselective reduction of β-ketosulfoxides

In fact, in the presence of a chelating agent such as $ZnCl_2$ or $ZnBr_2$, the β-ketosulfoxide adopts a twisted conformation after coordination of the oxygens. Moreover, the preferential conformation will be the one represented in III, where the *p*-tolyl group is in a pseudo-equatorial position and the steric hindrance with DIBAL-H is minimized. After this chelation step, the complexation of DIBAL-H with oxygen and a well-positioned halogen atom leads to a bimetallic bridged-species where aluminium is dsp^3 hybridized. The intramolecular transfer of hydride from the DIBAL-H takes place leading to the *syn* product (**Figure II.3**).

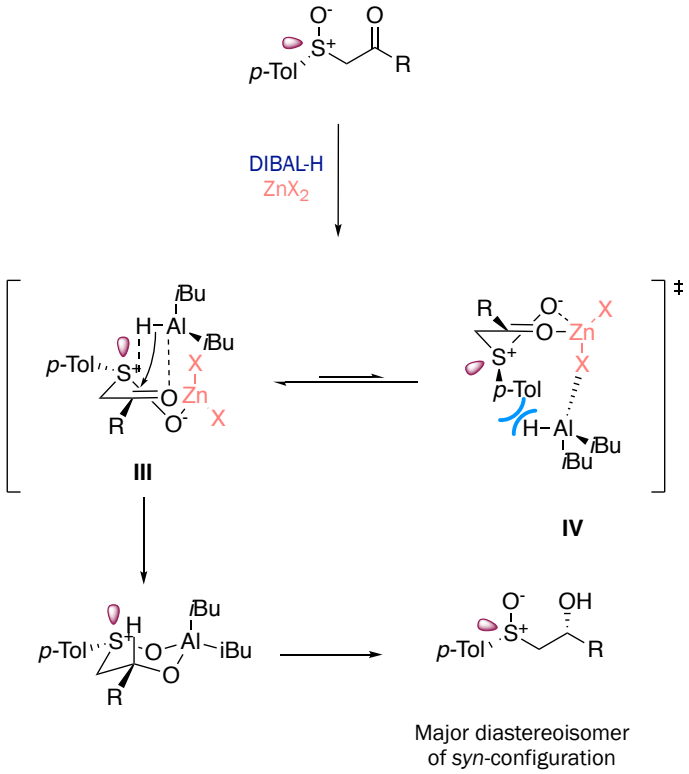
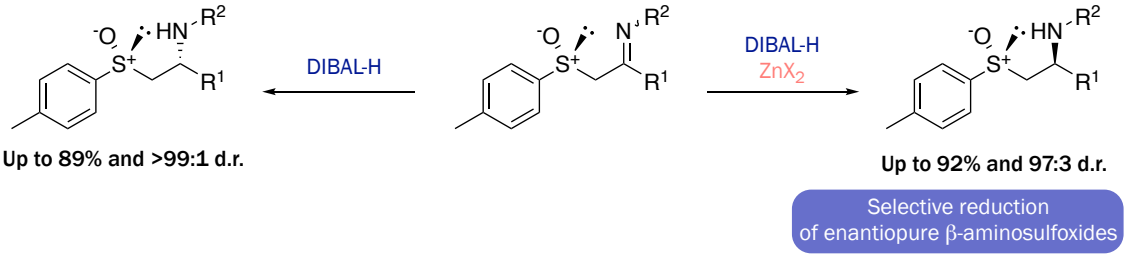


Figure II.3. Model of diastereoselective reduction of β-ketosulfoxides in the presence of a chelating agent

It is noteworthy that the attribution of each diastereoisomer of the obtained β-ketosulfoxides can be done by NMR. In fact, the diastereotopic protons of the methylene group in α-position of the sulfoxide gives non equivalent ABX systems for each one of the diastereoisomers.[311]

Similarly to the selective reductions of β-ketosulfoxides, α-sulfinyl ketimines have also been synthesized from the corresponding β-ketosulfoxides[314] and their highly stereoselective reduction has been described by Imanishi[315] and Garcia Ruano (**Scheme II.68**).[316,317]

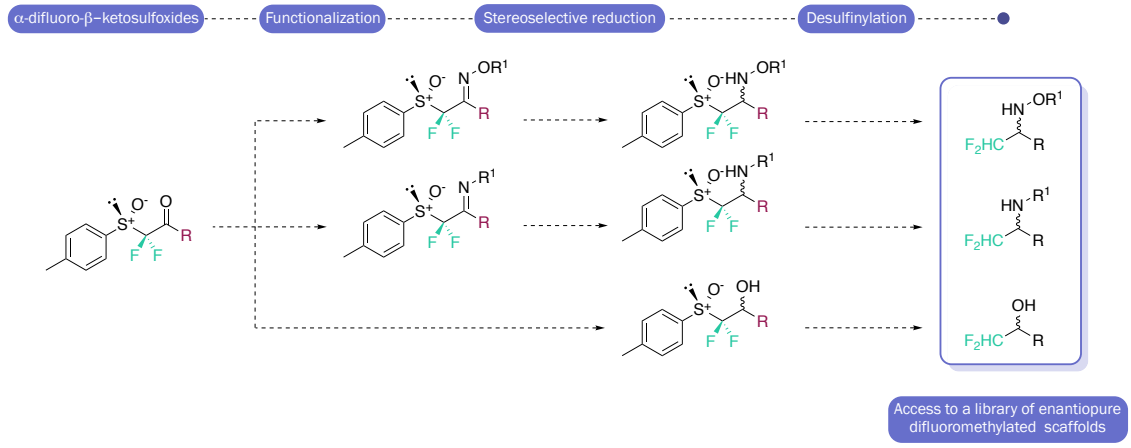


Scheme II.68. Diastereoselective reduction of β-iminosulfoxides

2. Strategy

In view of these results, we thought it would be interesting to apply this strategy to α-difluoro-β-ketosulfoxides as an alternative access to α-difluoro-β-sulfinyl alcohols or amines and thus to their desulfinylated counterparts (**Scheme II.69**). The access to α-difluoro-β-sulfinyl amines will be detailed in part d of *section C*.

Surprisingly, this strategy had, to the best of our knowledge, not been used on α-fluorosulfoxides in literature.

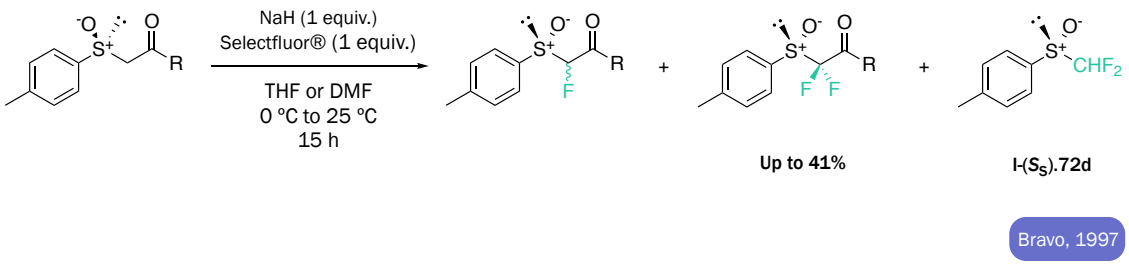


Scheme II.69. Strategy for the diastereoselective reduction of β-ketosulfoxides and its imino derivatives

To tackle this objective, we first had to prepare the key α-difluoro-β-ketosulfoxides.

3. Fluorinated β-ketosulfoxides reported in literature

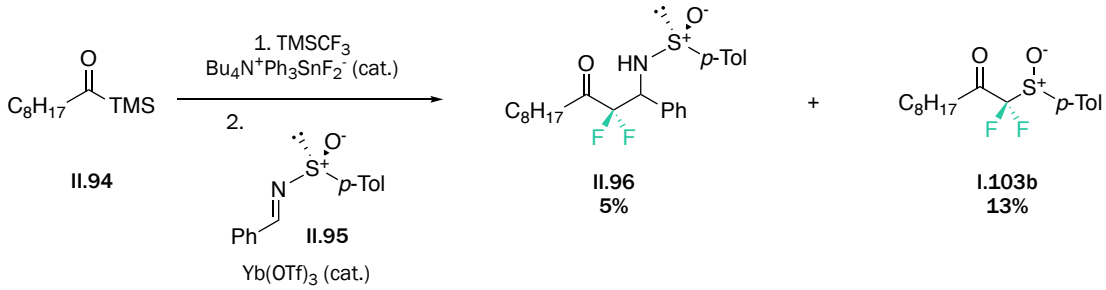
In 1997, Bravo reported the α-monofluorination of β-ketosulfoxides by Selectfluor®.[62] During this study, they observed the further fluorination of α-monofluoro-β-ketosulfoxides to provide the corresponding α-difluorinated derivatives in yields up to 41% (**Scheme II.70**).



Scheme II.70. Difluoromethylation of enantiopure β-ketosulfoxides with Selectfluor®

However, they were not able to improve this yield and obtain exclusively the α-difluoro-β-ketosulfoxide as they readily observed a deacylation giving the corresponding aryl difluoromethyl sulfoxide.

In 2005, Brigaud and Portella studied the synthesis of β-amino-α-difluoroketones via an imino aldol reaction starting from acylsilanes and the Ruppert-Prakash reagent.[318] However, in one case, the use of $Yb(OTf)_3$ as additive furnished the expected β–amino ketone in a very low yield whereas α-difluoro-β-ketosulfoxide was the major product, resulting from the attack of the difluoroenoxysilane (**Scheme II.71**).



Scheme II.71. Imino aldol reaction serendipitously revealing the presence of an α-difluoro-β-ketosulfoxide

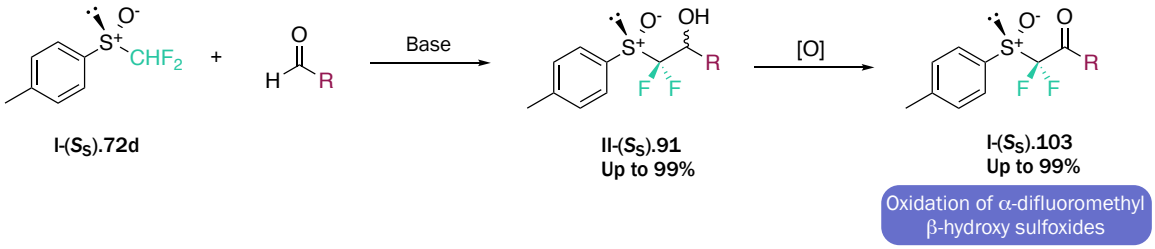
To the best of our knowledge, these authors noticed the formation of these interesting products but no further studies were performed on these derivatives and their possible synthetic application.

4. Methods used to access difluorinated β-ketosulfoxides

i. Oxidation of difluoromethyl sulfinyl alcohols

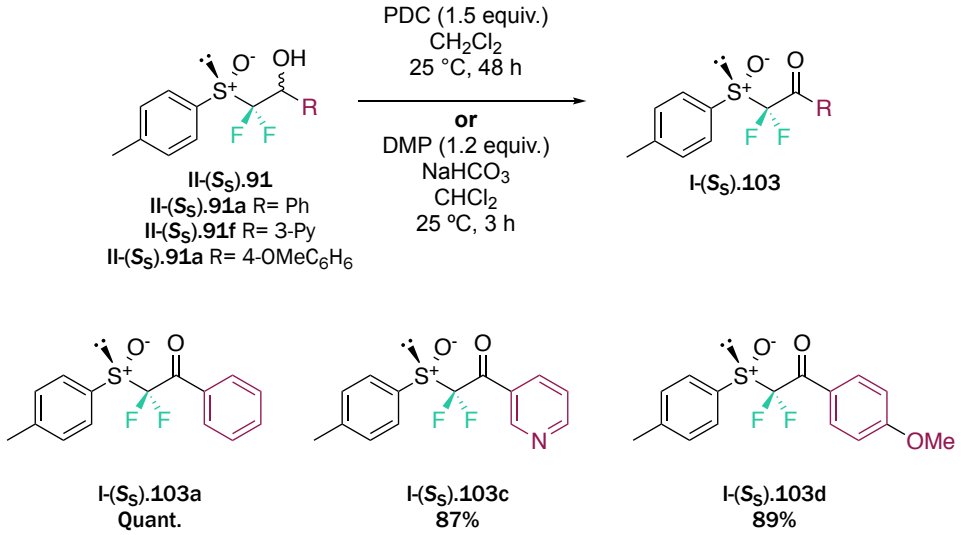
Performed with Chloé Batisse, PhD, and Amélia Messara, MSc.

Previously in the group, the synthesis of a α-difluoro-β-ketosulfoxide was successfully performed by oxidizing the corresponding difluoromethyl hydroxysulfoxide with pyridinium dichromate. This reaction led to the desired product in quantitative yield (**Scheme II.72**).



Scheme II.72. First method used in our group to access to α-difluoro-β-ketosulfoxides by oxydation of the corresponding difluoromethyl sulfinyl alcohols

Different α-difluoro–β-ketosulfoxides were then accessed through oxidation of the previously synthesized α-difluoro-β-hydroxysulfoxides with PDC or DMP as described in our latest paper (**Scheme II.73**).[65]



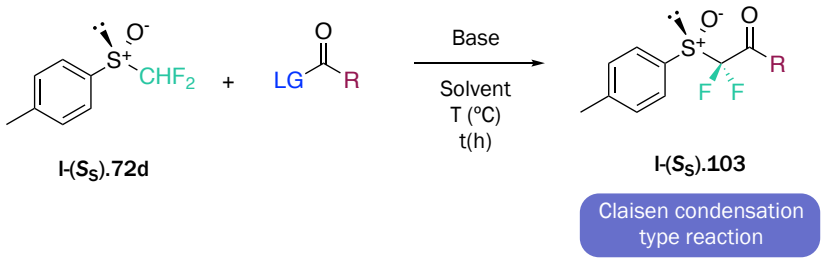
Scheme II.73. Synthesis of α-difluoro-β-ketosulfoxides

Thanks to this method, we were able to use α-difluoro-β-ketosulfoxides for the synthesis of diastereopure α-difluoromethyl β-hydroxysulfoxides, as described in *part 5* of this section.

However, the synthetic pathway, consisting in synthesizing the difluoromethyl hydroxysulfoxide starting from the difluoromethyl aryl sulfoxide, condensing it onto an aldehyde and then performing the oxidation, is not the most direct way to obtain these compounds. A new strategy for their synthesis was then required.

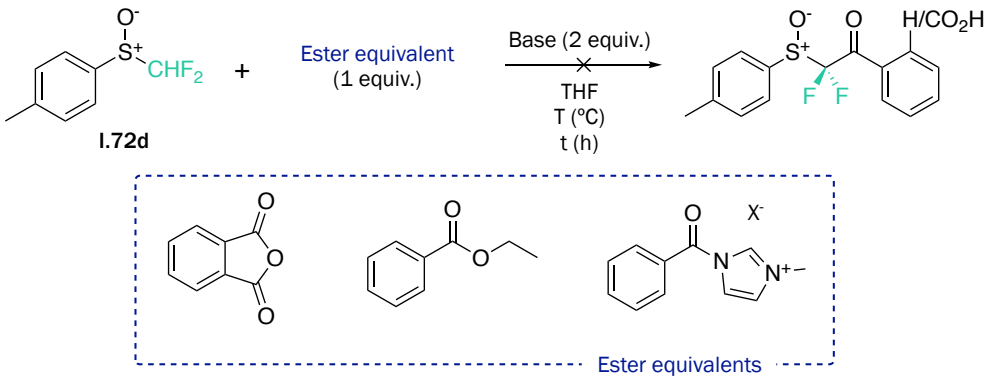
ii. Claisen condensation

The first alternate strategy chosen to access α-difluoro-β–ketosulfoxides was inspired from a method developed in the group for the one-pot synthesis of sulfinyl alcohols: a deprotonation of the corresponding difluoromethyl sulfoxide followed by the addition to an electrophile. Our adapted method consisted in performing a Claisen-type reaction between difluoromethyl *p*-tolyl sulfoxide and a range of ester equivalents (**Scheme II.74**).



Scheme II.74. Strategy to synthesize α-difluoro-β-ketosulfoxides *via* Claisen type condensations

Many attempts were carried out starting from the racemic sulfoxide and using various electrophiles (including anhydrides, esters, a carbonyl imidazolium and benzoyl chloride). These electrophiles were tested in presence of bases such as *t*-BuOK, KHMDS, LiHMDS and the phosphazene P$_4$*t*-Bu. For the ''potassium containing'' bases, the cryptand K222 was used as an additive in order to generate an ion exposed (''naked''). Despite its efficiency for the synthesis of difluoromethyl alcohols, the use of *t*-BuOK was inefficient for this synthesis and was then excluded. The reactions performed in THF, DMF or DCM were also unfruitful. Low temperature (-30 °C) was tried, as the additions of difluoromethyl *p*-tolyl sulfoxide **I.72d** to carbonyls, but the conversion not evolving, the reactions were let to reach room temperature. Moreover, the reaction times were extended to a long period of time (up to 3 days) without any improvement (**Scheme II.75**).



Scheme II.75. First attempts of synthesis of α-difluoro-β-ketosulfoxides

In the previous cases, we mainly observed either the unchanged starting material or side products on the crude NMR. The isolation of one of these side-products, difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95**, led us to perform some mechanistic tests and to propose mechanisms for this reaction. These tests are described in part E of this chapter.

During this optimization, the initial conditions consisted in performing the deprotonation of the difluoromethyl sulfoxide and slowly adding the resulting anion onto the elecrophile. However, with these conditions the β-ketosulfoxide was not formed. Instead we observed the formation of difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95**. In order to avoid this, different procedures were tested, by changing the addition order of the reactions. Conditions reported by Hu for the condensation of difluoromethyl phenyl sulfoxide to carbonyls consisted in mixing the electrophile and the sulfoxide, then adding the suitable base. These conditions were then used. We also tried to prepare a mixture of the electrophile and the base before adding difluoromethyl *p*-tolyl sulfoxide **I.72d**, and to perform the deprotonation in a separate batch then add to a solution containing the electrophile (**Figure II.4**).

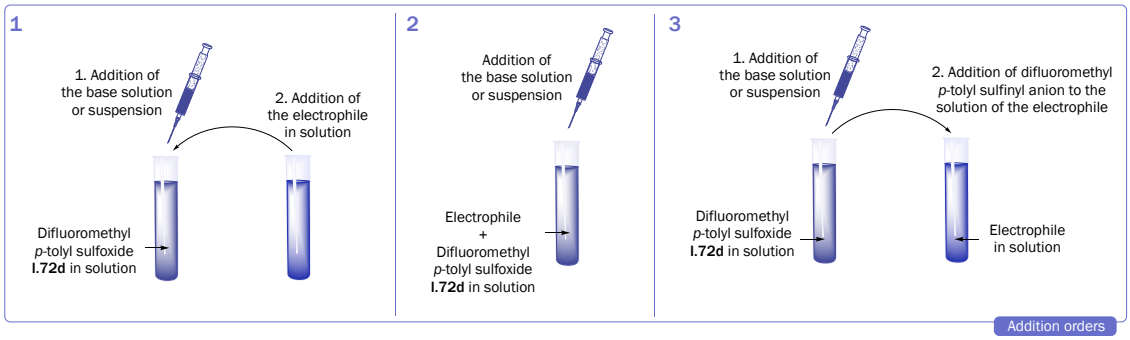
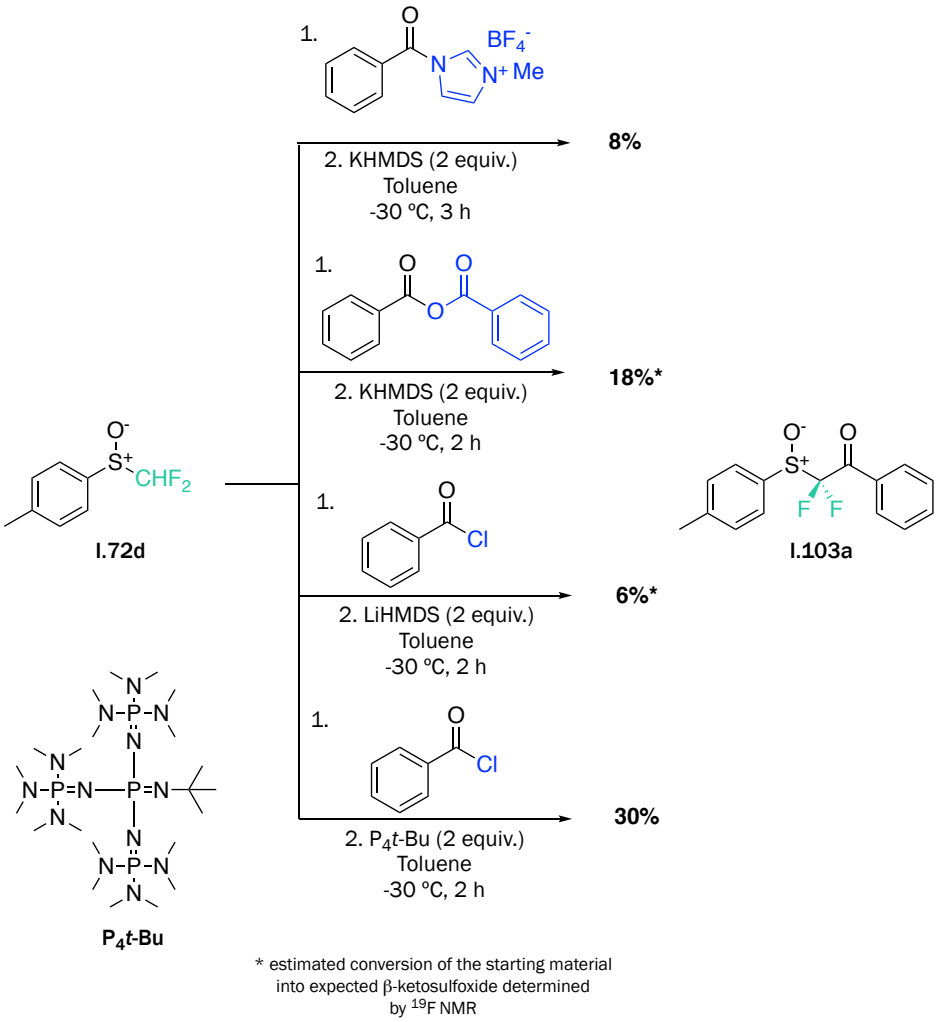


Figure II.4. Reagents addition order changes to improve the reaction of difluoromethyl *p*-tolyl sulfoxide and ester equivalents

Unfortunately, no improvement was observed with these different addition orders.

Continuing with the optimization for the synthesis of α-difluoro-β-ketosulfoxides, and inspired by procedures described by Hu *et al.* where toluene was preferred for nucleophilic difluoromethylations, the reaction was performed using this solvent. To our delight, we started observing the formation of the desired product, despite the presence of side products or the low conversion of the starting material in some cases. The most convenient conditions appeared to be the addition of the base onto a mixture of sulfoxide **I.72d** and electrophile, showing a smaller amount of side products on the crude NMR spectra (**Scheme II.76**).



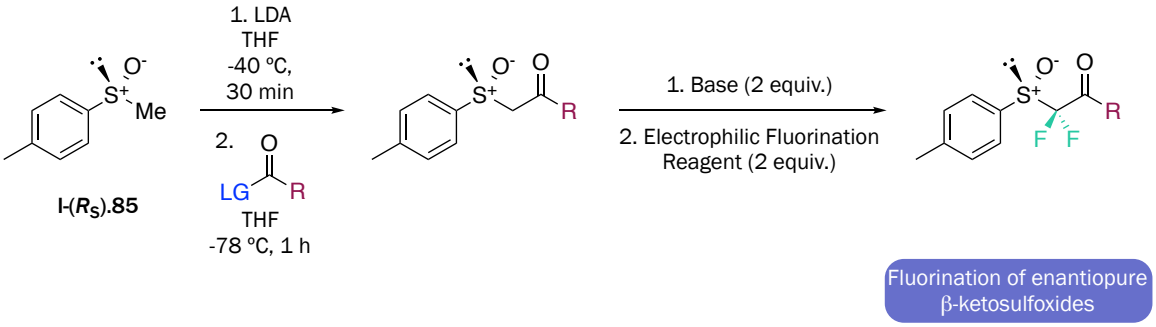
Scheme II.76. Successful attempts leading to α-difluoro-β-ketosulfoxides

An interesting 30% yield was obtained when using benzoyl chloride as electrophile, in presence of a phosphazene superbase P$_4$*t*-Bu. We also observed the formation of a small amount of the β-ketosulfoxide upon trapping by either *N*-benzoylimidazole activated by Meerwein's salt or benzoic anhydride, using either KHMDS or LiHMDS as base. At this point, the desired product was obtained in low to moderate yields, and the best conditions giving the least side products on the NMR spectrum of the crude are the ones using P$_4$*t*-Bu and benzoyl chloride.

Despite these attempts, the desired compound could not be obtained in satisfying yields, with the maximum yield achieved being 30%, the formation of side-products remaining a difficulty. In view of these results, we decided to explore a more efficient synthetic pathway to access enantiopure α-difluoro-β-ketosulfoxides.

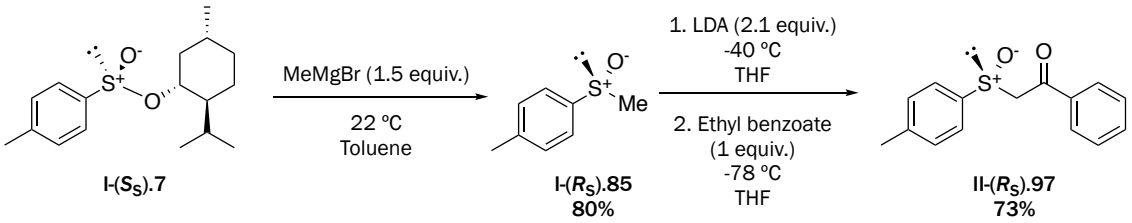
iii. Fluorination of β-ketosulfoxides with electrophilic fluorination reagents

Namely, we reconsidered Bravo's group work using Selectfluor® to fluorinate β-ketosulfoxides (**Scheme II.77**).[62]



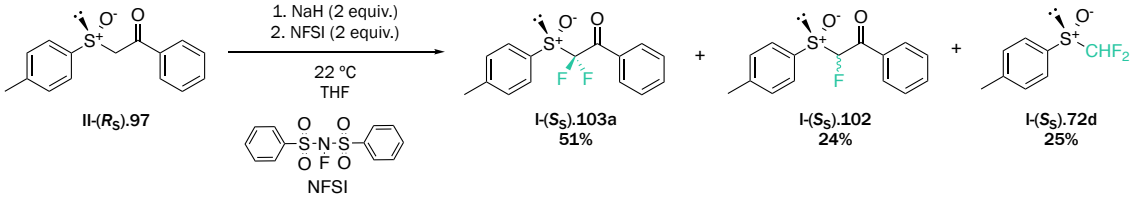
Scheme II.77. Strategy for the fluorination of enantiopure β-ketosulfoxides using electrophilic fluorination reagents

The access to enantiopure methyl *p*-tolyl sulfoxide and further transformation to β-ketosulfoxides of high optical purity was performed using conditions developed within by Solladié.[170] Enantiopure α-phenyl β-ketosulfoxide was prepared as model substrate for the difluorination study with 58% overall yield (**Scheme II.78**).



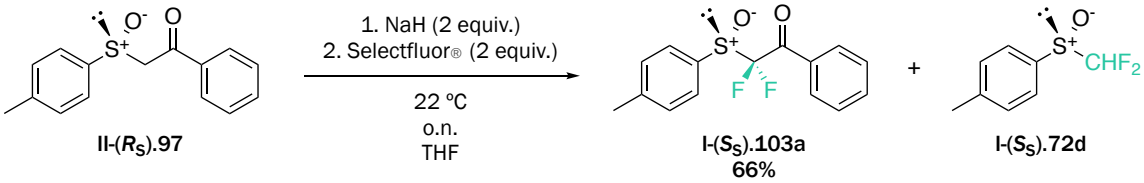
Scheme II.78. Synthesis of a model enantiopure β-ketosulfoxides

For the difluorination, we first decided to try the conditions of Bravo and co-workers, namely the use of NaH followed by NFSI as the fluorination reagent. These conditions led to both the α-monofluoro-β-ketosulfoxide and the α-difluoro-β-ketosulfoxide. The α-difluorinated-β-ketosulfoxide was obtained with a 51% yield and the mono-fluorinated species with a 24% yield. We also noticed the formation of the enantiopure difluoromethyl sulfoxide (98% e.e.), as described by Bravo and co-workers, in 25% yield (**Scheme II.79**).



Scheme II.79. Difluorination of enantiopure β-ketosulfoxide using NFSI

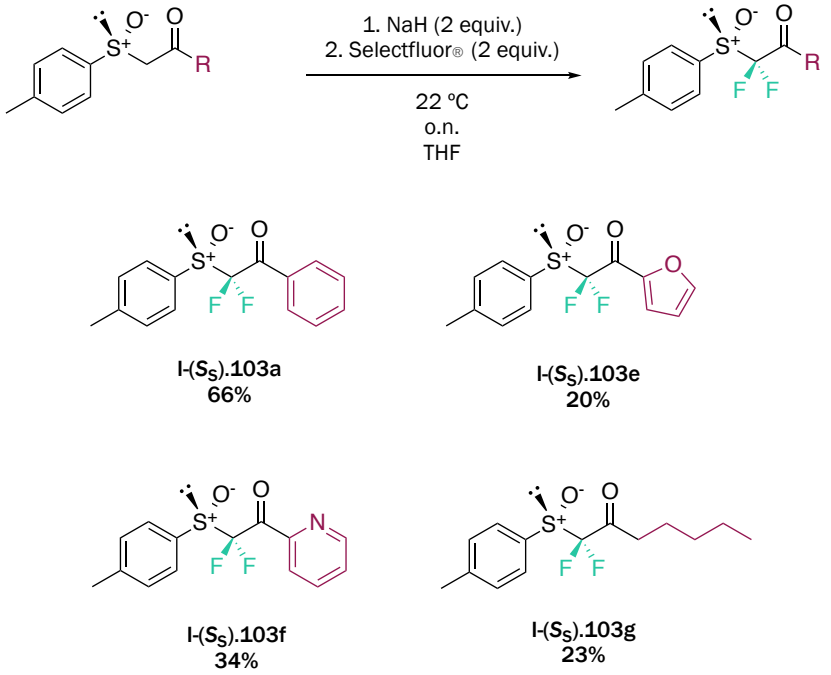
The difluorination performed with Selectfluor® allowed us to obtain the desired enantiopure α,α-difluoro-β-ketosulfoxide in a more satisfying 66% yield without the presence of α-monofluoro-β-ketosulfoxide (**Scheme II.80**).



Scheme II.80. Difluorination of an enatiopure β-ketosulfoxide using NaH as base and Selectfluor® as electrophilic fluorine source

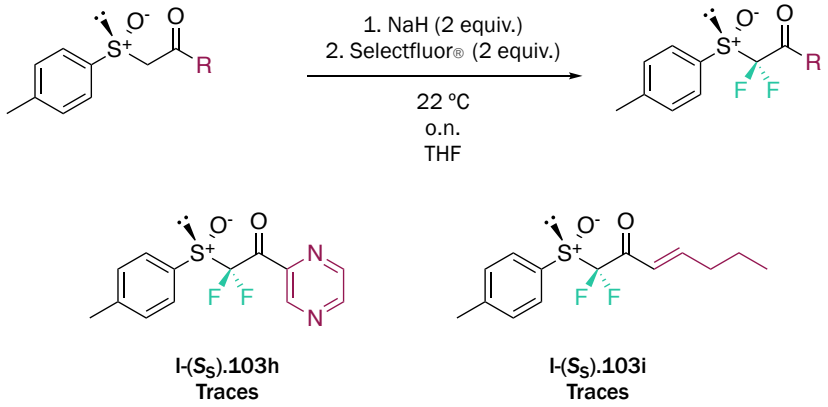
It is noteworthy that this methodology can be used for the synthesis of a range of enantiopure α-difluoro-β-ketosulfoxides on gram-scale, in contrast to the previous one due to the high cost of the reagent employed.

We used the best conditions mentioned above on a small series of substrates, bearing different substituents such as 2-pyridyl, 2-furyl or an alkyl chain (**Scheme II.81**).



Scheme II.81. Difluorination of a range of enantiopure β-ketosulfoxides

However, we noticed that the formation of the cleavage product, *p*-tolyl difluoromethyl sulfoxide, is a limitation in these syntheses, as the yields of the desired α-difluoro-β–ketosulfoxide remain moderate and compounds **I.103e** and **I.103f** were not stable in time. Despite the full consumption of the starting material, and in some cases were just corresponding to trace amounts as illustrated in **Scheme II.82**. The major product obtained is difluoromethyl *p*-tolyl sulfoxide.

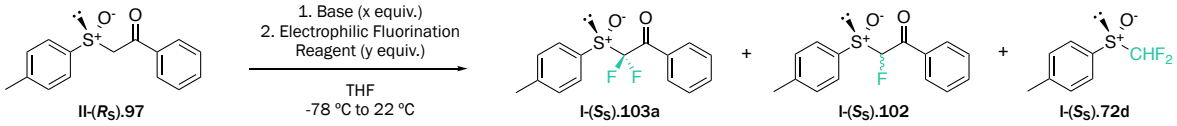


Scheme II.82. Unsuccessful examples of difluorination of β–ketosulfoxides

The formation of the fragmentation product, difluoromethyl *p*-tolyl sulfoxide **II.72d,** in all of these cases could probably be explained by a retro-Claisen reaction that takes place in the presence of bases. A similar difluorination/fragmentation process was described by Pattisson, who valorized it in order to obtain the corresponding difluoromethyl ketones.[319] The deprotonation of an *in situ* formed hydrate of the β-ketosulfoxide would lead to this retro-Claisen-like process.

We decided then to vary some reaction conditions, e.g. using other bases than sodium hydride, in order to minimize the formation of this product and improve the yield of the corresponding β-ketosulfoxides (**Table II.2**).

Table II.2. Difluorination trials using electrophilic fluorination reagents



Entry	Base	Fluorination reagent	Ratios** I-(S_S).103a	I-(S_S).102	I-(S_S).72d
1	No base	NFSI (2 equiv.)	0	0	0
2		Selectfluor® (2 equiv.)	0	0	0
3	Et_3N (2 equiv.)	NFSI (2 equiv.)	0	0	0
4		Selectfluor® (2 equiv.)	0	0	0
5	KHMDS (2.1 equiv.)	NFSI (2 equiv.)	55*	26*	0
6	LDA (2.1 equiv.)	NFSI (2.1 equiv.)	25	63	8
7		Selectfluor® (2.1 equiv.)	46	54	Traces
8	Na_2CO_3 (2.1 equiv.)	Selectfluor® (2.1 equiv.)	Traces	Traces	0%

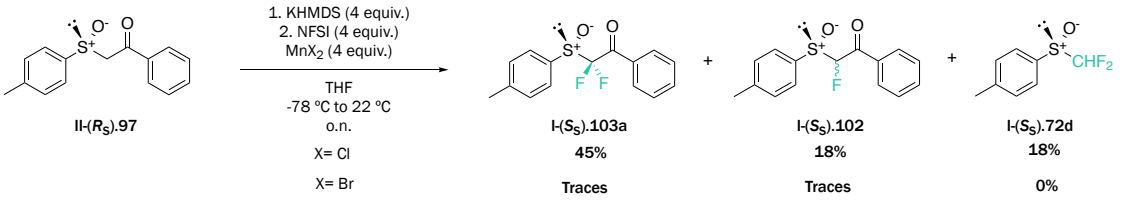
*Isolated yield

** Determined by ^{19}F NMR

In some cases, the synthesis of difluorinated compounds by reacting dicarbonyls with electrophilic fluorination reagents in absence of a base was described.[320,321] We therefore carried out experiments adapting our conditions in which the non-fluorinated β-ketosulfoxide was reacted exclusively with NFSI or Selectfluor® (Table, Entries 1 and 2). However, we did not observe the fluorinated product. The same result was observed with the use of triethylamine as a milder base than NaH. The starting material was fully recovered (Table, Entries 3 and 4).

More conditions were then tested to perform the difluorination. In litterature, KHMDS or LDA have been used for electrophilic fluorination.[322] An example of difluorination of β-ketosulfones has also been described by Loghmani-Khouzani and coworkers using Na_2CO_3 as a base.[323] Using these three bases, the mono and difluorinated β-ketosulfoxides were obtained as well as the *p*-tolyl difluoromethyl sulfoxide in the proportions presented in (Table, Entries 6 to 8).

Matsumura and co-workers described a fluorination strategy applied to the α-fluorination of carbonyl compounds.[324] Their studies showed that the most appropriate electrophilic fluorination reagent is NFSI, the reaction being performed with KHMDS as a base and in the presence of manganese bromide. We tried to apply these conditions to our substrate, unfortunately, the results obtained either with manganese bromide or chloride were worst than the ones without the use of a manganese halide (**Scheme II.83).**



Scheme II.83. Difluorination of β-ketosulfoxides in the presence of manganese halides

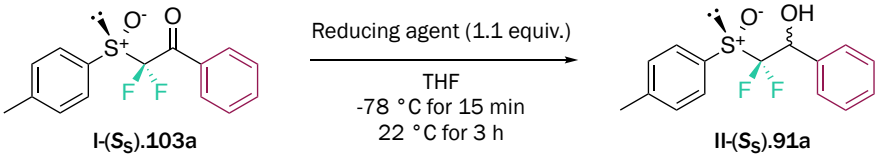
With these results in hand, we decided to continue the strategy using KHMDS as a base and NFSI as these conditions seem to limit the undesired formation of difluoromethyl *p*-tolyl sulfoxide.

5. Reduction of difluorinated β-ketosulfoxides to access difluoromethyl alcohols

The reduction of a model of an enantiopure α-difluoro β-ketosulfoxide was performed using conditions described in literature by Solladié and co-workers[312] on non-fluorinated analogues using different reducing hydrides.

The agents that were used for this transformation are $NaBH_4$, $LiAlH_4$, DIBAL-H, $LiBH_4$ and L-Selectride® as it is described in **Table II.3**.

Table II.3. Reduction of α-difluoro-β-ketosulfoxide by hydrides

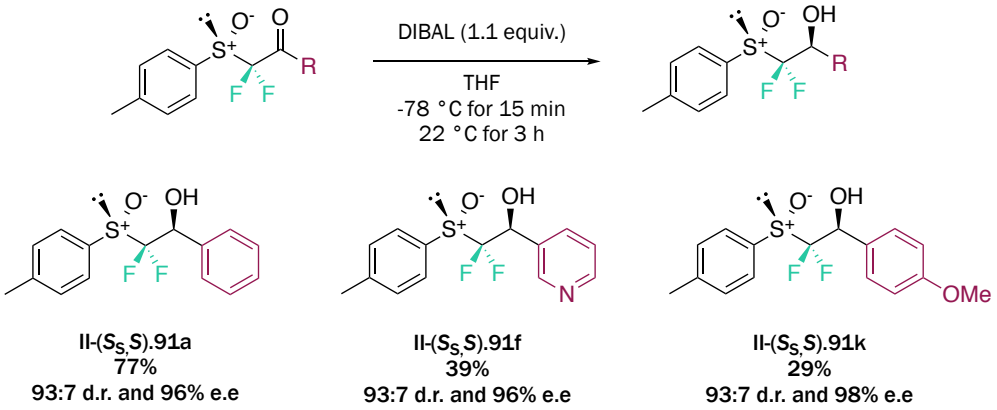


Entry	Reducing agent	Yield	d.r.
1	$NaBH_4$	72%	66:34
2	$LiAlH_4$	62%	49:51
3	DIBAL-H	77%	2:98
4	$LiBH_4$	Quant.	82:18
5	L-Selectride®	96%*	74:26

*Estimated by fluorine NMR

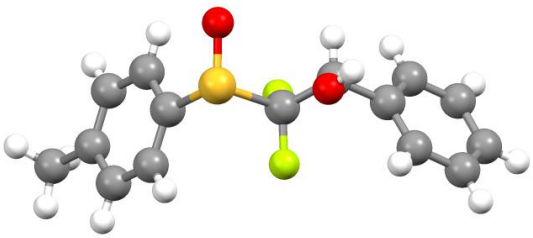
As previously described and similarly to Solladié's work, we expected to access diastereopure β-hydroxysulfoxides depending on the reaction conditions.[313] The reduction of the β–ketosulfoxide when using $NaBH_4$ or $LiAlH_4$ led to good yields and moderate diastereoselectivities, respectively up to 72% and 62:38. As expected, the use of DIBAL-H led to a single diastereomer with a 77% yield and a diastereomeric excess of 96%. The use of $LiBH_4$ and L-Selectride® gave a favoured diastereomer opposite to the one obtained when the reduction was performed with DIBAL-H with very good yield and d.r. up to 74:26.

To confirm the efficiency of the reaction in terms of diastereoselectivity, three examples of enantiopure α-difluoro-β-ketosulfoxides were prepared by previously described strategies and reduced with DIBAL-H (**Scheme II.84**).



Scheme II.84. Selective reduction of α-difluoro-β-ketosulfoxides with DIBAL-H

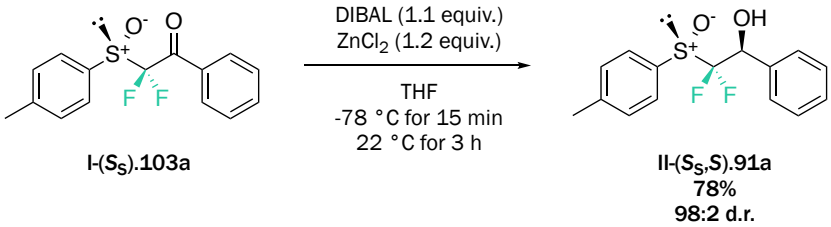
We were able to obtain exclusively one diastereomer of the expected α-difluoro-β-hydroxysulfoxides with high diastereoselectivities (93:7 to 98:2) and an excellent e.e. (96-98%) of the major diastereomer. A X-ray crystallographic structure of one of the crystallized major diastereomers was obtained and confirmed that the product of the diastereoselective reduction is the *anti* isomer (**Scheme II.85**). This configuration confirms our hypothesis concerning the transition states of reduction with DIBAL-H on the difluorinated compounds, corresponding also to the ones of the non-fluorinated β-ketosulfoxides, described in *part 1* of this section.



Scheme II.85. X-ray crystallographic structure of α-difluoro-β-sulfinyl alcohol II-($S_{S,}S$).91a

In the previous studies performed in the group, by condensation of the difluoromethyl sulfoxide anion to carbonyls involving P_4*t*-Bu, it was possible to access highly enantioenriched α-difluoro-β-hydroxysulfoxides of opposite relative configuration. The reduction strategy **(Table II.3 and Scheme II.95)** represents therefore an efficient method complementary to the previously described one.

In order to complete our study regarding the stereoselective reduction of α-monofluoro-β-ketosulfoxides, we decided to perform this reaction in the presence of a chelating agent to have access to the *syn* diastereoisomer, as it was reported on β-ketosulfoxides. However, we were surprised to observe that in the presence of $ZnCl_2$, the same diastereomer was obtained —with a 78% yield and a diastereomeric excess of 96%—, which clearly contrasts with the case of the non-fluorinated analogues (**Scheme II.86**).



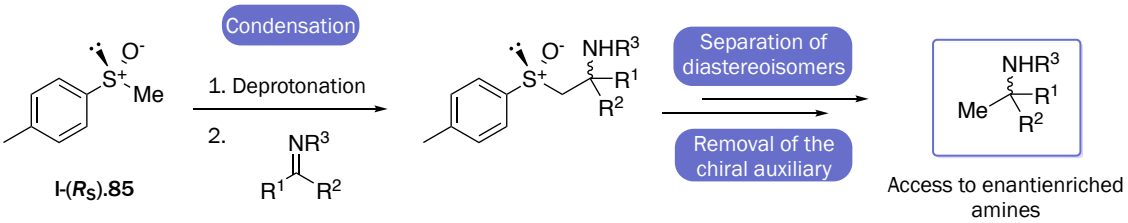
Scheme II.86. Selective reduction to access an α-(arenesulfinyldifluoromethyl)benzyl alcohol

This may indicate that the presence of the two fluorine atoms prevents the double coordination of the ketosulfoxide to the zinc halide, which is assumed to be responsible for the formation of the *syn* diastereomer.

C. Access to difluoromethylated amines by means of difluoromethyl sulfoxides

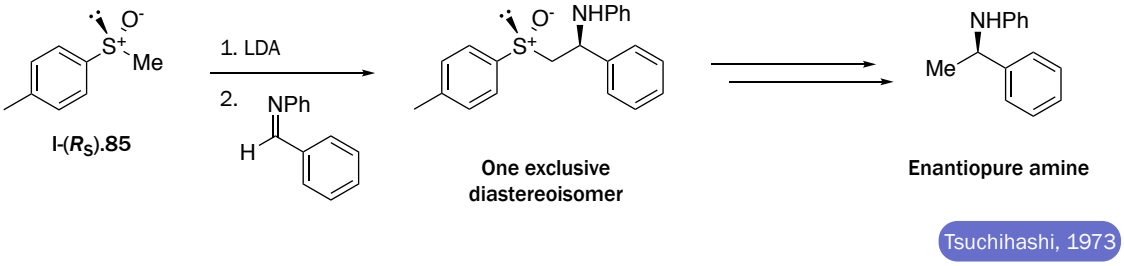
a. State of the art: non-fluorinated series

As in the case of chiral alcohols, among the multiple methods to access chiral amines, sulfoxides proved being valuable stereoinducers, as we will describe hereafter (**Scheme II.87**).



