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Design, synthesis and biological evaluation of new platelet aggregation inhibitors and novel methodologies for the preparation of CF_2R containing molecules.

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Equipments and conventional techniques

Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Avance 500, 400 and 300 spectrometers. ^{1}H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using [δ (C***H***Cl_3) = 7.26 ppm] as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS, using [δ (***C***DCl_3) = 77.0 ppm] as internal reference. ^{19}F NMR spectra: δ (F) are given in ppm relative to C***F***Cl_3 = 0.0 ppm as external reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (qt), multiplet (m) or br (broad).

Mass spectrometry

Mass spectral analyses have been performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) in Rennes (France).

Polarimeter

The optical rotation values have been measured with a Perkin-Elmer 141 Polarimeter, at 589 nm. The concentration was reported in gram per milliliter (c, g. ml^{-1}).

Solvents and reagents

All reagents were obtained commercially and used without further purification. The diethyl ether and the THF were distilled over sodium/benzophenone. The dichloromethane and toluene were distilled over calcium hydride.

Glass wares

Reactions that require anhydrous conditions have been carried out, under nitrogen or argon, by using oven dried (120 °C, 24 h) glassware.

Chromatography

The reactions have been monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of pentane, hexane, petroleum ether, diethyl ether and ethylacetate. Compounds were detected by UV light, *p*-anisaldehyde or potassium permanganate staining solution.

The purifications were performed by column chromatography or flash column chromatography using Acros silica gel (60, particle size 0.040–0.063 mm).

Melting points

The melting points were determined using Kofler apparatus.

Nomenclature

The names of the molecules were obtained using Chemdraw 8.0 software following the IUPAC nomenclature.

Abbreviations

- 12-HETE : 12-hydoxy-5Z,8Z,10E,14Z-eicosatetraenoic acid
- 13-HODE : 13-hydroxy-9Z,11E-octadecadienoic acid
- AA : Arachidonic acid
- LA : Linoleic acid
- Ac : acetate
- COX : Cyclooxyegnase
- DAST : Diethylaminosulfur trifluoride
- DCM : Dichloromethane
- DDQ : 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
- DMF : Dimethyl foramide
- DMSO : Dimethyl sulphoxide
- Et3N : Triethylamine
- EtOH : Ethanol
- Me : Methyl
- MeOH : Methanol
- NSAIDs : Non-steroidal anti-inflammatory drugs
- PG : Prostaglandin
- ppm : part per million
- THF : Tetrahydrofurane
- TLC : Thin layer chromatography
- TX : Thromboxane

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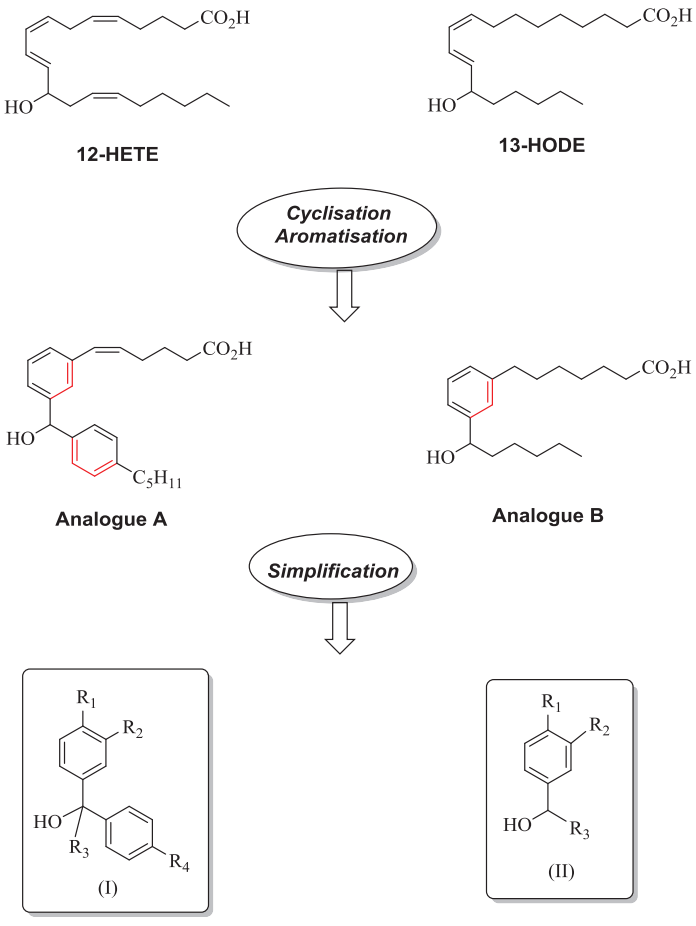
RESUME DE LA THESE EN FRANCAIS