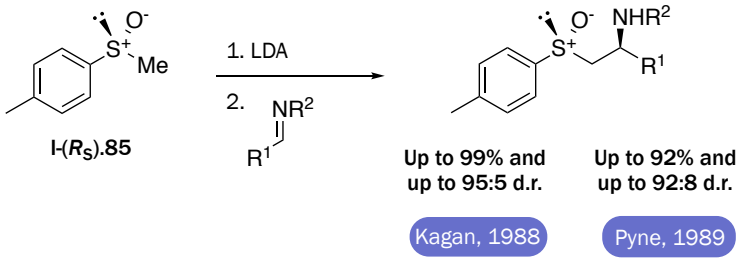
Scheme II.87. Strategy to access enantiopure α-amines using chiral sulfoxides

In 1973, Tsuchihashi reported the obtention of highly optically pure *N*-(1-phenylethyl)anilines after the condensation of methyl *p*-tolyl sulfoxide onto aryl imines (**Scheme II.88**).[325]



Scheme II.88. Obtention of an enantiopure α-arylamine from the condensation of enantiopure methyl *p*-tolyl sulfoxide onto the corresponding imine

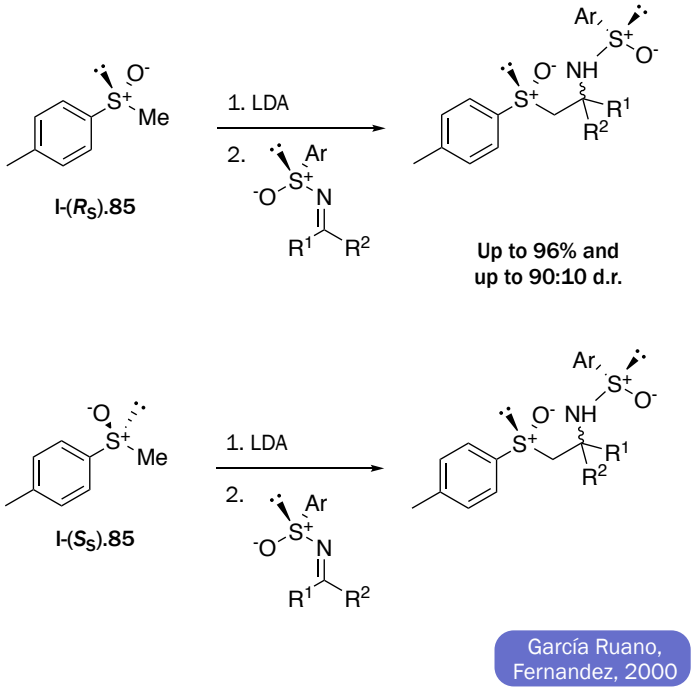
A decade later, Kagan followed by Pyne also studied the synthesis of diastereomerically pure aminosulfoxides.[326] They especially noticed the influence of the temperature of the two steps of the reaction. They were able to obtain the desired derivatives with excellent yields and diastereomeric ratios (**Scheme II.89**).



Scheme II.89. Addition of enantiopure methyl *p*-tolyl sulfoxide to a range of aldimines

After this reaction, only one diastereoisomer of the sulfinyl amine was obtained and after desulfinylation, allowed to access the enantiopure amine.

In the early 2000's, García Ruano and Fernandez described the addition of the lithium carbanions derived from both enantiomers of methyl *p*-tolyl sulfoxide onto *N*-(*S*)-arenesulfinyl)ketimines (**Scheme II.90**).[327,328]



Scheme II.90. Condensation of chiral methyl *p*-tolyl sulfoxides to enantiopure aryl sulfinyl ketimines

The reaction gave the corresponding sulfinylamines with high diastereoselectivities and yields. It is noteworthy that the relative configuration of the newly-formed quaternary carbon center relies on the *N*-sulfinylimine configuration. Thus, both diastereoisomers can be obtained by a proper choice of this substrate.

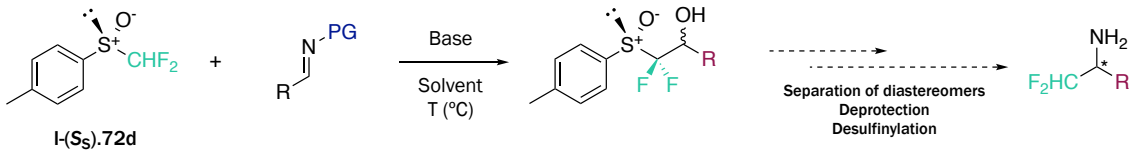
In addition to these methods, examples of the condensation of aryl sulfoxides onto *N*-(PMP)Arylaldimines[329,330] or onto Ellman's *tert*-butyl sulfinylimines[331] were reported with also very good diastereomeric ratios. These intermediates

were then used in the total synthesis of biologically actives compounds or ligands.

b. Attempts of (sulfinyl)difluoromethanide addition onto imines

As described in *part a.2.* of *section A*, and to the best of our knowledge the most representative methods reported to obtain chiral α-difluoromethyl amines involve the presence of a *tert*-butylsulfinyl group as an activating and powerful stereoinducing group on the imine substrate. Therefore, we can consider that new, non-substrate dependent, efficient approaches of a stereoselective introduction of a difluoromethyl group are needed to access building blocks for medicinal research.

We attempted to use the enantiopure difluoromethyl sulfoxide to introduce a difluoromethyl moiety on activated imines, in analogy to the work that has been performed on carbonyl compounds described in *section B* of this chapter (**Scheme II.91**).



Scheme II.91. Strategy to access enantioenriched difluoromethyl amines by means of chiral sulfoxides

Difluoromethyl *p*-tolyl sulfoxide has shown in the previous condensation trials some reactivity limitations towards electrophiles. A substrate that would be activated enough was thus required.

According to electrophilicity scales that have been reported by Mayr (**Figure II.5**),[332] we chose *N*-tosylimines as model substrates for first experiments.

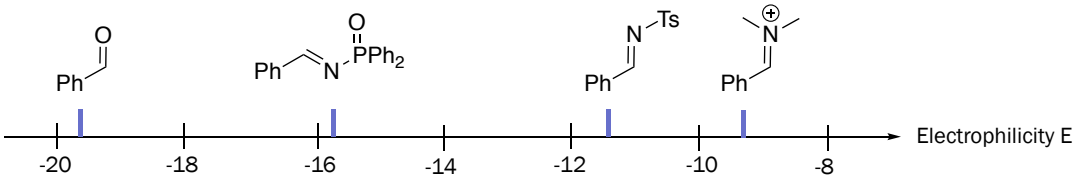
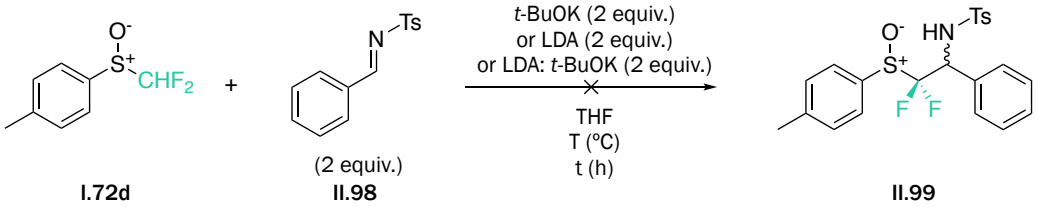


Figure II.5. Electrophilicity scale of aryl imines compared to benzaldehyde

In analogy with the conditions we developed for the condensation onto carbonyls, we first used *t*-BuOK as the corresponding base at -30 ºC (**Scheme II.92**).



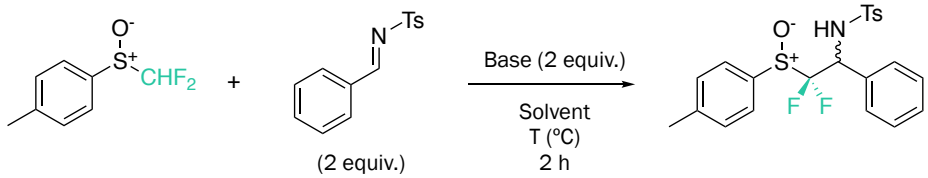
Scheme II.92. Attempts of difluoromethylation of a model tosylimine

Unfortunately, only a minimal conversion of the starting material into the desired amine was observed after some hours. The starting materials were recovered. Moreover, the examples regarding non-fluorinated aryl sulfoxides added to imines often use LDA and led to excellent results. In our case, it was not possible to observe the expected product. The combination of lithiated bases with alkali metal enolates resulting into a strong base with low nucleophilicity was also tested without success.

In some of our previous experiences, the use of toluene allowed us to perform condensation reactions of difluoromethyl *p*-tolyl sulfoxide onto electrophiles (*section B, part c*). This solvent was then tested with different bases in order to find the best reaction conditions for this nucleophilic addition. P_4*t*-Bu, KHMDS, LiHMDS and a combination of LiHMDS and TMEDA were tested.

KHMDS and P_4*t*-Bu allowed us to obtain difluorinated tosylamines with yields up to 34%. However, the diastereomeric ratio remains around 4:6 for these trials. Reactions with LiHMDS led to mixtures for which a low d.r. could only be determined. Since the best yield was obtained when using P_4*t*-Bu, we also evaluated THF as solvent, and we did not observe major differences in terms of diastereomeric ratio. As a better yield was obtained in THF, this solvent was then used for further experiments (**Table II.4**).

Table II.4. Difluoromethylation of *N*-tosyl benzaldimine

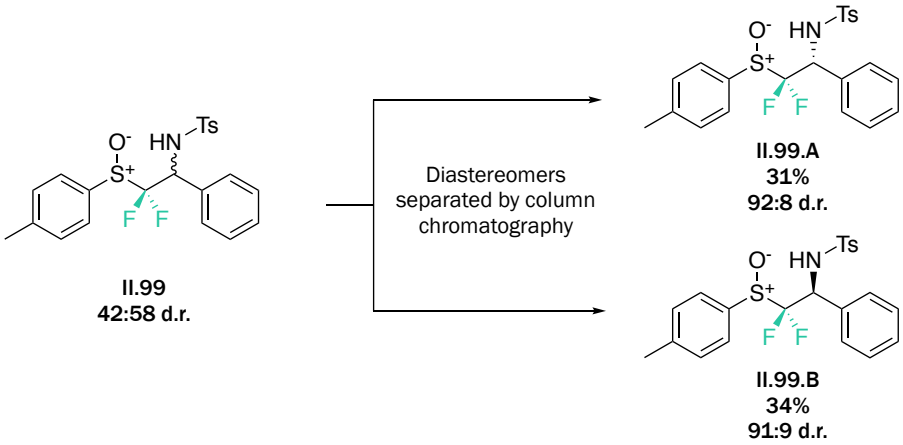


Entry	Base	Solvent	T (°C)	Yield	d.r.
1	LiHMDS	Toluene	-30	Undetermined	48:52
2	LiHMDS + TMEDA	Toluene	-30	Undetermined	50:50
3	KHMDS	Toluene	-30	30%	49:51
4	P_4*t*-Bu	Toluene	-30	34%	40:60
5		THF	-78	59% conversion*	34:66
6			-30	54%	42:58
7			0	Undetermined	36:64
8			22	Undetermined	39:61

*estimated by ^{19}F NMR

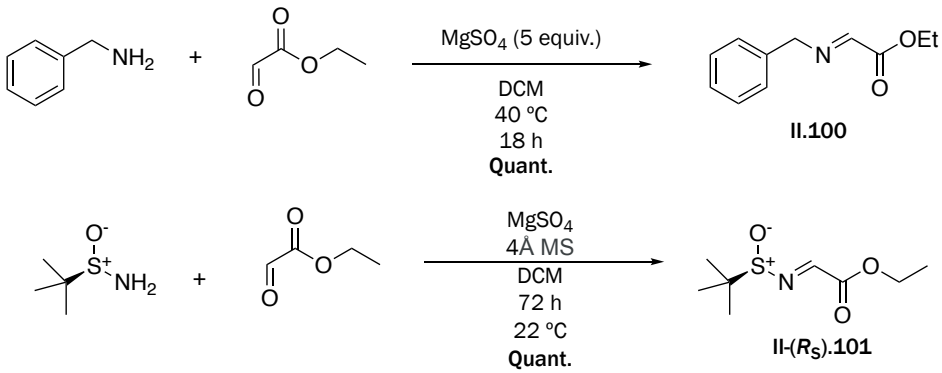
A qualitative ^{19}F NMR monitoring of the reaction after 5, 15, 45 and 120 minutes was performed at -78, -30, 0 and 22 ºC, using phosphazene superbase P_4*t*-Bu in order to evaluate if a kinetic resolution could take place as in the case of α-difluoro-β–sulfinyl alcohols, described in *section B, part a.3.* The diastereomeric ratios observed did not show significant changes with temperature or time of reaction.

To our delight, starting from a mixture of diastereoisomers of 42:58 d.r., we were able to obtain single diastereomers after a column chromatography using a dichloromethane/ methanol eluent system in flash chromatography, after the a first purification using cyclohexane/ ethyl acetate. (**Scheme II.93**).



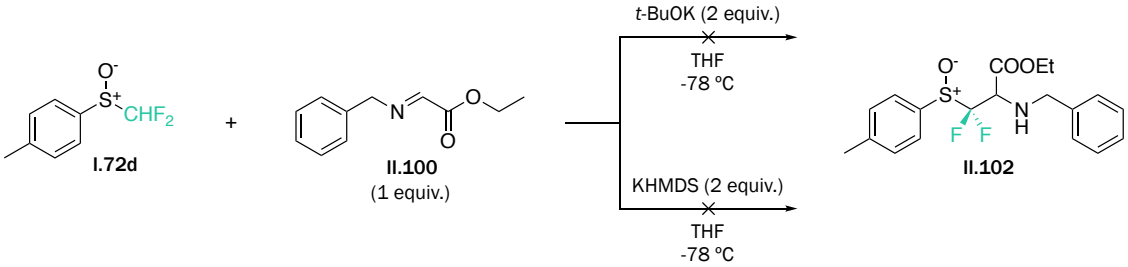
Scheme II.93. Separation of diastereoisomers derived from the condensation of difluoro(*p*-toluenesulfinyl)methanide onto a model *N*-tosyl benzaldimine

After using *N*-tosylimines as electrophiles, we focused on other imino-derivatives. We prepared iminoacetates, first the benzyl derivative and also one enantiomer from an *N*-(*tert*-butanesulfinyl) iminoacetate following the conditions described by Wei and coworkers.[333] To our delight, we were able to obtain quantitative yield in all cases (**Scheme II.94)**.



Scheme II.94. Preparation of *tert*-butyl sulfinyl iminoacetates

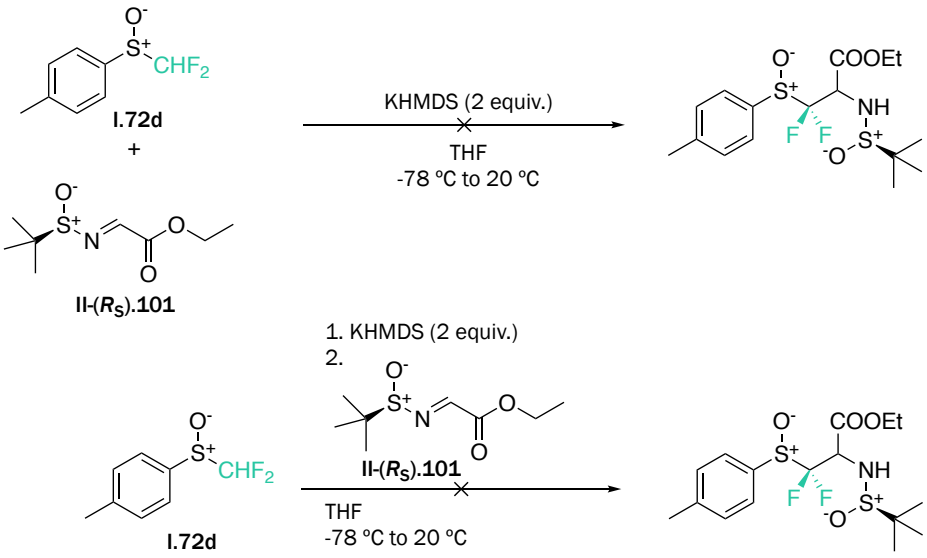
N-benzyl-O-ethyl iminoacetate was then first submitted to the reaction with racemic **I.72d.** (**Scheme II.95**).



Scheme II.95. Addition of difluoromethyl *p*-tolyl sulfoxide to *N*-benzylimino acetate

Unfortunately, the expected difluoromethylated amine could not be obtained under these conditions. As we mentioned in the first part of this section, we suspect this to be due to the lack of activation of the imine derivative, or the required used of a stronger base, for example P_4*t*-Bu. We decided then to test the chiral *N-(tert*-butanesulfinyl)imine prepared, as these kind of derivatives have already been used for difluoromethylation reaction using either difluoromethyl aryl sulfones or difluoromethyl trimethylsilylane.

Racemic difluoromethyl sulfoxide was first reacted with the (*R*)-*N*-*tert*-butylsulfinylimine. Unfortunately, we only could observe a minimal amount of a fluorinated product formed in the medium, and although the coupling constants seemed to correspond to the ones of a difluorinated *N*-sulfinylamine, the conversion was not satisfying whichever the order of the reagents. Moreover, we also observed the formation of the usual side product, difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95** (**Scheme II.96**).



Scheme II.96. Addition of difluoromethyl *p*-tolyl sulfinyl anion to Ellman's *tert*-butyl sulfinyl imines derived from ethyl glyoxalate

One could think this lack of reactivity may come from the mismatch effect related to the configuration of the two sulfoxides, affecting the reaction as the starting material is the racemic difluoromethyl *p*-tolyl sulfoxide. However, one could expect to observe at least a partial conversion on the expected product

II.103. In order to confirm this, it would be useful to perform the addition of **I.72d** onto the opposite enantiomer of *N-(tert*-butanesulfinyl)imine **II-(S_s).101**.

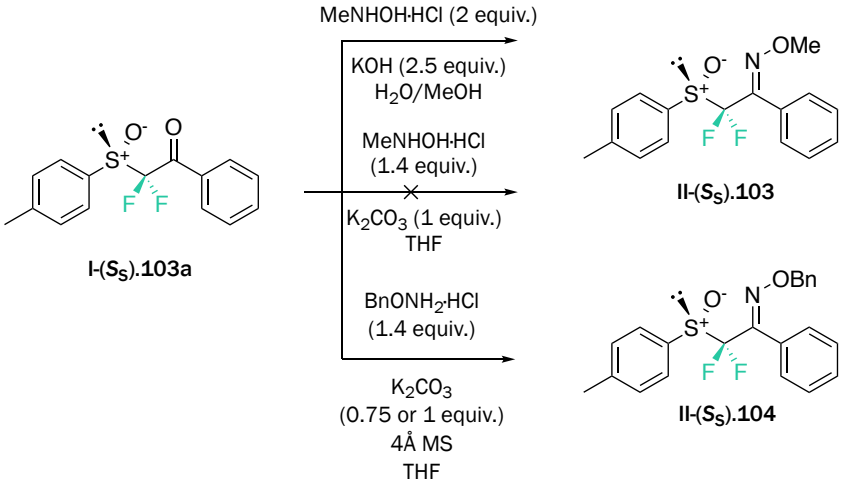
Despite our efforts, in the case of *N*-benzyl-O-ethyl iminoacetate and *N-(tert*-butanesulfinyl)imine we could not observe the formation of the desired product. We recovered the starting material as well as traces of unknown fluorinated products observed by ^{19}F NMR.

Thus, it seemed that it would be worthy to screen other imine derivatives, such as iminium salts or other activated imines not bearing a chiral inductor, so as to benefit from the sole stereoinduction of difluoromethyl *p*-tolyl sulfoxide.

c. Alternative access to difluorinated amines: functionalization of α-difluoro-β-ketosulfoxides into difluorinated β-ketoximes and attempts of reduction

The functionalization of α-difluoro-β-ketosulfoxides could give access to a range of enantiopure α-difluoro-β-sulfinylimines or α-difluoro-β-sulfinylketoximes that, after selective reduction, would provide a library of optically pure difluorinated amines.

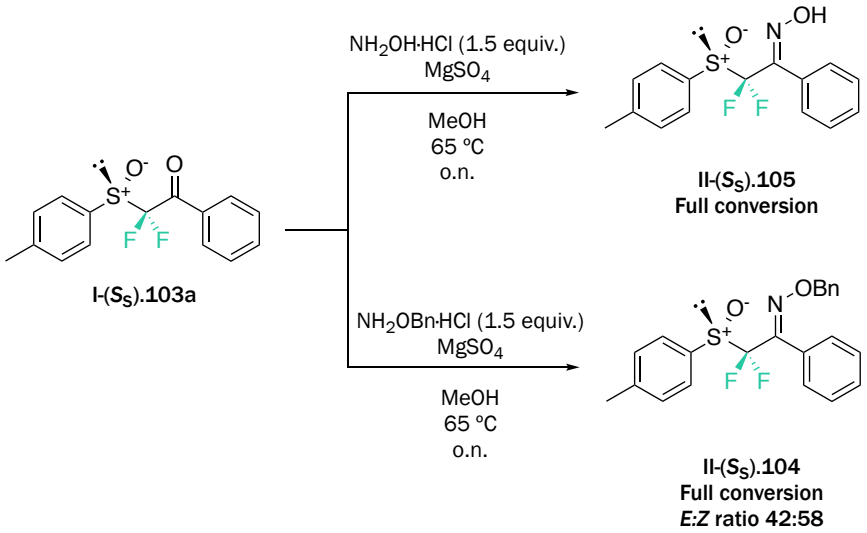
Some attempts of derivatization of the readily synthesized α-difluoro-β-ketosulfoxides were performed. Three methods inspired from procedures described by Dallimore and co-workers for the functionalization of fluorinated sulfones[334] and by Bravo and co-workers[335] for the functionalization of mono-fluorinated sulfoxides were used to try to access fluorinated β-sulfinyl oximes (**Scheme II.97**).



Scheme II.97. Attempts of functionalization of α-difluoro-β-ketosulfoxide to oximes

In all cases, we only could observe partial conversion of the starting material. We able to observe a small amount of the desired product by ^{1}H and ^{19}F NMR, unfortunately, after purification by flash chromatography only the starting α-difluoro-β-ketosulfoxide was recovered. We presume that hydrolysis of the oxime took place, as it was previously described by Fustero and co-workers for similar β-imino sulfoxides.[336]

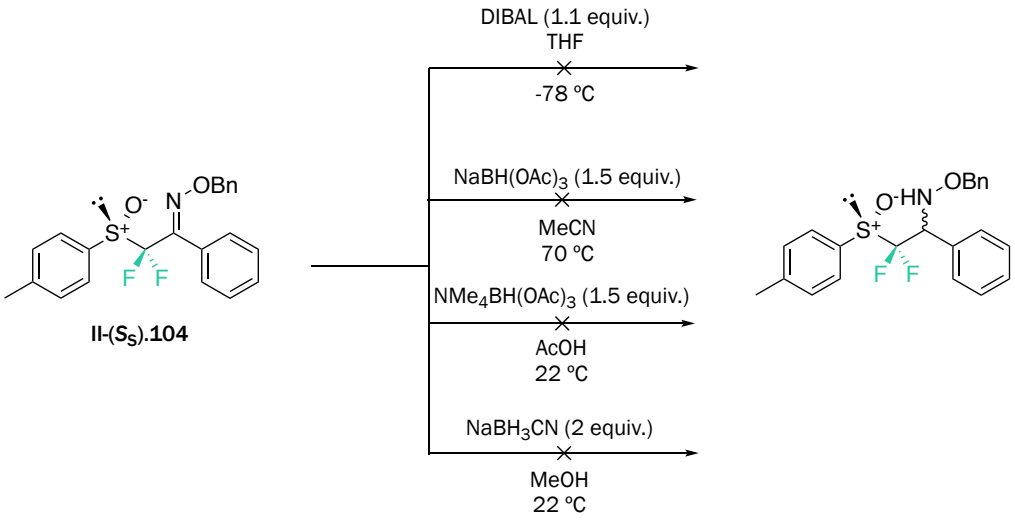
Another method was then used, by reacting the model α-difluoro-β-ketosulfoxide with hydroxylamine or O-benzylhydroxylamine hydrochloride in the presence of magnesium sulfate. To our delight, we were able to obtain a full conversion into the desired α-difluoro-β–sulfinylketoximes (**Scheme II.98**).



Scheme II.98. Successful attempts of synthesis of α-difluoro-β-ketoximes starting from α-difluoro-β-ketosulfoxides

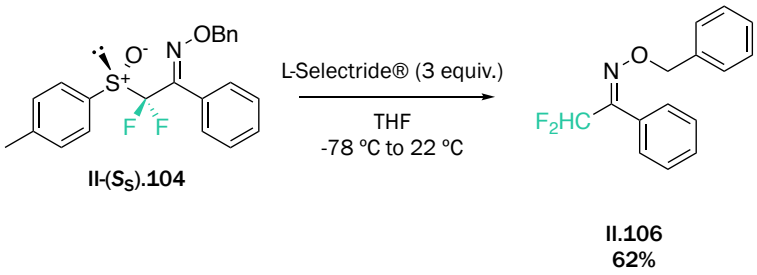
To avoid the previous hydrolysis problems encountered after flash chromatography, we decided to use these compounds without further purification, thanks to their clean and full conversion.

We then focused on their selective reduction in order to access the amino derivatives with a high diastereoselectivity. We applied conditions that had been employed with non-fluorinated analogues, namely the use of DIBAL as well as of $NaBH(OAc)_3$. Unfortunately these reagents did not allow us to obtain the corresponding α-difluoro-β-sulfinyl amines. In the case of DIBAL, unidentified side-products were obtained, as well as a partial amount of the starting α-difluoro-β-ketoxime II-(S_c).104. In the group, the use of $NMe_4BH(OAc)_3$ or $NaBH_3CN$ for the reduction of sulfinyl ketoximes showed good results, but in our case we only recovered the starting material (**Scheme II.99**).



Scheme II.99. Attempts of reduction of α-difluoro-β-ketoxime

We reacted our substrate with L-Selectride®, which is also described to be an efficient selective reducing agent for this kind of compounds (**Scheme II.100**) and that was used previously for the reduction of α–difluoro-β-ketosulfoxides (*section B* of this chapter).[315,316]



Scheme II.100. Reduction of α-difluoro-β-ketoxime with L-Selectride®

To our surprise, instead of obtaining the reduction product, we observed a cleavage of the S-CF_2 bond. The α-difluoromethyl *O*-benzyloxime **II.106** was obtained with a 62% yield.

To date, it was not possible to reduce our model α-difluoro-β-ketoxime derivative with classical reduction methods for non-fluorinated analogues.

d. Condensation of difluoromethyl *p*-tolyl sulfoxide on nitrones

In the previous section, we attempted without success to access α-difluoro-β-sulfinyl amines from the reduction of α-difluoro-β-ketoximes. We explored then another method in order to obtain these compounds.

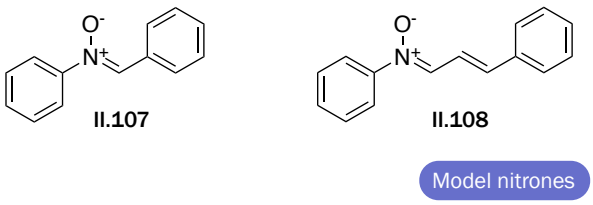
As more electrophilic analogues of imines, we considered nitrones and oximes for the addition of difluoromethyl *p*-tolyl sulfoxide to nitrones was studied, by analogy to the trifluoromethylation pathways of nitrones described in the litterature. The use of nitrones as an intermediate for the nucleophilic addition of the difluoromethyl moiety represented an alternative to access difluoromethyl amino derivatives, as it has been similarly done for trifluoromethylation reactions by Nelson *et al.*[337,338], and Kaliappan *et al.*[339] Moreover, two examples of successful and selective additions of the non-fluorinated analogue, methyl *p*-tolyl sulfinyl anion, have been reported by Cinquini[340] and Pyne.[341]

In addition, previous work has been reported for the addition of an aryl sulfonylmethyl analogue on oximes.[342] Moreover, oximes were worth trying to complete the evaluation of the different electrophiles tested during this project. To the best of our knowledge, at the beginning of this work no asymmetric or racemic synthetic pathway was described to introduce a -CHF_2 group into nitrones. The first example found was reported earlier in 2019 by Dilman.[343] He described a bromodifluoromethylation strategy of nitrones based on visible light promoted radical addition. He also showed that the bromodifluoromethyl group could be transformed again via radical processes to cleave the carbon–bromine bond and access a range of derivatives, among them the ones bearing a -CHF_2 group.

Inspired by the work of Nelson, we chose two model compounds to perform the different addition experiments. Indeed, the nitrone bearing a phenyl group in a-position was an analogue of the previous model electrophiles that we tested. In addition, we also used its vinilogue, since it was described by Nelson to lead to less side-reactions under trifluoromethylation conditions.

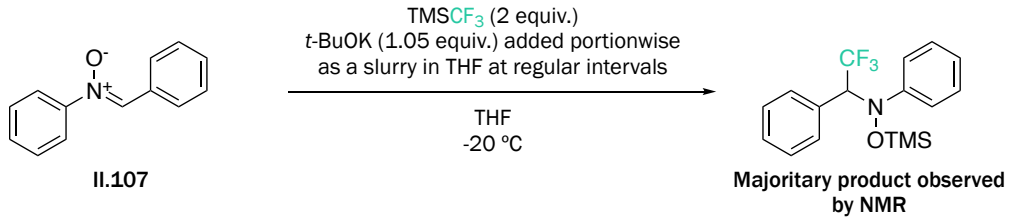
The synthesis of the substrates was performed starting from nitrobenzene and

the desired aldehyde in the presence of zinc to obtain the compounds presented in **Scheme II.101**.



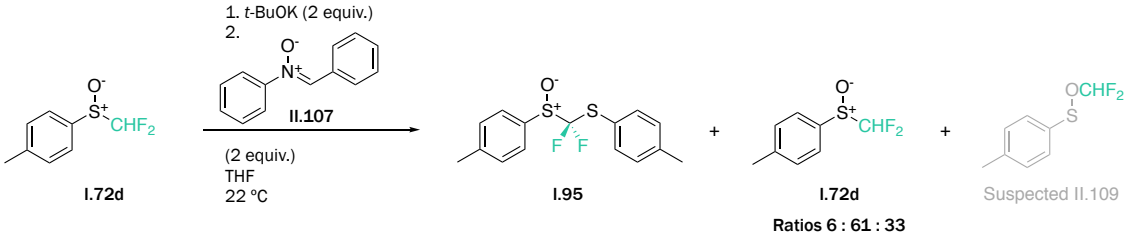
Scheme II.101. Model nitrones synthesized

After having reproduced Nelson's results on model nitrone II.104, we then decided to apply *t*-BuOK deprotonation conditions to perform the difluoromethylation on this substrate at room temperature (**Scheme II.102)**.



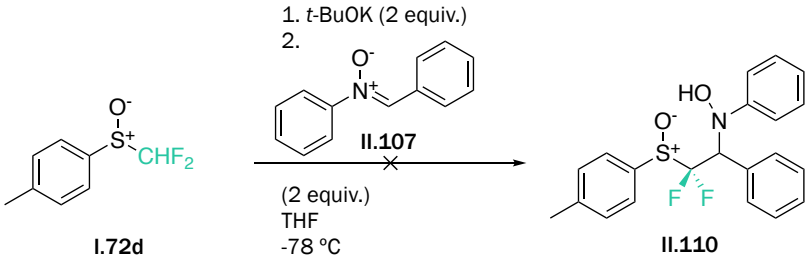
Scheme II.102. Trifluoromethylation of one of the model nitrones with the Ruppert-Prakash reagent

However, we observed the formation of difluoro(*p*-toluenesulfanyl)methyl *p*-tolyl sulfoxide **I.95** as a side-product, remaining starting sulfoxide as well as the side-product, suspected to be the difluoromethyl *p*-tolyl sulfenic ester (**Scheme II.103**). The hypotheses raised regarding these side-products and its formation will be discussed and can be find in *section E* of this chapter.



Scheme II.103. Attempt of difluoromethylation of a model nitrone at room temperature

In an attempt to minimize the formation of side-products, we reproduced the reaction at -78 °C. In this case, the starting materials were fully recovered (**Scheme II.104**).



Scheme II.104. Difluoromethylation of nitrone at low temperature

Although *t*-BuOK was known to efficiently deprotonate difluoromethyl *p*-tolyl sulfoxide, the resulting anion did not react with our model nitrone to give the corresponding difluoromethylated siloxamine.

We decided then to perform the reaction mediated by trimethylsilyl trifluoromethane sulfonates, in analogy to the enol silane additions to *N*-phenyl nitrones reported in literature by Downey.[344]

In fact, in our case we can compare use of difluoromethyl sulfinyl anion with the use of enolates, the stabilized negative charge being delocalized over the sulfur or carbon and the oxygen. Moreover, as in the case of enolates, the difluoromethyl sulfoxide anion is reactive towards electrophiles at carbon (**Figure II.6**).

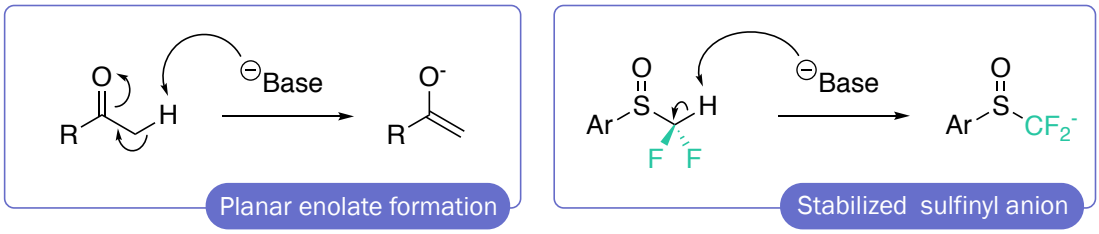
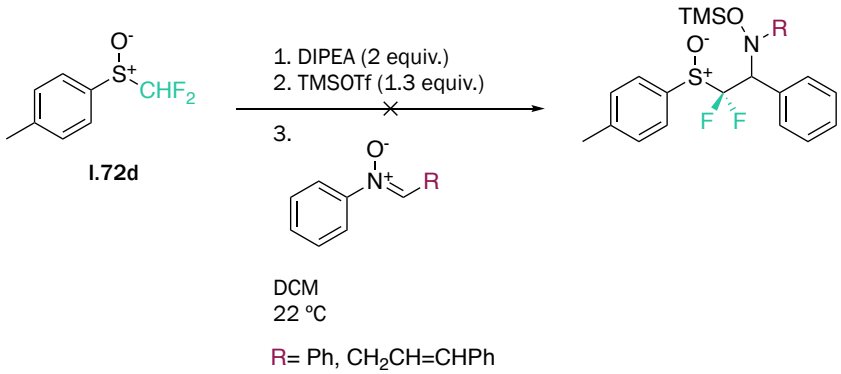
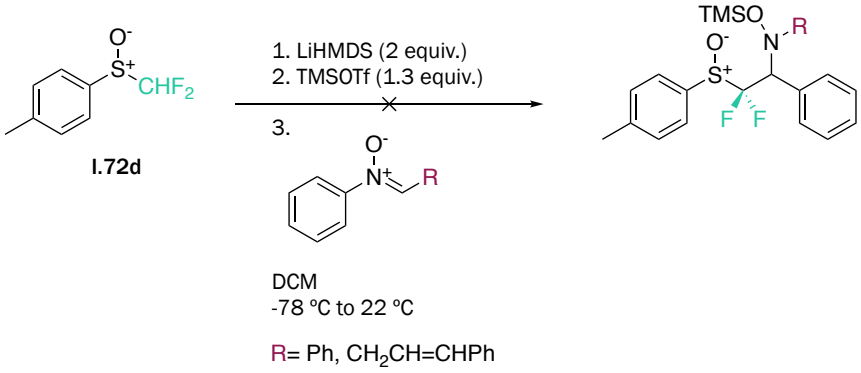


Figure II.6. Comparison of reactivity of enolates and difluoromethyl *p*-tolyl sulfinyl anion

In our case, we employed DIPEA (as Downey) or LiHMDS as the nitrogenated base (**Schemes II.105 and 106)**.



Scheme II.105. Use of DIPEA and TMSOTf for the difluoromethylation of nitrones



Scheme II.106. Attempts of difluoromethylation of nitrones using TMSOTf as an activator

Unfortunately, in both cases, we were not able to isolate the desired compound. Instead, we observed the almost quantitative formation of the recurrent difluorinated side-product difluoro(*p*-toluenesulfanyl)methyl *p*-tolyl sulfoxide **I.95**.

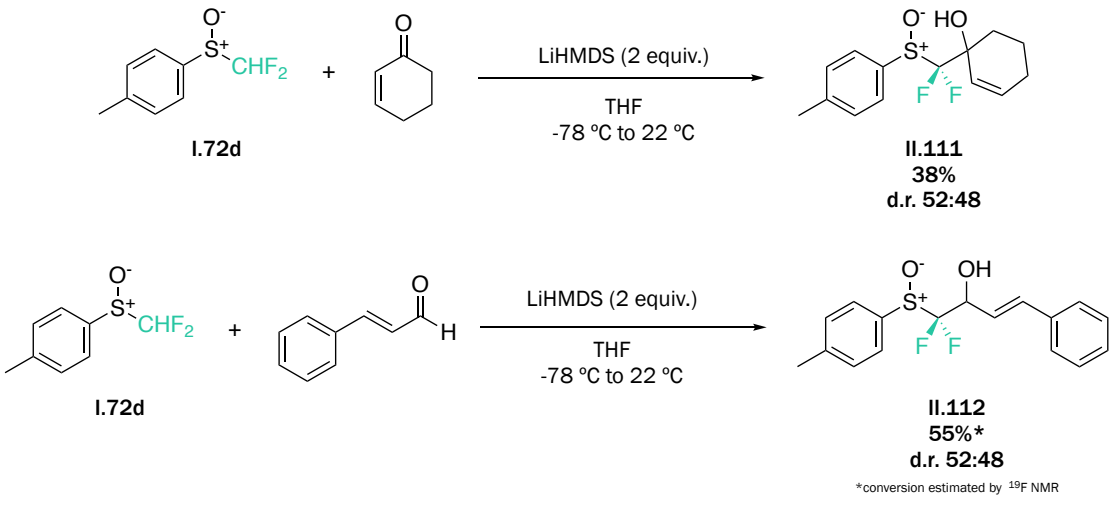
Due to these difficulties in the reactivity of difluoromethyl *p*-tolyl sulfoxide towards the model nitrones that were tested, and the recurrent observation of side-products, it was decided to discard this idea and we decided to try to investigate the mechanism of their formation. These aspects will be described respectively in *section E* of this chapter.

D. Conjugate additions of difluoromethyl *p*-tolyl sulfoxide to 1,4-unsaturated systems

Due to the presumably soft nature of the difluoro(sulfinyl)methanide anion, we wondered whether a softer electrophile than the ones described in the previous sections would be better suited for an efficient addition. We thus turned our attention to alpha,beta-unsaturated ketones or esters, which would have the additional advantage of providing addition products that could not be accessible via the methods described above in this chapter.

Hu's group described in 2008 the addition of a (benzenesulfonyl)difluoromethyl anion to α,β-enones, in which the 1,2-addition was favoured when using LiHMDS as a base at low temperature.[345] They were able to slightly tune this preference and obtain the 1,4-addition product in the presence of HMPA. This result does not seem surprising, as the use of organolithium species is known to favour this kind of selectivity.

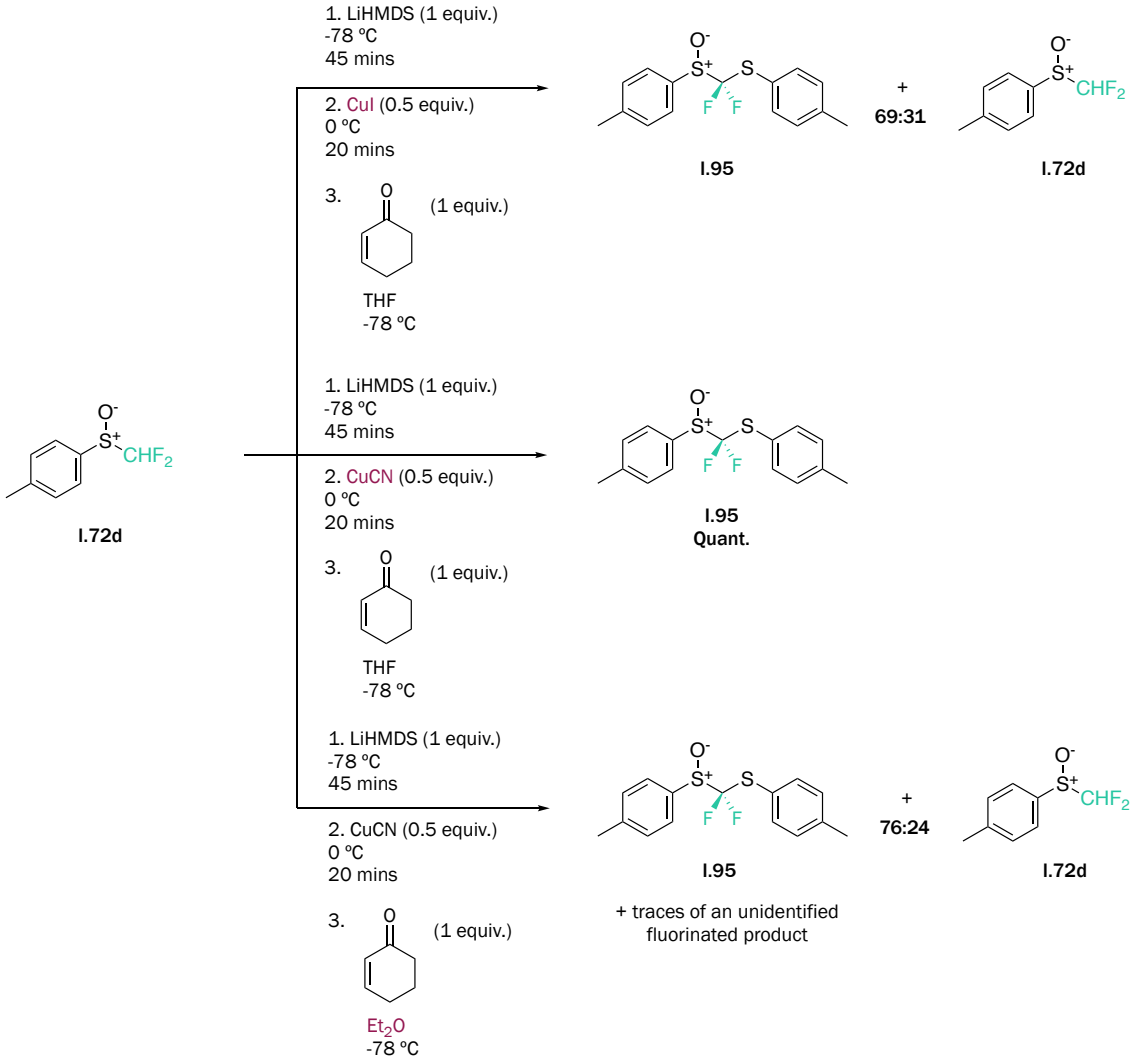
First experiments consisted in performing the addition of the lithiated anion of the difluoromethyl sulfoxide to some α,β–unsaturated systems. As model substrates were chosen cinnamaldehyde and cyclohexenone (**Scheme II.107**). The reactivity of cinnamaldehyde was noticed to be lower than the one of cyclohexenone. Not surprisingly, in both cases, we obtained the product corresponding to the 1,2 addition of the sulfoxide when LiHMDS was used as the base. It is noteworthy that the addition of HMPA to solvate the lithium counterion as described by Hu, and then obtain the 1,4-addition product did not have any influence in our case, as the 1,2-addition product was the only obtained.



Scheme II.107. Attempts of introduction of difluoromethyl *p*-tolyl sulfinyl anion to α,β-unsaturated systems

Lithiated species, combined to copper reagents are described for their use in the addition of nucleophiles to α,β–unsaturated systems.[346,347] The use of these organocopper reagents offers an efficient way for coupling two carbon moieties, and they are known to favour 1,4-addition over 1,2-addition. We

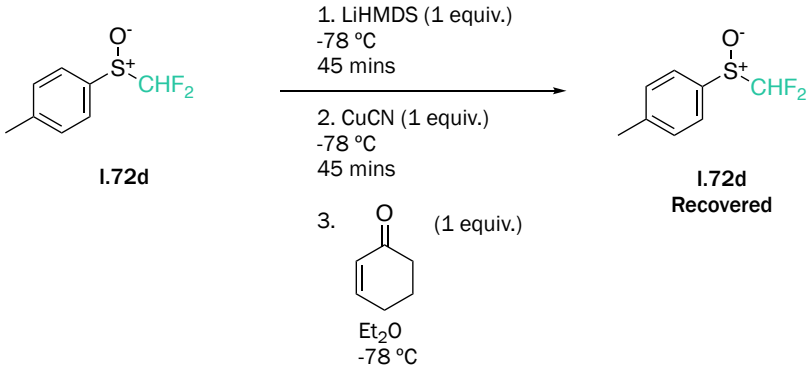
decided to use this approach, by performing the transmetallation of the corresponding lithiated difluoromethyl sulfoxide anion. In a first series of experiments, the difluoromethyl sulfoxide was deprotonated by a freshly prepared solution of LiHMDS, then this lithiated intermediate was added to a solution of a copper (I) reagent, namely copper iodide or copper cyanide. To allow the formation of the organocopper specie, the temperature of the reaction was allowed to reach 0 °C for 20 mins, then it was cooled back to -78 °C and the α,β-unsaturated system was added to the mixture (**Scheme II.108**).



Scheme II.108. Attempts of organocopper catalyzed addition of difluoromethyl *p*-tolyl sulfinyl anion to cyclohexenone

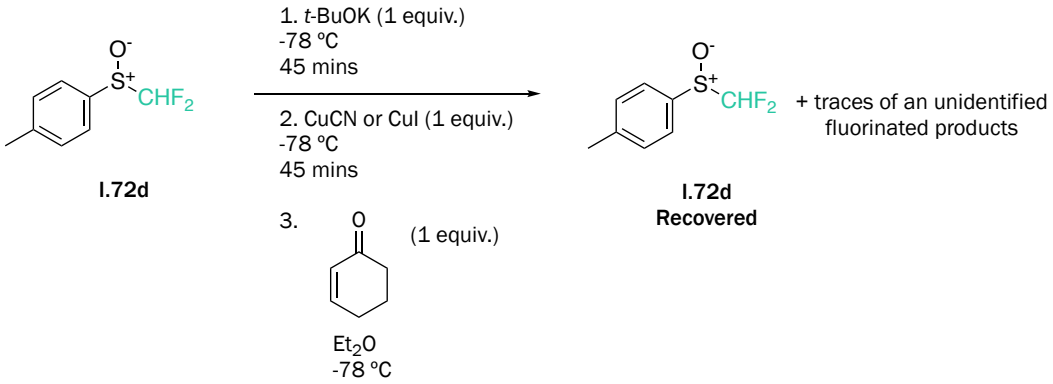
Unfortunately, only the signals corresponding to the difluorinated disulfoxide were observed by NMR. When cyclohexenone or *trans*-cinnamaldehyde were reacted with difluoromethyl *p*-tolyl sulfoxide in the presence of a base and copper iodide as a catalyst, we only could observe the formation of side-product **I.95** and unreacted starting difluoromethyl *p*-tolyl sulfoxide.

The influence of the temperature may impact the formation of side-product **I.95**. The next step consisted in performing the reaction at -78 ºC without changes (**Scheme II.109**).



Scheme II.109. Attempt of addition of difluoromethyl *p*-tolyl sulfinyl anion to α,β-unsaturated systems at a constant temperature

At this point, we mainly observed the unreacted starting material and traces of a fluorinated product. We decided then to use a different base, *t*-BuOK, in combination with copper iodide or copper cyanide. With these conditions, the same previous result was obtained (**Scheme II.110**).



Scheme II.110. Unsuccessful attempts of addition of difluoromethyl *p*-tolyl sulfinyl anion to α,β-unsaturated systems

As the tested conditions were not satisfying to add the masked difluoromethyl moiety to conjugated substrates, and since the pathway to form the difluorinated side-product remains unexplained, this strategy was discarded at this point. Future work may consist in evaluating other copper (I) sources, the stabilized CuBr.SMe$_2$ for example, with different compatible bases. We could also think that the presence of the sulfoxide will interfere with the reaction due to a possible coordination to copper. The addition of a ligand may be efficient to overcome this coordination issue, and could even have a positive impact also on the diastereoselectivity of the reaction. In addition to that, using a phosphazene superbase, which generates a non-coordinating [P$_4$*t*-Bu/H]$^+$ would also avoid a coordination between the sulfoxide and copper, or even *t*-BuO$^-$ and (TMS)$_2$N$^-$ from the employed bases. Furthermore, performing

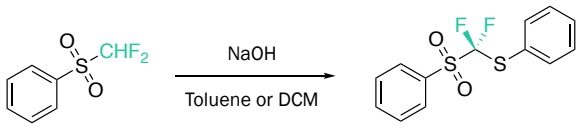
analytical experiences to confirm the formation of the organocopper intermediate prior to the addition of the electrophile would be interesting.

E. Reactivity observations

During the course of the project, we regularly observed side-reactions that limited the applications we contemplated for the difluoromethylation using difluoromethyl *p*-tolyl sulfoxide **I.72d**. Some side-products appeared regularly during nucleophilic additions. At this point, we carried out some experiments that could help us to elucidate the formation of these side-products and the reactivity of our compounds.

The most common side-product was first observed during the Claisen-type condensation reactions performed to synthesize α-difluoro-β-ketosulfoxides (*see section B, part c*). After isolation and characterization, we were able to determine its structure, being difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95.** We also observed it in several additions of the difluoromethyl *p*-tolyl sulfoxide anion to carbonyls along the project, as well as the bromination or silylation attempts.

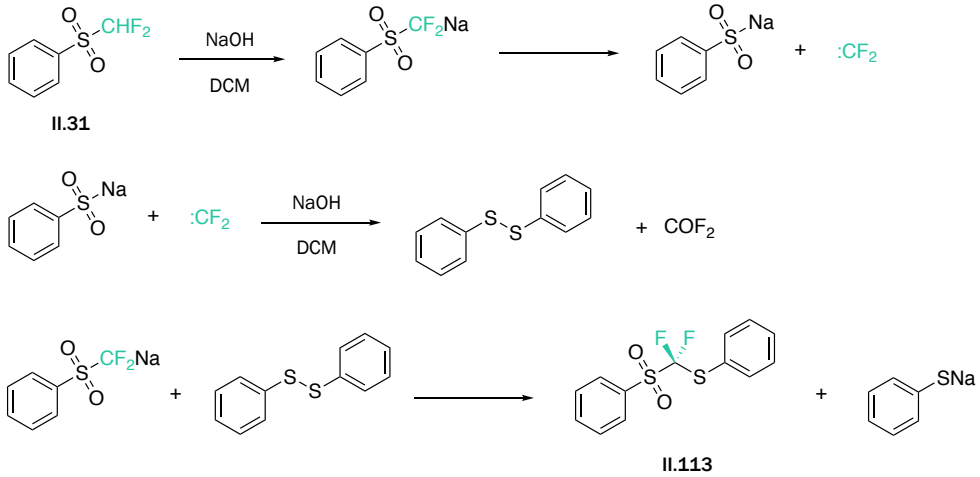
In analogy, we found in litterature the description of the sulfone analogue of this side-product described by Stahly[348] when performing the nucleophilic addition of difluoromethyl phenyl sulfone to aldehydes. He noticed that the treatment of the difluoromethyl phenyl sulfone **II.31** with standard conditions (Brönsted base) in absence of an electrophile led to the formation of difluoro(phenylsulfonyl)methyl phenyl sulfide **II.113** (**Scheme II.111**).



II.31 **II.113**

Scheme II.111. Observations regarding difluoromethyl sulfone under basic conditions

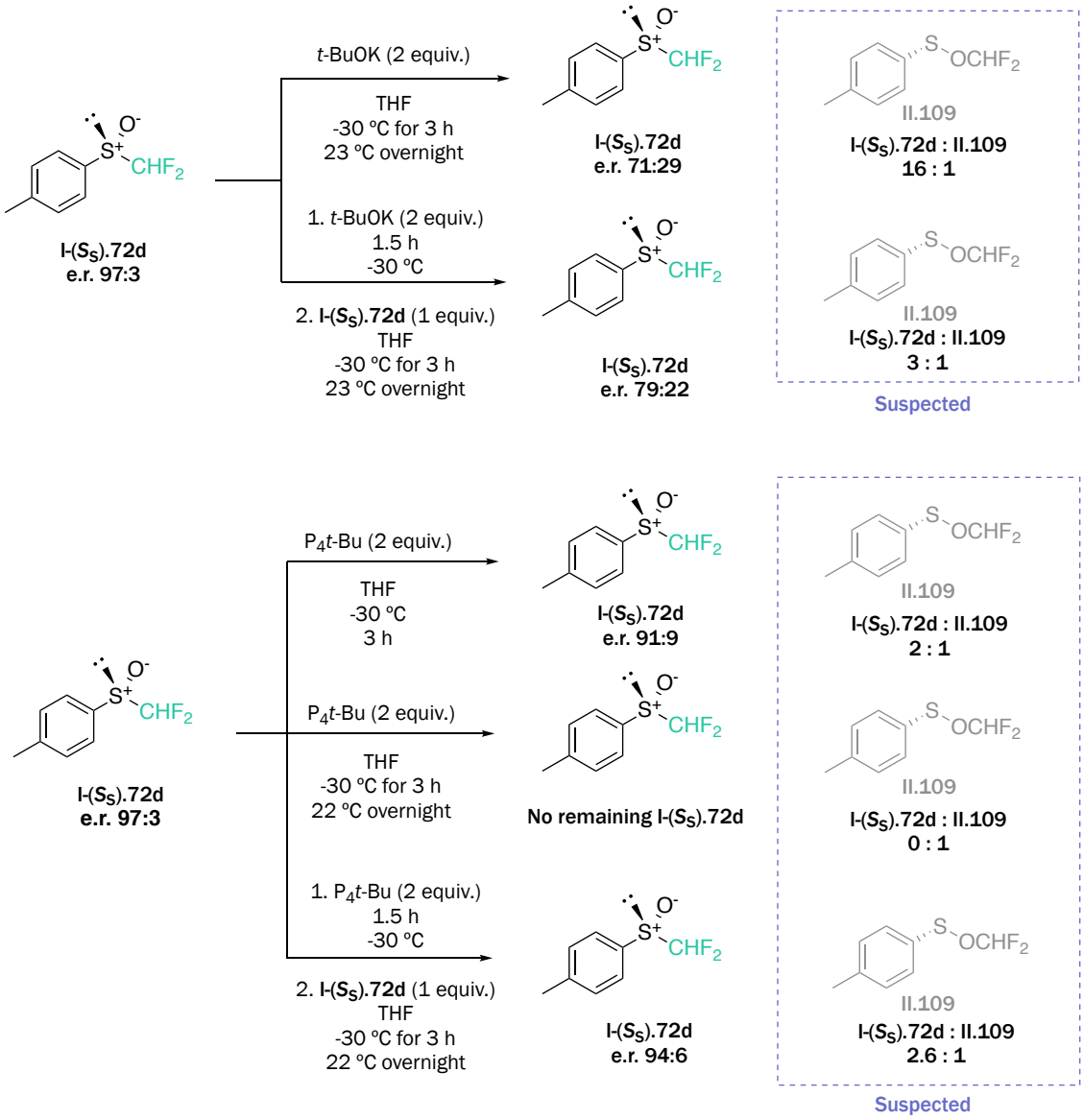
A mechanism was also proposed for the formation of this product (**Scheme II.112**).



II.31 **II.113**

Scheme II.112. Proposed mechanism for the formation of side-products of difluoromethyl phenyl sulfone under basic conditions

Inspired by this description, and not being sure if it can be transposed the case of the corresponding sulfoxide, some experiments were performed in order to try to explain the formation of difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95**. Enantiopure difluoromethyl *p*-tolyl sulfoxide **I-(S_S).72d** in the most common reaction conditions: -30 °C in THF using potassium *tert*-butoxide and P_4*t*-Bu as a base (**Scheme II.113**).

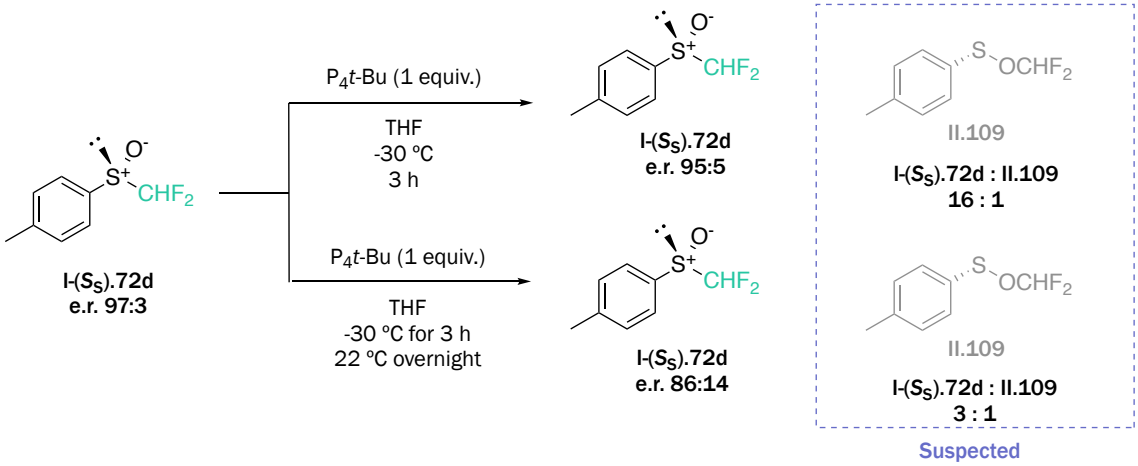


Scheme II.113. Evolution of enantioenriched difluoromethyl *p*-tolyl sulfoxide in the presence of a base and in the absence of an electrophile

First of all, in almost all of these experiences, we observed the remaining presence of difluoromethyl *p*-tolyl sulfoxide **I-(S_S).72d**, and its partial racemization. A part from variable amounts of unidentified side-products and from the latter starting sulfoxide, we observed by proton NMR a signal corresponding to another $-CHF_2$ moiety. However, we were not able to isolate this compound. The corresponding signal of this compound is a triplet having a classical coupling value for the $-CHF_2$ group, i.e. 55 Hz, at 6.7 ppm. In fluorine NMR, a signal was also detected at -91 ppm when this byproduct was observed.

In addition, the crude mixture analysis by UPLC-MS only revealed a major peak having the corresponding mass of difluoromethyl *p*-tolyl sulfoxide **I-(*S*$_S$).72d**. Based on these observations, we supposed the side-product is the corresponding difluoromethyl sulfenic ester **II.109**.

We also carried out experiments where only one equivalent of P$_4$*t*-Bu was used to evaluate the effect on the enantiomeric ratio of difluoromethyl *p*-tolyl sulfoxide after 3 h at -30 ºC in one case and when allowing the medium to reach room temperature in the other case. The results are presented in **Scheme II.114**.

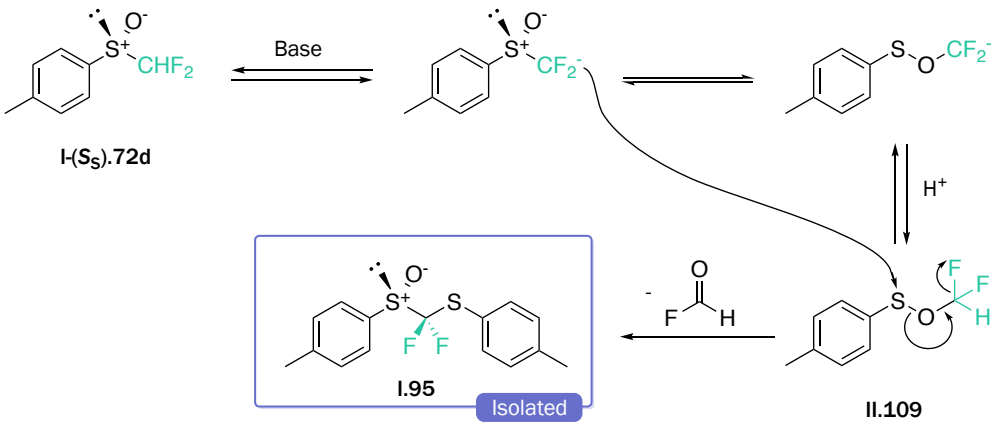


Scheme II.114. Attempt of racemization of difluoromethyl *p*-tolyl sulfoxide using only one equivalent of superbase

Once again, we observed a partial racemization of the difluoromethyl *p*-tolyl sulfoxide. These observations are surprising as **I-(*S*$_S$).72d** was proved to be stable in solution at room temperature. An additional analytical study is underway in our group, in collaboration with Dr. Nicolas Vanthuyne (ISM2 – UMR7313, Marseille) and his coworkers, in order to determine the inversion barriers of aryl difluoromethyl sulfoxides.

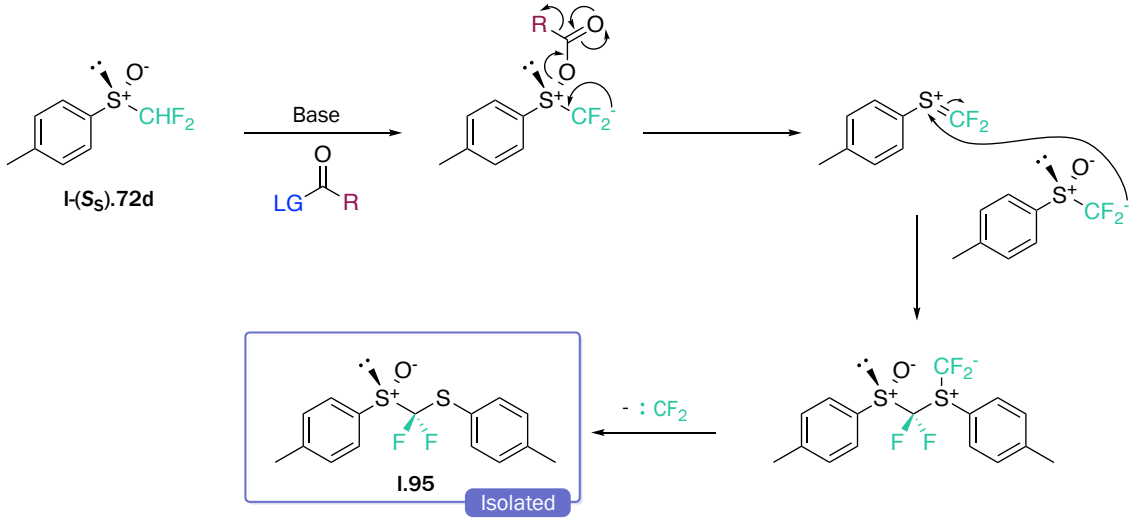
Complementary analytical trials are currently being performed in the group, in collaboration of an analytical partner facility to determine rotational barriers and behavior of our difluoromethyl aryl sulfoxides. We are confident about these informations helping us to have a better understanding of the reactivity of these –CHF$_2$ surrogates.

As we mentioned on several occasions in this chapter, during a large number of experiments, we were able to observe the signals corresponding to the presumed sulfenic ester **II.109**, as well as the concomitant formation of difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95**. If the side-product observed is indeed the difluoromethyl sulfenic ester, this species could be an intermediate in the formation of **I.95** following the mechanism proposed in **Scheme II.115**, with formation of volatile formyl fluoride as driving force.



Scheme II.115. Proposed mechanism accounting for the observation of presumed sulfenic ester II.109 as well as for the formation of side-product I.95

However, the signals of the assumed sulfenic ester were not detected in all reactions were **I.95** was formed. Consequently, this led us to imagine another possible mechanism, when a leaving group was present in the electrophile as in the case of Claisen-type condensations (**Scheme II.116**).



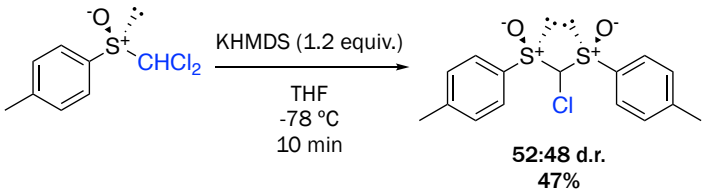
Scheme II.116. Second hypothetical mechanism of formation of difluoro(*p*-toluenesulfanyl)methyl sulfoxide I.95

This mechanism would consist in a Pummerer reaction, where the sulfoxide would be activated at the oxygen atom by the electrophile, leading after elimination of a carboxylate, to a α-difluorosulfenium, which would be attacked by another molecule of deprotonated sulfoxide **I.72d**. After loss of difluorocarbene, the usual byproduct **I.95** would be generated.

With these results and hypotheses in hand, we could partially explain some observations and difficulties encountered before. In fact, the transposition of the -CHF_2 of the sulfoxide **I.72d** to give the sulfenic ester intermediate **II.107** could be in agreement with the fact that the best results for nucleophilic

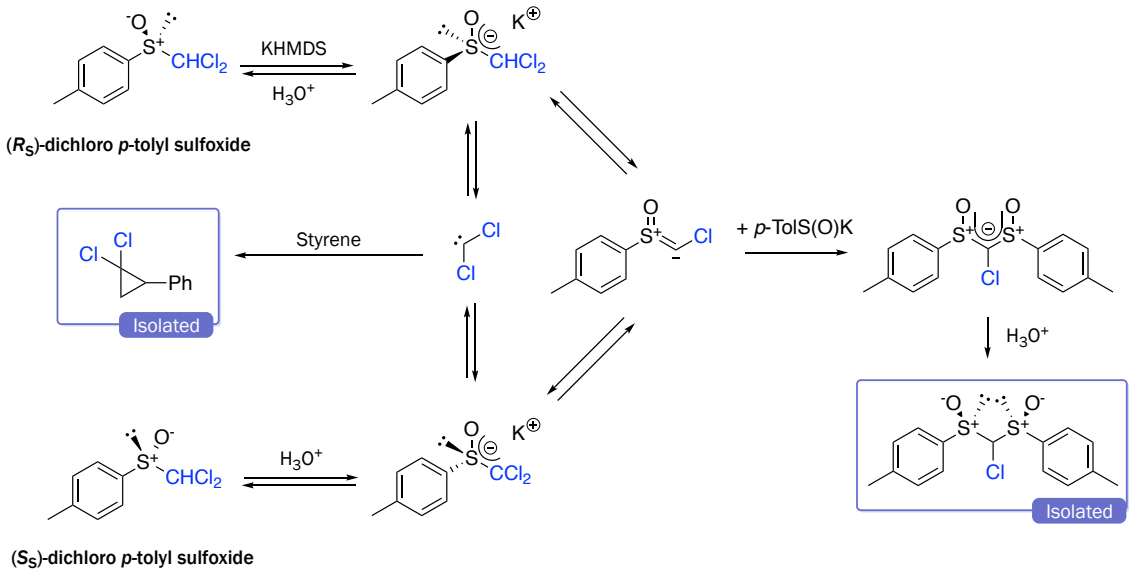
additions to carbonyls were obtained when the electrophile was in the medium with difluoromethyl *p*-tolyl sulfoxide **I.72d** and the base was added to the solution. The rapid reaction with the electrophile may prevent the transposition; accordingly, no signals corresponding to this intermediate were observed before. On the other hand, in the case of imines for which the attack of the deprotonated sulfoxide appears less efficient, the latter is now allowed to evolve into the difluoromethyl sulfenate **II.109** into difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95** that we observed regularly as a product of the reaction. Last, in the case of acyl chlorides and analogues as electrophiles, where **I.95** is also observed, it is presently difficult to distinguish between the two possible mechanisms, namely the one involving the sulfenic ester *vs* the Pummerer reaction type, and both could actually take place in the same reaction medium.

In analogy to our case, Kimura's group studied the stability of enantiopure (R_S)-dichloromethyl *p*-tolyl sulfoxide after observing its racemization in the presence of KHMDS.[349] In their case, they identified chloro(*p*-tolylsulfinyl)methane as major side-product (**Scheme II.117**), but they do not observe a similar dichloro(*p*-toluenesulfanyl)methyl sulfoxide specie as in our case with the difluorinated analogue.



Scheme II.117. Experimental observations of the behaviour (R_S)-dichloro *p*-tolyl sulfoxide in the presence of KHMDS

Moreover, the addition (R_S)-dichloromethyl *p*-tolyl sulfoxide onto styrene using the previous conditions with a longer reaction time led to a low formation of (2,2-dichlorocyclopropyl)benzene. The identification of byproducts obtained led the authors to propose a mechanism for the racemization of (R_S)-dichloromethyl *p*-tolyl sulfoxide in the presence of KHMDS (**Scheme II.118**).



Scheme II.118.Plausible mechanism of racemization of enantiopure dichloromethyl *p*-tolyl sulfoxide proposed by Kimura

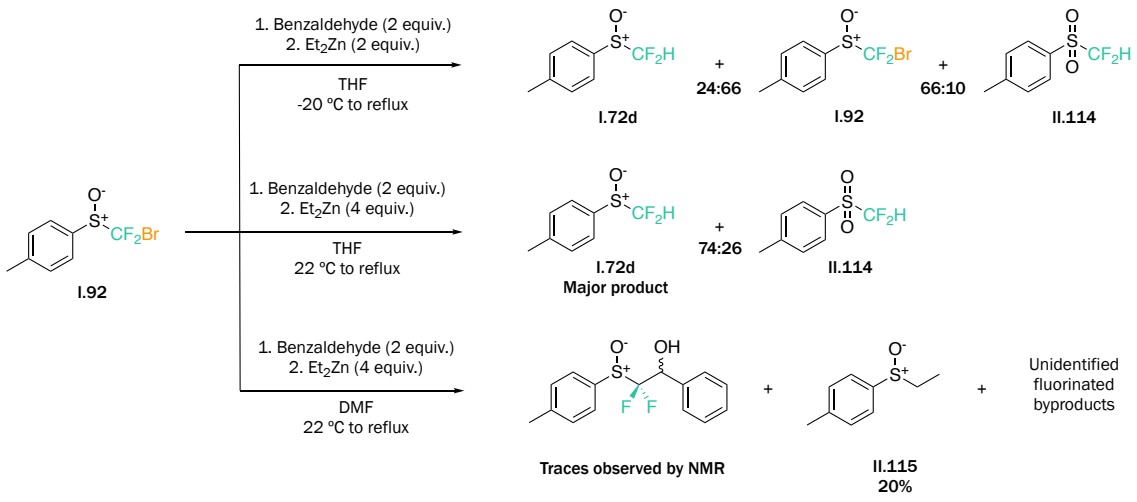
The findings of Kimura would support the fact that enantiopure dihalogenated *p*-tolyl sulfoxides are susceptible to racemization, in contrast to usual chiral non-racemic sulfoxides. Nevertheless, their proposed mechanism seems not appear to apply to difluoromethyl *p*-tolyl sulfoxide, as we did obtain different side-products in basic medium. Further experimental and computational studies would help in the elucidation of the racemization process of enantiopure difluoromethyl *p*-tolyl sulfoxides.

F. Reformatsky-type reactions from bromodifluoromethyl sulfoxides

As described in the first chapter, we aimed to synthesize difluorinated sulfoxide derivatives in order to try different transformations, complementary to the nucleophilic additions previously described.

We were able to access a bromodifluoromethyl sulfoxide by electrophilic bromination of difluoromethyl *p*-tolyl sulfoxide with a moderate yield. The next step consisted then in using this new substrate with a model electrophile to evaluate its reactivity and further applications. The experiments were performed starting from the racemic derivative.

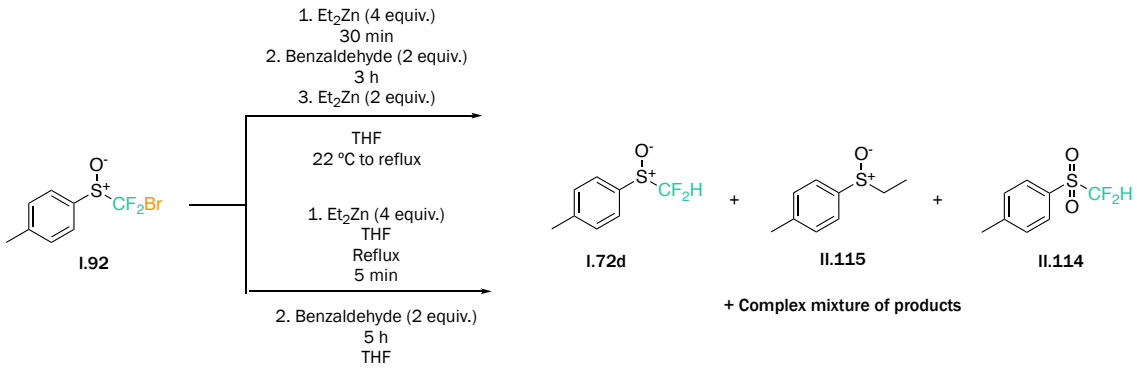
In the past, the Reformatsky-type reaction of ethyl bromodifluoroacetate was used in our team to prepare ethyl difluoro (*p*-toluenesulfinyl)acetate in highly enantioenriched form from a diastereo- and enantiopure *N*-sulfinyl oxazolidinone by means of diethylzinc. We first transposed these reaction conditions to bromodifluoromethyl *p*-tolyl sulfoxide (**Scheme II.119**). As a model substrate, we chose benzaldehyde, which was previously used also as a model substrate for nucleophilic additions of difluoromethyl *p*-tolyl sulfoxide.



Scheme II.119. Reformatsky type reaction performed with bromodifluoromethyl *p*-tolyl sulfoxide

Unfortunately, when using 2 or 4 equivalents of diethyl zinc, in the presence of an excess of benzaldehyde, either in DMF or THF as solvents, we mostly observed no conversion, or reduction of the bromodifluoromethyl *p*-tolyl sulfoxide into the corresponding difluoromethyl *p*-tolyl sulfoxide. Moreover, we also observed the addition of an ethyl chain to the sulfoxide, with loss of the difluoromethyl fragment, as well as the difluoromethyl *p*-tolyl sulfone **II.115** in the specified relative proportions that were determined by proton and fluorine NMR. We then changed the order of addition of the reagents, by forming first the fluorinated organozinc intermediate and then adding it to the aldehyde.

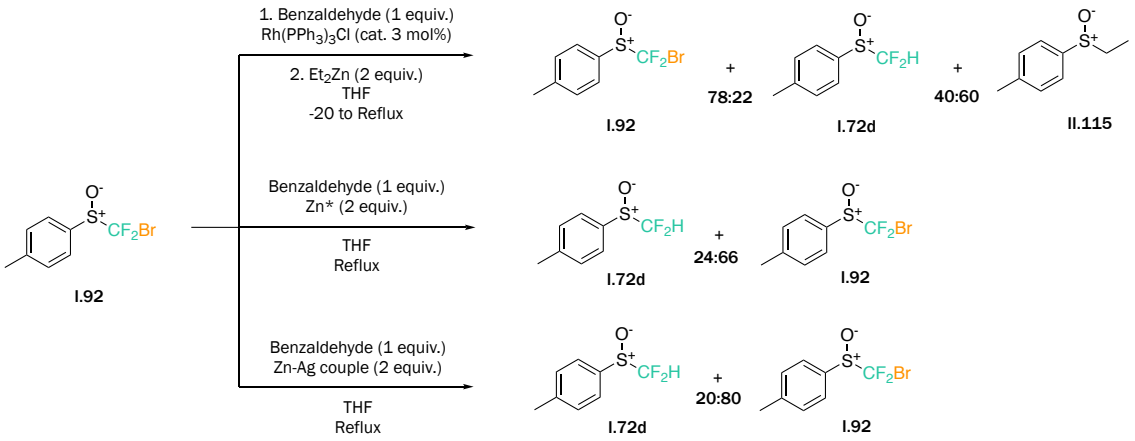
In a first experiment, as the reaction was not evolving in time towards the desired product, after 3 h 2 supplementary equivalents of diethylzinc were added to the medium (**Scheme II.120**).



Scheme II.120. Reformatsky type reactions using diethyl zinc and bromodifluoromethyl *p*-tolyl sulfoxide

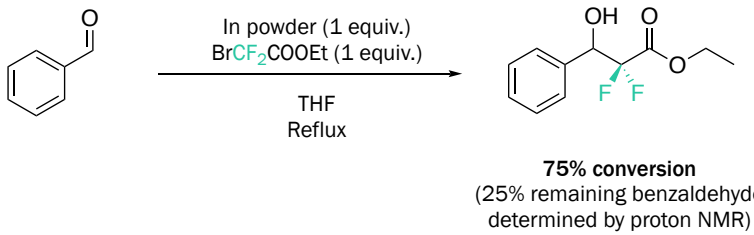
Unfortunately, this addition did not improve the reaction and the desired sulfinyl alcohol was not obtained. The same results were observed when the formation of the organozinc reagent was tried in a shorter time (5 minutes). We only were able to observe the formation of the alkylated sulfoxide as well as the reduction of the bromodifluro *p*-tolyl sulfoxide derivative, small amount of **II.114** and other unidentified side-products in a complex mixture.

We performed the reaction in the presence of a catalytic amount of Wilkinson's catalyst, which is used in the Honda-Reformatsky-type reactions and has been used, among others, for the synthesis of α-difluoro-β-amino acids by Poisson and Linclau.[183] Unfortunately, these conditions only led to the reduction or alkylation of our substrate as in the previous conditions. On another attempt to perform this addition to benzaldehyde, we used pre-activated zinc powder, in order to avoid the alkylation and removal of the fluorine atoms in the molecule. However, a large amount of the starting material was recovered and the substrate that reacted was only reduced to the difluoromethyl p-tolyl sulfoxide. Recently, Konno and coworkers reported an efficient way to perform the zinc insertion in a CF_2-Br bond in alkene derivatives. Indeed, he used a zinc-silver couple Zn(Ag) instead of silver powder, which led to excellent results as the insertion took place very smoothly.[350] We prepared the Zn(Ag) couple and performed the reaction by replacing zinc powder with it. This time, we only observed an increased amount of reduced sulfoxide formed and remaing starting material, but still no addition to the aldehyde (**Scheme II.121**).



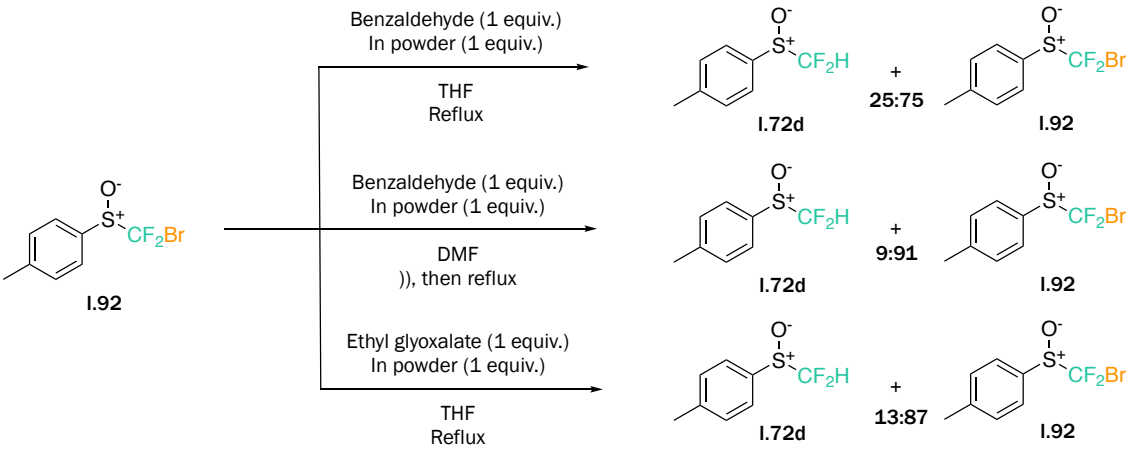
Scheme II.121. Use of diferent zinc systems to perform Reformatsky type reactions

Regrettably, we were not able to obtain the corresponding sulfinyl alcohol under these conditions, and once again only bromodifluoromethyl *p*-tolyl sulfoxide **I.92**, difluoromethyl *p*-tolyl sulfoxide **I.72d** and ethyl *p*-tolyl sulfoxide **II.115** were observed. As the zinc derivatives were not efficient for this transformation, we tried indium as an alternative metal source for the Reformatsky-type reactions.[184] We first performed a reference test to confirm the addition of difluoroacetate to benzaldehyde in the presence of indium when using commercially available ethyl bromodifluoroacetate (**Scheme II.122**).



Scheme II.122. Validation of an indium mediated difluoromethylation Reformatsky type reaction

After validation of these conditions, we applied them to bromodifluoromethyl *p*-tolyl sulfoxide in DMF and THF. We performed the addition on ethyl glyoxalate and benzaldehyde. In one case, the mixture was sonicated (**Scheme II.123**).



Scheme II.123. Indium-mediated Reformatsky type reactions

Unfortunately, we observed the same products as before, namely the reduced difluoromethyl *p*-tolyl sulfoxide **I.72d** and the starting material **I.92**. In view of these results, this strategy was discarded. In the previous reactions, we could notice an apparent lack of reactivity of the organometallic specie resulting from bromodifluoromethyl *p*-tolyl sulfoxide towards a model electrophile. However, it would be interesting to verify the efficiency of the insertion of the metals tested, namely zinc and indium, into bromodifluoromethyl *p*-tolyl sulfoxide.

Complementary studies may consist in the synthesis of organomagnesium reagents derived from **I.88** that could be more reactive than the organozinc or organoindium species prepared in the course of this project.

G. Summary and conclusion

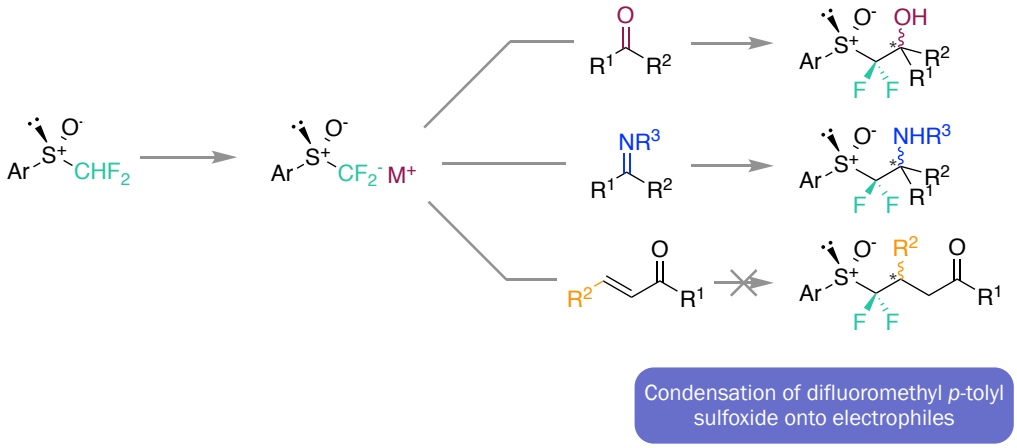
In the course of this project, we aimed to develop an efficient method to synthesize highly optically pure derivatives by means of the use of chiral aryl difluoromethyl sulfoxides.

As described in the first chapter, a gram-scalable and efficient synthetic pathway to obtain enantiopure difluoromethyl sulfoxides was developed and its use in nucleophilic additions to electrophiles was studied. We wished to use this strong chiral inductor in order to obtain a range of diastereoenriched derivatives from carbonyls, imines, nitrones and α,β-unstaturated derivatives.

First of all, inspired by previous work performed within the research team, we studied the condensation of difluoromethyl *p*-tolyl sulfoxide onto aldehydes and ketones. Results described in the group for this reaction in the presence of a phosphazene superbase revealed excellent diastereoselectivities. A hypothetical mechanism was proposed; involving a kinetic resolution explaining how high diastereomerically enriched α-difluoromethyl-β-sulfinyl alcohols were obtained. However during the course of the project some interrogations were raised regarding this kinetic resolution. To shed the light on the mechanism of this resolution, a ca. 1:1 mixture of diastereomers of α-difluoro-β-sulfinyl alcohol **II.91a** was submitted to various basic conditions. In all experiments involving P_4*t*-Bu as the base, a variation of the d.r. was observed, but to varying amplitudes depending on the conditions. These experiments did not allow us to distinguish between two mechanisms, namely a second deprotonation by the superbase *vs* spontaneous elimination of fluoride, leading in both cases to the same outcome, being the formation of the α–monofluoro-β-ketosulfoxide byproduct and formal release of HF.

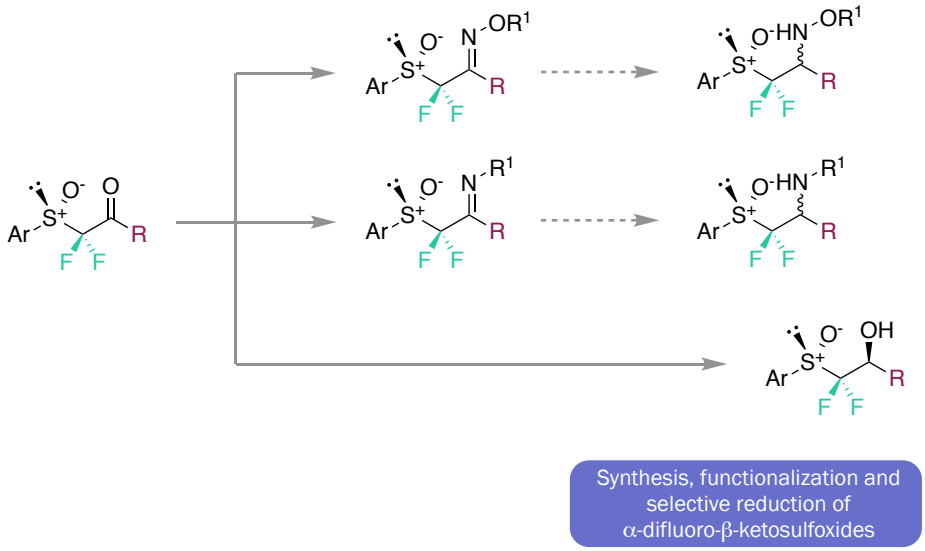
Nevertheless, it was of great interest to apply this condensation strategy in order to access difluoromethylated building blocks of pharmaceutical interest. A selected serie of *N*-heterocyclic ketones and aldehydes were studied as substrates in order to synthesize their corresponding difluoromethyl alcohols. We successfully synthesized difluoromethylated 4-, 5- and 6-membered saturated *N*-heterocycles as well as thiazole derivatives that were used for further functionalization. Details of these aspects will be described in *chapter III.*

On another hand, we decided to screen some electrophiles that could be involved in difluoromethylation reactions with difluoromethyl *p*-tolyl sulfoxide **I.72d**. Model imines, nitrones and α,β-unstaturated systems were tested. Concerning imines, satistfying results were obtained in the case of tosylated imines, as they led, despite a limited diastereoselectivity of the reaction, to diastereomerically pure difluoromethylated *N*-sulfinylamines after separation of diastereomers. The suitable derivatives from imino acetate could not be obtained, and nitrones and α,β-unstaturated did not give the corresponding products as expected (**Scheme II.124**).



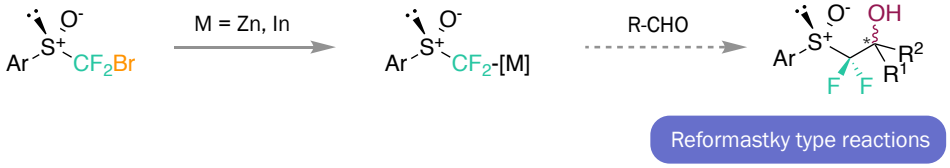
Scheme II.124. Difluoromethylation strategy by condensation of difluoromethyl *p*-tolyl sulfoxide onto electrophiles

A second strategy allowing the access to highly enantioenriched α-difluoro-β-sulfinyl alcohols was the use of their corresponding α-difluoro-β-ketosulfoxides and performing a stereoselective reduction. We decided to study this strategy by first focusing on developing an efficient synthesis of α-difluoro-β-ketosulfoxides. Previously in the group, their preparation was performed by oxidation of a mixture of the two diastereoisomers of difluoromethyl sulfinyl alcohols. We tried to prepare them in a more direct way by performing a Claisen-type condensation of difluoromethyl *p*-tolyl sulfoxide onto ester equivalents. Unfortunately, the results were not as efficient as we expected. We performed then the difluorination of enantiopure β-ketosulfoxides. Once again, we encountered some issues, as a cleavage of a C-C bond took place, probably by a retro-Claisen reaction, leading to enantiopure difluoromethyl *p*-tolyl sulfoxide **I-(S_S).72d**. Nevertheless, then the obtained α-difluoro-β-ketosulfoxides where selectively reduced with DIBAL-H and we were able to obtain a range of derivatives of high optical purity. It is noteworthy that this method is complementary to the condensation of difluoromethyl *p*-tolyl sulfoxides onto carbonyls, which led to α–difluoro-β-sulfinyl alcohols of *syn* configuration, whereas the selective reduction of α-difluoro-β-ketosulfoxides affords the *anti* products. We were also able to functionalize a model α-difluoro-β-ketosulfoxide into α-difluoro-β-ketoximes, their selective reduction remaining non conclusive for the moment (**Scheme II.125**).



Scheme II.125. Study of α-difluoro-β-ketosulfoxides

Finally, in the first chapter, we described the successful synthesis of bromodifluoromethyl *p*-tolyl sulfoxide. This derivative was engaged in Reformatsky type reactions mediated by zinc and indium. Unfortunately, its reactivity was very limited towards model electrophiles and the formation of side-products was recurrent (**Scheme II.126**). More experiments should be carried out to assess the usefulness of bromodifluoromethyl *p*-tolyl sulfoxide.



Scheme II.126. Use of bromodifluromethyl *p*-tolyl sulfoxide for Reformatsky type reactions

During the course of this project, we were able to notice regularly the formation of side-products, specially difluoro(*p*-toluenesulfanyl)methyl sulfoxide **I.95** that was isolated and characterized. Trying to explain its formation led us to perform a series of experiments on the possible decomposition or racemization of difluoromethyl *p*-tolyl sulfoxide. Hypothetical mechanisms were proposed based on experimental observations, however we are not yet able to confirm the exact course of the reaction. The determination of the rotational barrier of enantiopure difluoromethyl *p*-tolyl sulfoxide as well as the determination of its pKa are currently underway in the group in order to bring more elements that could elucidate the mechanisms involved in the reactions that were performed and showed interesting but still unexplained results.

In the next chapter, the use of the diverse compounds that could be synthesized starting from difluoromethyl *p*-tolyl sulfoxide will be described. Our first aim after synthesizing a range of difluoromethanesulfinyl derivatives

consisted in studying the removal of the chiral auxiliary, then performing transformations of the different functional groups present in the molecules.

H. Experimental part

a. Synthesis of α-difluoro-β-sulfinyl alcohols

The diastereomeric ratios of the products were determined by ^{19}F NMR.

1. First strategy: Condensation of difluoromethyl *p*-tolyl sulfoxide onto carbonyl derivatives

General procedure 1a : use of *t*-BuOK

In a reaction tube under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **I.57d** (1 equiv., 50 mg, 0.26 mmol) and the carbonyl derivative (1 equiv., 0.53 mmol) in 1 mL of the appropriate anhydrous solvent (THF or DMF). The mixture was stirred at –30 °C for 5 minutes. Potassium *tert*-butoxide (2 equiv., 60 mg, 0.53 mmol) previously suspended or solubilised in 1 mL of the same anhydrous solvent was added dropwise to the previous solution. The reaction mixture was stirred at –30 °C for 40 minutes, then quenched with water at –30 °C. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with a saturated solution of ammonium chloride and with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

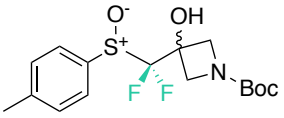
General procedure 1b : Use of KHMDS

To a solution of difluoromethyl *p*-tolyl sulfoxide **I.57d** (1 equiv., 750 mg, 3.94 mmol) and the carbonyl derivative (2 equiv., 3.94 mmol) in 12 mL of anhydrous THF (Tetrahydrofuran) (2 ml) at -30 °C, was added very quickly a commercial solution of potassium bis(trimethylsilyl)amide (15.8 mL, 7.89 mmol, 0.5 M in hexane). The mixture was stirred for 3 h at -30 °C. A saturated solution of ammonium chloride was added to the mixture. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo.

General procedure 1c : use of P_4*t*-Bu

Hexane was removed under vacuum from 0.2 mL of the commercially available solution of superbase P_4*t*-Bu (0.8 M in hexane, 2 equiv., 0.2 mL, 160 μmol). The solid obtained was dissolved in 0.7 mL of freshly distilled THF (or another solvent for tests) previously cooled to –30 °C. To a solution of α,α-difluoromethyl *p*-tolyl sulfoxide **I.57d** (1 equiv., 15 mg, 0.080 mmol) and carbonyl derivative (1 equiv., 0.079 mmol) dissolved in 1.8 mL of freshly distilled THF (or another solvent for tests) at –30 °C was added dropwise the previous solution of P_4*t*-Bu in THF (or another solvent for tests). The reaction mixture was stirred at –30 °C for 2 h, then quenched with water at this temperature. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

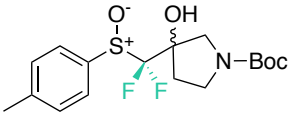
tert-Butyl-3-(difluoro(*p*-tolylsulfinyl)methyl)-3-hydroxyazetidine-1-carboxylate II.91r



II.91r

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to pure ethyl acetate). 22% yield. Yellow oil. **^{1}H NMR (600 MHz, DMSO, 373 K)** δ (ppm) 7.65 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 7.7 Hz, 2H), 4.23 (d, J = 10.1 Hz, 1H), 3.88 (d, J = 10.2 Hz, 1H), 3.81 – 3.67 (m, 2H), 3.07 (s, 9H), 2.43 (s, 3H). **^{19}F NMR (565 MHz, DMSO, 373 K)** δ (ppm) –118.62 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 222.9 Hz, $\Delta\nu_{AB}$ = 1534 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 144.4, 130.4, 126.4, 122.3, 80.5, 72.8, 58.1, 28.4, 21.8. **HRMS (ESI)** m/z calculated for $[C_{16}H_{21}F_2NNaO_4S]^+$: 384.1052, found: 384.1061. **IR (cm^{-1})** 2973, 2322, 1707, 1673, 1399, 1258, 1052, 800.

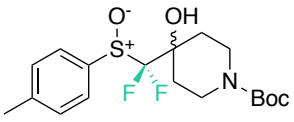
tert-Butyl-3-(difluoro(*p*-tolylsulfinyl)methyl)-3-hydroxypyrrolidine-1-carboxylate II.91p



II.91p

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to pure ethyl acetate). 57% yield. 48:52 d.r. Yellow oil. The diastereomeric ratio and the enantiomeric excess of the product were determined by HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH= 80/20, flow rate 0.5 mL/min, λ = 204 nm, τ = 19.1 min, 21.2 min, 23.4 min, 30.9 min). **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 7.61 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 4.74 (s, 0H), 3.75 – 3.46 (m, 2H), 2.43 (s, 1H), 2.32 – 2.03 (m, 1H), 1.43 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ (ppm) First diastereomer: –112.04 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224 Hz, $\Delta\nu_{AB}$ = 2783 Hz, 2F). Second diastereomer: –112.94 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224 Hz, $J_{BX} = J_{H\text{-}F}$ = 41.8 Hz, $\Delta\nu_{AB}$ = 3445 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 143.8, 132.5, 120.0, 126.8, 80.1, 54.2 (d, J= 25.7 Hz), 44.95, 44.35, 33.28 (d, J = 15.2 Hz), 28.55, 28.48, 21.71. **HRMS (ESI)** m/z calculated for $[C_{17}H_{23}F_2NNaO_4S]^+$: 398.1208, found: 398.1235. **IR (cm^{-1})** 2973, 2322, 1707, 1673, 1399, 1258, 1052, 800.

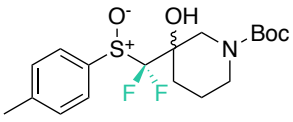
tert-Butyl-4-(difluoro(*p*-tolylsulfinyl)methyl)-4-hydroxypiperidine-1-carboxylate II.91u



II.91u

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 30:70). 45% yield. Yellow oil. **^{1}H NMR (400 MHz, DMSO, 373K)** δ (ppm) 7.19 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 3.43 (dd, J = 13.1, 3.3 Hz, 2H), 2.65 (t, J = 12.6 Hz, 2H), 1.60 (d, J = 14.3 Hz, 1H), 1.26 (m, 3H), 1.00 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -108.73 (*app.* dd, J = 221.3, 102.6 Hz, 1F), -122.09 (*app.* d, J = 221.6 Hz, 1F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 143.9, 130.1, 126.8, 79.9, 74.8 (t, J = 22.1 Hz), 38.5, 31.4, 30.2, 28.6, 21.7. **HRMS (ESI)** m/z calculated for $[C_{18}H_{25}F_2NNaO_4S]^+$: 412.1365, found: 412.1358. **IR (cm^{-1})** 3373, 2976, 1694, 1670, 1477, 1426, 1367, 1251, 1166, 1086, 1052, 812.

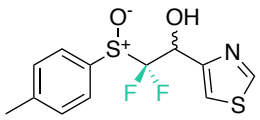
tert-Butyl-3-(difluoro(*p*-tolylsulfinyl)methyl)-3-(4-nitrophenoxy)piperidine-1-carboxylate II.91v



II.91v

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 30:70). 38%. Yellow oil. **^{1}H NMR (600 MHz, DMSO, 373 K)** δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 4.28 (d, *J* = 13.7 Hz, 0.4H), 3.80 (d, *J* = 13.4 Hz, 0.4H), 3.78 – 3.68 (m, 1.6H), 2.98 – 2.78 (m, 0.6H), 3.07 (s, 2H), 2.08 (d, *J* = 13.9 Hz, 1H), 1.92 (dd, *J* = 17.3, 7.9 Hz, 1H), 1.82 – 1.67 (m, 2H), 1.57 – 1.48 (m, 1H), 1.40 (s, 9H). **^{19}F NMR (565 MHz, DMSO, 373 K)** *δ* (ppm) -108.93 (*app.* d, *J* = 219.6 Hz, 0.6F), -109.94 (*app.* d, *J* = 220.8 Hz, 0.4F), -119.94 (*app.* d, *J* = 220.4 Hz, 1F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.6, 129.9, 126.9, 80.62, 74.6 (dd, *J* = 22.1, 19.2 Hz), 28.6, 28.5, 21.7. **HRMS (ESI)** m/z calculated for $[C_{18}H_{25}F_2NNaO_4S]^+$: 412.1365, found: 412.1340. **IR (cm^{-1})** 3388, 2976, 2934, 1673, 1427, 1366, 1280, 1160, 1111, 809.

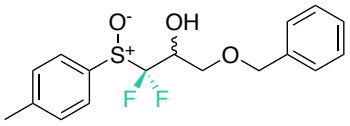
2,2-Difluoro-1-(thiazol-4-yl)-2-(*p*-tolylsulfinyl)-ethan-1-ol II.91q



II.91q

Prepared by general procedure 1a and 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to pure ethyl acetate). 47 % yield. Dark yellow oil. When using procedure 1a, 28:72 d.r., when using procedure 1b, 64:36 d.r. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) First diastereomer 8.85 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 5.37 (dd, *J* = 15.3, 8.2 Hz, 1H), 2.44 (s, 3H), Second diastereomer 8.83 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 5.60 (d, *J* = 21.7, 1H), 2.45 (s, 0.81H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) First diastereomer –115.1 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 219.5 Hz, $\Delta\nu_{AB}$ = 2190 Hz, 2F), Second diastereomer –115.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224.6 Hz, $\Delta\nu_{AB}$ = 1281 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 153.2, 150.6, 143.7, 141.7, 130.1, 129.8, 126.5, 126.5, 125.5, 118.0, 68.3, 29.9, 21.5. **IR (cm^{-1})** 3290, 2921, 1597, 1406, 1194, 1114, 1086, 991, 809, 521, 450. **HRMS (ESI)** m/z calculated for $[C_{12}H_{12}F_2NO_2S_2]^+$: 304.0272, found: 304.0282.

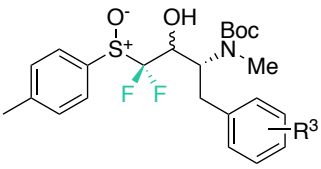
3-(Benzyloxy)-1,1-difluoro-1-(*p*-tolylsulfinyl)propan-2-ol II.91s



II.91s

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate as gradient (from pure heptane to pure ethyl acetate). 10% yield. Yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 7H), 4.85 – 4.44 (m, 2H), 3.89 – 3.73 (m, 2H), 3.31 (d, *J* = 6.5 Hz, 0.6H), 2.95 (d, *J* = 5.1 Hz, 0.4H), 2.45 (s, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** *δ* (ppm) First diastereomer –114.1 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 227.4 Hz, $\Delta\nu_{AB}$ = 2363 Hz, 2F), Second diastereomer –116.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 225.1 Hz, $\Delta\nu_{AB}$ = 241 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.4, 137.3, 131.6, 130.1, 129.3, 127.5, 126.3, 73.9, 68.1, 67.6, 21.4. **IR (cm^{-1})** 1258, 1096, 1025, 800. **HRMS (ESI)** m/z calculated for $[C_{17}H_{18}F_2NaO_3S]^+$: 363.0837, found: 363.0849.

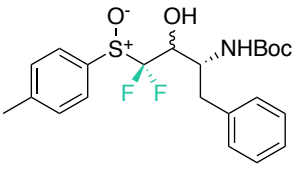
tert-Butyl-((2R)-1-(aryl)-4,4-difluoro-3-hydroxy-4-(*p*-tolylsulfinyl)butan-2-yl)(methyl)carbamate II.91y



II.91y

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 20:80). 17% yield. Yellow oil. 49:51 d.r. *Due to confidentiality reasons, aromatic substituents are not disclosed.* **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm) 4.73 (*app.* d, J = 27.4 Hz, 1H), 3.45 (d, J= 12.0 Hz, 1H), 2.90 (d, J = 10.9 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H, 1.45 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -117.76 (*app.* d, J = 121.0 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 163.0 (d, J = 11.7 Hz), 162.4 (d, J = 11.8 Hz), 161.1 (d, J = 11.9 Hz), 160.4 (d, J = 11.8 Hz), 157.1, 143.9, 143.4, 132.7, 132.6, 132.3 (t, J = 8 Hz), 130.2, 129.9, 129.93, 129.6, 126.8, 123.10, 121.6, 111.4, 103.7, 28.4, 21.4. **HRMS (ESI)** m/z calculated for $[C_{23}H_{27}F_4NNaO_4S]^+$: 512.1489, found: 512.1481.

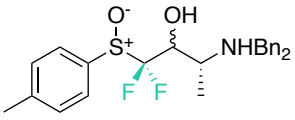
tert-Butyl-((2R)-4,4-difluoro-3-hydroxy-1-phenyl-4-(p-tolylsulfinyl)butan-2-yl)carbamate II.91x



II.91x

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to pure ethyl acetate). 25% yield. Yellow oil. Mixture of 4 diastereomers, 51:49 d.r. and 43:57 e.r. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 – 7.54 (m, 3H), 7.47 – 7.25 (m, 6H), 5.66 – 5.18 (m, 1H), 5.16 – 4.96 (m, 1.5H), 4.83 (d, J = 8.2 Hz, 0.5H), 4.64 (d, J = 24.4 Hz, 0.5H), 4.34 (dd, J = 22.4, 6.0 Hz, 0.5H), 4.25 – 4.01 (m, 2H), 3.16 – 2.84 (m, 1H), 2.49 (s, 3H), 1.43 (m, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** First diastereomer, δ (ppm) –113 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 222.6 Hz, $\Delta\nu_{AB}$ = 2566 Hz, 2F); Second diastereomer, δ (ppm) –113.6 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 225.4 Hz, $\Delta\nu_{AB}$ = 2401 Hz, 2F); Third diastereomer, δ (ppm) –115.3 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 224.9 Hz, $\Delta\nu_{AB}$ = 974 Hz, 2F); Fourth diastereomer, δ (ppm) –115.1 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 220.0 Hz, $\Delta\nu_{AB}$ = 481 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 143.6, 137.5, 130.1, 130.0, 129.82, 129.5, 128.7, 126.7, 126.5, 126.1, 70.3, 68.1, 53.9, 51.8, 37.6, 28.4, 21.8. **IR** (cm^{-1}) 3332, 2978, 1693, 1496, 1393, 1367, 1168, 1087, 1046, 811, 757, 701. **HRMS (ESI):** m/z calculated for $[C_{22}H_{27}F_2NNaO_4S]^+$: 462.1521, found: 462.1521.

(3*S*)-3-(Dibenzylamino)-1,1-difluoro-1-(*p*-tolylsulfinyl)butan-2-ol II.91w

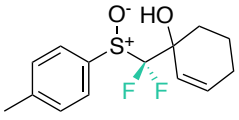


II.91w

Prepared by general procedure 1b. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 30:70). 81% yield. Yellow oil. 50:50 d.r. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.59 (d, J = 7.9 Hz, 2H), 7.43 – 7.28 (m, 12H), 3.87 (t, J = 13.2 Hz, 2H), 3.74 – 3.57 (m, 2H), 3.50 (d, J = 14.4 Hz, 0.6H), 3.27 (d, J = 14.6 Hz, 0.4H), 2.85 – 2.62 (m, 1H), 2.43 (s, 3H), 1.32 (m, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** First diastereomer, δ (ppm) –112.7 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 223.6 Hz, $\Delta\nu_{AB}$ = 3836 Hz, 2F); Second diastereomer, δ (ppm) –113.8 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 220.7 Hz, $\Delta\nu_{AB}$ = 3373 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.1 (d, J= 2.8 Hz), 138.3, 138.0, 129.6, 129.4 (d, J = 4.4 Hz), 128.9, 128.5 (d, J = 2.4 Hz), 128.4, 127.5 (d, J = 3.4 Hz), 126.8 (d, J = 2.1 Hz), 126.8, 74.5 (ddd, J = 33.9, 22.7, 19.6 Hz), 58.67, 59.66, 57.85, 56.32, 21.58. **IR (cm^{-1})** 3388, 3032,

2798, 1495, 1455, 1084, 976, 812, 745, 700. **HRMS (ESI)** m/z calculated for $[C_{25}H_{28}F_2NO_2S]^+$: 444.1803, found: 444.1800.

1-(difluoro(*p*-tolylsulfinyl)methyl)cyclohex-2-en-1-ol II.111



II.111

In a reaction tube under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **I.72d** (1 equiv., 30 mg, 0.16 mmol), cyclohexenone (1 equiv., 0.03 mL, 0.16 mmol) in 1 mL of THF. The mixture was stirred at –30 °C for 10 minutes. In the meanwhile, to a solution of distilled HMDS (2 equiv., 0.07 mL, 0.32 mmol) in 1.5 mL of dry THF at –78 °C was added dropwise butyllithium (2 equiv., 1.54 M, 0.21 mL, 0.32 mmol). This solution was stirred at –30 °C for 20 minutes. The mixture was added dropwise to the previous solution. The reaction mixture was stirred at –30 °C for 2 h. A saturated solution of ammonium chloride was added to the mixture. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude mixture was purified by silica gel flash chromatography using a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 30:70). 38% yield. 52:48 d.r. Colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.9 Hz, 2H), 7.37 (dd, *J* = 8.3, 3.0 Hz, 2H), 6.21 (ddd, *J* = 10.2, 4.7, 3.0 Hz, 0.54H), 6.15 (ddd, *J* = 10.2, 5.0, 2.6 Hz, 0.46H), 6.01 – 5.94 (m, 1H), 3.33 (d, *J* = 34.1 Hz, 1H), 2.44 (d, *J* = 1.3 Hz, 3H), 2.19 – 2.00 (m, 4H), 1.85 – 1.74 (m, 2H). **^{19}F NMR (471 MHz, $CDCl_3$)** δ (ppm) First diastereomer –113,4 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 219.1 Hz, $\Delta\nu_{AB}$ = 5965 Hz, 2F). Second diastereomer –113.3 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 221.5 Hz, $\Delta\nu_{AB}$ = 5351 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.6 (d, *J* = 10.5 Hz), 136.3, 120.0, 126.8, 124.0 (dt, *J* = 43.2, 3.1 Hz), 73.9 (dd, *J* = 20.0, 3.2 Hz), 37.5, 30.8, 29.9, 24.6, 24.2, 21.8, 17.7, 17.5. **HRMS (ESI)** m/z calculated for $[C_{14}H_{17}F_2O_2S]^+$: 287.0912, found: 287.0895.

2. Second strategy – Diastereoselective reduction of α-difluoro-β-ketosulfoxides

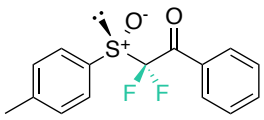
b. Synthesis of α-difluoro-β-ketosulfoxides

General procedure 2a.

Use of PDC as oxidizing agent

4 Å molecular sieves and PDC (1.5 equiv.) were added to a solution of the corresponding α-difluoro-β-sulfinyl alcohol **II-(*S*$_S$).91a or II-(*S*$_S$).91d** (1 equiv.) in anhydrous CH_2Cl_2. The resulting suspension was stirred at room temperature for 43 h. Diethyl ether and water were added to the reaction mixture that was then filtered. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

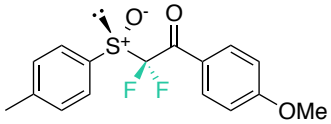
(S)-2,2-Difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-one I-(S_S,*S*).103a



I-(S_S).103a

The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 50:50). Quantitative yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 8.01 (dd, *J* = 1.1 Hz, 8.6 Hz, 2H), 7.67 (tt, *J* = 1.2 Hz, 7.5 Hz, 1H), 7.56-7.48 (m, 4H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H). **^{19}F NMR (471 MHz, $CDCl_3$)** δ (ppm) –103.7 (AB system, J_{AB} = $J_{F\text{-}F}$ = 237.7 Hz, $\Delta\nu_{AB}$ = 1223.8 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 185.5 (t, *J* = 22.7 Hz), 144.1, 135.3, 132.8, 132.5, 130.7, 130.2, 129.0, 126.4, 21.8. **IR (cm^{-1})** 2924, 1694, 1597, 1493, 1450, 1274, 1142, 1090, 1067, 974, 810. **HRMS (ESI)** calculated for [$C_{15}H_{13}F_2O_2S$]: 295.0598, found: 295.0584.

(S)-2,2-Difluoro-1-(4-methoxyphenyl)-2-(*p*-toluenesulfinyl)-ethan-1-one I-(S_S,*S*).103d



I-(S_S).103d

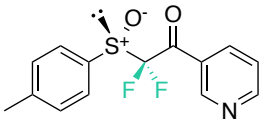
The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient (from pure cyclohexame to 80 :20). 89% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** *δ* (ppm) 8.02 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H), 2.42 (s, 3H). **^{19}F NMR (471 MHz, $CDCl_3$)** *δ* (ppm) –104.9 (AB system, J_{AB} = $J_{F\text{-}F}$ = 235.8 Hz, $\Delta\nu_{AB}$ = 1385 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** *δ* (ppm) 183.3, 165.4, 143.9, 133.4, 132.9, 130.1, 126.3, 114.2, 55.8, 21.8. **IR (cm^{-1})** 2924, 1694, 1597, 1493, 1450, 1274, 1142, 1090, 1067, 974, 810. **HRMS (ESI)** calculated for [$C_{15}H_{13}F_2O_2S$]: 295.0598, found: 295.0584. IR (cm^{-1}) 1684, 1598, 1269, 1147, 603. HRMS (ESI) calcd for $C_{16}H_{14}F_2O_3SK$: 363.0263, found: 363.0253.

General procedure 2b.

Use of DMP as oxidizing agent

DMP (1.2 equiv., 565 mg, 0.41 mL, 1.33 mmol) was added to a solution of α-difluoro-β-sulfinyl alcohol **II-(S_S).91f** (1 equiv., 330 mg, 1.11 mmol) 21a-6 and $NaHCO_3$ (4 equiv., 373 mg, 4.44 mmol) in 8 mL of anhydrous CH_2Cl_2 at 25 ºC. The mixture was stirred for 30 min. A saturated solution of $NaHCO_3$ was added to the reaction mixture. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

(*S*)-2,2-Difluoro-1-(3-pyridinyl)-2-(*p*-toluenesulfinyl)-ethan-1-one I-(S_S).103c



I-(S_S).103c

The crude was purified by chromatography on demetalled silica gel with a cyclohexane :ethyl acetate gradient (100 :0 to 20 :80). 87% yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 9.12 (dd, *J* = 2.3, 1.0 Hz, 1H), 8.84 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.31 (dq, *J* = 9.0, 1.9 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.45 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H), 7.36 – 7.30 (m, 2H), 2.42 (s, 3H). **^{19}F NMR (471 MHz, $CDCl_3$)** δ (ppm) –104.3 (AB system, J_{AB} = $J_{F\text{-}F}$ = 238.4 Hz, $\Delta\nu_{AB}$ = 1907,6 Hz, 2F).**^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 185.1 (t, *J* = 24.6 Hz), 154.9, 151.5, 144.4, 138.0, 132.3, 130.3, 129.8, 128.6, 126.1, 123.6, 21.8. **IR**

(cm^{-1}) 1699, 1585, 1140, 1089, 810, 700, 515. **HRMS (ESI)** calcd for $C_{14}H_{11}F_2O_2SNNa$: 318.0371, found: 318.0360.

General procedure 2c.

To a solution of difluoromethyl *p*-tolyl sulfoxide **I.72d** (1 equiv., 15 mg, 0.0789 mmol) and benzoyl chloride (1 equiv., 0.009 mL, 0.0789 mmol) in 2.3 mL of dried toluene at -30 ºC, P_4*t*-Bu (2 equiv., 0.8 M in *n*-hexane, 0.197 mL, 0.158 mmol) was added dropwise. The mixture was stirred for 2h at -30 ºC. The reaction mixture was quenched with water and extracted three times with diethyl ether. The product was purified by column chromatography with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 70:30 gradient).

(S)-2,2-Difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-one I-(S_S).103a

Prepared using procedure 2c. **I-(S_S).103a** obtained with 30% yield. Yellow oil.

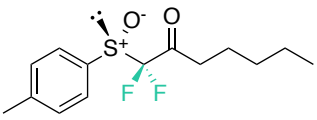
General procedure 2d.

To a suspension of NaH (2.1 equiv.) in freshly distilled THF under argon at 0 ˚C was added a solution of the corresponding β-ketosulfoxide **II.97** (1 equiv.) dissolved in freshly distilled THF. This solution was stirred at 0 ˚C for 30 minutes and then for 1.5 h at 22 ºC. Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) (2.1 equiv.) was added as a solid to the mixture, which was then stirred at room temperature overnight. The mixture was quenched with a saturated solution of ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure.

(S)-2,2-Difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-one I-(S_S,*S*).103a

Prepared using procedure 2d. The product was purified by column chromatography with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 70:30 gradient). **I-(S_S).103a** obtained with 66% yield. Yellow oil.

1,1-Difluoro-1-(*p*-tolylsulfinyl)heptan-2-one I-(S_S).103g



I-(S_S).103g

Prepared using procedure 2d. The crude was purified by chromatography on demetalled silica gel with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 20:80). 87% yield. Light orange oil. **^{1}H NMR (500 MHz, $CDCl^3$)** δ (ppm) 7.56 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 2.71 – 2.49 (m, 2H), 2.44 (s, 3H), 2.43 – 2.33 (m, 1H), 1.59 – 1.47 (m, 2H), 1.38 – 1.16 (m, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR (471 MHz, $CDCl_3$)** δ (ppm) –111.4 (AB system, $J_{AB} = J_{F\text{-}F}$ = 229.6 Hz, $\Delta\nu_{AB}$ = 1766.5 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 196.43, 144.15, 136.97, 132.63, 130.33, 130.28, 129.92, 125.98, 119.27, 40.52, 30.96, 22.40, 21.90, 21.77, 13.95. **HRMS (ESI)** calculated for $C_{14}H_{19}F_2O_2S$: 289.1068, found: 289.1058.

c. Diastereoselective reductions of α-difluoro-β-ketosulfoxides

General procedures to access to highly diastereo- and enantioenriched α-difluoro-β-sulfinyl alcohols (S_S,*S*)-II.91

General procedure 3a.

Reduction with L-Selectride

A solution of L-Selectride (3 equiv., 1 M in THF) was added dropwise to a solution of enantioenriched (S)-2,2-Difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S) (1 equiv.) in freshly distilled THF (ca. 5 mL /mmol) under argon at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 3 hours. The mixture was sequentially treated with water, methanol and a 1M solution of NaOH. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

General procedure 3b.

Reduction with $NaBH_4$

$NaBH_4$ (1.1 equiv.) was added portionwise to a solution of enantioenriched (*S*)-2,2-difluoro-1-(het)aryl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S)- (1.1 equiv.) in dried THF (*ca.* 5 mL /mmol) under argon at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 3 h. A saturated solution of ammonium chloride was slowly added. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

General procedure 3c.

Reduction with $LiBH_4$

$LiBH_4$ (1.1 equiv.) was added portionwise to a solution of enantioenriched (*S*)-2,2-difluoro-1-(het)aryl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S)-**I-(S_S).103a** (1.1 equiv.) in dried THF (*ca.* 5 mL /mmol) under argon at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 3 hours. A saturated solution of ammonium chloride was slowly added. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

General procedure 3d.

Reduction with $LiAlH_4$

A solution of $LiAlH_4$ (1.1 equiv., 2 M in THF,) was added dropwise to a solution of enantioenriched (*S*)-2,2-difluoro-1-(het)aryl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S) **I-(S_S).103** (1 equiv.) in freshly distilled THF (*ca.* 5 mL /mmol) under argon

at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 40 min when no remaining starting material was observed. The mixture was cooled to 0 ºC and a saturated solution of sodium sulphate was added to the mixture. The cooling bath was removed, and the mixture was stirred for 15 minutes at 22 ºC. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

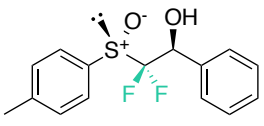
General procedure 3e.

Reduction with DIBAL-H

A solution of DIBAL-H (1.1 equiv., 1 M in THF,) was added dropwise to a solution of enantioenriched (S)-2,2-difluoro-1-(het)aryl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S) **I-(*S*$_S$).103** (1 equiv.) and when chosen, $ZnCl_2$ (1.2 equiv.) in freshly distilled THF (*ca.* 5 mL /mmol) under argon at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 3 h. The mixture was cooled to 0 ºC and diluted with diethyl ether. Water was slowly added, followed by a 1M solution of NaOH. The cooling bath was removed, and the mixture was stirred for 15 minutes at 22 ºC. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

(*S*)-2,2-Difluoro-1-phenyl-2-((*S*)-*p*-tolylsulfinyl)ethan-1-ol (*S*$_S$,*S*)

- Prepared by procedure 3a. The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 50:50). 96% yield. 74:26 d.r.
- Prepared by procedure 3b. The crude was purified by chromatography on silica gel with *n*-heptane:ethyl acetate (from pure *n*-heptane to 50:50). 72% yield. 66:34 d.r.
- Prepared by procedure 3c. The crude was purified by chromatography on silica gel with a *n*-heptane:ethyl acetate gradient (from pure *n*-heptane to 50:50). Quantitative yield. 82:18 d.r.
- Prepared by procedure 3d. The crude was purified by chromatography on silica gel with a *n*-heptane:ethyl acetate gradient (from pure *n*-heptane to 50:50). 62% yield. 49:51 d.r.
- Prepared by procedure 3e. The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 50:50). 77% yield. 98:2 d.r., 96% e.e.
-



II-(S$_S$,*S*).91a

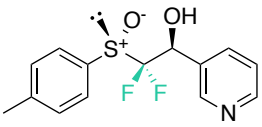
One diastereomer **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 7.62 (d, *J* = 7.9 Hz, 2H), 7.49-7.45 (m, 2H), 7.39-7.34 (m, 5H), 5.42 (ddd, *J* = 1.4 Hz, 5.0 Hz, 22.6 Hz, 1H), 4.67 (d, *J* = 5.5 Hz, 1H), 2.43 (s, 3H). **^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm)** –114.7 (ABX system, $J_{AB} = J_{F\text{-}F} = 225.4$ Hz, $J_{BX} = J_{H\text{-}F} = 22.5$ Hz, $\Delta\nu_{AB} = 2417$ Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 143.6, 134.7, 132.3, 130.1, 129.2, 128.5, 128.0, 126.5, 124.4 (dd, *J* = 297.5, 305.6 Hz), 70.9 (dd, *J* = 20.0, 28.6 Hz), 21.7. The diastereomeric ratio and the enantiomeric excess of the product were determined by HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH= 80/20,

flow rate 0.5 mL/min, λ = 205 nm, τ = 9.4 min, 10.8 min, 20.0 min, 23.6 min). **$[\alpha]_{589}$** = +125.07 (20 °C, 0.895 g/100 mL, $CHCl_3$). **IR** (cm^{-1}) 3225, 2924, 1494, 1456, 1112, 1086, 1042, 809, 729, 698. **HRMS (ESI)** calculated for $C_{15}H_{15}F_2O_2S$: 297.0755, found: 297.0747.

Crystallographic data for (S)-2,2-Difluoro-1-phenyl-2-((S)-p-tolylsulfinyl)ethan-1-ol (S_s,S) II-(S,S_s).91a

Formule	$C_{15}H_{14}F_2O_2S$	Cell volume	834.251 $Å^3$
M (g/mol)	296.32	Z, Calculated density	4, 1.301 Mg/m^3
Temperature (K)	173 (2)	F(000)	616
Wavelength	0.71073	Crystal size	0.240 x 0.180 x 0.120 mm
Crystalline structure	Orthorhombic	Theta range for data collection	2.720 to 28.016
Space group	P 2_1 2_1 2_1		
a	7.2232 (4) Å	Z	0
b	7.7962 (4) Å	Z'	0
c	26.8653 (15) Å	Configuration	*S*
α _	90 °	Flack parameter	- 0.04 (3)
β _	90 °	R1	3.4%
γ _	90 °		

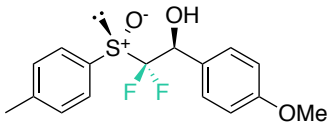
(*S*)-2,2-Difluoro-1-(3-pyridinyl)-2-((*S*)-*p*-tolylsulfinyl)ethan-1-ol II-(S_s,*S*).91f



II-(S_S,S).91f

Prepared by procedure 2e. The crude was purified by chromatography on demetalled silica gel with cyclohexane:ethyl acetate (from pure cyclohexane to 30:70). 39% yield. 93:7 d.r., 96% e.e. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 8.66 (s, 2H), 7.89 (d, *J* = 6.8 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 3H), 5.51 (d, *J* = 22.9 Hz, 1H), 2.41 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) *δ* (ppm) –114.4 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 225.4 Hz, J_{BX} = $J_{H\text{-}F}$ = 23.2 Hz, $\Delta\nu_{AB}$ = 2245 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 149.9, 148.9, 143.8, 136.2, 132.0 (d, *J* = 3.7 Hz), 131.5, 130.1, 126.6, 123.7, 68.4 (dd, *J* = 29.4, 19.6 Hz), 21.7. The diastereomeric ratio and the enantiomeric excess of the product were determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 207 nm, τ = 20.6 min; 23.6 min ; 49.1 min and 59.5 min.). **IR** (cm^{-1}) 3056, 1699, 1585, 1420, 1280, 1140, 1065, 810, 700, 515. **HRMS (ESI)** calculated for $C_{14}H_{11}F_2NaNO_2S$: 318.0371, found: 318.0360.

(*S*)-2,2-Difluoro-1-(4-anisyl)-2-((*S*)-*p*-tolylsulfinyl)ethan-1-ol II-(S_s,*S*).91k



II-(S_S,S).91k

Prepared by procedure 2e. The crude was purified by chromatography on demetalled silica gel with cyclohexane:ethyl acetate (from pure cyclohexane to 50:50). 29% yield. 93:7 d.r., 98% e.e. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 7.60 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.37 (d, *J* = 22.6 Hz, 1H), 3.79 (s, 2H), 2.43 (s, 2H). **^{19}F NMR (471 MHz, $CDCl_3$)** *δ* (ppm) –114,0 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224.2 Hz, $J_{BX} = J_{H\text{-}F}$ = 22.3 Hz, $\Delta\nu_{AB}$ = 3035.4 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 160.30, 143.51, 132.32, 130.00, 129.58, 129.25, 126.79, 126.52, 113.90, 70.39 (dd, *J* = 28.9, 19.4 Hz), 55.39, 21.70. The diastereomeric ratio and the enantiomeric excess of the product were determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 204 nm, τ = 13,0 min ; 15,5 min ; 31,7 min and 41,7 min.). IR (cm^{-1}) 3326, 1611, 1513, 1250, 1085, 1034, 975, 789, 522. **HRMS (ESI)** calculated for $C_{16}H_{16}F_2KO_3S$: 365.0420, found: 365.0432.

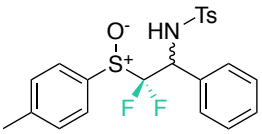
d. Synthesis of α-difluoro-β-sulfinyl amines

1. First strategy – Condensation of difluoromethyl *p*-tolyl sulfoxide onto *N*-tosylimine model substrate

In a microwave tube under argon were dissolved 4-(difluoromethanesulfinyl)toluene (1 equiv., 15 mg, 0.079 mmol) and freshly prepared 4-methyl-*N*-[(1*E*)-phenylmethylidene]benzene-1-sulfonamide (1 equiv., 20.5 mg, 0.079 mmol) in freshly distilled THF. After some minutes of stirring at the corresponding temperature, 2 equiv. of the solution of the base were added dropwise. The solution turned yellow then orange, then brown. This solution was stirred at the corresponding temperature until full conversion of the starting material. The reaction mixture was quenched with water. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by column chromatography on demetalled silica gel with cyclohexane:ethyl acetate (100:0 to 30:70 gradient).

When P_4*t*-Bu (2 equiv., 0.158 mmol) was used as the base at 0 °C, the product was obtained as a mixture of diastereomers as a white solid (54%, 19 mg, 0.0423 mmol, d.r. 37:63 (measured by ^{1}H and ^{19}F NMR)). The two diastereomers were separated by column chromatography with a MeOH:dichloromethane mixture (0:100 to 0.5:100 gradient) and were obtained as white solids.

N-tosyl 2,2-difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethanamine II.99



II.99

First diastereomer **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.55 (d, *J* = 8.2 Hz, 4H), 7.52 (d, *J*= 8.4 Hz, 4H), 7.33 (d, *J*= 8.6 Hz, 2H), 7.27 – 7.22 (m, 3H), 7.09 (d, *J* = 8.6 Hz, 2H), 5.62 (d, *J* = 8.8 Hz, 1H), 5.14 (ddd, *J* = 17.3, 10.9, 8.8 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -110.99 (dd, $J_{F\text{-}F}$= 218.5, $J_{H\text{-}F}$= 17.2 Hz), -113.84 (dd, $J_{F\text{-}F}$=

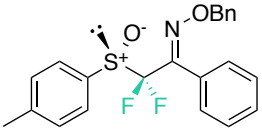
218.5, J_{H-F}= 10.9 Hz). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 146.9, 130.8, 129.8, 129.4, 129.3, 128.8, 128.6, 127.1, 126.7, 126.64, 77.2, 69.9, 62.9, 59.2, 29.8, 22.7, 21.6, 21.4. **HRMS (ESI):** m/z calculated for $[C_{22}H_{22}F_2NO_3S_2]^+$: 450.1010, found: 450.1004. Second diastereomer **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.59 (d, *J*= 8.0 Hz, 2H), 7.52 (d, *J*= 8.0 Hz, 2H), 7.34 (d, *J*= 8.0 Hz, 2H), 7.12 (d, *J*= 8.1 Hz, 2H), 6.32 (d, *J* = 9.3 Hz, 1H), 5.23 (ddd, *J*= 18.2, *J*= 9.3, *J*= 3.9 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ (ppm) -108.21 (dd, *J*= 224.3, *J*= 18.1 Hz, 1F), -109.89 (dd, J_{F-F} = 224.2, J_{H-F} = 4.4 Hz, 1F). **HRMS (ESI):** m/z calculated for $[C_{22}H_{21}F_2NNaO_3S_2]^+$: 472.0816, found: 472.0823

2. Second strategy – Functionalization of α-difluoro-β-ketosulfoxides

General procedure

In a sealable tuve were added (*S*)-2,2-Difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S) **I-(S_S).103a (**1 equiv., 0.34 mmol), hydroxylamine or benzyloxyhydroxylamine hydrochloride (1.5 equiv., 0.51 mmol), anhydrous magnesium sulfate (excess) and methanol (1 mL). The tube was sealed and heated to 65 ˚C for 16 h or until the starting material full consumption. The reaction mixture was quenched with water. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. No purification was performed.

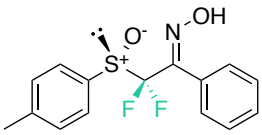
2,2-difluoro-1-phenyl-2-(*p*-tolylsulfinyl)ethan-1-one O-benzyl oxime II-(S_S).104



II-(S_S).104

Full conversion. Visqueous light yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.50 – 7.33 (m, 10H), 7.12 (d, *J* = 6.6 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 5.07 (s, 0.5H), 5.25 (d, *J* = 5.1 Hz, 1H), 5.07 (s, 0.5H), 2.40 (s, 3H), 1.93 – 1.86 (m, 2H). **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* (ppm) First diastereomer –100,2 (ABX system, J_{AB} = J_{F-F} = 232 Hz, $\Delta\nu_{AB}$ = 202 Hz, 2F). Second diastereomer –103,1 (ABX system, J_{AB} = J_{F-F} = 225 Hz, $\Delta\nu_{AB}$ = 734 Hz, 2F). **HRMS (ESI):** m/z calculated for $[C_{22}H_{19}F_2KNO_2S]^+$: 438.0736, found: 438.0732.

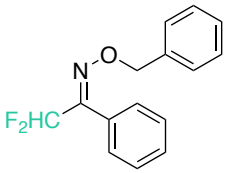
2,2-difluoro-1-phenyl-2-(*p*-tolylsulfinyl)ethan-1-one oxime II-(S_S).105



II-(S_S).105

Full conversion. Visqueous colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.70 (d, *J* = 7.9 Hz, 2H), 7.57 – 7.33 (m, 8H), 2.44 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ (ppm) First diastereomer –99.71 (ABX system, J_{AB} = J_{F-F} = 239.5 Hz, $\Delta\nu_{AB}$ = 6579 Hz, 2F). Second diastereomer –103,0 (ABX system, J_{AB} = J_{F-F} = 236.7 Hz, J_{BX} = J_{H-F} = 5.8 Hz, $\Delta\nu_{AB}$ = 2460 Hz, 2F). **HRMS (ESI):** m/z calculated for $[C_{15}H_{14}F_2NO_2S]^+$: 310.0708, found: 310.0705.

2,2-difluoro-1-phenylethan-1-one O-benzyl oxime II.106



II.106

A solution of L-Selectride (3 equiv., 1 M in THF) was added to a solution of **II-(S_s).104** (1 equiv.) in freshly distilled THF (ca. 5 mL /mmol) under argon at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 3 hours. The mixture was sequentially treated with water, methanol and a 1M solution of NaOH. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by column chromatography on demetalled silica gel with cyclohexane:ethyl acetate (from pure cyclohexane to 20:80). 62% yield. Colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 – 7.66 (m, 1H), 7.63 – 7.56 (m, 2H), 7.44 – 7.31 (m, 7H), 6.26 (t, *J* = 54.7 Hz, 0.5H), 6.26 (t, *J* = 53.8 Hz, 0.5H), 5.36 – 5.15 (m, 2H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ (ppm) -115.17 (*app.* d, *J* = 54.6 Hz), -122.69 (*app.* d, *J* = 53.8 Hz). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 137.0, 136,7, 130.1, 129.1, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 127.7, 117.13, 114.8 (t, *J* = 239.9 Hz), 106.93 (t, *J* = 240.6 Hz), 112.4, 109.3, 104.5, 77.8, 77.6. **HRMS (ESI):** m/z calculated for $[C_{15}H_{14}F_2NO]^+$: 262.1038, found: 262.1048.

Chapter III

Functionalization of difluoromethyl derivatives

Table of contents

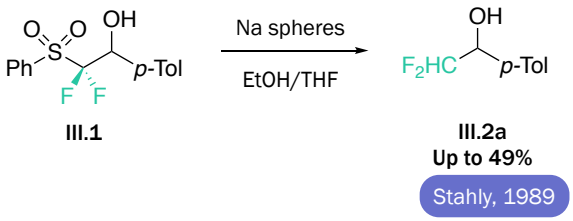
A. Access to enantioenriched difluoromethylated scaffolds from difluoromethyl sulfinyl derivatives: removal of the chiral auxiliary

One of the final and crucial steps of this methodology is the desulfinylation step, in which the sulfinyl moiety is removed with retention of the configuration of the difluoromethylated stereocenters. Some soft and efficient methods have been reported before to perform the desulfinylation on non-fluorinated sulfoxide derivatives and were presented in *Chapter I*. Moreover, some strategies have also been applied to fluorinated analogues, but consist mostly in desulfonylation reactions. These methods will be succinctly described, followed by the attempts that have been performed within our team.

a. State of the art: Methods used in the fluorinated series

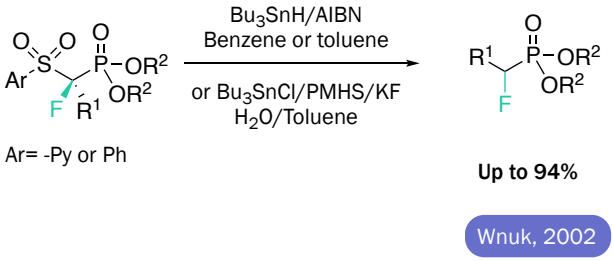
The removal of a sulfinyl group used as a chiral auxiliary in fluorinated derivatives was not reported at the beginning of this project. In fact, only methanesulfonyl analogues have been previously used and the removal of the arenesulfonyl group was described using diverse methods that will be presented in this part.

In the 1990's, Stahly performed the synthesis of a α–difluoromethyl β-hydroxysulfone and some transformations of this compound. Its desulfonylation was carried out in ethanol/THF mixture using sodium spheres, leading to the corresponding α-difluoromethyl alcohols with moderate yields (**Scheme III.1**).[348]



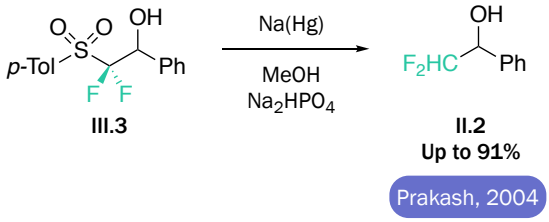
Scheme III.1. Desulfonylation of an aryl difluoromethyl sulfonyl derivative using sodium spheres

A decade later, Wnuk's group synthesized alkyl fluoro(benzenesulfonyl)methylphosphonates and tried to perform the removal of the sulfone moiety with sodium amalgam, but this later resulted in cleavage of the phosphorus-carbon bond instead of the sulfur-carbon one. The use of Raney nickel also failed to produce the expected fluorophosphonates. A radical desulfonylation system was then used, namely Bu_3SnH/AIBN that gave access to the fluorophosphonates (**Scheme III.2**). In order to reduce toxicity and purification problems associated with the use of Bu_3SnH, they used Bu_3SnCl/AIBN/PMHS/KF/H_2O/toluene system was employed and afforded satisfying desulfonylation results.[351]



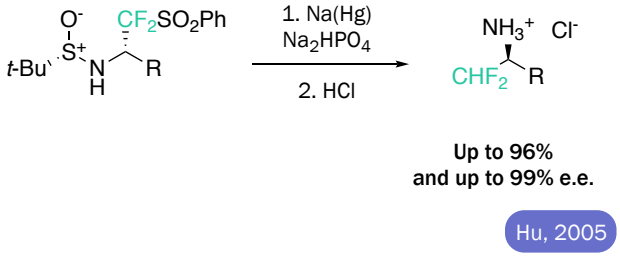
Scheme III.2. Desulfonylation of fluoro(phenylsulfonyl)methylphosphonates

In the course of his studies regarding fluorinated derivatives, Prakash reported a reductive desulfonylation, to replace the arylsulfonyl groups by a hydrogen atom. The use of sodium metal in ethanol or methanol appeared to be inefficient, which led them to prepare a sodium/ mercury amalgam system to perform these desulfonylations (**Scheme III.3**). In presence of a sodium monohydrogenphosphate buffering agent to control the pH, difluoromethyl alcohols were obtained with very good yields.[352]



Scheme III.3. Desulfonylation using sodium/mercury amalgam

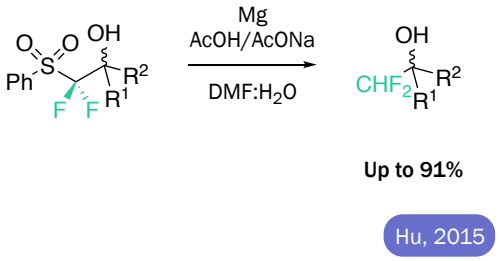
Similarly, Hu used this strategy in 2005 in order to access enantiopure difluoromethyl amines prepared by nucleophilic addition of difluoromethyl phenyl sulfone to Ellman's *tert*-butanesulfinyl imines. The yields and enantiomeric excess obtained were excellent (**Scheme III.4**).[353]



Scheme III.4. Desulfonylation with sodium/mercury amalgam leading to difluoromethyl amines

Continuing with the use of metal amalgam species, the high efficiency of aluminium/mercury amalgam was also described by Hu. The desulfonylation leading to monofluoromethyl-substituted tertiary alcohols was efficiently

performed with this amalgam, giving the expected products with high yields and optical purity (**Scheme III.5**).[354]



Scheme III.5. Magnesium mediated desulfonylation

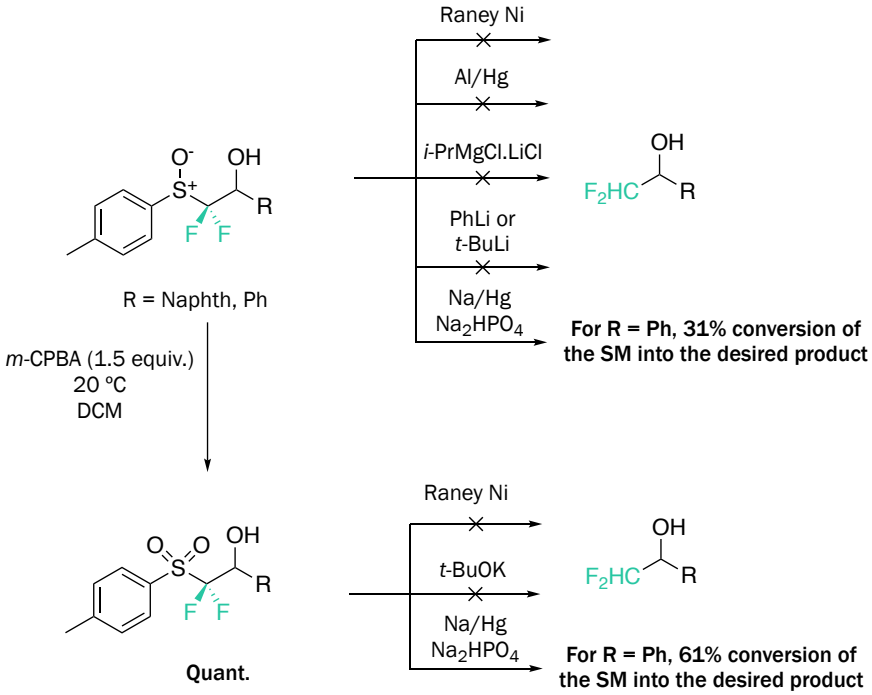
Inspired by these conditions, and the ones described in *part A* of *Chapter I* regarding non-fluorinated analogues, several experiments were performed within our research group.

b. Methods used in the group

1. Attempts performed for the removal of the chiral auxiliary

Previously, our team had a strong interest in the synthesis of highly enantioenriched α-difluoro-β-hydroxysulfoxides, as described in *Chapter II*. Desulfinylation attempts were performed on these compounds using several conditions inspired by the literature and mentioned in Chapter 1 as well as in the previous section. The largely known desulfinylation reagent Raney nickel was used without satisfying results. The use of *i*PrMgCl·LiCl, and of an aluminium/ mercury amalgam did not lead to the desired compound either.

On the other hand, strategies were also described in the literature for the desulfonylation of fluorinated derivatives. The oxidation of α-difluoro-β-hydroxysulfoxides with *m*-CPBA was found to be very efficient to obtain the corresponding sulfonyl analogues in quantitative yield. The subsequent desulfonylation by means of Raney nickel was again unfruitful (**Scheme III.6**). Other methods were found to be efficient for the desulfinylation of the non-fluorinated, mono-fluorinated or halogenated analogues of our compounds. The use of organolithium reagents was reported by Suzuki and co-workers[355] and Garcia Ruano and co-workers.[171] When phenyllithium or *tert*-butyllithium have been employed, only traces of the corresponding difluoromethyl alcohol were observed by ^{19}F NMR.



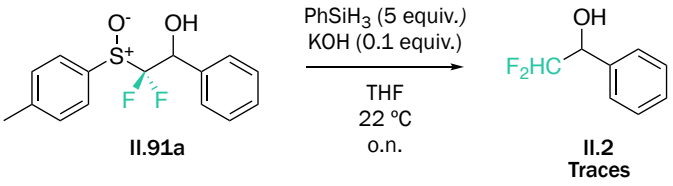
Scheme III.6. Desulfinylation and desulfonylation attempts of α–difluoro-β-hydroxysulfoxides

More promising results were however obtained with either the sulfinyl- or sulfonyldifluoromethyl-derived alcohols when using a sodium/mercury amalgam, with the desired product being formed in 31% and 61% yield respectively.

However, the acute toxicity of mercury, and therefore the limitations in the pharmaceutical field of its use, led us to abandon this option and to look for an alternative way for this transformation.

2. Use of a silane-based system

In 2017, Midura and co-workers reported on the use of phenylsilane in a KOH-catalyzed system as an effective and novel desulfinylation reagent.[70] We applied this method to our fluorinated compounds. The use of the optimized conditions gave a low conversion of the starting material into the desired product (**Scheme III.7**).



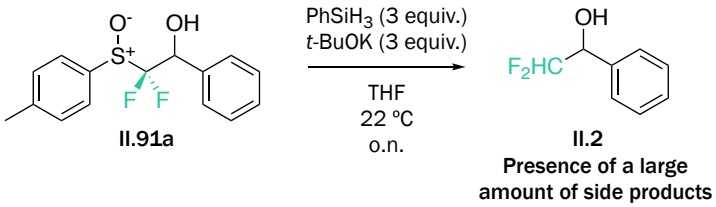
Scheme III.7. Use of Midura's conditions of desulfinylation

This reaction was repeated with an increased amount of base (0.5 then 1 equiv.). After one night, we could observe full conversion of the starting material and

presence of the desired compound. However, the formation of a large amount of side products was observed by ^{1}H NMR. The reaction was performed once again, this time with 10 equivalents of phenylsilane and 3 equivalents of KOH. The reaction was faster, and a total consumption of the starting material was observed after 3 hours, but still with the undesired side products. Unfortunately, after purification by column chromatography, impurities were eluted together with the difluoromethyl alcohol.

The ^{1}H NMR of the major side product showed a large number of signals for aromatic protons and no signals in ^{19}F NMR. This led us to presume that a silylated side product was present. An acidic work-up using hydrochloric acid was performed on the crude mixture without satisfying results. The resulting mixture was then treated with a solution of TBAF overnight, to try to cleave the presumed silylated ether, again without success.

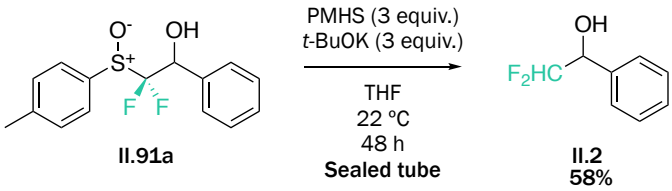
The use of *t*-BuOK giving the same results as KOH, it was preferred for the following tests, to try to avoid the formation of polyhydroxisiloxanes. With 3 equivalents of phenylsilane, a full conversion of the starting material into the desired difluoromethyl alcohol was observed, and the crude material appeared much cleaner by ^{1}H and ^{19}F NMR than under previous conditions (**Scheme III.8)**.



Scheme III.8. Desulfinylation attempts using a phenylsilane-mediated method

However, the purification of the desired desulfinylated product still remained a difficulty as the difluoromethyl alcohol could not be isolated after work-up and flash chromatography due to the impurities present using this method.

Our hypothesis being that silylated polymers formed in the medium could not be removed, another reagent than phenylsilane was used to facilitate the purification. The use of PMHS (polymethylhydrosiloxane) in the presence of simple bases (*t*-BuOK or KOH) has been described by Nikonov to reduce ketones and esters.[356] This system was used, as a substitution for phenylsilane (**Scheme III.9**).

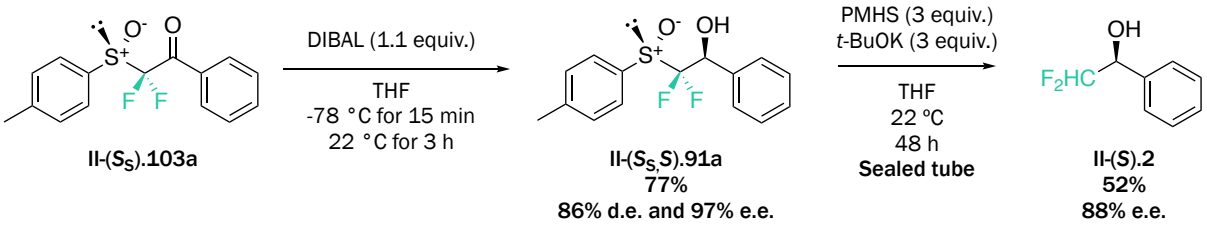


Scheme III.9. PMHS/*t*-BuOK mediated desulfinylation

To our delight, the expected racemic α-difluoromethyl benzyl alcohol was obtained with 58% yield.

Our strategy being focused on the access to enantiopure difluoromethylated products, we performed the reaction on the diastereopure sulfinyl alcohol, obtained

by selective reduction of the enantioenriched α-difluoro-β-ketosulfoxide (**Scheme III.10**).



Scheme III.10. PMHS mediated desulfinylation applied to an enantio- and diastereopure α-difluoromethyl β-hydroxysulfoxide

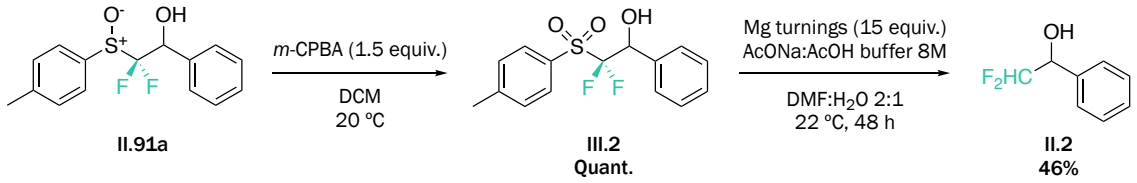
The alcohol was obtained with 52% yield and full retention of configuration at the stereogenic carbon was confirmed by chiral HPLC, one enantiomer of this alcohol being mainly observed.

Thus, this method presents a promising strategy adapted to our substrates to achieve the obtention of enantiopure difluoromethylated building blocks.

3. Mg(0)-mediated desulfonylation

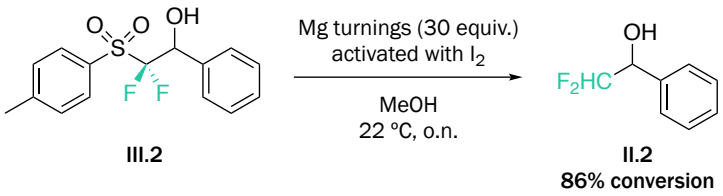
In parallel to the latter approach we decided to investigate another strategy, described by Hu and coworkers,[219] where enantiopure difluoromethylated alcohols can be obtained from the corresponding difluoro hydroxysufones with retention of configuration using magnesium turnings in the presence of an acetate buffer.[219,224,357]

Their conditions were applied to a model sulfoxide **II.91a** and afforded the desired compound in 46% yield (**Scheme III.11**). However, the corresponding alcohol could only be obtained one time with a 46% yield, instead of 93% described in literature.



Scheme III.11. Magnesium mediated desulfonylation strategy in the presence of an acetate buffer

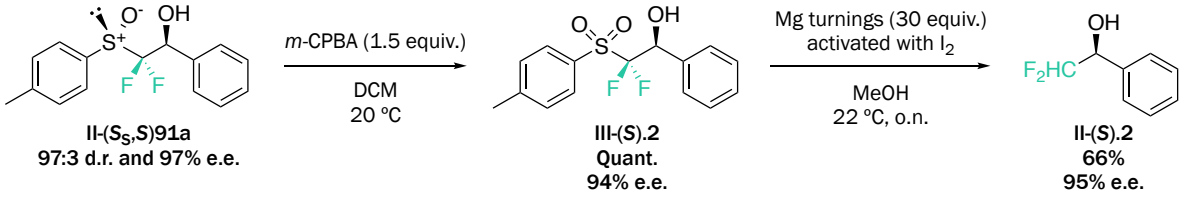
In order to understand why this reaction was not reproducible in our hands, more experiences were carried out by changing the proton source and the activation mode (**Scheme III.12**).



Scheme III.12. Desulfonylation method using activated magnesium turnings

The use of 30 equivalents of iodine-activated magnesium in methanol allowed us to obtain a high conversion of the β-hydroxysulfone in the corresponding difluoromethyl alcohol.

In addition, the application of this strategy to the corresponding enantiopure β-sulfonyl alcohol **II-(*S*).2** led gratifyingly to the desired enantiopure difluoromethyl alcohol (**Scheme III.13**).

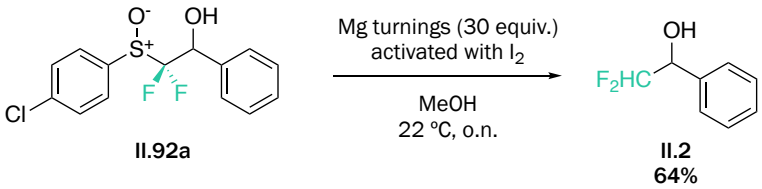


Scheme III.13. Magnesium mediated desulfonylation applied to a diastereopure derivative

The enantiomeric excess of this product was determined by chiral HPLC and we were pleased to confirm that this desulfonylation method gave once again full retention of configuration.

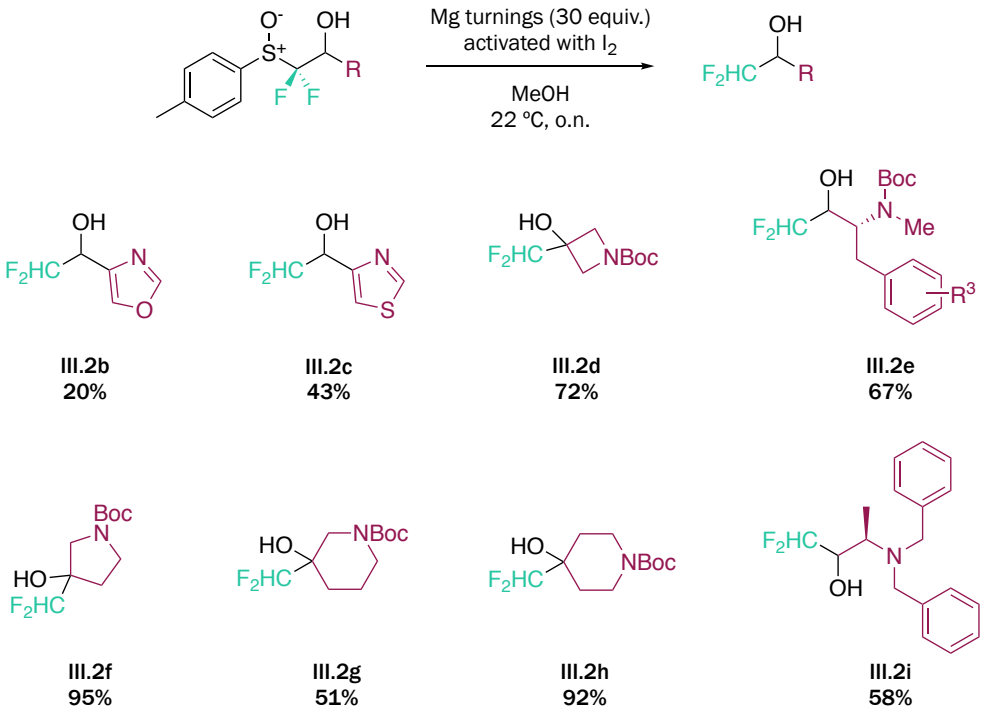
4. Mg(0)-mediated desulfinylation

After the development of efficient desulfonylation methods, presented in the previous section, we tried to apply the Mg(0) mediated conditions directly on α–difluoromethyl β-hydroxysulfoxide. To our delight, when the phenyl-derived α-difluoromethyl β-hydroxy sulfoxide —without prior conversion to the corresponding sulfone— was reacted with magnesium in the presence of a catalytic amount of iodine, we observed full consumption of the starting material and formation of the desired difluoromethyl alcohol (**Scheme III.14**).



Scheme III.14. Magnesium mediated desulfinylation reaction

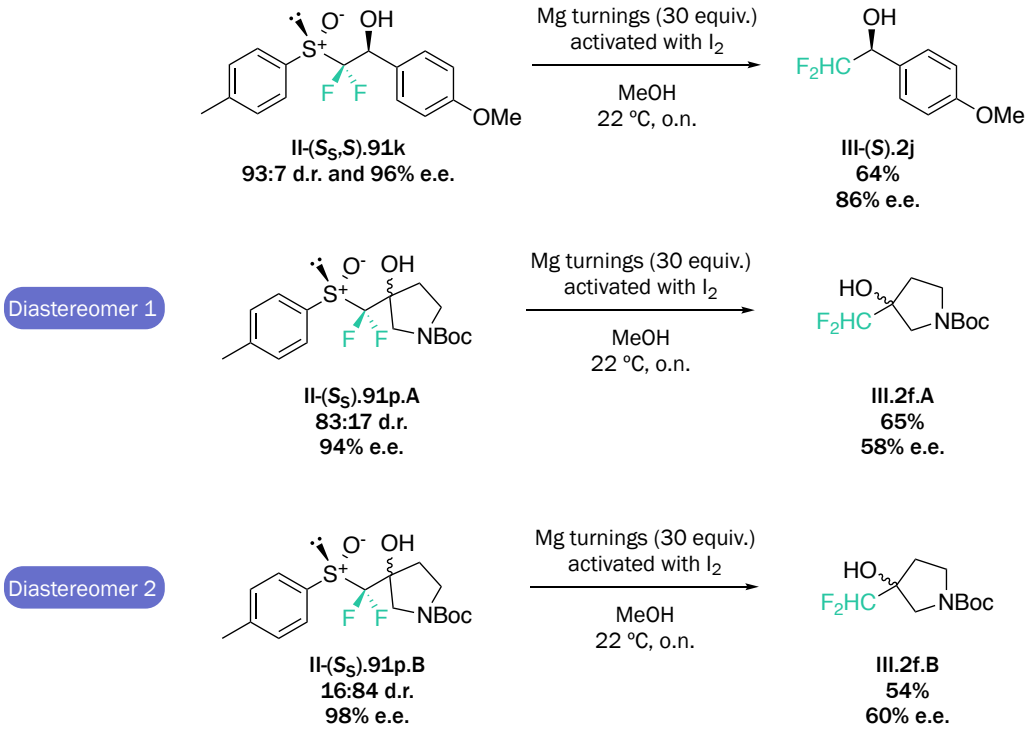
These conditions were then used to desulfinylate the α-difluoromethyl β-sulfinyl alcohols bearing heterocycles that were prepared during the course of the project (**Scheme III.15**).



Scheme III.15. Desulfinylation reaction scope using activated Mg(0)

We were able to obtain the expected difluoromethyl alcohols in moderate to excellent yields.

In order to confirm that the diastereoenriched sulfinyl alcohols could give access to their corresponding alcohols without loss of optical purity, we performed the desulfinylation using magnesium turnings on diastereo and enantioenriched compounds (**Scheme III.16**).



Scheme III.16. Activated Mg(0) mediated desulfinylation applied to enantio- and diastereoenriched derivatives

Regarding the anisyl-derived alcohol, we were pleased to confirm the high enantiomeric excess obtained. The moderate e.e. observed for the pyrrolidinol (around 60%) is due to an uncomplete diastereomeric separation of the sulfinyl alcohols in the previous step.

Except for this last example, highly enantioenriched α-difluoromethylated alcohols could then be obtained by two different methods of desulfinylation of highly diastereo and enantioenriched α-difluoro-β-hydroxysulfoxides, using either iodine-activated magnesium or PMHS/*t*-BuOK. Moreover, the stereoenrichment at the carbon center can be preserved.

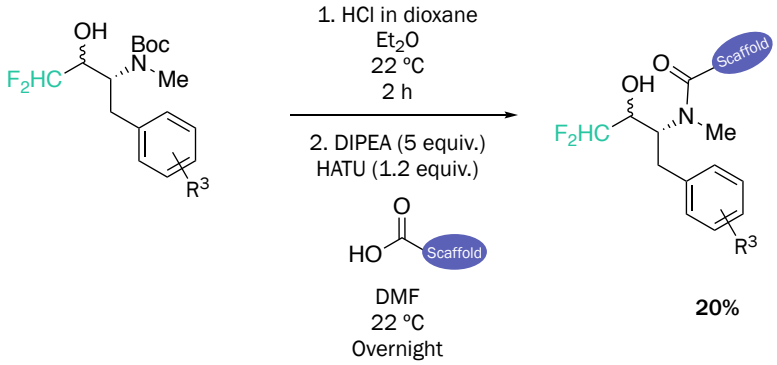
5. Application to the synthesis of a pharmaceutical candidate

In the second chapter, we described our interest in the addition of difluoromethyl *p*-tolyl sulfoxide to amino aldehydes in order to access enantioenriched difluoromethylated amino alcohols. These compounds are of great interest in medicinal chemistry as they can be used to access a large number of nitrogenated derivatives bearing a -CHF_2 group.

An example of application of these compounds is currently being studied in the medicinal chemistry team at Sanofi. Analogues of a lead compound in a drug discovery project are currently being synthesized, and as it was described in *part F* of *chapter II*, amino alcohols bearing -CH_2F, -CHF_2 and -CF_3 are going to be tested to evaluate their potential therapeutic activity.

Using our methodology, we were able to synthesize the corresponding α-difluoromethyl β-sulfinyl alcohol and the protected amino alcohol derived from the substituted phenylalanine was successfully obtained after desulfinylation using magnesium(0).

The deprotection of *N*-Boc β-amino α-difluoromethyl alcohol was performed in acidic conditions and the unprotected amine reacted with the unprotected carboxylic acid group of a platform furnished by our collaborators in the presence of DIPEA and HATU as the coupling activator (**Scheme III.17**).



Scheme III.17. Peptide coupling applied to a difluoromethyl-substituted amino alcohol of pharmaceutical interest

We are able to obtain the expected final product with 20% yield. This synthesis was performed on small scale and with the racemic precursor. In order to obtain both enantiomers of the corresponding difluoromethylated amino alcohol, a separation of the two diastereomers of the preceeding α'-amino- α-difluoromethyl-β-sulfinyl alcohols should be performed after the introduction of the –CHF_2 surrogate.

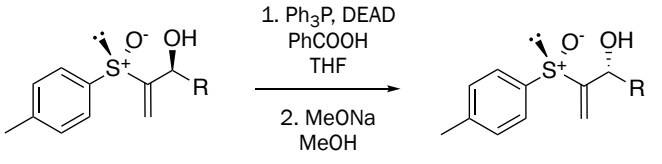
B. Attempts of Mitsunobu type reactions on α-difluoromethyl alcohols

a. State of the art of Mitsunobu type reactions on fluorinated compounds

The Mitsunobu reaction is widely known to be an efficient and useful stereospecific transformation to replace a hydroxy group by a nucleophile. This transformation has been widely used in synthetic organic chemistry and mostly occurs under mild conditions involving a redox system: oxidizing azo reagent and a reducing phosphine reagent.[358] Over the decades, huge improvements have been accomplished and this reaction gained popularity due to its numerous applications in organic chemistry. For detailed information, readers are invited to consult recent reviews describing the progress and applications of Mitsunobu reactions.[359,360]

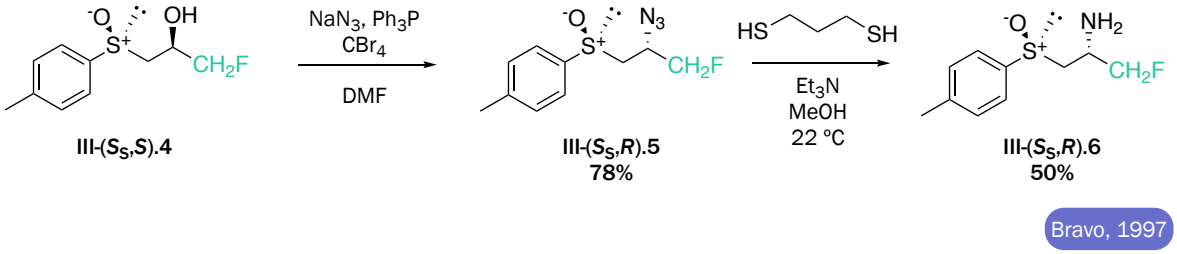
We have previously studied and developed the access to difluoromethylated building blocks of high optical purity, mostly difluoromethyl alcohols. In order to valorize this methodology and expand the scope of difluoromethylated derivatives, Mitsunobu type reactions were explored for their known efficiency to access difluoromethyl amines, among others, as we will se bellow.

In literature, only a few examples have been reported for Mitsunobu type reactions performed with non-fluorinated aryl sulfinyl alcohols. A representative example was decribed by Toru in 2002,[361] where the access to both diastereoisomers was ensured by performing a Mitsunobu reaction with benzoic acid, followed by ester cleavage to the corresponding alcohol under inversion of configuration (**Scheme III.18**). This strategy was successfully applied to similar sulfinyl alcohols by Pradilla in 2003.[362]



Scheme III.18. Mitsunobu reaction developped by Toru

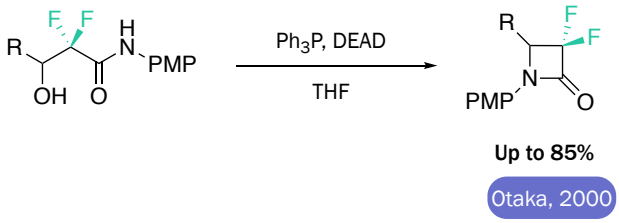
Another example of a Mitsunobu reaction performed on sulfinyl alcohols, but also including a fluorinated substituent has been described by Bravo in 1997 using a monofluoromethylated sulfinyl alcohol to access the corresponding amines *via* the transformation of the alcohol to an azide (**Scheme III.19**).[363]



Scheme III.19. Azidation protocol of fluorinated sulfinyl alcohol

To the best of our knowledge, there are no other examples of this reaction on sulfinyl alcohols. However, more extensive studies have been done regarding Mitsunobu reactions on fluorinated alcohols. An account of some of these methods will be presented.

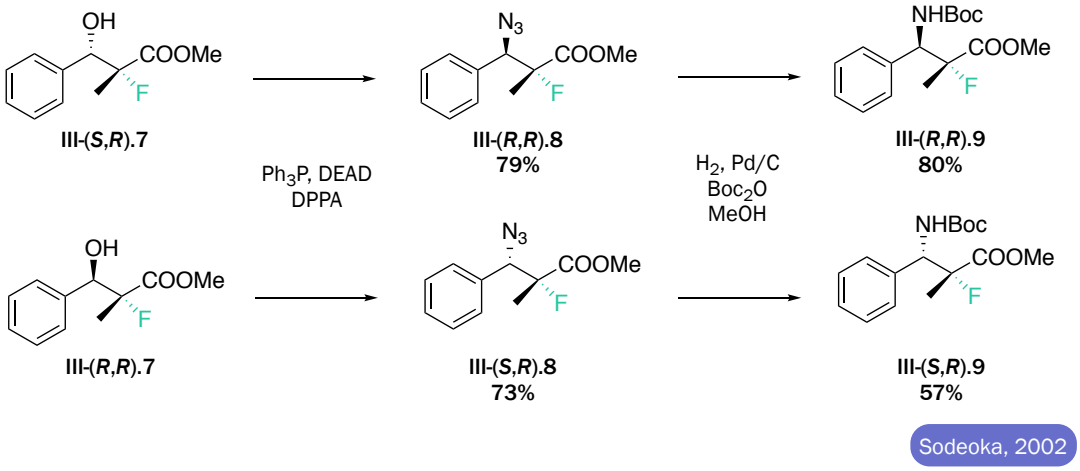
In 2000, Otaka tried to synthesize (*Z*)-fluoroalkene dipeptide isosteres. His strategy involved the synthesis of fluorinated β-lactams followed by a ring opening and other transformations leading to the desired fluoroalkene dipeptide isosteres.[364] The synthesis of the intermediate β-lactams went through an intramolecular Mitsunobu reaction of α-difluoro-β-hydroxy amides with Ph_3P-DEAD in THF (**Scheme III.20**).



Scheme III.20. Intramolecular Mitsunobu reaction of a difluoromethylated hydroxy amide

Another example involving an intramolecular Mitsunobu reaction leading to β-lactams was reported by Skrydstrup a few years ago.[365]

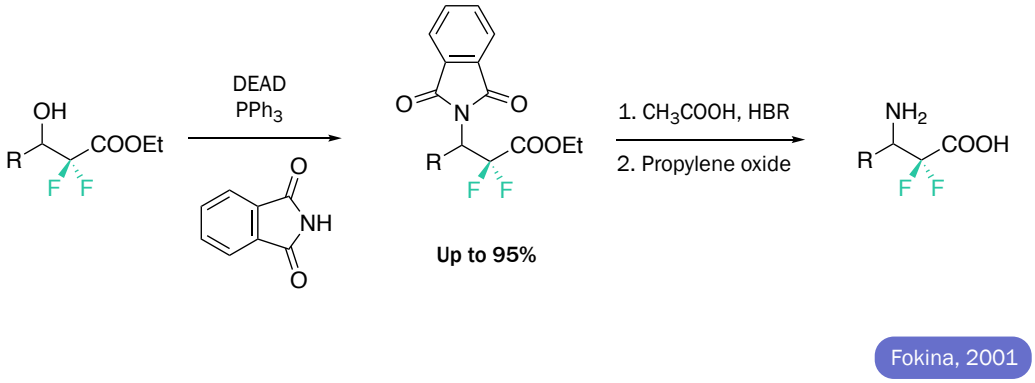
Sodeoka's group focused on the synthesis of fluorinated derivatives of β-amino acids. This group started from enantiopure α-fluoro-β-hydroxy esters that were converted after azidation and reduction into the corresponding diastereopure α-fluoro-β-amino esters (**Scheme III.21**).[366]



Scheme III.21. Azidation of diastereopure α-fluoro-β-aminoesters

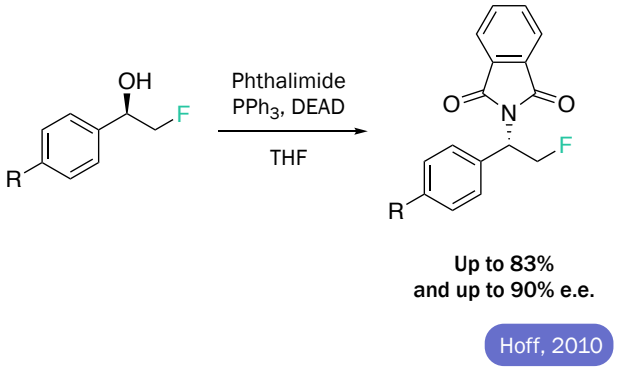
Similar synthetic pathways were described by Stanton[367] and Silverman[368] to access fluorinated amine derivatives after a Mitsunobu azidation.

Furthermore, an alternative route to fluorinated amines from the corresponding alcohols consists in performing Mitsunobu reactions using phthalimide.[369] Fokina's group described the synthesis of α-difluoro-β-amino acids, where the key step is a Mitsunobu amination (**Scheme III.22**).[370]



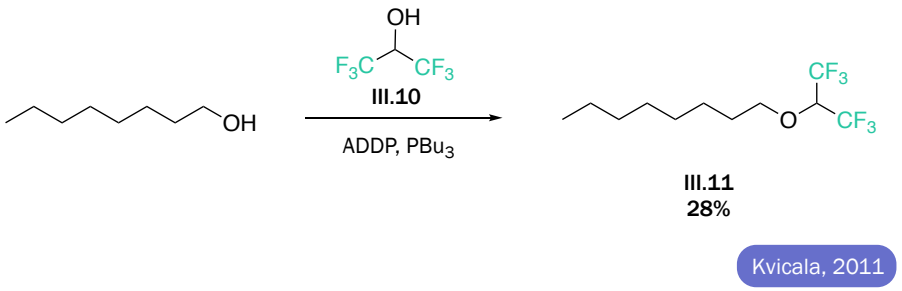
Scheme III.22. Mitsunobu amination of difluorinated ethyl acetates

Hoff reported the reaction of enantiopure α-fluoroalcohols with phthalimide in the presence of diethyl azodicarboxylate and triphenylphosphine to obtain the *N*-substituted phthalimides. In some cases, the yields were very good and the products were obtained with a perfect inversion of the stereochemistry (**Scheme III.23**).[371]



Scheme III.23. Mitsunobu reaction leading to a fluorinated amine intermediate

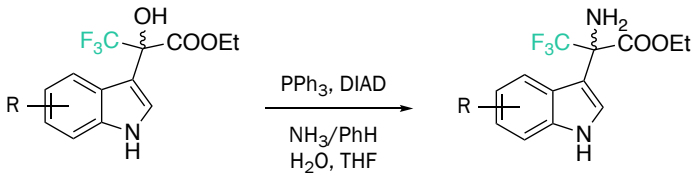
In order to prepare fluorinated cyclopentadienes and the derived cyclopentadienide sandwich complexes, Kvicala and co-workers studied the synthesis of fluorinated tripyrazolylmethanes. They first performed a model reaction with octan-1-ol and HFIP that under Mitsunobu conditions led to the target molecule bearing the two trifluoromethyl moieties with a low yield (**Scheme III.24**).[372]



Scheme III.24. Mitsunobu reaction from octan-1-ol and HFIP

Unfortunately, the authors also reported that when they applied this strategy to their substrate of interest, tripyrazolylethanol, only starting materials were recovered, showing the limits of the transformation.

A last representative example was reported by Zhou in 2014. Chiral indole-based α-amino acids were synthesized by the Mitsunobu reaction of indol-3-yl trifluoropyruvate derivatives as potential HIV-1 transcriptase inhibitors.[373] In fact, racemic trifluoromethylated indoles have already been studied and the authors wanted to understand the effect of both enantiomers of these indole derivatives, and also find more efficient small molecular inhibitors. They developed an indole-based α-amino acid library by replacing the –OH group of their trifluoromethylated derivatives by an amine group using diisopropyl azodicarboxylate, triphenylphosphine and ammonia (**Scheme III.25**).



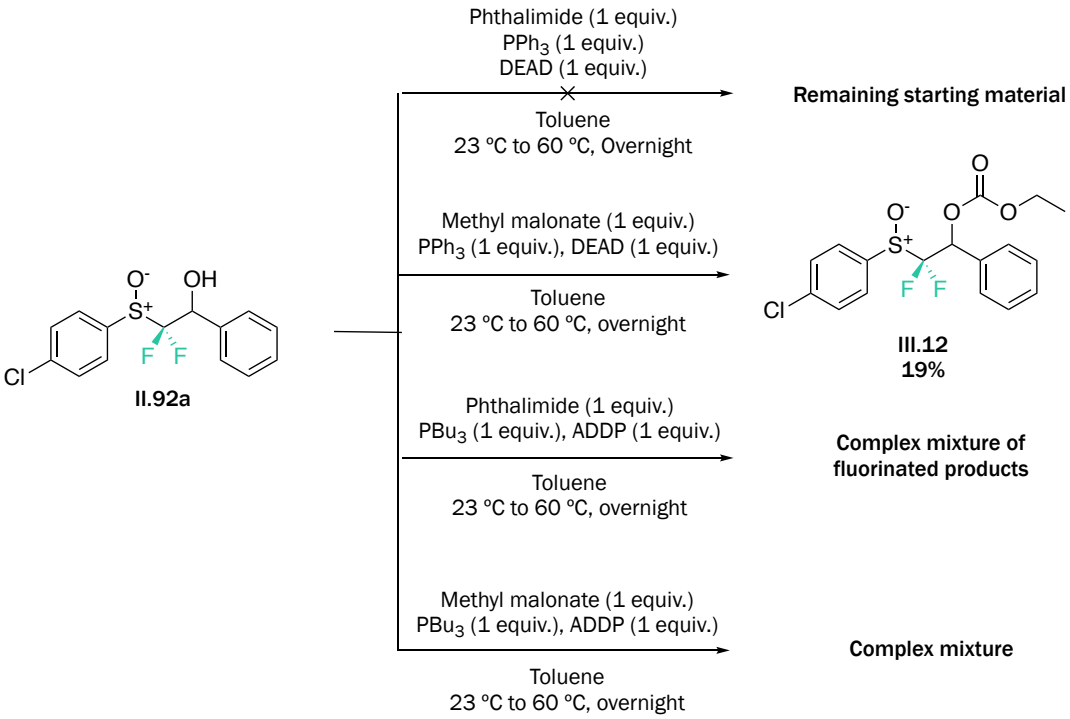
Up to 51%
and up to 90% e.e.

Zhou, 2014

Scheme III.25. Mitsunobu reaction using ammonia as pronucleophile

b. Attempts performed on α-difluoro-β-sulfinyl alcohols

Inspired by the previous cited conditions and their promising results, we aimed to replace the –OH moiety directly on the α-difluoromethyl β-sulfinyl alcohols, in order to take advantage of the stereochemistry induced by the sulfoxide. We used the standard redox system: diethyl azodicarboxylate and triphenylphosphine. In addition, we also tried an alternative system, being PBu_3 and ADDP (1,1'-(azodicarbonyl)dipiperidine), as shown in **Scheme III.26**. The nucleophiles used for these tests were phthalimide in order to introduce an amine moiety, and also a malonate.



Scheme III.26. Mitsunobu reactions using PPh_3-DEAD or PBu_3-ADDP systems on α-difluoromethyl β–sulfinyl alcohol

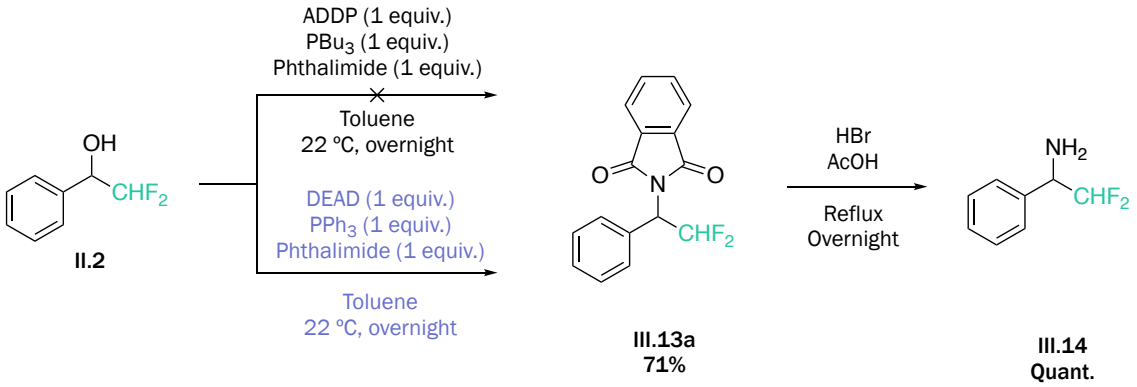
However, the desired products were not obtained. We only were able to observe complex mixtures after the reaction, and in one case, we were able to isolate the major compound, where the hydroxy moiety was carbonylated by the diethyl azodicarboxylate.

Next, reactions were performed directly on the difluoromethyl alcohol, in absence of the chiral auxiliary, to check if the lack of reactivity is due to its presence in the molecule.

c. Attempts on α-difluoromethyl alcohols

The cleavage of the C-S bond on α-difluoromethyl β-sulfinyl alcohols was performed using the magnesium mediated desulfinylation conditions described in *part A* of this chapter.

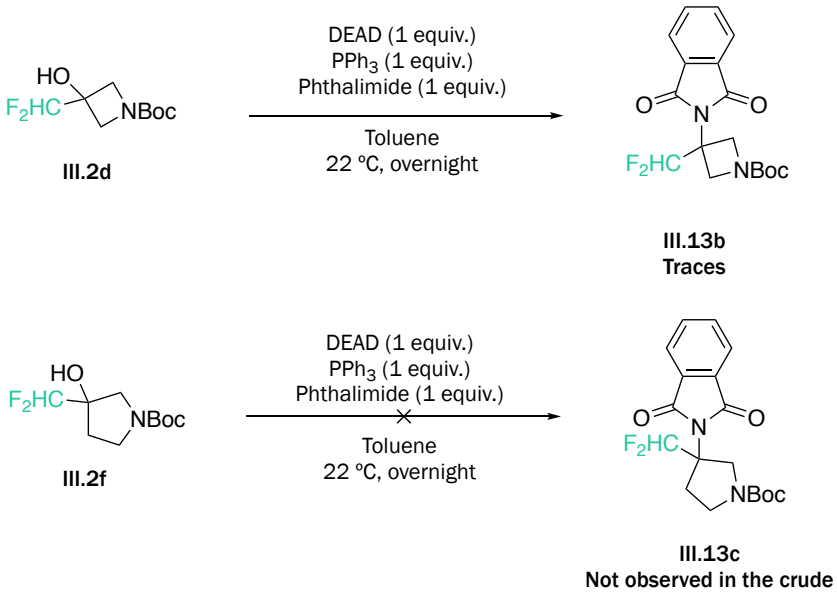
We were then able to test the Mitsunobu conditions on the model difluoromethyl alcohol **II.2** (**Scheme III.27**).



Scheme III.27. Mitsunobu reaction on a model difluoromethyl alcohol leading to a difluoromethyl amine

When using ADDP in combination with PBu_3, no reaction was observed, and the starting alcohol was unchanged. To our delight, when the redox system was triphenyl phosphine and diethyl azodicaboxylate, we were able to isolate the desired product **III.13a** with a satisfying yield of 71%. The deprotection of the phthalimide to access the free amine was carried out by using hydrobromic acid in acetic acid, and led to **III.14**. Another possible phthalimide cleavage employs hydrazine, which would proceed under milder conditions.

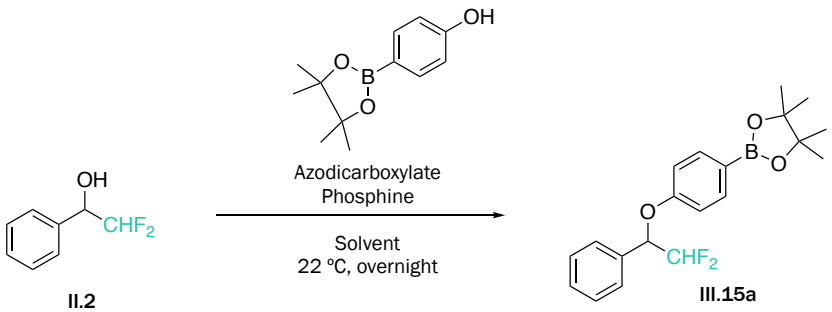
Unfortunately, when the Mitsunobu amination of the azetidine derivative **III-2d** was tried with phthalimide, only a small amount of the corresponding product was observed. Despite our efforts, only traces of the product could be recovered after purification by flash chromatography followed by preparative HPLC (**Scheme III.28**). Similarly, the pyrrolidine derivative **III.13c** could not be observed under the same reaction conditions.



Scheme III.28. Mitsunobu reactions performed on *N*-heterocyclic difluoromethyl alcohols

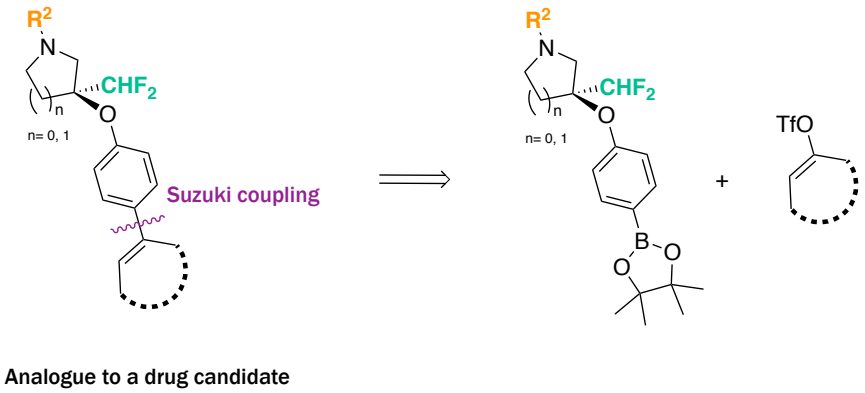
Nevertheless, as the Mitsunobu reaction was efficient directly on the model difluoromethyl alcohol, a phenol bearing a boronic ester group was used as another type of useful nucleophile. The presence of this group will give us access to difluoromethylated building blocks that can be readily used for Suzuki-Miyaura couplings. Some tests were performed on the model substrate, the difluoromethyl phenyl carbinol (**Table III.1**). TMAD (tetramethylazodicarboxamide) was previously used in the chemistry team to perform the Mitsunobu reaction with hydroxyphenyl boronic pinacol ester. The standard redox system (DEAD and PPh_3) was also tested in THF and toluene.

Table III.1. Mitsunobu attempts on a model difluoromethyl alcohol to access a boronic ester derivative



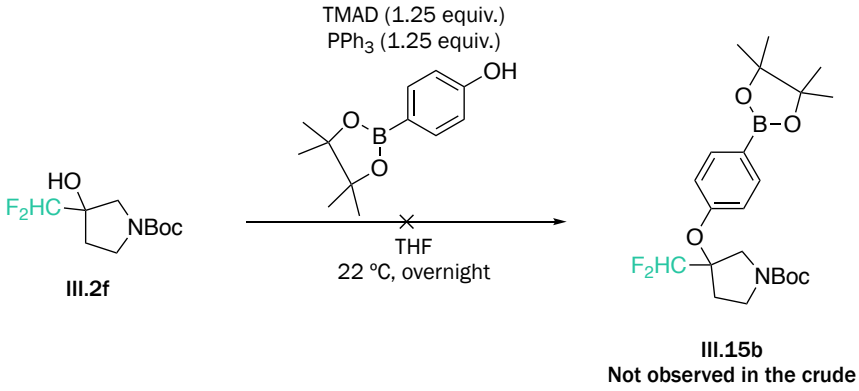
Entry	Phosphine	Azodicarboxylate or amide	Solvent	Yield
1	PPh_3 (1.25 equiv.)	TMAD (1.25 equiv.)	THF	**III.15a** 74%
2	PPh_3 (1 equiv.)	DEAD (1 equiv.)	THF	**III.15a** 53%
3	PPh_3 (1 equiv.)	DEAD (1 equiv.)	Toluene	**III.15a** 34%

We were able to isolate the desired product **III.15a** with yields from 34 to 74%. With these conditions in hands, the reaction was applied on the difluoromethylated *N*-heterocyclic derivatives. We focused on the transformation of the azetidine and pyrrolidine derivatives, as the difluoromethyl derivatives of these substrates are of great interest for the medicinal chemistry team. The non-fluorinated compounds have shown interesting activities in a drug discovery program. Synthesizing analogues of these derivatives bearing a difluoromethyl moiety could provide beneficial effects to their activity, such as a hydrogen-bond donor effect among others or can have an impact on their lipophilicity and then enhance their activity, being known effects of the difluoromethyl group. The proposed strategy consisted in performing a Suzuki coupling between the difluoromethyl *N*-heterocycles bearing a phenyl boronic ester and a coupling partner that has been prepared in the chemistry team bearing a triflate group as pseudohalide (**Scheme III.29**).



Scheme III.29. Suzuki strategy to access a drug candidate analogue bearing a difluoromethyl group

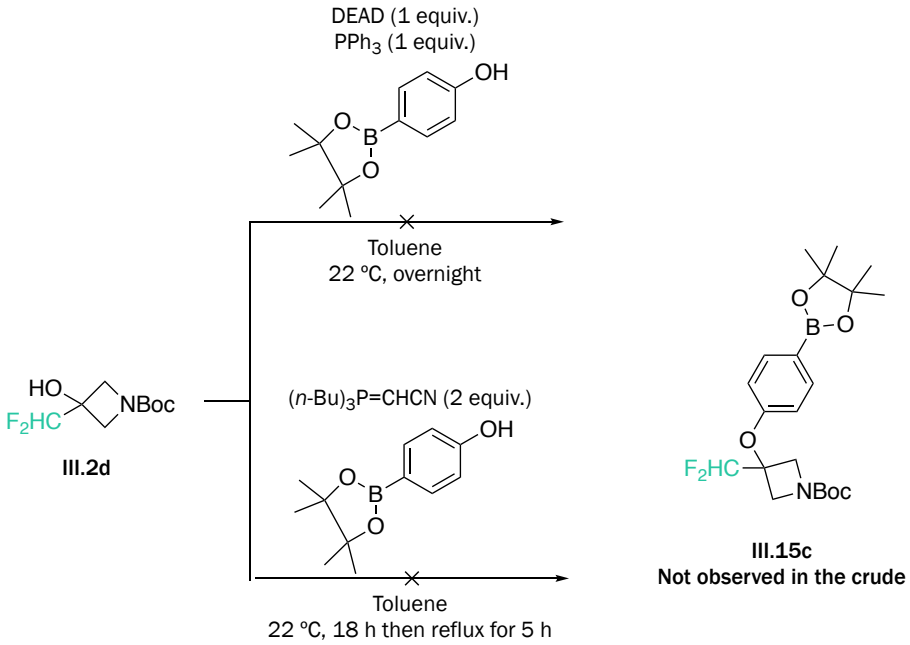
In order to access the other partner for the coupling, Mitsunobu reactions were then tried with 4-hydroxybenzene boronic pinacol ester with the previous best conditions of **Table III.1**, entry 1 (**Scheme III.30**).



Scheme III.30. Mitsunobu reaction to access a phenyl boronic ester derivative of difluoromethyl pyrrolidine

However, for the pyrrolidine substrate, when using the diamide-triphenyl phosphine combination the transformation did not take place and the starting material was recovered unchanged.

For the azetidine derivative, we used the DEAD-PPh_3 combination and also the Tsunoda reagent, a different Mitsunobu reagent known to be an efficient alternative (**Scheme III.31**).[374]



Scheme III.31. Mitsunobu reactions on difluoromethylated azetidine

Unfortunately, the desired products **III.15** bearing the phenyl boronic pinacol ester were not obtained.

More experiments were performed in THF, and as it is regularly described, an excess of alcohol was used. However, these results did not lead to the desired product either, not surprisingly as the carbon sterically hindered difficults the S_N2 type reaction. Finally, the presence of an added base, triethylamine, was tried for this experience, as it was shown in some literature cases to be beneficial for the reaction. Regrettably, in our case, this did not help the reaction and only starting materials were recovered.[374]

Another approach was then proposed, in order to functionalize the difluoromethyl alcohols bearing N-heterocycles. This will be described in the next section.

C. Nucleophilic aromatic substitutions

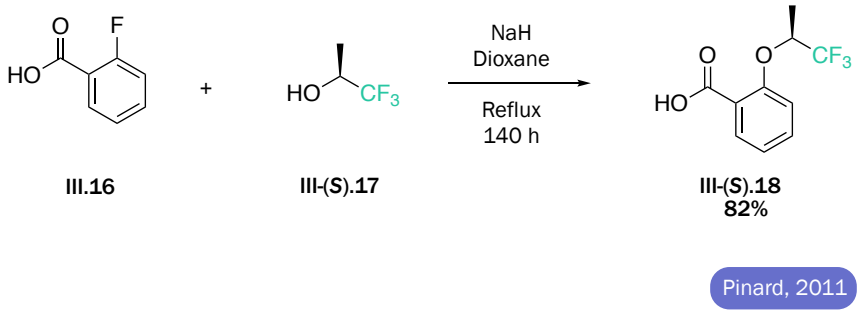
a. State of the art: examples of S_NAr type reactions on fluorinated derivatives

Nucleophilic aromatic substitutions represent a powerful tool in organic synthesis. Many derivatives can be obtained by replacing the halides of electron-deficient aromatic rings in the presence of a nucleophile. One can then have access to a large number of derivatives by properly choosing the nucleophile.

We considered then to use this strategy specific to alcohols starting from our readily prepared difluoromethylated alcohols as nucleophiles.

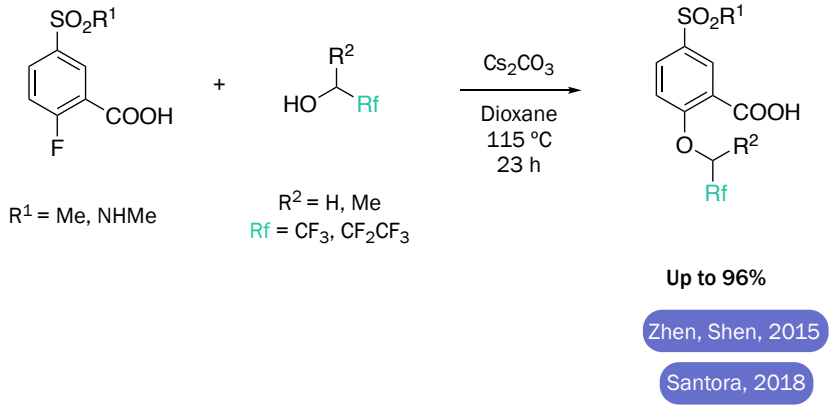
In literature, the examples of S_NAr reactions with alcohols bearing fluoroalkyl substituents are limited. In fact, the electron withdrawing effect of fluorine atoms in β-position of the alcohol makes of the deprotonated species a weaker nucleophile, requiring then harsh reaction conditions or the use of a highly activated aromatic ring as counterpart. Representative examples of this reaction will be listed in this section.

The use of fluorinated propanols was described a few times. In 2011, Pinard used **III-(*S*).17** with 2-fluorobenzoic acid in the presence of NaH to obtain the propan-2-yl derivative **III-(*S*).18** bearing a -CF_3 group (**Scheme III.32**).[375]



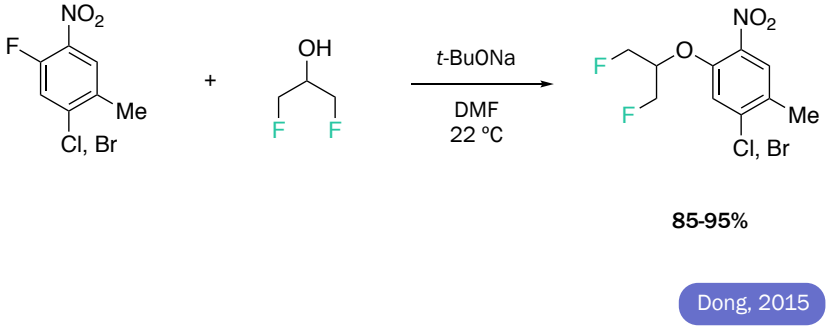
Scheme III.32. S_NAr using a trifluoromethylated alcohol

Later on, Zhen and Shen in 2015, followed by Santora's group in 2018 described a similar strategy where fluoroalkyl alcohols were reacted with trisubstituted aryls using cesium carbonate (**Scheme III.33**).[376,377] The expected fluoroalkylated molecules were obtained with good to excellent yields.



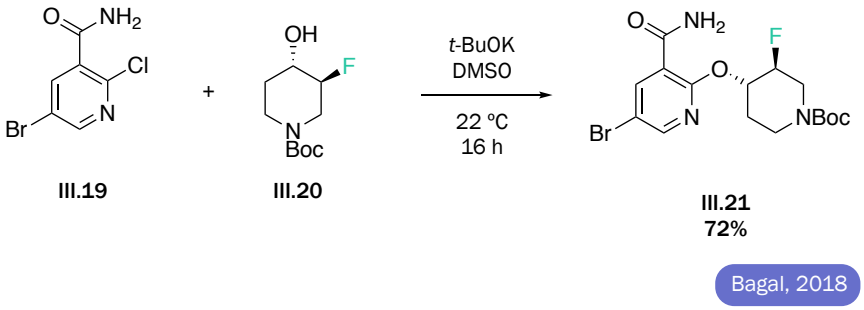
Scheme III.33. Cs_2CO_3 mediated S_NAr using fluoroalkylated alcohols

In 2015, Dong used 1,3-difluoropropan-2-ol to perform the nucleophilic aromatic substitution of tetrasubstituted aryls.[378] The use of *t*-BuONa allowed the group to replace the fluorine substituent of the aromatic ring with yields up to 95% (**Scheme III.34**).



Scheme III.34. S_NAr of tetrasubstituted aryls using *t*-BuONa

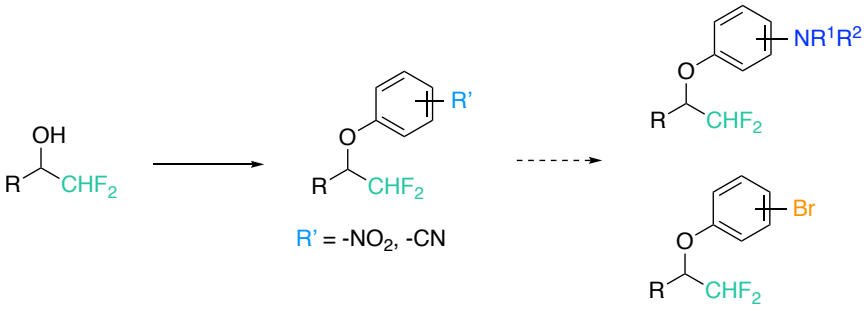
Recently, an additional interesting example of S_NAr was reported by Bagal using an alcohol derived from piperazine and bearing a fluorine atom, and a trisubstituted pyridine.[379] The chlorine atom in position 2 was successfully substituted and the monofluorinated product **III.21** was obtained in a very satisfying yield (**Scheme III.35**).



Scheme III.35. S_NAr reaction of halogenated pyridine using *t*-BuOK

b. Optimization of the reaction conditions

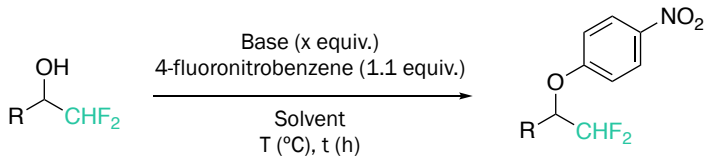
In view of the lack of reactivity of our azetidine and pyrrolidine substrates in Mitsunobu type reactions, aromatic nucleophilic substitutions were envisaged instead. This approach would allow us to add aromatic rings that after further functionalization can lead to amino substrates or halogenated aryl ethers for coupling reactions (**Scheme III.36**).

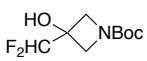
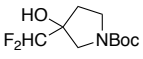


Scheme III.36. Possible derivatives obtained after functionalization of difluoromethyl alcohols by nucleophilic aromatic substitutions

The S_NAr were carried out using potassium *tert*-butoxide, sodium hydride and potassium carbonate as bases, in the presence of fluoronitrobenzene, in order to obtain the nitrophenyl derivative bearing the corresponding difluoromethyl-substituted *N*-heterocycle (**Table III.2**).[380]

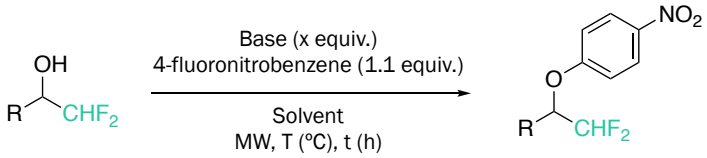
Table III.2. S_NAr reactions on azetidine and pyrrolidine-derived difluoromethylated alcohols

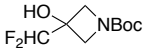
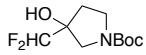


Entry	Substrate	Base (equiv.)	t (h)	T (°C)	Solvent	Yield
1	 **III.2d**	*t*-BuOK (1.1 equiv.)	20	22	THF	**III.22a** 52%
2		NaH (1.1 equiv.)	20	22	THF	**III.22a** 0%
3		K_2CO_3 (1.1 equiv.)	20	22	DMF	**III.22a** Traces
4	 **III.2f**	*t*-BuOK (1.1 equiv.)	20	22	THF	**III.22b** 34%

We were able to obtain the expected compounds with moderate yields when using *t*-BuOK. Furthermore, this transformation was improved using microwave-assisted synthesis. The optimization of the reaction is presented in **Table III.3**.

Table III.3. Microwave assisted S_NAr reactions

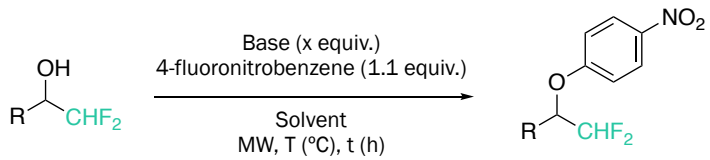


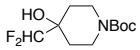
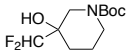
Entry	Substrate	Base (equiv.)	t (h)	T (°C)	Solvent	Yield
1	 **III.2d**	Cs_2CO_3 (2.9 equiv.)	1	110	DMF	**III.22a** 94%
2		K_2CO_3 (1.1 equiv.)	1	110	DMF	0%
3		K_2CO_3 (1.1 equiv.)	1	110	NMP	0%
4		1. K_2CO_3 (2.9 equiv.) 2. K_2CO_3 (2.9 equiv.)	2 1.25	110 110	DMF	1. 50% conversion* 2. Isolated yield 32%
5	 **III.2f**	Cs_2CO_3 (2.9 equiv.)	1	110	DMF	**III.22b** 0%
6		Cs_2CO_3 (2.9 equiv.)	2	140	DMF	82%
7		K_2CO_3 (1.1 equiv.)	1	110	DMF	0%
8		K_2CO_3 (1.1 equiv.)	1	110	NMP	0%
9		1. K_2CO_3 (2.9 equiv.) 2. K_2CO_3 (2.9 equiv.) 3. K_2CO_3 (2.9 equiv.)	2 1.5 1.5	140 140 140	DMF	1. Traces 2. 50% conversion* 3. Isolated yield 30%
10		K_2CO_3 (2.9 equiv.)	3	170	DMF	50% conversion*

*estimation made by proton NMR

In entries 4 and 9, we can observe that the conversion of the reaction was not total. An additional time of reaction was required, as well as the addition of reagents. To our delight, we were able to obtain satisfying conditions leading to the expected nitrophenyl derivative **III.22b** bearing the corresponding difluoromethyl *N*-heterocycle with excellent yields up to 94% for the azetidine derivative and 82% for the pyrrolidine derivative. These conditions, using Cs_2CO_3, were then applied to the 6 membered *N*-heterocycles (**Table III.4**).

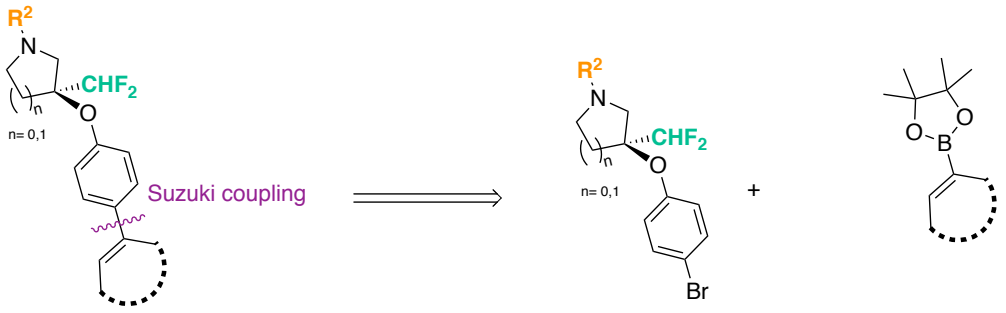
Table III.4. S_NAr reaction on 6 membered *N*-heterocycles



Entry	Substrate	Base (equiv.)	t (h)	T (°C)	Solvent	Yield
1	 **III.2h**	1. Cs_2CO_3 (2.9 equiv.) 2. Cs_2CO_3 (2.9 equiv.)	1 1	110 120	DMF	**III.22c** 1. Traces 2. Isolated yield 57%
2	 **III.2g**	1. Cs_2CO_3 (2.9 equiv.) 2. Cs_2CO_3 (2.9 equiv.) 3. Cs_2CO_3 (2.9 equiv.)	1 1 1.5	120 140 140	DMF	**III.22d** 1. Traces 2. *ca.* 50:50 of SM : product 3. Isolated yield 54%

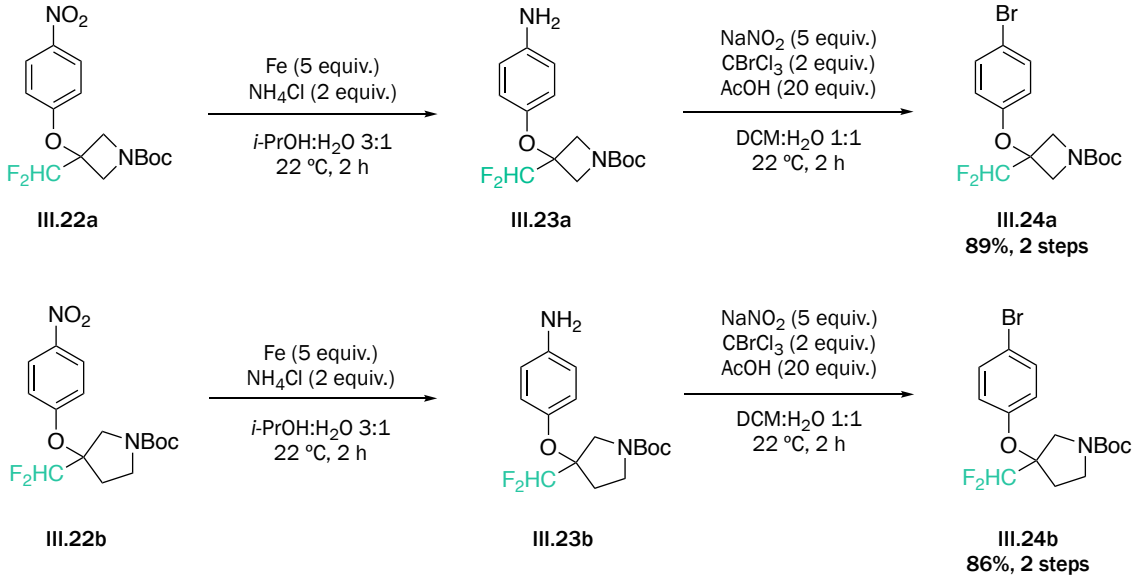
A larger reaction time and additional reagents were required in order to achieve a full conversion of the substrate into the expected product. We were able to obtain these compounds in moderate yields up to 54% for the *N*-Boc-3-substituted piperidine **III.22d** and 57% for the *N*-Boc-4- substituted piperidine **III.22c**.

As it was mentioned in Part B, we aimed to prepare a coupling partner for Suzuki-Miyaura couplings between difluoromethylated 4 and 5-membered *N*-heterocycles and scaffolds of a drug discovery project. The attempts for the synthesis of substituted difluoromethyl azetidine and pyrrolidines bearing a phenyl boronic ester were not successful and led us to consider an inversion of the chemical functions of the coupling partners. The *N*-heterocycle substituted with a *p*-bromophenyl bromide was then synthesized *via* a S_NAr reaction in order to be coupled with the available coupling partner having the boronic ester function (**Scheme III.37**).



Scheme III.37. Strategy to access a drug candidate analogue from a difluromethylated pyrrolidine bearing a *p*-bromophenyl bromide group

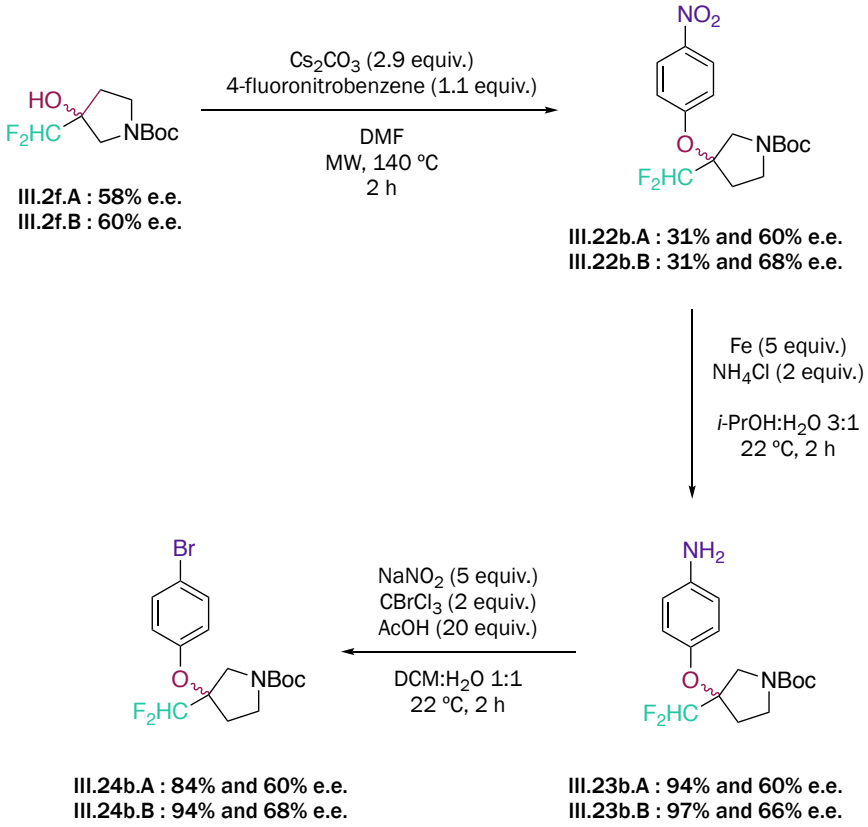
To access this bromobenzene derivative, the reduction of the nitro function was performed on two aryl ether obtained by S_NAr, bearing difluoromethyl azetidine and pyrrolidine moieties. The use of iron powder in the presence of ammonium chloride led to excellent yield for the reduction into anilines. Then the transformation of the latter to the phenyl bromide was performed by halogen abstraction from $CBrCl_3$ under weakly acidic conditions[381] with a very good yield (**Scheme III.38**).



Scheme III.38. Access to bromobenzene derivatives bearing a difluoromethylated *N*-heterocycle

In view of these results, the same conditions were applied to both enantiomers of *N*-boc 3-(difluoromethyl)pyrrolidin-3-ol. To achieve this, the enantiomers were prepared following our methodology starting from the condensation of difluoromethyl *p*-tolyl sulfoxide onto *N*-Boc pyrrolidinone. Both diastereomers were separated by column chromatography, and after desulfinylation, we were able to obtain enantioenriched 3-(difluoromethyl)pyrrolidinols **III.2f.A** and **III.2f.B**.

Each starting enantiomer **III.2f.A** and **III.2f.B** has an enantiomeric excess of *ca.* 60%, and both were submitted to the S_NAr conditions to obtain first the nitrophenyl derivatives, which were then reduced into the anilines **III.23b.A** and **III.23b.B** and finally transformed into the bromophenyl derivatives **III.24b.A** and **III.24b.B** (**Scheme III.39**). The enantiomeric ratio of the S_NAr product was verified by chiral HPLC and showed retention of configuration at the stereogenic carbon center. We were glad to confirm that the configuration was also preserved after the reduction of the nitro moiety and the conversion of the aniline to the aryl bromide. This validated sequence can then be applied to other derivatives, knowing that the initial enantiomeric ratio of the difluoromethyl alcohol can be improved from the previous steps.



Scheme III.39. S_NAr reactions and functionalization applied to enantiopure difluoromethylated pyrrolidines

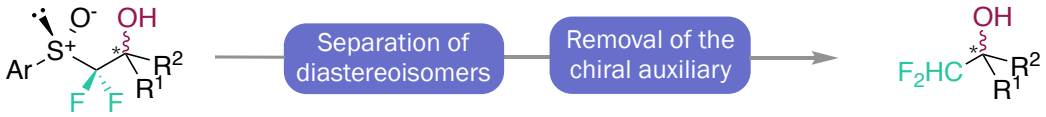
The readily prepared enantiomers bearing a bromophenyl group can then be involved in the Suzuki-Miyaura coupling reactions to obtain the final compounds.

D. Summary and conclusions

Continuing our studies to access enantiopure difluoromethylated compounds using chiral difluoromethyl aryl sulfoxides as $-CHF_2$ surrogates, we focused our efforts on the functionalization of α-difluoromethyl-β-sulfinyl alcohols.

In the previous chapter, we reported the different strategies that were used to introduce the difluoromethyl moiety by deprotonation and nucleophilic addition of the corresponding anion onto a range of electrophiles. The most successful results were obtained when the (arenesulfinyl)-difluoro-methanide was added to carbonyls. We focused then on the possibilities of functionalization of these compounds.

First, the desulfinylation was explored. Several methods described in the literature for the non-fluorinated analogues were tested without success. Moreover, desulfonylation protocols described to be efficient for difluoromethylated sulfonyl compounds were also tried and some reproducibility issues were raised. However, we were able to develop efficient conditions for this procedure. In addition to that, the same conditions used for the desulfonylation involving activated Mg(0) were efficiently applied to the sulfinyl derivatives. In the course of our studies, we also investigated a recently described system for desulfinylation: phenylsilane in basic medium. After an optimization of the reaction conditions and with the alternative use of PMHS instead of phenylsilane, we had access to a second desulfinylation method. It is noteworthy that retention of configuration at the freshly formed carbon center was confirmed in both cases, making this methodology reliable (**Scheme III.40**).

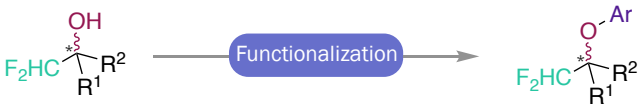


Scheme III.40. Access to enantioenriched difluoromethyl alcohols from α-difluoromethyl-β-hydroxysulfoxides

Moreover, we aimed to valorize the synthesized difluoromethyl alcohols. The final part of this project consisted then in studying their transformations of the different functional groups contained in these molecules, in order to establish them as a highly valuable platform towards various chiral difluoromethylated building-blocks of high interest, particularly in medicinal chemistry.

First, we considered the Mitsunobu reaction. Indeed, the possibility to introduce a large number of functionalities by properly choosing the pronucleophile seemed very attractive for this project. This was complementary to the fact that the inversion of configuration of the carbon center during the transformation would be of great interest to access numerous enantiopure difluoromethylated compounds. The first attempts of functionalization of α-difluoromethyl-β-hydroxysulfoxides were unfortunately unfruitful. We focused then on the functionalization of difluoromethyl derivatives after removal of the sulfinyl chiral auxiliary. We were glad to observe that our model substrate reacted very well in the Mitsunobu conditions to afford the corresponding amine and boronate-substituted aryl ether. However, when this strategy was applied to selected *N*-heterocycles, results were not satisfying, and we could not obtain the expected products.

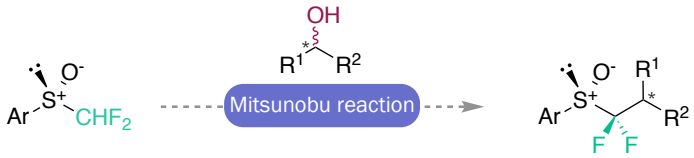
We finally proceeded with another challenging transformation of our substrates: nucleophilic aromatic substitutions using difluoromethyl alcohols as the corresponding nucleophiles. To our delight, the different 4, 5 and 6-membered *N*-heterocyclic alcohols showed excellent results. As an extension of the study, we synthesized in racemic and enantioenriched fashion the bromophenyl ether of 3-(difluoromethyl)pyrrolidin-3-ol to be used in the synthesis of a building block of pharmaceutical interest. Three steps were involved in this synthesis (the key step being a S_NAr), and we were able to confirm the retention of configuration at the carbon stereocenter all along the process (**Scheme III.41**).



Scheme III.41. Functionalization of enantioenriched difluoromethyl alcohols

Furthermore, the functionalizations performed using nucleophilic aromatic substitutions opened the way to access new derivatives, and it will be worth completing the study by synthesizing a range of aryl ethers bearing the -CHF_2 moiety, as proposed in **Scheme III.36**.

Regarding the Mitsunobu type reactions that did not afford satisfying results, it would be also interesting to use enantiopure difluoromethyl *p*-tolyl sulfoxide as the pronucleophile to evaluate its reactivity (**Scheme III.42**).



Scheme III.42. Mitsunobu reaction between difluoromethyl *p*-tolyl sulfoxide and chiral alcohols

E. Experimental Part

a. Desulfinylation of α-difluoro-β-sulfinyl alcohols

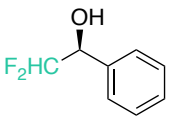
General procedure for the Mg(0)-mediated desulfinylation

Magnesium turnings (30 equiv., 2.59 mmol) were previously placed under vacuum. 0.3 mL of methanol and a minimal amount of iodine were added to the medium. The mixture was cooled to 0 ºC. A solution of the corresponding α-difluoro-β-sulfinyl alcohol **II.91** (1 equiv., 0.086 mmol) in 0.7 mL of methanol was added. The reaction mixture was allowed to warm to 20 ºC and stirred at this temperature for 16 h. The reaction was quenched with a saturated solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

PMHS/*t*-BuOK-mediated desulfinylation

To a stirred solution of 2,2-difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-ol (S_S,*S*) **II-(*S*,S_S).91a** (1 equiv., 50.0 mg, 169 mmol) and *t*-BuOK (3 equiv., 56.8 mg, 506 mmol) in freshly distilled THF was added dropwise PMHS (3 equiv., 0.14 mL, 506 mmol). The mixture was stirred at 20 ºC for 48 h in a sealed tube, then quenched with a solution of KOH in a water/methanol (1:1, V/V) mixture and left under stirring for 2 h. The aqueous phase was extracted three times with diethyl ether. The combined organic phases were washed with a saturated solution of sodium carbonate and with brine dried over anhydrous sodium sulfate, filtered over Celite® and activated charcoal and concentrated under reduced pressure.

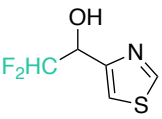
(*S*)-2,2-Difluoro-1-phenylethan-1-ol II-(*S*).2



II-(*S*).2

Prepared by PMHS/*t*-BuOK-mediated desulfinylation. The crude was purified by chromatography on silica gel with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 70:30). 52% yield. 88% e.e. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.46-7.35 (m, 5H), 5.77 (td, J = 4.8 Hz, 55.9 Hz, 1H), 4.84 (td, J = 4.6 Hz, 10.1 Hz, 1H), 2.43 (br s, 1H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ (ppm) -127.2 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 284.1 Hz, J_{AX} = $J_{H\text{-}F}$ = 55.9 Hz, J_{BX} = $J_{H\text{-}F}$ = 9.5 Hz, ΔνAB = 278.5 Hz, 1F) and -128.0 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 284.1 Hz, J_{AX} = $J_{H\text{-}F}$ = 55.9 Hz, J_{BX} = $J_{H\text{-}F}$ = 10.9 Hz, ΔνAB = 278.8 Hz, 1F). In agreement with previously reported data.[382] The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (*n*-hexane:*i*-PrOH 95:5, flow rate: 0.5 mL/min, λ = 207 nm, τ = 10.7 min and 11.7 min).

2,2-Difluoro-1-(thiazol-4-yl)ethan-1-ol III.2c



III.2c

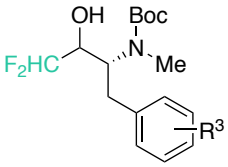
Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 30:70). 43% yield. Orange oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 8.84 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 6.01 (td, J = 55.7, 3.9 Hz, 1H), 5.22 – 4.92 (m, 1H), 3.17 (br, 1H), 2.42 – 2.26 (m, 1H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -129.3 (ABX system, J_{AB}=$J_{F\text{-}F}$= 284.8 Hz, ΔνAB=226 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 153.55, 130.4, 117.50, 116.9, 115.06 (t, J = 245.4 Hz). **HRMS (ESI):** m/z calculated for $[C_5H_6F_2NO_2]^+$: 150.0361, found: 150.0362.

tert-Butyl-3-(difluoro(*p*-toluenesulfinyl)methyl)-3-hydroxypiperidine-1-carboxylate III.2d

III.2d

Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 30:70). 38% yield. Yellow oil. White solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 5.81 (td, *J* = 55.7, 1.2 Hz, 1H), 4.11 (d, *J* = 9.8 Hz, 2H), 3.87 (d, *J* = 9.8 Hz, 2H), 2.88 (br, 1H), 1.44 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) -134.16 (*app.* d, *J* = 2.9 Hz). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 156.3, 116.9, 114.6 (t, *J* = 244.7 Hz), 112.1, 80.6, 77.5, 77.2, 76.8, 69.8, 69.6 (t, *J* = 24.8 Hz)., 69.4, 56.7, 28.5. **HRMS (ESI):** m/z calculated for $[C_9H_{15}F_2NNaO_3]^+$: 246. 0912, found: 246.0919. **IR (cm^{-1})** 3354, 2979, 1654, 1498, 1433, 1228, 1169, 1068, 625.

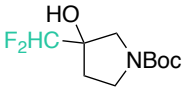
tert-Butyl-((2*R*)-1-(aryl)-4,4-difluoro-3-hydroxybutan-2-yl)(methyl)carbamate III.2e



III.2e

Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl gradient (from pure heptane to 50:50). 67% yield. Colorless oil. *Due to confidentiality reasons, aromatic substituents are not disclosed.* **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 5.75 (td, *J* = 55.7, 3.8 Hz, 1H), 4.21 – 4.06 (m, 1H), 3.62 (d, *J* = 11.1 Hz, 1H), 3.30 (dd, *J* = 14.2, 11.3 Hz, 1H), 3.01 – 2.90 (m, 1H), 2.52 (s, 3H), 1.43 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -129.2 (t, *J* = 288.0 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 163.3 (d, *J* = 12.0 Hz), 160.8 (d, *J* = 12.0 Hz), 157.0, 132.3, 115.3 (t, *J* = 243.5 Hz), 111.3 (dd, *J* = 20.9, 3.7 Hz), 103.8 (t, *J* = 25.8 Hz), 80.9, 74.0 (t, *J* = 23.1 Hz), 61.4, 37.5, 28.4, 26.4. **HRMS (ESI):** m/z calculated for $[C_{16}H_{21}F_4NNaO_3]^+$: 374.1250, found: 374.1326

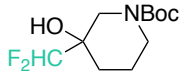
tert-Butyl 3-(difluoromethyl)-3-hydroxypyrrolidine-1-carboxylate III.2f



III.2f

Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 95% yield. Colorless solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm) 5.75 (t, *J* = 55.8 Hz, 1H), 3.65 – 3.47 (m, 4H), 3.48 – 3.33 (m, 1H), 3.33 – 3.18 (m, 1H), 2.12 – 1.99 (m, 1H), 1.99 – 1.84 (m, 1H), 1.44 (s, 9H). **^{19}F NMR (471 MHz, $CDCl_3$)** δ (ppm) -130.27, (*app.* d, *J* = 54.4 Hz), -130.25 (*app.* d, *J* = 56.1 Hz), -130.20 (*app.* d, *J* = 55.8 Hz). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 115.5 (t, *J* = 245.8 Hz), 80.0, 79.4 (dt, *J* = 107.7, 22.2 Hz), 53.1, 52.8, 44.5, 44.1, 32.5, 32.0, 28.6. **HRMS (ESI):** m/z calculated for $[C_{10}H_{17}F_2NNaO_3]^+$: 260.1069, found: 260.1081. **IR (cm^{-1})** 3299, 1647, 1545, 1499, 1289, 1236, 1014, 872, 814, 591, 504. The enantiomeric ratio of the product was determined by HPLC using a Chiracel IC column (*n*-hexane:*i*-PrOH= 90:10, flow rate 0.5 mL/min, λ = 205 nm, τ = 11.1 min, 15.1 min).

tert-Butyl 3-(difluoromethyl)-3-hydroxypiperidine-1-carboxylate III.2g

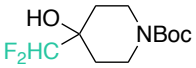


III.2g

Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 51% yield. Colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 5.57 (t, *J* = 55.8 Hz, 1H), 3.92 (d, *J* = 13.4 Hz, 1H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.52 (s, 0H), 3.18 – 2.98 (m, 2H), 1.92 – 1.57 (m, 3H), 1.46 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -134.00 (*app.* d, *J* = 3.3 Hz, 1F), -134.02 (*app.* s, 1F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm)

156.4, 116.5 (t, *J* = 221.5 Hz), 79.9, 70.3, 66.4, 50.5, 43.8, 28.5. **HRMS (ESI):** m/z calculated for $[C_{11}H_{19}F_2NNaO_3]^+$: 274.1225, found: 274.1232.

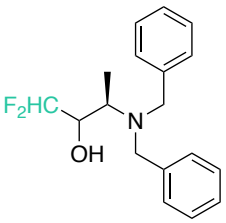
tert-Butyl 4-(difluoromethyl)-4-hydroxypiperidine-1-carboxylate III.2h



III.2h

Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 92% yield. Light yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 5.49 (t, *J* = 56.3 Hz, 1H), 4.24 – 3.76 (m, 2H), 3.08 (t, *J* = 13.1 Hz, 2H), 1.67 (m, 2H), 1.61 – 1.50 (m, 2H), 1.46 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -129.14 (app. d, *J* = 3.5 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** (ppm) 154.8, 117.4 (t, *J* = 247.1 Hz), 79.9, 70.3 (t, *J* = 21.3 Hz), 67.8, 38.5, 34.2, 28.5. **HRMS (ESI):** m/z calculated for $[C_{11}H_{19}F_2NNaO_3]^+$: 274.1225, found: 274.1215. **IR (cm^{-1})** 3410, 2973, 1670, 1427, 1366, 1249, 1166, 1065, 972.

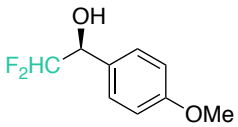
(3*S*)-3-(Dibenzylamino)-1,1-difluorobutan-2-ol III.2i



III.2i

Prepared by Mg(0)-mediated desulfinylation. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 58% yield. Light yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.47 – 7.14 (m, 10H), 5.40 (t, *J* = 56.6 Hz, 1H), 3.95 – 3.57 (m, 5H), 2.85 (d, *J* = 14.5 Hz, 1H), 2.56 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.05 (s, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -131.9 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 279.7 Hz, ΔνAB= 1490 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 138.6, 129.3, 128.7, 127.7, 117.2 (t, *J* = 247.8 Hz), 71.7, 71.2, 60.2, 57.5, 20.2. **HRMS (ESI):** m/z calculated for $[C_{18}H_{22}F_2NO]^+$: 305.1664, found: 306.1655.

(*S*)-2,2-Difluoro-1-(4-anisyl)-ethan-1-ol III-(*S*).2j



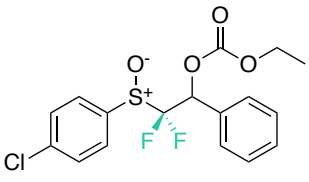
III-(S).2j

Prepared by Mg(0)-mediated desulfinylation. The crude product was purified by chromatography on silica gel using with a cyclohexane:ethyl acetate gradient (from pure cyclohexane to 60:40). 64% yield. 86% e.e. **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm)** 7.34 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.74 (td, *J* = 5.1 Hz, 56.3 Hz, 1H), 4.77 (td, *J* = 4.7 Hz, 10.3 Hz, 1H), 3.81 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm)** -127.5 (*app.* dd, *J* = 56.2, *J* = 9.5 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm)** 160.3, 131.8, 130.0, 129.7, 129.6, 128.6, 117.9, 116.0, 114.3, 114.0, 113.9, 73.4 (d, *J* = 26 Hz), 55.5, 29.8. **IR (cm^{-1})** 3414, 2924, 1515, 1250,1068, 832, 552. **HRMS (ESI)** calculated for $C_9H_9F_2O_2$: 187.0576, found: 187.0591. **$[\alpha]_{589}$** = + 13.40 (20 ºC, 0.7 g/100 mL, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (*n*-hexane:*i*-PrOH 98:2, flow rate: 0.5 mL/min, λ = 224 nm, τ = 27.2 min and 30.7 min).

b. Mitsunobu type reactions

2-((4-Chlorophenyl)sulfinyl)-2,2-difluoro-1-phenylethyl ethyl carbonate III.12

To a solution of 2-((4-chlorophenyl)sulfinyl)-2,2-difluoro-1-phenylethan-1-ol (60.0 mg, 0.189 mmol), triphenylphosphine (50,2 mg, 0.189 mmol) and dimethyl malonate (25.0 mg, 0.189 mmol) in anhydrous toluene (2 ml) was added dropwise at 0 °C diethyl azodicarboxylate (0.035 ml, 0.189 mmol). The solution was stirred overnight at room temperature. As starting material was still observed, the mixture was heated at 60 °C for 5 h. The mixture was filtered over Celite® and the volatiles were evaporated under reduced pressure.



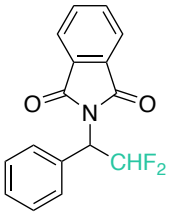
III.12

The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure *n*-heptane to pure ethyl acetate). 14 mg, 0.036 mmol, 19% yield. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.49 – 7.34 (m, 5H), 6.22 (dd, *J* = 14.3, 11.0 Hz, 1H), 4.32 – 4.21 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -113.39 (*app.* d, *J* = 2.0 Hz). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 153.0, 129.7, 128.8, 128.4, 127.9, 73.7 (dd, *J* = 28.6, 25.7 Hz), 73.5, 65.6, 14.3. **HRMS (ESI):** m/z calculated for $[C_{17}H_{15}ClF_2KO_4S]^+$: 426.9979, found: 426.9967

2-(2,2-Difluoro-1-phenylethyl)isoindoline-1,3-dione III.13a

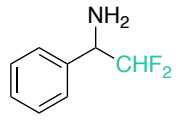
To a solution of phthalimide (48.97 mg, 0.32 mmol) in anhydrous toluene (2 ml) was added 2,2-difluoro-1-phenylethan-1-ol (50 mg, 0.32 mmol) (in solution in toluene) and triphenylphosphine (83.76 mg, 0.32 mmol) (as a solid). Diethyl azodicarboxylate (58 μL, 0.32 mmol) was added dropwise and the mixture was stirred overnight at room temperature. The mixture was filtered through a small pad of silica, washed with dichloromethane. The volatiles were evaporated under reduced pressure. The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 20:80) twice. 71% yield. Light yellow solid.



III.13a

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.56 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.44 – 7.30 (m, 3H), 6.99 (td, *J* = 56.6, 7.6 Hz, 1H), 5.50 (ddd, *J* = 11.1, 9.5, 7.6 Hz, 1H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -126.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ =246.1 Hz, $J_{AX} = J_{H\text{-}F}$ = 56.6 Hz, 7.6 Hz, ΔνAB=635 Hz, 2F). **^{13}C NMR (126 MHz, $CDCl_3$)** δ (ppm) 167.70, 134.7, 133.8, 131.71, 129.3, 129.2, 128.9, 123.8, 113.3 (dd, *J* = 246.0, 243.5 Hz), 57.5 (dd, *J* = 25, 30 Hz). **HRMS (ESI):** m/z calculated for $[C_{16}H_{12}F_2NO_2]^+$: 288.0831, found: 288.0831. **IR (cm^{-1})** 1781, 1716, 1384, 1108, 1067, 1052, 720, 696, 499.

2,2-Difluoro-1-phenylethan-1-amine III.14



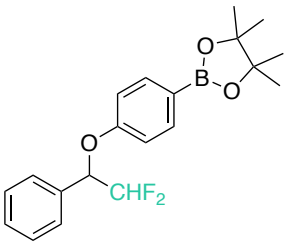
III.14

A mixture of 2-(2,2-difluoro-1-phenylethyl)isoindoline-1,3-dione (25 mg, 87 μmol), acetic acid (0.2o mL, 3.5 mmol) and hydrobromic acid (0.2 ml, 1.77 mmol) was stirred at 120 °C overnight. The mixture was allowed to reach room temperature, was filtered and washed with methanol. A saturated solution of sodium carbonate in water was

added to the mixture and the aqueous phase was extracted three times with dichloromethane. The volatiles were evaporated under reduced pressure. No purification was performed. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.63 – 7.01 (m, 5H), 5.77 (td, *J* = 56.7, 4.6 Hz, 1H), 4.19 (ddd, *J* = 13.8, 9.7, 4.5 Hz, 1H). In agreement with previously reported data.[261]

2-(4-(2,2-Difluoro-1-phenylethoxy)phenyl)-pinacolborane III.15a

To a solution of 4-hydroxyphenyl pinacolborane (69 mg, 32 μmol) in anhydrous THF (2 ml) was added 2,2-difluoro-1-phenylethan-1-ol (50 mg, 32 μmol) (in solution in THF) and triphenylphosphine (84 mg, 316 μmol) as a solid. (*E*)-*N1,N1,N2,N2*-tetramethyldiazene-1,2-dicarboxamide (68 mg, 40 μmol) was added portionwise and the mixture was stirred overnight at room temperature. The mixture was filtered through a small pad of silica, washed with dichloromethane. The filtrate was concentrated under reduced pressure.



III.15a

The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to pure ethyl acetate). 74% yield. Light yellow oil.

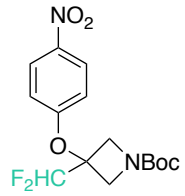
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (d, *J* = 8.6 , 2H), 7.44 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.99 (td, *J* = 55.5, 4.2 Hz, 1H), 5.31 (td, *J* = 10.1, 4.2 Hz, 1H), 1.30 (s, 12H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -126,6 (ABX system, J_{AB} = $J_{F\text{-}F}$=285.8 Hz, 7.6 Hz, ΔνAB= 962.2 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 159.5, 136.6, 133.5, 129.3, 128.9, 127.7, 115.4, 114.6, 83.77, 79.0, 78.8, 78.5, 24.9. IR (cm^{-1}) 3290, 2921, 1597, 1406, 1194, 1114, 1086, 991, 809, 521, 450. **HRMS (ESI):** m/z calculated for $[C_{20}H_{24}BF_2O_3]^+$: 361.1785, found: 361.1787.

c. Nucleophilic aromatic substitutions

General procedure

In a microwave tube, the corresponding difluoromethyl alcohol (135 μmol, 1 equiv.) was dissolved in DMF and 4-fluoronitrobenzene (16 μl, 148 μmol, 1.1 equiv.) was added followed by cesium carbonate (128 mg, 391 μmol, 2.9 equiv.). The reaction mixture was heated under microwave irradiation at the appropriate temperature for the time indicated. A saturated solution of ammonium chloride was added to the solution and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixtures were purified by silica gel flash chromatography.

tert-Butyl 3-(difluoromethyl)-3-(4-nitrophenoxy)azetidine-1-carboxylate III.22a



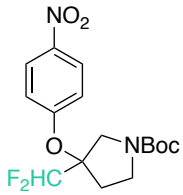
III.22a

Reaction time: 1 h. Reaction temperature: 110 °C.

The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 30:70). 94% yield. Light yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 8.23 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 6.10 (t, *J* = 55.0 Hz, 1H), 4.34 (d, *J* = 10.3 Hz, 2H), 4.19 (d, *J* = 11.2 Hz, 1H), 1.45 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -131.27 (*app.* s). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 159.17, 155.86, 143.13, 126.15, 117.16, 111.3 (t, *J* = 247.5 Hz),

81.08, 75.6 (t, J = 25.6 Hz), 54.34, 28.39. **HRMS (ESI):** m/z calculated for $[C_{15}H_{18}F_2KN_2O_5]^+$: 383.0815, found: 383.0815. **IR (cm^{-1})** 2977, 1704, 1593, 1520, 1391, 1344, 1246, 1111, 1083, 1062, 853, 751.

tert-Butyl 3-(difluoromethyl)-3-(4-nitrophenoxy)pyrrolidine-1-carboxylate III.22b



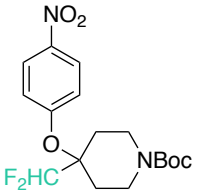
III.22b

Reaction time: 2 h. Reaction temperature: 140 ºC.

The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 10:90). 82% yield. Yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.37 – 7.93 (m, 2H), 7.13 – 6.78 (m, 2H), 5.98 (t, J = 55.0 Hz, 1H), 4.16 – 3.35 (m, 4H), 2.38 – 2.15 (m, 2H), 1.37 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ (ppm) 159.3, 154.2, 143.9, 126.3, 125.7, 122.2, 115.8, 114.3, 80.6, 49.8, 44.2, 28.5. **HRMS (ESI):** m/z calculated for $[C_{16}H_{20}F_2N_2NaO_5]^+$: 381.1232, found: 381.1222. **IR (cm^{-1})** 2918, 2850, 1698, 1523, 1412, 1344, 1240, 1163, 1068, 871. The enantiomeric ratio of the product was determined by HPLC using a Chiracel IC column (*n*-hexane:*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 274 nm, τ = 35.8 min, 39.2 min).

tert-Butyl 4-(difluoromethyl)-4-(4-nitrophenoxy)piperidine-1-carboxylate III.22c

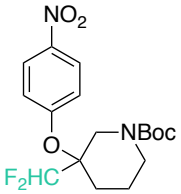


III.22c

Reaction time: 1 h at 110 ºC followed by 1 h at 120 ºC.

The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 57% yield. Light yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) 8.21 (d, J = 9.1 Hz, 2H), 7.21 (d, J = 9.1 Hz, 2H), 5.78 (t, J = 55.1 Hz, 1H), 4.19 – 3.77 (m, 2H), 3.26 – 2.87 (m, 2H), 2.06 (d, J = 13.9 Hz, 2H), 1.92 – 1.71 (m, 2H), 1.46 (s, 9H).**^{19}F NMR (282 MHz, CDCl$_3$)** δ (ppm) -115.33 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 221.2 Hz, ΔνAB= 2331 Hz, 0.39F), -114.8 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 226.1 Hz, ΔνAB= 1231 Hz, 0.61F). **^{13}C NMR (101 MHz, CDCl$_3$)** δ (ppm) 160.1, 154.6, 143.9, 125.6, 122.5, 115.78 (t, J = 249.3 Hz), 80.44 (t, J = 21.0 Hz), 80.3, 40.4, 38.8, 28.5. **HRMS (ESI):** m/z calculated for $[C_{17}H_{22}F_2N_2NaO_5]^+$: 395.1389, found: 395.1392. **IR (cm^{-1})** 2973, 1692, 1591, 1520, 1345, 1164, 1068, 864.

tert-Butyl 3-(difluoromethyl)-3-(4-nitrophenoxy)piperidine-1-carboxylate III.22d



III.22d

Reaction time: 1 h at 120 ºC, 1h at 140 ºC and 1.5 h at 140 ºC.

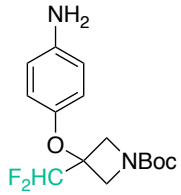
The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 57% yield. Yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) 8.27 – 8.07 (m, 2H), 7.22 (d, J = 9.1 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 6.61 (d, J = 9.4 Hz, 1H), 5.84 (t, J = 54.8 Hz, 1H), 4.38 (dd, J = 8.0, 4.5 Hz, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.12 (s, 2H), 2.14 – 2.02 (m, 1H), 1.92 – 1.72 (m, 1H), 1.43 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ (ppm) 110.1, 115.4, 123.1, 125.8, 40.4, 28.6, 27.8, 20.0. **HRMS (ESI):** m/z calculated for $[C_{17}H_{22}F_2N_2NaO_5]^+$: 395.1389, found: 395.1376.

d. Reduction of nitrophenyl derivatives

General procedure

Reduced iron powder (0.30 mmol, 5 equiv.) and ammonium chloride (0.13 mmol, 2 equiv.) were added to a solution of the nitroaryl derivative (0.060 mmol) in an mixture isopropanol:water (1:3, V/V) mixture. The solution was refluxed for 2 h. The mixture was cooled to room temperature and poured into water, extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

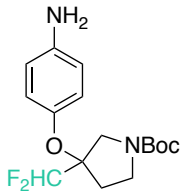
***tert*-Butyl 3-(4-aminophenoxy)-3-(difluoromethyl)azetidine-1-carboxylate III.23a**



III.23a

Quantitative yield. Light yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$) δ** (ppm) 6.74 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.01 (t, *J* = 55.5 Hz, 1H), 4.28 – 3.95 (m, 4H), 1.43 (s, 5H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 145.96, 142.97, 121.03, 113.12 (t, *J* = 245.9 Hz), 116.26, 110.68, 80.40, 75.61 (t, *J* = 25.0 Hz), 54.10, 28.40. **HRMS (ESI):** m/z calculated for $[C_{15}H_{21}F_2N_2O_3]^+$: 315.1515, found: 315.1495. **IR (cm^{-1})** 3356, 2976, 1698, 1509, 1392, 1226, 1167, 1107, 835, 629.

***tert*-Butyl 3-(4-aminophenoxy)-3-(difluoromethyl)pyrrolidine-1-carboxylate III.23b**



III.23b

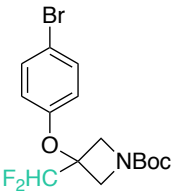
The crude mixture was filtered through a pad of silica gel using ethyl acetate as eluent. 97% yield. Light yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 6.69 (d, *J* = 8.5 Hz, 2H), 6.49 (d, *J* = 8.3 Hz, 2H), 5.84 (t, *J* = 55.4 Hz, 1H), 3.78 – 3.15 (m, 6H), 2.18 – 1.86 (m, 2H), 1.35 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -128.93 (1F), -129.43 (d, *J* = 6.5 Hz, 1F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 154.37, 145.53, 143.70, 124.55, 114.3, 115.84, 87.8, 49.73, 44.16, 28.60. **HRMS (ESI):** m/z calculated for $[C_{16}H_{22}F_2N_2NaO_3]^+$: 351.1491, found: 351.1479. The enantiomeric ratio of the product was determined by HPLC using a Chiracel ID column (*n*-hexane/*i*-PrOH= 80:20, flow rate 0.5 mL/min, λ = 204 nm, τ = 18.78 min, 21.77 min).

e. Conversion of anilines to aryl bromides

General procedure

Aryl amine (0.03 mmol, 1 equiv.), $NaNO_2$ (0.15 mmol, 5 equiv.), bromotrichloromethane (0.06 mmol, 2 equiv.), and solvent system (0.4 mL each of organic solvent and H_2O) were stirred (5 min) at room temperature. Acetic acid (20 equiv.) was then added in one portion and the reaction stirred under argon for 1 h. After separation of the organic layer, the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure.

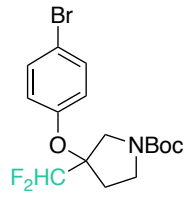
tert-Butyl 3-(4-bromophenoxy)-3-(difluoromethyl)azetidine-1-carboxylate III.24a



III.24a

The crude mixture was filtered through a pad of silica gel using a *n*-heptane:ethyl acetate The crude mixture was purified by silica gel flash chromatography using a *n*-heptane:ethyl acetate gradient (from pure heptane to 50:50). 57% yield. Light yellow oil. (20:80). 89% yield. Dark orange oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.42 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.05 (t, *J* = 55.3 Hz, 1H), 4.24 (d, *J* = 10.0 Hz, 2H), 4.12 (d, *J* = 10.3 Hz, 2H), 1.44 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -132.38 (*app*. s, 2F). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 156.0, 153.1, 132.9, 119.9, 115.1, 112.6 (t, *J* = 246.7 Hz), 80.8, 75.3 (t, *J* = 25.3 Hz), 54.2, 28.4. **HRMS (ESI):** m/z calculated for $[C_{15}H_{18}F_2BrNNaO_3]^+$: 400.0330, found: 400.0349. **IR (cm^{-1})** 3358, 2977, 1704, 1643, 1486, 1391, 1209, 1169, 1111, 631.

tert-Butyl 3-(4-bromophenoxy)-3-(difluoromethyl)pyrrolidine-1-carboxylate III.24b



III.24b

The crude mixture was filtered through a pad of silica gel using ethyl acetate as eluent. 86% yield. Dark orange oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.42 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.97 (t, *J* = 55.2 Hz, 1H), 3.78 (d, *J* = 12.7 Hz, 0.4H), 3.68 (d, *J* = 13.2 Hz, 0.6H), 3.63 – 3.34 (m, 3H), 2.30 – 2.05 (m, 2H), 1.44 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -128.01 (d, *J* = 26.3 Hz), -128.50 (d, *J* = 21.4 Hz). **^{13}C NMR (101 MHz, $CDCl_3$)** δ (ppm) 132.6, 124.7, 152.9, 118.1, 117.9, 80.1, 49.8, 44.1, 28.5. **HRMS (ESI):** m/z calculated for $[C_{16}H_{20}F_2BrNNaO_3]^+$: 414.0487, found: 414.0493. **IR (cm^{-1})** 2918, 2806, 1704, 1593, 1520, 1394, 1348, 1246, 1169, 1111, 1080, 853, 751. The enantiomeric ratio of the product was determined by HPLC using a Chiracel ID column (*n*-hexane:*i*-PrOH = 95:5, flow rate 0.5 mL/min, λ = 222 nm, τ = 13.48 min, 14.58 min).

Conclusion and perspectives

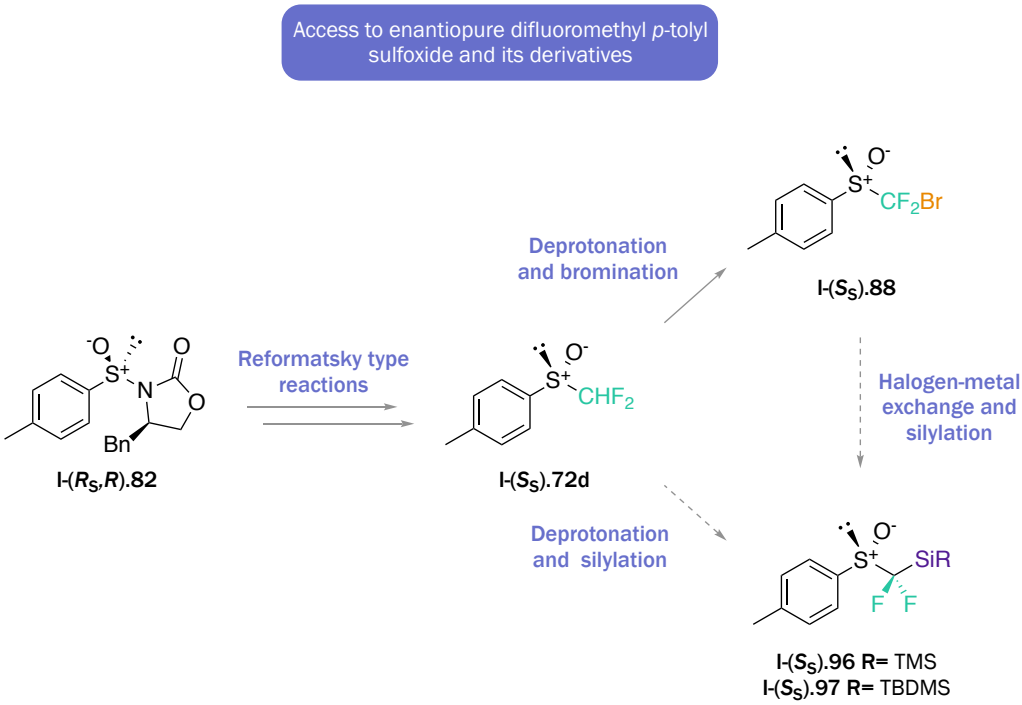
Conclusion and perspectives

Many examples reported in the literature in the last decades have disclosed the importance of organofluorine chemistry in life sciences (*cf.* Introduction chapter). The introduction of a fluorine atom or a fluorinated group in a molecule can deeply impact its physical, chemical and biological properties. The increasing number of fluorinated compounds currently used in pharmaceutical and agrochemical research evidence the importance of developing new efficient synthetic strategies for their preparation. Although several research groups have achieved major accomplishments in the introduction of fluorinated substituents, a major challenge in this field remains their stereoselective introduction.

The difluoromethyl group among other Emergent Fluorinated Substituents (EFS) offers features that render it an interesting functional group for pharmaceutical applications. Its use as a bioisostere of thiol or hydroxyl group has been recognized in biologically active compounds, due to a similar stereoelectronic arrangement and to its ability to perform hydrogen bonding and thus allowing improved interactions with biological targets. Moreover, the CHF_2 group can modify the acidity of neighboring groups in the molecule as well as its lipophilicity. Only a few methods have been published for the stereoselective introduction of the CHF_2 group.

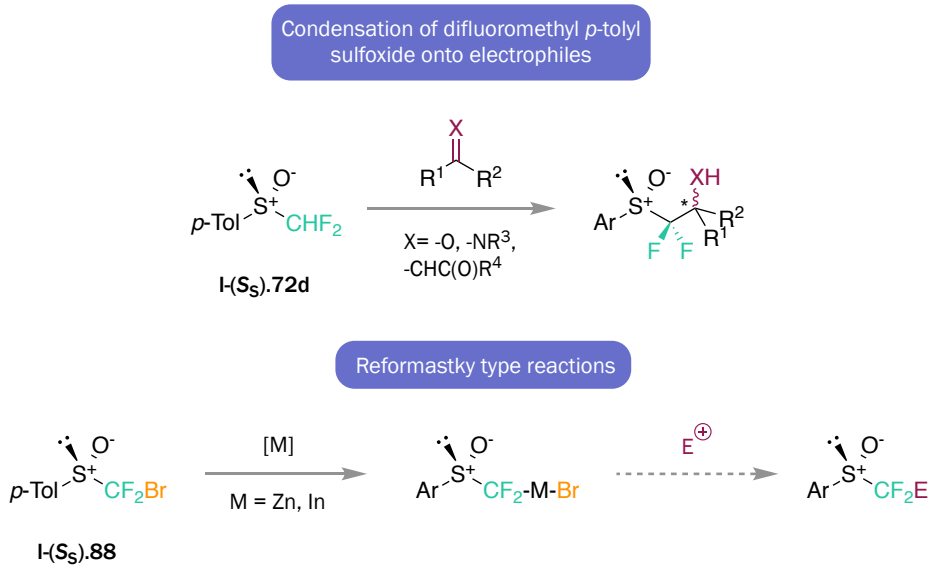
Sulfoxides proved to be highly efficient chiral auxiliaries in asymmetric synthesis. Within our research group, we aimed to combine the remarkable chiral induction ability of sulfoxides with the fluorinated group of interest, CHF_2. In this context, we got inspired by the work performed by Hu and Prakash[383] to design new chiral difluoromethyl surrogates, namely difluoromethyl aryl sulfoxides.

Firstly, we developed a new, more efficient and more reproducible synthesis of enantiopure difluoromethyl sulfoxides, which had been described only in two reports in literature. Pursuing a remarkable work performed in our group in the course of the synthesis of these compounds, we were able to obtain enantiopure (*S*)-difluoromethyl *p*-tolyl sulfoxide **I-(*S*$_S$).72d** with an excellent optical purity.[65] Then, we used this compound to try to synthesize further derivatives, namely bromodifluoromethyl *p*-tolyl sulfoxide **I.88** and difluoromethyltrialkylsilyl *p*-tolyl sulfoxides **I.96** and **I.97** (**Scheme C.1**). The synthesis of these derivatives was aimed to provide additional reactivities and broaden the scope of difluoromethylation using sulfoxides. We were able to obtain bromodifluoromethylated derivative **I.88**, however the attempts to access difluoro(trialkylsilyl)methyl counterparts remained unsuccessful.



Scheme C.1. Synthesis of difluoromethyl *p*-tolyl sulfoxide and its bromo and silyl derivatives

After synthesizing new chiral difluoromethyl surrogates, a first project was dedicated to the introduction of difluoromethyl *p*-tolyl sulfoxide and bromodifluoromethyl *p*-tolyl sulfoxide onto electrophiles (*cf. Chapter 1*, **Scheme C.2**).



Scheme C.2. Introduction of the difluoromethyl moiety by condensation of difluoromethyl *p*-tolyl sulfoxide onto electrophiles

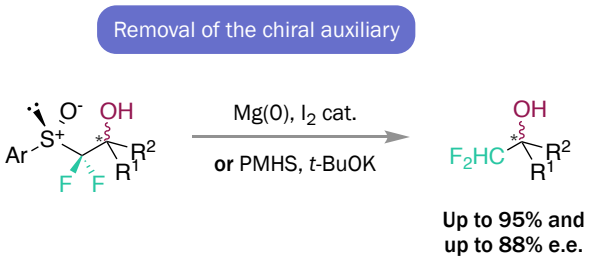
α-Difluoro-β-sulfinyl alcohols were successfully obtained by the condensation of difluoromethyl *p*-tolyl sulfoxide **I.72d** onto carbonyls, and α-difluoro-β-sulfinyl alcohols bearing heterocycles of pharmaceutical interest were synthesized. Although our methodology suffered from moderate diastereoselectivities (up to

28:72 d.r.), the separation of the obtained diastereomers of α-difluoro-β-sulfinyl derivatives allowed for the isolation of diastereo- and enantioenriched compounds.

Aiming at obtaining diastereoenriched derivatives more efficiently, we developed the synthesis of α-difluoro-β-ketosulfoxides **I.103** as precursors of α-difluoro-β-sulfinyl alcohols. The diastereoselective reductions of α-difluoro-β-ketosulfoxides were successfully performed and the desired products were obtained with good yields and excellent enantio- and diastereomeric ratios (up to 77% yield, 98:2 d.r. and 96% e.e.). These two complementary methodologies represent a straightforward access to α-difluoro-β-sulfinyl alcohols.

Regarding α-difluoro-β-amino derivatives, the reaction of difluoromethyl *p*-tolyl sulfoxide **I.72d** with aza electrophiles was not as efficient as expected. We were able to use a model imine substrate and obtain a mixture of the corresponding diastereomers of α-difluoro-β-sulfinyl amines (up to 34:66 d.r.), which were separated after column chromatography. The reactivity towards α,β-unsaturated systems was insufficient and unfortunately, we were not able to obtain the desired Michael products. The attempted Reformatsky type reactions of bromodifluoromethyl *p*-tolyl sulfoxide **I.88** and carbonyls were not efficient enough to obtain the corresponding α-difluoro-β-sulfinyl alcohols **(Scheme C.2)**. It will be worth evaluating the reactivity of **I.88** with other electrophiles or in other transformations, for example photocatalyzed reactions with electron-deficient alkenes.[384,385]

The last part of this project was dedicated to the post-functionalization of α-difluoro-β-sulfinyl alcohols (*cf. Chapter III*, **Scheme C.3**). The objective was to develop efficient approaches to functionalize the previously synthesized derivatives and obtain novel difluoromethylated building blocks. For this purpose, we primarily focused on the removal of the chiral auxiliary. Interestingly, and despite several unfruitful attempts we could discover two convenient and efficient desulfinylation methods leading to α-difluoromethyl alcohols with good yields and enantiomeric excesses.

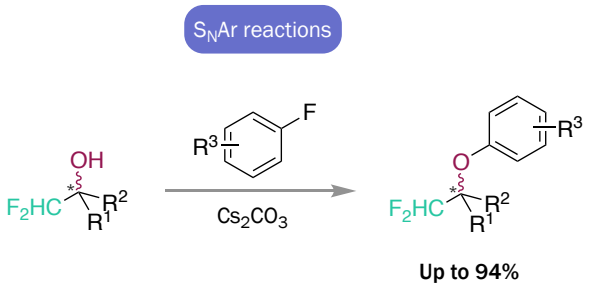


Scheme C.3. Desulfinylation methods leading to enantioenriched α-difluoromethyl alcohols

In order to functionalize α-difluoro-β-sulfinyl alcohols, we studied Mitsunobu reactions considering the extensive versatility of this transformation. Standard Mitsunobu conditions were applied to α-difluoro-β-sulfinyl alcohols without success. The next attempts consisted in using directly α-difluoromethyl alcohols after removal of the sulfoxide. In the case of our model substrate, the functionalization was possible but the extension to other substrates did not lead to the desired products.

We decided to pursue our efforts by performing nucleophilic aromatic substitution reactions (S_NAr) to introduce various functional groups, which will pave the way for

further derivatization. α-Difluoromethyl alcohols were used as pronucleophiles, and we succeeded in synthesizing a range of α-difluoromethyl oxyaryls in racemic and enantiopure form (**Scheme C.4**).

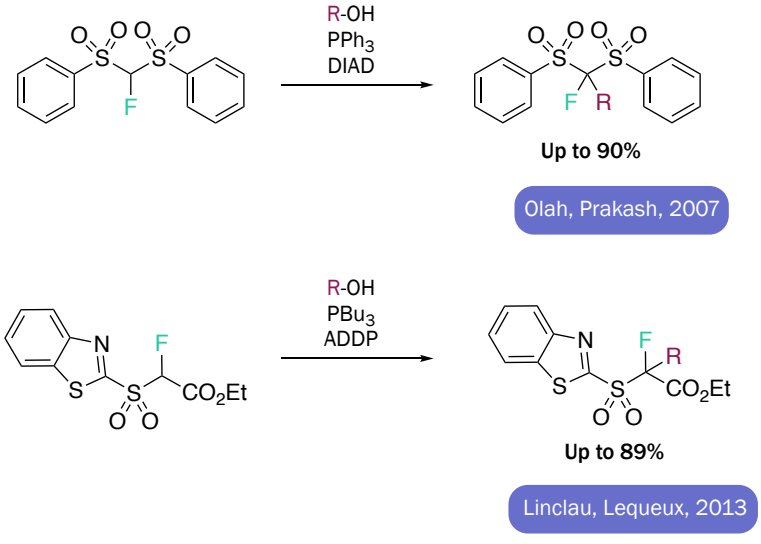


Scheme C.4. Nucleophilic aromatic substitutions of α-difluoromethyl alcohols

α-Difluoromethyl oxyaryl derivatives offer an interesting reactivity when bearing halogens, among others, for further substitution reactions, metallo-catalyzed couplings or halogen-metal exchange reactions. Moreover, a main outlook would consist in using other aromatic partners, such as pyridines, to increase the scope of the reaction.

During this project, we were able to develop a new difluoromethylation strategy. Enantioenriched derivatives were synthesized starting from enantiopure difluoromethyl *p*-tolyl sulfoxide and their derivatization with a versatile transformation (S_NAr) was studied. The results obtained open new perspectives for the synthesis of fluorinated derivatives of pharmaceutical or agrochemical interest.

It would be interesting to expand the use of difluoromethyl *p*-tolyl sulfoxide, for example as a pronucleophile in Mitsunobu reactions. Only a few examples have been reported for this transformation with fluorinated alkyl derivatives. The monofluoroalkylations of primary and secondary alcohols have been described by Olah and Prakash by using fluoro-bis(phenylsulfonyl)methane as a fluorocarbon nucleophile.[386] Linclau and Lequeux also described in 2013 the use of a benzothiazolyl-based fluorosulfone in Mitsunobu reactions with racemic and enantiopure alcohols with good results **(Scheme C.5)**.[387]

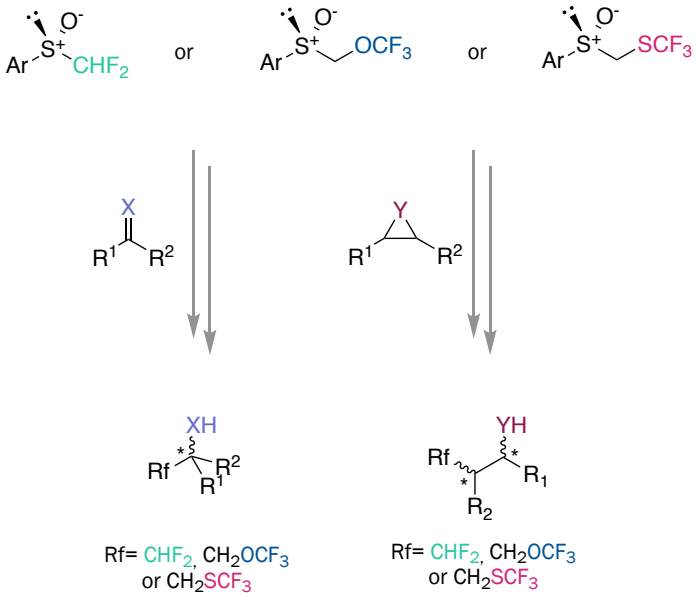


Scheme C.5. Mitsunobu reactions using fluorinated sulfones

These two examples seem encouraging for the possibility of performing new Mitsunobu reactions to introduce the CHF_2 moiety.

Furthermore, several mechanistic inquiries were raised to explain the condensation process of difluoromethyl *p*-tolyl sulfoxide onto carbonyls with phosphazene superbase P_4*t*-Bu.[227] In addition, the mechanism of formation of the recurrent side product difluoro(*p*-tolyl-thio)methyl-*p*-tolyl sulfoxide **I.95**, could not be determined yet. Nevertheless, two distinct hypothetical mechanistic paths have been proposed. Further studies to elucidate these mechanisms would be of great interest.

Finally, in view of the achievements obtained for the -CHF_2 group, one could imagine performing the stereoselective introduction of other EFS by means of sulfoxides as chiral inductors. Stereoselective introduction of EFS as OCF_3 or SCF_3 is underexplored and appear as highly challenging projects (**Scheme C.6**). These studies are ongoing in our research group.



Scheme C.6. Strategy towards enantiopure -OCF_3 and -SCF_3-containing molecules by means of chiral sulfoxides

References

1 Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.

2 Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1887.

3 Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.

4 *Fluorine in medicinal chemistry and chemical biology*; Ojima, I., Ed.; John Wiley & Sons Ltd., **2009**; Ojima, I., Ed.

5 Maienfisch, P.; Hall, R. G.; Maienfisch, P. *Chimia* **2004**, *58*, 93–99.

6 Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506.

7 Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16–29.

8 Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. *Chem. Eur. J.* **2019**, *25*, 1–24.

9 Agricola, G. In *Sive De Re Metallica*; Froben, Ed.; Basel, **1530**; pp 121–126.

10 Corsi Romano, F. *Delle pietre antiche trattato*, 3rd ed.; Di Gaetano, P., Ed.; Roma: Rome, **1845**; Di Gaetano, P., Ed.

11 Loewental, A. I.; Harden, D. B.; Bromehead, C. E. N. *J. Rom. Stud.* **1949**, *39*, 31–37.

12 Banks, R. E. *J. Fluorine Chem.* **1986**, *33*, 3–26.

13 Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141–152.

14 Deng, H.; O'Hagan, D.; Schaffrath, C. *Nat. Prod. Rep.* **2004**, *21*, 773–784.

15 O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127–133.

16 Lide, D. R. *CRC Handbook of Chemistry and Physics*, 97th ed.; CRC Press Taylor and Francis: Boca Raton, FlL, **2016**.

17 Campbell, M. G.; Mercier, J.; Genicot, C.; Gouverneur, V.; Hooker, J. M.; Ritter, T. *Nat. Chem.* **2016**, *9*, 1–3.

18 Cole, E.; Stewart, M.; Littich, R.; Hoareau, R.; Scott, P. *Curr. Top. Med. Chem.* **2014**, *14*, 875–900.

19 Jacobson, O.; Chen, X. *Curr. Top. Med. Chem.* **2010**, *10*, 1048–1059.

20 Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8998–9033.

21 Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, **1994**.

22 Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11.

23 Harsanyi, A.; Sandford, G. *Green Chem.* **2015**, *17*, 2081–2086.

24 Wakselman, C.; Kaziz, C. *J. Fluorine Chem.* **1986**, *33*, 347–359.

25 Okazoe, T. *Proc. Japan Acad. Ser. B Phys. Biol. Sci.* **2009**, *85*, 276–289.

26 Goldwhite, H. *J. Fluorine Chem.* **1986**, *33*, 109–132.

27 Ellis, J. F.; May, G. F. *J. Fluorine Chem.* **1986**, *33*, 133–147.

28 Davies, R. M.; Ellwood, R. P.; Davies, G. M. *Int. J. Dent. Hyg.* **2003**, *1*, 3–8.

29 Pizzo, G.; Piscopo, M. R.; Pizzo, I.; Giuliana, G. *Clin. Oral Investig.* **2007**, *11*, 189–193.

30 Walsh, T.; Worthington, H. V.; Glenny, A. M.; Marinho, V. C. C.; Jeroncic, A. *Cochrane Database Syst. Rev.* **2019**, *2019*, 1–244.

31 Zonghai, C.; Zhengcheng, Z.; Khalil, A. In *Advanced Fluoride-Based Materials for Energy Conversion*; Nakajima, T., Groult, H., Eds.; Elsevier, **2015**; pp 1–31.

32 von Aspern, N.; Röschenthaler, G. V.; Winter, M.; Cekic-Laskovic, I. *Angew. Chem. Int. Ed.* **2019**, *58*, 15978–16000.

33 Filler, R.; Saha, R. *Future Med. Chem.* **2009**, *1*, 777–791.

34 Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358–6383.

35 Rowley, M.; Hallett, D. J.; Goodacre, S.; Moyes, C.; Crawforth, J.; Sparey, T. J.; Patel, S.; Marwood, R.; Patel, S.; Thomas, S.; Hitzel, L.; O'Connor, D.; Szeto, N.; Castro, J. L.; Hutson, P. H.; Macleod, A. M. *J. Med. Chem.* **2001**, *44*, 1603–1614.

36 Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525–616.

37 Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973–980.

38 Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.

39 Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.

40 Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822–5880.

41 Theodoridis, G. *J. Chem. Inf. Model.* **2006**, *2*, 122–167.

42 Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626–1631.

43 Caminati, W.; Melandri, S.; Moreschini, P.; Favero, P. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 2924–2925.

44 Müller, K. *Chim. Int. J. Chem.* **2014**, *68*, 356–362.

45 Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 9325–9332.

46 Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. *J. Med. Chem.* **2017**, *60*, 797–804.

47 Zafrani, Y.; Sod-Moriah, G.; Yeffet, D.; Berliner, A.; Amir, D.; Marciano, D.; Elias, S.; Katalan, S.; Ashkenazi, N.; Madmon, M.; Gershonov, E.; Saphier, S. *J. Med. Chem.* **2019**, *62*, 5628–5637.

48 Zheng, B.; D'Andrea, S. V.; Sun, L. Q.; Wang, A. X.; Chen, Y.; Hrnciar, P.; Friborg, J.; Falk, P.; Hernandez, D.; Yu, F.; Sheaffer, A. K.; Knipe, J. O.; Mosure, K.; Rajamani, R.; Good, A. C.; Kish, K.; Tredup, J.; Klei, H. E.; Paruchuri, M.; Ng, A.; Gao, Q.; Rampulla, R. A.; Mathur, A.; Meanwell, N. A.; McPhee, F.; Scola, P. M. *ACS Med. Chem. Lett.* **2018**, *9*, 143–148.

49 Huchet, Q. A.; Kuhn, B.; Wagner, B.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Fluorine Chem.* **2013**, *152*, 119–128.

50 Xing, L.; Blakemore, D. C.; Narayanan, A.; Unwalla, R.; Lovering, F.; Denny, R. A.; Zhou, H.; Bunnage, M. E. *ChemMedChem* **2015**, *10*, 715–726.

51 Müller, K. *Chimia* **2014**, *68*, 356–362.

52 Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701–704.

53 Martínez, M. D.; Luna, L.; Tesio, A. Y.; Feresin, G. E.; Durán, F. J.; Burton, G. *J. Pharm. Pharmacol.* **2016**, *68*, 233–244.

54 Steinkühler, C.; Biasiol, G.; Brunetti, M.; Urbani, A.; Koch, U.; Cortese, R.; Pessi, A.; De Francesco, R. *Biochemistry* **1998**, *37*, 8899–8905.

55 Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633–2644.

56 Ni, C.; Wang, F.; Hu, J. *Beilstein J. Org. Chem.* **2008**, *4*, 1–6.

57 Shen, X.; Zhang, W.; Ni, C.; Gu, Y.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 16999–17002.

58 Aikawa, K.; Yoshida, S.; Kondo, D.; Asai, Y.; Mikami, K. *Org. Lett.* **2015**, *17*, 5108–5111.

59 Solladié, G. *Synthesis* **1981**, 185–197.

60 Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, 328–401.

61 Carreño, M. C.; Ribagorda, M.; Urbano, A.; Herna, G. *Chem. Commun.* **2009**, *41*, 6129–6144.

62 Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani, F.; Zanda, M.; Zappala, C. *J. Fluorine Chem.* **1997**, *84*, 79–82.

63 Dilman, A. D.; Levin, V. V. *Mendeleev Commun.* **2015**, *25*, 239–244.

64 Batisse, C.; Panossian, A.; Hanquet, G.; Leroux, F. R. *Chem. Commun.* **2018**, *54*, 10423–10426.

65 Batisse, C.; Céspedes Dávila, M. F.; Castello, M.; Messara, A.; Vivet, B.; Marciniak, G.; Panossian, A.; Hanquet, G.; Leroux, F. R. *Tetrahedron* **2019**, *75*, 3063–3079.

66 Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1687–1690.

67 Solladié, G.; Greck, C.; Demailly, G.; Solladié-Cavallo, A. *Tetrahedron Lett.* **1982**, *23*, 5047–5050.

68 Pyne, S.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932–1936.

69 Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843–2846.

70 Midura, W. H.; Rzewnicka, A.; Krysiak, J. A. *Beilstein J. Org. Chem.* **2017**, *13*, 1513–1517.

71 Arroyo, Y.; Meana, Á.; Sanz-Tejedor, M. A.; Ruano, J. L. G. *Org. Lett.* **2008**, *10*, 2151–2154.

72 Desbeaux, E. *Physique populaire*; Flammarion, E., Ed.; Librairie Marpon et Flammarion: Paris, **1891**; Flammarion, E., Ed.

73 Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 1–14.

74 Thiehoff, C.; Rey, Y. P.; Gilmour, R. *Isr. J. Chem.* **2017**, *57*, 92–100.

75 O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

76 Reichenbächer, K.; Süss, H. I.; Hulliger, J. *Chem. Soc. Rev.* **2005**, *34*, 22–30.

77 Uneyama, K. *Organofluorine Chemistry*; Uneyama, K., Ed.; Blackwell Publishing Ltd: Oxford, **2006**; Uneyama, K., Ed.

78 Spierings, G. A. C. M. *J. Mater. Sci.* **1993**, *28*, 6261–6273.

79 Jacobs, R. T.; Bernstein, P. R.; Cronk, L. A.; Vacek, E. P.; Newcomb, L. F.; Aharony, D.; Buckner, C. K.; Kusner, E. J. *J. Med. Chem.* **1994**, *37*, 1282–1297.

80 Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943–954.

81 Eriksson, T.; Bjöurkman, S.; Roth, B.; Fyge, Å.; Höuglund, P. *Chirality* **1995**, *7*, 44–52.

82 Takeuchi, Y.; Shiragami, T.; Kimura, K.; Suzuki, E.; Shibata, N. *Org. Lett.* **1999**, *1*, 1571–1573.

83 Olsen, J. A.; Banner, D. W.; Seiler, P.; Wagner, B.; Tschopp, T.; Obst-Sander, U.; Kansy, M.; Müller, K.; Diederich, F. *ChemBioChem* **2004**, *5*, 666–675.

84 Burger, A. *Prog. Drug Res.* **1991**, *37*, 287–371.

85 Kirk, K. L.; R., F. In *Biomedical Frontiers of Fluorine Chemistry - ACS Symposium Series*; Ojima, I., Welch, J. R., McCarthy, J. T., Eds.; American Chemical Society: Washington, **1996**; Vol. 639, pp 1–24.

86 Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.

87 Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315–8359.

88 Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acenã, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422–518.

89 Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Springer Berlin Heidelberg: Berlin, Heidelberg, **1986**; pp 125–259.

90 Lindberg, P.; Brandstrom, A.; Bjorn, W.; Hillevi, M.; Leif, R.; Hoffmann, K.-J. *Med. Res. Rev.* **1990**, *10*, 1–54.

91 Ramachandra, B. *Crit. Rev. Anal. Chem.* **2016**, *46*, 482–489.

92 Murillo-Rodríguez, E.; Barciela Veras, A.; Barbosa Rocha, N.; Budde, H.; Machado, S. *ACS Chem. Neurosci.* **2018**, *9*, 151–158.

93 Li, Y.; Koiso, Y.; Kobayashi, H.; Hashimoto, Y.; Iwasaki, S. *Biochem. Pharmacol.* **1995**, *49*, 1367–1372.

94 Morisaki, N.; Mitsui, Y.; Yamashita, Y.; Koiso, Y.; Shirai, R.; Hashimoto, Y.; Iwasaki, S. *J. Antibiot. (Tokyo).* **1998**, *51*, 423–427.

95 Joullié, M. M.; Berritt, S.; Hamel, E. *Tetrahedron Lett.* **2011**, *52*, 2136–2139.

96 Salom-Roig, X.; Bauder, C. *Synthesis* **2020**, *52*.

97 Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760.

98 Han, J.; Soloshonok, V. A.; Klika, K. D.; Drabowicz, J.; Wzorek, A. *Chemical Society Reviews*. Royal Society of Chemistry February 21, 2018, pp 1307–1350.

99 Sipos, G.; Drinkel, E. E.; Dorta, R. *Chem. Soc. Rev.* **2015**, *44*, 3834–3860.

100 Trost, B. M.; Ryan, M. C.; Rao, M. *Beilstein J. Org. Chem.* **2016**, *12*, 1136–1152.

101 Trost, B. M.; Rao, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 5026–5043.

102 Trost, B. M.; Rao, M.; Dieskau, A. P. *J. Am. Chem. Soc.* **2013**, *135*, 18697–18704.

103 Rayner, D. R.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4854–4860.

104 In *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*; Mikolajczyk, M., Drabowicz, J., Kielbasinski, P., Eds.; CRC Press LLC: Boca Raton, FL, **1997**; pp 47–56.

105 Kagan, H. B. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, **2008**; pp 1–30.

106 Wojaczyńska, E.; Wojaczyński, J. *Chem. Rev.* **2010**, *110*, 4303–4356.

107 Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, *2*, 173.

108 Fernandes, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789–6796.

109 Llera, J. M.; Fernhdez, I.; Alcudia, F. *Tetrahedron Lett.* **1991**, *32*, 1299–7302.

110 Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991–5999.

111 Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349–6358.

112 Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885–5888.

113 Han, Z.; Krishnamurthy, D.; Grover, P.; Wilkinson, H. S.; Fang, Q. K.; Su, X.; Lu, Z. H.; Magiera, D.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 2032–2035.

114 Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880–7881.

115 Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977–5985.

116 Maitro, G.; Vogel, S.; Sadaoui, M.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2007**, *9*, 5493–5496.

117 Abarca, B.; Ballesteros, R.; Ballesteros-Garrido, R.; Colobert, F.; Leroux, F. R. *Tetrahedron* **2007**, *63*, 10479–10485.

118 Colobert, F.; Ballesteros-Garrido, R.; Leroux, F. R.; Ballesteros, R.; Abarca, B. *Tetrahedron Lett.* **2007**, *48*, 6896–6899.

119 Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.

120 Zhao, S. H.; Samuel, O.; Kagan, H. B. *Org. Synth.* **1990**, *68*, 49.

121 Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135–5145.

122 Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325–326.

123 Diter, P.; Samuel, O.; Taudien, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1994**, *5*, 549–552.

124 Brunei, J.-M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086–8088.

125 Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sö, H.; Von Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819–3825.

126 Superchi, S.; Rosini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 349–352.

127 Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392–9395.

128 Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1997**, *62*, 8560–8564.

129 Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273–5276.

130 Bolm, C.; Dabard, O. A. G. *Synlett* **1999**, *3*, 360–362.

131 Furia, F. Di; Licini, G.; Modena, G.; Motterle, R.; Nugent, W. A. *J. Org. Chem.* **1996**, *61*, 5175–5177.

132 Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3873–3876.

133 Halterman, R. L.; Jan, S.-T.; Nimmons, H. L. *Synlett* **1991**, 791–792.

134 Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**, *33*, 7111–7114.

135 Noda, K.; Hosoya, N.; Irie, R.; Yamashita, Y.; Katsuki, T. *Tetrahedron* **1994**, *50*, 9609–9618.

136 Noda, K.; Hosoya, N.; Yanai, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1994**, *35*, 1887–1890.

137 Kokubo, C.; Katsuki, T. *Tetrahedron* **1996**, *52*, 13895–13900.

138 Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483–1486.

139 Skarzewski, J.; Ostrycharz, E.; Siedlecka, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3457–3461.

140 Skarzewski, J.; Wojaczyńska, E.; Turowska-Tyrk, I. *Tetrahedron: Asymmetry* **2002**, *13*, 369–375.

141 Bolm, C.; Bienewald, F. *Angew. Chem. Int. Ed.* **1995**, *34*, 2640–2642.

142 Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002**, 161–163.

143 Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

144 Barlan, A. U.; Zhang, W.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 6075–6087.

145 Mekmouche, Y.; Hummel, H.; Ho, R. Y. N.; Que, L.; Sch ¸nemann, V.; Thomas, F.; Trautwein, A. X.; Lebrun, C.; Gorgy, K.; Lepre, J.-C.; Collomb, M.-N.; Deronzier, A.; Fontecave, M.; Ménage, S. *Chem. Eur. J.* **2002**, *8*, 1196–1204.

146 Legros, J.; Bolm, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5487–5489.

147 Legros, J.; Bolm, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 4225–4228.

148 Legros, J.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 1086–1092.

149 Bryliakov, K. P.; Talsi, E. P. *Chem. Eur. J.* **2007**, *13*, 8045–8050.

150 Yamaguchi, T.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4729–4731.

151 Holland, H. L. *Nat. Prod. Rep.* **2001**, *18*, 171–181.

152 Matsui, T.; Dekishima, Y.; Ueda, M. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 7699–7706.

153 Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187–207.

154 Massa, A.; Siniscalchi, F. R.; Bugatti, V.; Lattanzi, A.; Scettri, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1277–1283.

155 Takata, T.; Ando, W. *Tetrahedron Lett.* **1986**, *27*, 1591–1594.

156 Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc* **1992**, *114*, 1428–1437.

157 Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274–7285.

158 Bulman Page, P. C.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M.; Robhason, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2911–2914.

159 Bohé, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 1211–1214.

160 Bohr, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141–154.

161 Del Río, R. E.; Wang, B.; Achab, S.; Bohé, L. *Org. Lett.* **2007**, *9*, 2265–2268.

162 Schoumacker, S.; Hamelin, O.; Téti, S.; Pécaut, J.; Fontecave, M. *J. Org. Chem.* **2005**, *70*, 301–308.

163 Akhatou, A.; Rahimi, M.; Cheboub, K.; Ghosez, L.; Hanquet, G. *Tetrahedron* **2007**, *63*, 6232–6240.

164 Imamoto, T.; Koto, H. *Chem. Lett.* **1986**, 967–968.

165 Varvoglis, A.; Koser, G. F.; Moriarty, R. M.; Prakash, O.; Baker, G. P.; Mann, F. G.; Sheppard, N.; Tetlow, A. J.; Leffler, J. E.; Jaffe, H.; Balthazor, T. M.; Miles, J. A.; Stults, B. R.; Schardt, B.; Hill, C. L.; Tanner, D. D.; Gidley, G. C.; Amey, R.; L; Martin, J. C.; Nguyen, T. T.; Wilson, S. R.; Martin, J. C.; Wettach, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 5672–5673.

166 Tsuchihashi, G.; Iriuchiyima, S.; Ishibashi, M.; Chemical, S. *Tetrahedron Lett.* **1972**, *45*, 4605–4608.

167 Sugiyama, S.; Kido, M.; Satoh, T. *Tetrahedron Lett.* **2005**, *46*, 6771–6775.

168 Fustero, S.; Pozo, C. Del; Catalań, S.; Alemán, J.; Parra, A.; Marcos, V.; Ruano, J. L. G. *Org. Lett.* **2009**, *11*, 641–644.

169 Node, M.; Nishide, K.; Shlgeta, Y.; Obata, K.; Shiraki, H.; Kunishige, H. *Tetrahedron* **1997**, *53*, 12883–12894.

170 Solladié, G.; Demailly, G.; Greck, C. *J. Org. Chem.* **1985**, *50*, 1552–1554.

171 Arroyo, Y.; Meana, Á.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *Tetrahedron* **2006**, *62*, 8525–8532.

172 Satoh, T.; Horiguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8235–8238.

173 Abramovitch, A.; Fensterbank, L.; Malacria, M.; Marek, I. *Angew. Chem. Int. Ed.* **2008**, *47*, 6865–6868.

174 Furukawa, N.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 5723–5726.

175 Satoh, T.; Kurihara, T.; Fujita, K. *Tetrahedron* **2001**, *57*, 5369–5375.

176 Solladié, G.; Bauder, C.; Arce-Dubois, E.; Pasturel-Jacopé, Y. *Tetrahedron Lett.* **2001**, *42*, 2923–2925.

177 Solladié, G. *Synthesis* **1981**, *66*, 185–196.

178 Posner, G. H.; Hulce, M. *Tetrahedron Lett.* **1984**, *23*, 3431–3434.

179 Annunziata, R.; Cinquini, M.; Cozzi, F.; Montanari, F.; Restelli, A. *J. Chem. Soc. Chem. Commun.* **1983**, No. 20, 1138–1139.

180 Matsnev, A. V; Kondratenko, N. V; Yagupolskii, Y. L.; Yagupolskii, L. M. *Tetrahedron Lett.* **2002**, *43*, 2949–2952.

181 Nehru, K.; Kim, S. S.; Kim, D. W.; Jung, H. C. *Synthesis* **2002**, 2484–2486.

182 Mason, J. D.; Murphree, S. S. *Synlett* **2013**, *24*, 1391–1394.

183 Fontenelle, Q.; Conroy, M.; Light, M.; Poisson, T.; Pannecoucke, X.; Linclau, B. *J. Org. Chem.* **2014**, *79*, 4186–4195.

184 Poisson, T.; Belhomme, M. C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277–9285.

185 Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert, F. *Chem. Soc. Rev.* **2013**, *42*, 937–949.

186 Xu, L.; Vicic, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 2536–2539.

187 Aikawa, K.; Ishii, K.; Endo, Y.; Mikami, K. *J. Fluorine Chem.* **2017**, *203*, 122–129.

188 Zhu, S. Q.; Xu, X. H.; Qing, F. L. *Org. Chem. Front.* **2015**, *2*, 1022–1025.

189 Du, G. F.; Wang, Y.; Gu, C. Z.; Dai, B.; He, L. *RSC Adv.* **2015**, *5*, 35421–35424.

190 Howard, J. L.; Schotten, C.; Alston, S. T.; Browne, D. L. *Chem. Commun.* **2016**, *52*, 8448–8451.

191 Ferguson, D. M.; Malapit, C. A.; Bour, J. R.; Sanford, M. S. *J. Org. Chem.* **2019**, *84*, 3735–3740.

192 Evans, D. a; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.

193 Sparrow, K. J.; Carley, S.; Söhnel, T.; Barker, D.; Brimble, M. A. *Tetrahedron* **2015**, *71*, 2210–2221.

194 Kuneida, N.; Nokami, J.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 256–259.

195 Tiensripojamarn, A.; Reutrakul, V.; Kusamran, K.; Nimgirawath, S. *Chem. Lett.* **1979**, 209–212.

196 Bennechel, T.; Strandel, P.; Oftebro, R.; Undheiml, K. *Eur J Med Chem* **1993**, *28*, 463–472.

197 Midura, W. H. *Synlett* **2006**, No. 5, 733–736.

198 Mollar, C.; Besora, M.; Maseras, F.; Asensio, G.; Medio-Simón, M. *Chem. Eur. J.* **2010**, *16*, 13390–13397.

199 Rodríguez, N.; Cuenca, A.; Ramírez De Arellano, C.; Medio-Simón, M.; Peine, D.; Asensio, G. *J. Org. Chem.* **2004**, *69*, 8070–8076.

200 Rodríguez, N.; Medio-Simón, M.; Asensio, G. *Adv. Synth. Catal.* **2007**, *349*, 987–991.

201 Medio-Simón, M.; Mollar, C.; Rodríguez, N.; Asensio, G. *Org. Lett.* **2005**, *7*, 4669–4672.

202 Liu, G.; Mori, S.; Wang, X.; Noritake, S.; Tokunaga, E.; Shibata, N. *New J. Chem.* **2012**, *36*, 1769–1773.

203 Urban, C.; Cadoret, F.; Blazejewski, J. C.; Magnier, E. *Eur. J. Org. Chem.* **2011**, No. 25, 4862–4867.

204 Urban, C.; Macé, Y.; Cadoret, F.; Blazejewski, J. C.; Magnier, E. *Adv. Synth. Catal.* **2010**, *352*, 2805–2814.

205 Burton, D. J.; Wiemers, D. M. *J. Fluorine Chem.* **1981**, *18*, 573–582.

206 Liu, G.; Mori, S.; Wang, X.; Noritake, S.; Tokunaga, E.; Shibata, N. *New J. Chem.* **2012**, *36*, 1769–1773.

207 Urban, C.; Macé, Y.; Cadoret, F.; Blazejewski, J.-C.; Magnier, E. *Adv. Synth. Catal.* **2010**, *352*, 2805–2814.

208 Wu, J.; Zhao, Q.; Wilson, T. C.; Verhoog, S.; Lu, L.; Gouverneur, V.; Shen, Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 2413–2417.

209 Sokolenko, L. V.; Orlova, R. K.; Filatov, A. A.; Yagupolskii, Y. L.; Magnier, E.; Pégot, B.; Diter, P. *Molecules* **2019**, *24*, 1249–1261.

210 Zhang, C. P.; Wang, Z. L.; Chen, Q. Y.; Zhang, C. T.; Xiao, J. C. *J. Fluorine Chem.* **2010**, *131*, 433–438.

211 Jiang, F.; Ni, C.; Hu, J. *J. Fluorine Chem.* **2016**.

212 Ismalaj, E.; Billard, T. *J. Fluorine Chem.* **2017**, *203*, 215–217.

213 Pohmakotr, M.; Sithikanchanakul, S. *Synth. Commun.* **1989**, *19*, 477–484.

214 Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786.

215 Krishnamoorthy, S.; Prakash, G. K. S. *Synthesis* **2017**, *49*, 3394–3406.

216 Huang, W.; Ni, C.; Zhao, Y.; Gao, B.; Hu, J. *J. Fluorine Chem.* **2012**, *143*, 161–166.

217 Huang, W.; Ni, C.; Zhao, Y.; Zhang, W.; Dilman, A. D.; Hu, J. *Tetrahedron* **2012**, *68*, 5137–5144.

218 Zhu, J.; Wang, F.; Huang, W.; Zhao, Y.; Ye, W.; Hu, J. *Synlett* **2011**, 899–902.

219 Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273–8277.

220 Liu, J.; Ni, C.; Wang, F.; Hu, J. *Tetrahedron Lett.* **2008**, *49*, 1605–1608.

221 Levin, V. V.; Elkin, P. K.; Struchkova, M. I.; Dilman, A. D. *J. Fluorine Chem.* **2013**, *154*, 43–46.

222 Uneyama, K. *J. Fluorine Chem.* **2008**, *129*, 550–576.

223 Huang, W.; Ni, C.; Zhao, Y.; Zhang, W.; Dilman, A. D.; Hu, J. *Tetrahedron* **2012**, *68*, 5137–5144.

224 Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342–5345.

225 Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457–4463.

226 Zhu, L.; Li, Y.; Ni, C.; Hu, J.; Beier, P. *J. Fluorine Chem.* **2007**, *128*, 1241–1247.

227 Batisse, C.; Panossian, A.; Hanquet, G.; Leroux, F. R. *Chem. Commun.* **2018**, *54*, 10423–10426.

228 Hugenberg, V.; Haufe, G. *J. Fluorine Chem.* **2010**, *131*, 942–950.

229 Venier, C. G.; Squires, T. G.; Chen, Y.; Hussmann, G. P.; Shei, J. C.; Smith, B. F. *J. Org. Chem.* **1982**, *47*, 3773–3774.

230 Kitir, B.; Baldry, M.; Ingmer, H.; Olsen, C. A. *Tetrahedron* **2014**, *70*, 7721–7732.

231 Ferreira, J.; Rees-Jones, S. C. M.; Ramaotsoa, V.; Msutu, A.; Hunter, R. *Org. Biomol. Chem.* **2016**, *14*, 1545–1549.

232 Kitazume, T.; Asai, M.; Tsukamoto, T.; Yamazaki, T. *J. Fluorine Chem.* **1992**, *56*, 271–284.

233 Nakamura, K.; Yamanaka, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2529–2533.

234 Borzecka, W.; Lavandera, I.; Gotor, V. *J. Org. Chem.* **2013**, *78*, 7312–7317.

235 Kato, K.; Nakamura, H.; Nakanishi, K. *Appl. Surf. Sci.* **2014**, *293*, 312–317.

236 Goushi, S.; Funabiki, K.; Ohta, M.; Hatano, K.; Matsui, M. *Tetrahedron* **2007**, *63*, 4061–4066.

237 Slungard, S. V.; Krakeli, T.-A.; Thvedt, T. H. K.; Fuglseth, E.; Sundby, E.; Hoff, B. H. *Tetrahedron* **2011**, *67*, 5642–5650.

238 Mikami, K.; Tasaki, T.; Matsukawa, S.; Maruta, M. *Synlett* **1995**, 1057–1058.

239 Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Tadafumi, U.; Maruta, M. *Asymmetric Catalysis of CarbonyI-Ene and Aldol Reactions with Fluoral by Chiral Binaphthol-Derived Titanium Complex*; **1996**; Vol. 52.

240 Funabiki, K.; Itoh, Y.; Kubota, Y.; Matsui, M. *J. Org. Chem.* **2011**, *76*, 3545–3550.

241 Funabiki, K.; Furuno, Y.; Yano, Y.; Sakaida, Y.; Kubota, Y.; Matsui, M. *Chem. - Asian J.* **2015**, *10*, 2701–2707.

242 Cabrera, J. M.; Tauber, J.; Zhang, W.; Xiang, M.; Krische, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 9392–9395.

243 Pluta, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2019**, *131*, 2481–2485.

244 Neves-Garcia, T.; Vélez, A.; Martínez-Ilarduya, J. M.; Espinet, P. *Chem. Commun.* **2018**, *54*, 11809–11812.

245 Van Der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 9053–9065.

246 Aikawa, K.; Yoshida, S.; Kondo, D.; Asai, Y.; Mikami, K. *Org. Lett.* **2015**, *17*, 5108–5111.

247 Matador, E.; de Gracia Retamosa, M.; Jiménez-Sánchez, A.; Monge, D.; Fernández, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2019**, 130–138.

248 Huang, W.-S.; Delcourt, M.-L.; Pannecoucke, X.; Charette, A. B.; Poisson, T.; Jubault, P. *Org. Lett.* **2019**, *21*, 7509–7513.

249 Kallwass, H. K. W.; Yee, C.; Blythe, T. A.; McNabb, T. J.; Rogers, E. E.; Shames, S. L. *Bioorg. Med. Chem.* **1994**, *2*, 557–566.

250 Kato, K.; Gong, Y.; Saito, T.; Yokogawa, Y. *J. Mol. Catal. B Enzym.* **2004**, *30*, 61–68.

251 Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313–315.

252 Chen, M. W.; Duan, Y.; Chen, Q. A.; Wang, D. S.; Yu, C. Bin; Zhou, Y. G. *Org. Lett.* **2010**, *12*, 5075–5077.

253 Sakamoto, T.; Horiguchi, K.; Saito, K.; Mori, K.; Akiyama, T. *Asian J. Org. Chem.* **2013**, *2*, 943–946.

254 Chen, M. W.; Yang, Q.; Deng, Z.; Ding, Q.; Peng, Y. *J. Org. Chem.* **2019**, *84*, 10371–10379.

255 Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun.* **2004**, *10*, 1928–1929.

256 Zhao, Q. Y.; Yuan, Z. L.; Shi, M. *Adv. Synth. Catal.* **2011**, *353*, 637–643.

257 Fustero, S.; Rodenes, M.; Román, R.; Sedgwick, D. M.; Aguado, J. E.; Soloshonok, V. A.; Han, J.; Mei, H.; Medio-Simon, M.; Barrio, P. *Adv. Synth. Catal.* **2019**, *361*, 3860–3867.

258 Liu, Y.; Liu, J.; Huang, Y.; Qing, F. L. *Chem. Commun.* **2013**, *49*, 7492–7494.

259 Dai, Y.; Xie, C.; Zhou, J.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Asian J. Org. Chem.* **2015**, *4*, 1020–1024.

260 You, Y.; Luo, S. *Org. Lett.* **2018**, *20*, 7137–7140.

261 Kanai, M.; Ueda, K.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Ootsuka, T.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *J. Fluorine Chem.* **2005**, *126*, 377–383.

262 Zhang, F.; Liu, Z. J.; Liu, J. T. *Org. Biomol. Chem.* **2011**, *9*, 3625–3628.

263 Li, P.; Sun, D. W.; Jiang, M.; Liu, J. T. *Tetrahedron* **2019**, *75*, 603–607.

264 Chen, H.; Yu, W.; Guo, X. H.; Meng, W. D.; Huang, Y. G. *Chinese Chem. Lett.* **2012**, *23*, 277–280.

265 Yang, J.; Zhang, J.; Meng, W.; Huang, Y. *Tetrahedron Lett.* **2015**, *56*, 6556–6559.

266 Liu, P.; Liu, Z. J.; Wu, F. *Adv. Synth. Catal.* **2015**, *357*, 818–822.

267 Liu, J.; Li, Y.; Hu, J. *J. Org. Chem.* **2007**, *72*, 3119–3121.

268 Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342–5345.

269 Volonterio, A.; Vergani, B.; Crucianelli, M.; Zanda, M.; Bravo, P. *J. Org. Chem.* **1998**, *63*, 7236–7243.

270 Li, G.; Van Der Donk, W. A. *Org. Lett.* **2007**, *9*, 41–44.

271 Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.

272 Rong, J.; Ni, C.; Hu, J. *Asian J. Org. Chem.* **2017**, *6*, 139–152.

273 Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. Eur. J.* **2017**, *23*, 14676–14701.

274 Gu, Y.; Lu, C.; Gu, Y.; Shen, Q. *Chinese J. Chem.* **2018**, *36*, 55–58.

275 Endo, Y.; Ishii, K.; Mikami, K. *Tetrahedron* **2019**, *75*, 4099–4103.

276 Kuneida, N.; Kinoshita, M.; Nokami, J. *Chem. Lett.* **1977**, 289–292.

277 Demailly, G.; Greck, C.; Solladie, G. *Tetrahedron Lett.* **1984**, *37*, 4113–4116.

278 Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* **1990**, *31*, 5349–5352.

279 Braun, M.; Hild, W. *Chem. Ber.* **1984**, *117*, 413–414.

280 Prat, D.; Hayler, J.; Wells, A. *Green Chem.* **2014**, *16*, 4546–4551.

281 Grey, M.; Snieckus, V.; Lebel, H. *Encycl. Reagents Org. Synth.* **2004**, 1–12.

282 Tshepelevitsh, S.; Kütt, A.; Lõkov, M.; Kaljurand, I.; Saame, J.; Heering, A.; Plieger, P. G.; Vianello, R.; Leito, I. *Eur. J. Org. Chem.* **2019**, *2019*, 6735–6748.

283 Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J. *ChemMedChem* **2007**, *2*, 1100–1115.

284 Schlosser, M. *Angew. Chem. Int. Ed.* **1998**, *110*, 1496–1513.

285 Durrat, F.; Sanchez, M. V.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, No. 19, 3286–3297.

286 Yoda, H.; Takahashi, M.; Sengoku, T. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH Verlag & Co, **2011**; pp 41–61.

287 Starmans, W. A. J.; Walgers, R. W. A.; Thijs, L.; de Gelder, R.; Smits, J. M. M.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 4991–5004.

288 Wang, D. X.; Booth, H.; Lerner-Marmarosh, N.; Osdene, T. S.; Abood, L. G. *Drug Dev. Res.* **1998**, *45*, 10–16.

289 Asif, M. *MOJ Bioorganic Org. Chem.* **2018**, *2*, 36–40.

290 Hart, T.; Macias, A. T.; Benwell, K.; Brooks, T.; D'Alessandro, J.; Dokurno, P.; Francis, G.; Gibbons, B.; Haymes, T.; Kennett, G.; Lightowler, S.; Mansell, H.; Matassova, N.; Misra, A.; Padfield, A.; Parsons, R.; Pratt, R.; Robertson, A.; Walls, S.; Wong, M.; Roughley, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4241–4244.

291 Evano, G.; Jensen, A. A.; Kusk, M.; Nielsen, B.; Rabasso, N. *Org. Biomol. Chem.* **2005**, *3*, 3926–3936.

292 Tomita, H.; Mitusaki, S.; Tamaki, E. *Biol. Chem.* **1964**, *28*, 451–455.

293 Delauney, A. J.; Verma, D. P. S. *Plant J.* **1993**, *4*.

294 Mercadé, E.; Zangrando, E.; Clotet, A.; Claver, C.; Godard, C. *Eur. J. Inorg. Chem.* **2019**, *2019*, 4211–4220.

295 Mukaiyama, T.; Asami, M. *Chiral pyrrolidine diamines as efficient ligands in asymmetric synthesis*; Asami, M., Ed.; Springer Verlag: Berlin, Heidelberg, **1985**; Asami, M., Ed.

296 Coskun, N.; Çetin, M.; Gronert, S.; Ma, J.; Erden, I. *Tetrahedron* **2015**, *71*, 2636–2642.

297 Flores, M.; García-García, P.; Garrido, N. M.; Marcos, I. S.; Sanz-González, F.; Díez, D. *J. Org. Chem.* **2013**, *78*, 7068–7075.

298 Hulin, B.; Cabral, S.; Lopaze, M. G.; Van Volkenburg, M. A.; Andrews, K. M.; Parker, J. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4770–4773.

299 Jurica, E. A.; Wu, X.; Williams, K. N.; Hernandez, A. S.; Nirschl, D. S.; Rampulla, R. A.; Mathur, A.; Zhou, M.; Cao, G.; Xie, C.; Jacob, B.; Cai, H.; Wang, T.; Murphy, B. J.; Liu, H.; Xu, C.; Kunselman, L. K.; Hicks, M. B.; Sun, Q.; Schnur, D. M.; Sitko, D. F.; Dierks, E. A.; Apedo, A.; Moore, D. B.; Foster, K. A.; Cvijic, M. E.; Panemangalore, R.; Flynn, N. A.; Maxwell, B. D.; Hong, Y.; Tian, Y.; Wilkes, J. J.; Zinker, B. A.; Whaley, J. M.; Barrish, J. C.; Robl, A.; Ewing, W. R.; Ellsworth, B. A. *J. Med. Chem.* **2017**, *60*, 1417–1431.

300 Yang, H. K.; Son, W. S.; Lim, K. S.; Kim, G. H.; Lim, E. J.; Gadhe, C. G.; Lee, J. Y.; Jeong, K. S.; Lim, S. M.; Pae, A. N. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 1460–1471.

301 Kashyap, S. J.; Garg, V. K.; Sharma, P. K.; Kumar, N.; Dudhe, R.; Gupta, J. K. *Med. Chem. Res.* **2012**, *21*, 2123–2132.

302 Pola, S. In *Scope of Selective Heterocycles from Organic and Pharmaceutical Perspective*; InTech, **2016**.

303 Bell, F. W.; Cantrell, A. S.; Högberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M.; Noréen, R.; Öberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Temansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *J. Med. Chem.* **1995**, *38*, 4929–4936.

304 Das, D.; Sikdar, P.; Bairagi, M. *Eur. J. Med. Chem.* **2016**, *109*, 89–98.

305 Deutsch, A.; Wagner, C.; Deutsch, C.; Hoffmann-Röder, A. *Eur. J. Org. Chem.* **2016**, 930–945.

306 Zhang, G. W.; Wang, L.; Nie, J.; Ma, J. A. *Adv. Synth. Catal.* **2008**, *350*, 1457–1463.

307 Neouchy, Z.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2018**, *20*, 6017–6021.

308 Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem.* **2004**, 1558–1566.

309 Becker, H. D.; Mikol, G. J.; Russell, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3410–3414.

310 Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639–1640.

311 Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435–438.

312 Carreño, M. C.; Garcia Ruano, J. L.; Martin, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120–2128.

313 Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6649–6652.

314 Ogura, K.; Ishida, M.; Tomori, H.; Fujita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*.

315 Miyashita, K.; Toyoda, T.; Miyabe, H.; Imanishi, T. *Synlett* **1995**, *211*, 1229–1931.

316 García Ruano, J. L.; Lorente, A.; Rodríguez, J. H. *Tetrahedron Lett.* **1992**, *33*, 5637–5640.

317 García Ruano, J. L.; Cifuentes, M. M.; Lorente, A.; Rodríguez Ramos, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 4607–4618.

318 Jonet, S.; Cherouvrier, F.; Brigaud, T.; Portella, C. *Eur. J. Org. Chem.* **2005**, 4304–4312.

319 Leng, D. J.; Black, C. M.; Pattison, G. *Org. Biomol. Chem.* **2016**, *14*, 1531–1535.

320 Howard, J. L.; Sagatov, Y.; Repusseau, L.; Schotten, C.; Browne, D. L. *Green Chem.* **2017**, *19*, 2798–2802.

321 Stavber, G.; Stavber, S. *Adv. Synth. Catal.* **2010**, *352*, 2838–2846.

322 Differding, E.; Rtiegg, G. M.; Lang, R. W. *Tetrahedron Lett.* **1991**, *15*, 1779–1782.

323 Loghmani-Khouzani, H.; Poorheravi, M. R.; Sadeghi, M. M. M.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 7419–7425.

324 Matsumura, Y.; Nakano, T.; Mori, N.; Morizawa, Y. *Chimia* **2004**, *58*, 148–152.

325 Tsuchihashi, G.; Iriuchijima, S.; Maniwa, K. *Tetrahedron Lett.* **1973**, *36*, 3389–3392.

326 Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6101–6104.

327 García Ruano, J. L.; Alcudia, A.; Del Prado, M.; Barros, D.; Maestro, M. C.; Fernández, I. *J. Org. Chem.* **2000**, *65*, 2856–2862.

328 García Ruano, J. L.; Alemán, J.; Del Prado, M.; Fernández, I. *J. Org. Chem.* **2004**, *69*, 4454–4463.

329 Zucca, C.; Bravo, P.; Corradi, E.; Meille, S. V.; Volonterio, A.; Zanda, M. *Molecules* **2001**, *6*, 424–432.

330 Borrego, L. G.; Recio, R.; Álvarez, E.; Sánchez-Coronilla, A.; Khiar, N.;

Fernández, I. *Org. Lett.* **2019**, *21*, 6513–6518.

331 Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 498–501.

332 Appel, R.; Mayr, H. *J. Am. Chem. Soc.* **2011**, *133*, 8240–8251.

333 Huang, W.; Ye, J.; Zheng, W.; Dong, H.; Wei, B. *J. Org. Chem.* **2013**, *78*, 11229–11237.

334 Dallimore, J.; El Qacemi, M.; Koza-Kiewicz, A.; Longstaff, A.; Mclachlan, M.; Peace, J. Herbicidal isoxazoline derivatives. WO2011/033251A1, 2011.

335 Bravo, P.; Resnati, G.; Zappalà, C. *J. Fluorine Chem.* **1992**, *59*, 153–156.

336 Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210–6219.

337 Nelson, D. W.; Easley, R. A.; Pintea, B. N. V. *Tetrahedron Lett.* **1999**, *40*, 25–28.

338 Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572–2582.

339 Khangarot, R. K.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2013**, 2692–2698.

340 Annunziata, R.; Cinquini, M. *Synthesis* **1982**, 929–931.

341 Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1992**, *48*, 9385–9390.

342 Curtin, M. L.; Dai, Y.; Davidsen, S. K.; Dellaria, J. F. J.; Florjancic, A. S.; Gong, J.; Guo, Y.; Heyman, H. R.; Holms, J. H.; Michaelides, M. R.; Stacey, J. R.; Steinman, D. H.; Wada, C. K.; Lianhong, X. Reverse Hydroxamate Inhibitors of Matrix Metalloproteinases. US6294573 B1, 2001.

343 Dmitriev, I. A.; Supranovich, V. I.; Levin, V. V.; Dilman, A. D. *Eur. J. Org. Chem.* **2019**, No. 26, 4119–4122.

344 Downey, C. W.; Dombrowski, C. M.; Maxwell, E. N.; Safran, C. L.; Akomah, O. A. *Eur. J. Org. Chem.* **2013**, 5716–5720.

345 Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699–5713.

346 Posner, G. H. *Org. React.* **1972**, 12–14.

347 Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 198–200.

348 Stahly, G. P. *J. Fluorine Chem.* **1989**, *43*, 53–66.

349 Kimura, T.; Tsuru, T.; Momochi, H.; Satoh, T. *Heteroat. Chem.* **2009**, *24*, 131–137.

350 Tamamoto, K.; Yamada, S.; Konno, T. *Beilstein J. Org. Chem.* **2018**, *14*, 2375–2383.

351 Wnuk, S. F.; Bergolla, L. A.; Garcia, P. I. *J. Org. Chem.* **2002**, *67*, 3065–3071.

352 Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315–4317.

353 Li, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5882–5886.

354 Shen, X.; Miao, W.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 775–779.

355 Uno, H.; Sakamoto, K.; Semba, F.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 210–217.

356 Revunova, K.; Nikonov, G. I. *Chem. Eur. J.* **2014**, *20*, 839–845.

357 Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 786–789.

358 Hughes, D. L. In *Organic reactions vol. 42*; Paquette, L., Ed.; Wiley Online Library, **1992**; pp 335–395.

359 But, T. Y. S.; Toy, P. H. *Chem. - An Asian J.* **2007**, *2*, 1340–1355.

360 Fletcher, S. *Org. Chem. Front.* **2015**, *2*, 739–752.

361 Mase, N.; Watanabe, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **2000**, *65*, 7083–7090.

362 Fernández de la Pradilla, R.; Manzano, P.; Montero, C.; Priego, J.; Martínez-Ripoll, M.; Martínez-Cruz, L. A. *J. Org. Chem.* **2003**, *68*, 7755–7767.

363 Bravo, P.; Cavicchio, G.; Crucianelli, M.; Poggiali, A.; Zanda, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2811–2815.

364 Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 285–287.

365 Andersen, T. L.; Frederiksen, M. W.; Domino, K.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 10396–10400.

366 Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530–14531.

367 Stanton, M. G.; Stauffer, S. R.; Gregro, A. R.; Steinbeiser, M.; Nantermet, P.; Sankaranarayanan, S.; Price, E. A.; Wu, G.; Crouthamel, M. C.; Ellis, J.; Lai, M. T.; Espeseth, A. S.; Shi, X. P.; Jin, L.; Colussi, D.; Pietrak, B.; Huang, Q.; Xu, M.; Simon, A. J.; Graham, S. L.; Vacca, J. P.; Selnick, H. *J. Med. Chem.* **2007**, *50*, 3431–3433.

368 Juncosa, J. I.; Groves, A. P.; Xia, G.; Silverman, R. B. *Bioorg. Med. Chem.* **2013**, *21*, 903–911.

369 Kolb, M.; Barth, J.; Heydt, J. georges; Jung, M. J. *J. Med. Chem.* **1987**, *30*, 267–272.

370 Fokina, N. A.; Kornilov, A. M.; Kukhar, V. P. *J. Fluorine Chem.* **2001**, *111*, 69–76.

371 Thvedt, T. H. K.; Fuglseth, E.; Sundby, E.; Hoff, B. H. *Tetrahedron* **2010**, *66*, 6733–6743.

372 Skalická, V.; Rybáčková, M.; Skalický, M.; Kvíčalová, M.; Cvačka, J.; Březinová, A.; Čejka, J.; Kvíčala, J. *J. Fluorine Chem.* **2011**, *132*, 434–440.

373 Han, X.; Wu, H.; Wang, W.; Dong, C.; Tien, P.; Wu, S.; Zhou, H. B. *Org. Biomol. Chem.* **2014**, *12*, 8308–8317.

374 Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, No. April, 2551–2651.

375 Pinard, E.; Burner, S.; Cueni, P.; Hartung, T.; Norcross, R. D.; Schmid, P.; Waldmeier, P.; Zielinski, G.; Ravert, H. T.; Holt, D. P.; Dannals, R. F. *J. Label. Compd. Radiopharm.* **2011**, *54*, 702–707.

376 Liu, Y.; Guo, L.; Duan, H.; Zhang, L.; Jiang, N.; Zhen, X.; Shen, J. *RSC Adv.* **2015**, *5*, 40964–40977.

377 Santora, V. J.; Almos, T. A.; Barido, R.; Basinger, J.; Bellows, C. L.; Bookser, B. C.; Breitenbucher, J. G.; Broadbent, N. J.; Cabebe, C.; Chai, C. K.; Chen, M.; Chow, S.; Chung, D. M.; Crickard, L.; Danks, A. M.; Freestone, G. C.; Gitnick, D.; Gupta, V.; Hoffmaster, C.; Hudson, A. R.; Kaplan, A. P.; Kennedy, M. R.; Lee, D.; Limberis, J.; Ly, K.; Mak, C. C.; Masatsugu, B.; Morse, A. C.; Na, J.; Neul, D.; Nikpur, J.; Peters, M.; Petroski, R. E.; Renick, J.; Sebring, K.; Sevidal, S.; Tabatabaei, A.; Wen, J.; Yan, Y.; Yoder, Z. W.; Zook, D. *J. Med. Chem.* **2018**, *61*, 6018–6033.

378 Zhang, P.; Dong, J.; Zhong, B.; Zhang, D.; Jin, C.; Meng, X.; Sun, D.; Xu, X.; Zhou, Y.; Liang, Z.; Ji, M.; Li, H.; Xu, T.; Song, G.; Zhang, L.; Chen, G.; Yuan, H.; Shih, J.; Zhang, R.; Hou, G.; Jin, Y.; Yang, Q. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3738–3743.

379 Bagal, S. K.; Andrews, M.; Bechle, B. M.; Bian, J.; Bilsland, J.; Blakemore, D. C.; Braganza, J. F.; Bungay, P. J.; Corbett, M. S.; Cronin, C. N.; Cui, J. J.; Dias, R.; Flanagan, N. J.; Greasley, S. E.; Grimley, R.; James, K.; Johnson, E.; Kitching, L.; Kraus, M. L.; Mcalpine, I.; Nagata, A.; Ninkovic, S.; Omoto, K.; Scales, S.; Skerratt, S. E.; Sun, J.; Tran-dube, M.; Waldron, G. J.; Wang, F.; Warmus, J. S. **2018**.

380 Weïwer, M.; Xu, Q.; Gale, J. P.; Lewis, M.; Campbell, A. J.; Schroeder, F. A.; Van De Bittner, G. C.; Walk, M.; Amaya, A.; Su, P.; Dordevic, L.; Sacher, J. R.; Skepner, A.; Fei, D.; Dennehy, K.; Nguyen, S.; Faloon, P. W.; Perez, J.; Cottrell, J. R.; Liu, F.; Palmer, M.; Pan, J. Q.; Hooker, J. M.; Zhang, Y. L.; Scolnick, E.; Wagner, F. F.; Holson, E. B. *ACS Chem. Biol.* **2018**, *13*, 1038–1047.

381 Leas, D. A.; Dong, Y.; Vennerstrom, J. L.; Stack, D. E. *Org. Lett.* **2017**, *19*, 2518–2521.

382 Ramachandran, P. V.; Teodorovic', A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1075–1086.

383 Zhu, L.; Li, Y.; Ni, C.; Hu, J.; Beier, P.; Wang, Y.; Surya Prakash, G. K. K.; Olah, G. A. *J. Fluorine Chem.* **2007**, *128*, 1241–1247.

384 Tang, X. J.; Zhang, Z.; Dolbier, W. R. *Chem. Eur. J.* **2015**, *21*, 18961–18965.

385 Lin, Q. Y.; Xu, X. H.; Qing, F. L. *Org. Biomol. Chem.* **2015**, *13*, 8740–8749.

386 Prakash, G. K. S.; Chacko, S.; Alconcel, S.; Stewart, T.; Mathew, T.; Olah, G. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4933–4936.

387 Larnaud, F.; Malassis, J.; Pfund, E.; Linclau, B.; Lequeux, T. *Org. Lett.* **2013**, *15*, 2450–2453.

Scientific contribution

Presentations

- **Poster presentations**

Towards the enantioselective C(sp^3) difluoromethylation : Batisse, C., Céspedes Dávila M. F., Panossian, A., Hanquet, G., Leroux, F. R., Regio-Symposium **2017**, Liestal – Switzerland, 06-08.09.2017

New insights into enantioselective difluoromethylation by means of sulfoxides as chiral and traceless auxiliaries : Batisse, C., Céspedes Dávila M. F., Panossian, A., Vivet, B., Heng, R., Marciniak, G., Hanquet, G., Leroux, F. R. :

Ecole thématique Le Fluor (GIS Fluor) **2018**, La Rochelle – France, 14-17.05.2018

22th International Symposium on Fluorine Chemistry ISFC **2018**, Oxford – United-Kingdom, 22-27.07.2018

2nd Swiss industrial chemistry symposium **2018**, Basel – Switzerland, 19.10.2018

- **Oral communications**

Stereoselective synthesis of a library of building blocks bearing emergent fluorinated substituents, Céspedes Dávila, M. F., 1st LIMA Scientific Day **2018**, Mulhouse – France, 25.06.2018.

New insights into enantioselective difluoromethylation by means of sulfoxides as chiral and traceless auxiliaries, Batisse, C., Céspedes Dávila M. F., Panossian, A., Vivet, B., Heng, R., Marciniak, G., Hanquet, G., Leroux, F. R., 19th European Symposium on Fluorine Chemistry **2019**, Warsaw – Poland, 25-31.08.2019

Publication

Efficient asymmetric synthesis of aryl difluoromethyl sulfoxides and their use to access enantiopure α-difluoromethyl alcohols, Batisse, C., Céspedes Dávila M. F., Castello, M., Messara, A., Vivet, B., Marciniak, Panossian, A., Hanquet, G., Leroux, F. R., *Tetrahedron* **2019**, *75*, 3063-3079; *https://doi.org/10.1016/j.tet.2019.04.037*.

Université de Strasbourg

Maria F. CESPEDES DAVILA

New insights into the stereoselective synthesis of difluoromethylated building blocks of pharmaceutical interest

SANOFI

Résumé

L'introduction d'un atome de fluor ou d'un groupement fluoré dans des molécules biologiquement actives permet d'améliorer remarquablement leurs propriétés physico-chimiques et biologiques. La chimie organique du fluor a connu une croissance très importante durant les dernières décennies, ce qui transparaît dans le grand nombre de principes actifs fluorés parmi les composés pharmaceutiques ou agrochimiques sur le marché. Les propriétés additionnelles du groupement -CHF_2, considéré comme un bioisostère des groupements hydroxyle ou thiol pouvant jouer le rôle de donneur de liaison hydrogène, ainsi que le nombre limité d'exemples de difluorométhylation énantiosélective dans la littérature nous ont amené à nous intéresser au développement de nouvelles méthodes de synthèse efficaces pour accéder à des briques synthétiques difluorométhylées potentiellement valorisables en chimie médicinale. La stratégie de ce projet consiste à utiliser un sulfoxyde difluorométhylé énantiopur afin d'étudier l'introduction stéréosélective du groupement difluorométhyle. Cette approche nous a permis de développer des voies d'accès à une librairie de composés qui, après désulfinylation, ont donné accès à des molécules difluorométhylées de haute pureté optique. La post-fonctionnalisation des composés a également été étudiée afin d'accéder à des intermédiaires difluorométhylés intéressants en chimie médicinale. Les différents résultats obtenus au cours de ce projet seront exposés dans ce manuscrit.

Mots clés : synthèse asymétrique, chimie du fluor, -CHF_2, sulfoxyde, inducteur de chiralité, post-fonctionnalisation

Résumé en anglais

The introduction of a fluorine atom or a fluorinated group in bioactive molecules can deeply modify their structure, reactivity and function. During the last decades, the emergence of organofluorine chemistry has been particularly noticeable. This is illustrated by the large amount of pharmaceuticals and agrochemicals currently commercialised containing at least one fluorine atom. The outstanding properties of the –CHF_2 group as a bioisostere of hydroxyl and thiol such as its hydrogen bond donor character, and the limited number of enantioselective difluoromethylations reported in literature led us to develop a new synthetic pathway to access difluoromethylated building blocks for medicinal research. The use of an enantiopure difluoromethyl sulfoxide has been the guideline for the project. This approach allowed us to study the stereoselective introduction of the difluoromethyl group in a library of molecules that, after desulfinylation, led to enantioenriched difluoromethylated compounds. The post-functionalization of these compounds was also investigated in order to expand the scope of the study and give access to difluoromethylated intermediates of interest in medicinal chemistry. The results obtained in the course of this project are discussed in this manuscript.

Keywords: asymmetric synthesis, fluorine chemistry, -CHF_2, sulfoxide, chiral inductor, post-functionalization