Chapitre 1 Synthèse et évaluation biologique de nouveaux composés à activité antiagrégante plaquettaire

1-Introduction

L'acide 12-hydroxy-5*Z*,8*Z*,10*E*,14*Z*-eicosatetraenoique (12-HETE) et l'acide 13-hydroxy-9*Z*,11*E*-octadecadienoique (13-HODE) sont des composés biologiquement actifs, derivés de l' acide arachidonique via l'action de la 12-lipoxygénase pour le premier et de l'acide linoléique via la 15-lipoxygénase pour le second. Ces métabolites ont démontré des activités antiagrégante plaquettaires. Il a été montré, par A. Hachem et al., que des analogues stabilisés par aromatisation (Analogues des Séries A et B, **Schéma 1**) étaient aussi de bons inhibiteurs de l'agrégation plaquettaire induite par le thromboxane.

Schéma 1: Analogues simplifiés du 12-HETE et du 13-HODE



Sur cette base, nous nous sommes donc proposés de préparer, et tester en antiagrégant plaquettaire, de nouveaux analogues encore plus simples, les composés des séries (I) et (II).

2- Synthèse des composés de la famille (I)

La préparation des composés de ce type emploie essentiellement des réactions de Grignard, des aménagements fonctionnels et des réactions de couplage au palladium. Elles sont mentionnées ci-après, sous forme de schémas récapitulaitifs:

Schéma 4. Synthèse de l'acide *meta*-carboxylique **3**

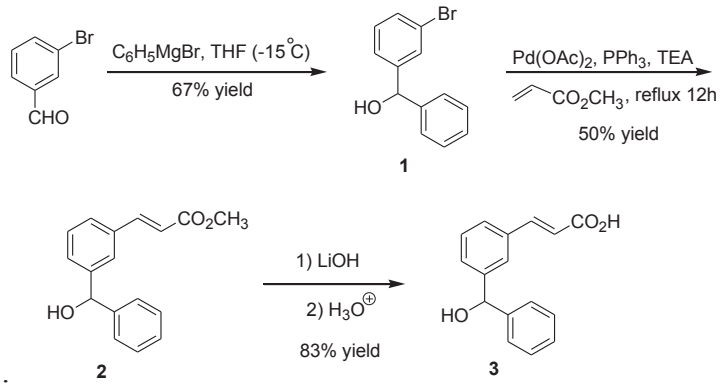


Schéma 5. Synthèse de l'acide *ortho*-carboxylique **6**

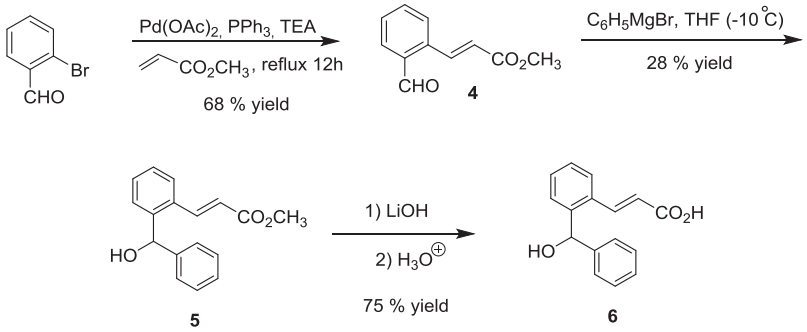


Schéma 7. Synthèse de l'acide *meta*-carboxylique **10**

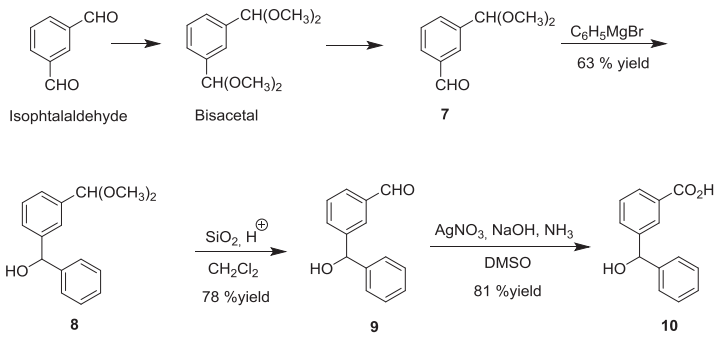


Schéma 9. Synthèse de l'acide *ortho*-substitué **15**

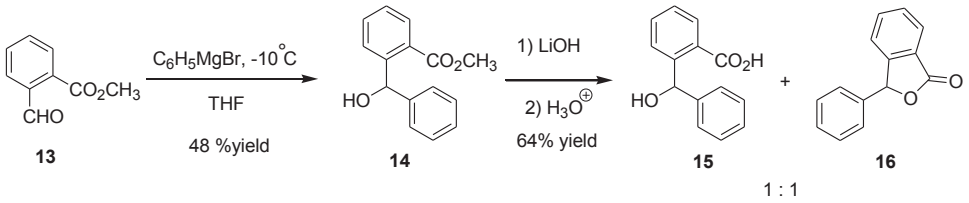
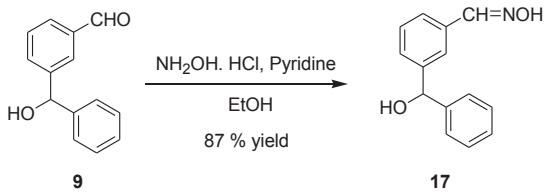
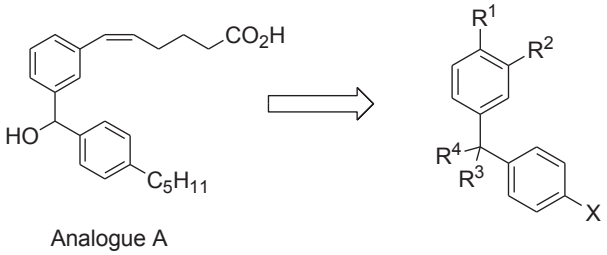


Schéma 10. Synthèse de l'oxime **17**



Il est bien connu que les composés phénoliques présentent des activités biologiques puissantes: on peut mentionner le 2-(3,4-dihydroxyphenyl)ethanol (DHPE) composant de l'huile d'olive ou le resveratrol bien connu dans le vin. Nous avons donc préparé aussi un certain nombre de composés de type (I) avec des composantes phénoliques sur les noyaux aromatiques, comme indiqué dans le tableau 1.

Tableau 1. Analogues phénoliques de A.



Analogue A

Composé	R_1	R_2	R_3	R_4	X
18	OH	OCH_3	OH	H	H
19	OH	OCH_3	OH	H	F
20	OH	OCH_3	OH	CH_3	H
21	OH	OCH_3	-	CH_2	H
22	H	OH	OH	H	H

Ces composés ont été préparés par des réactions de Grignard à partir des dérivés carbonylés appropriés et les schémas 11 et 12 donnent des exemples représentatifs de ces synthèses.

Schéma 11. Préparation du phenol **18** et de son analogue fluoré **19.**

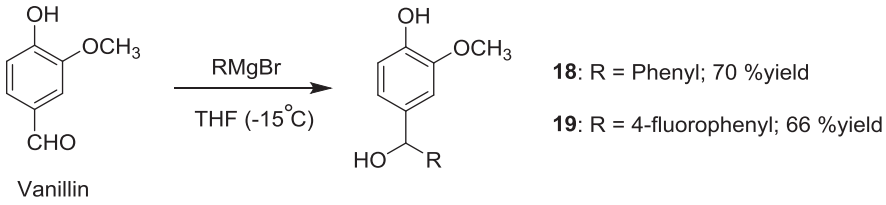
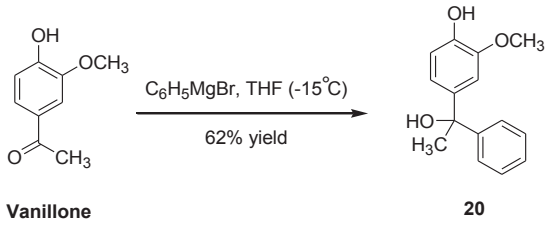


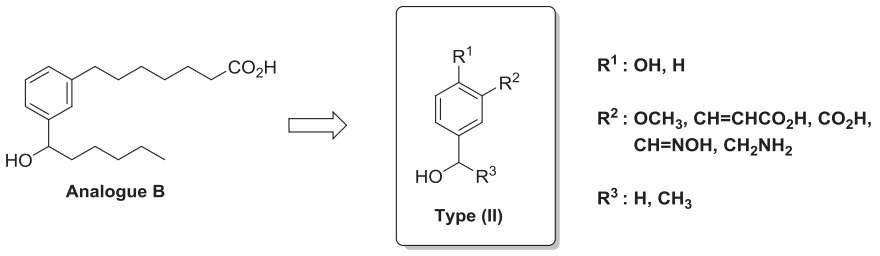
Schéma 12. Préparation du phenol **20**.



3 Synthèse des composés de type (II)

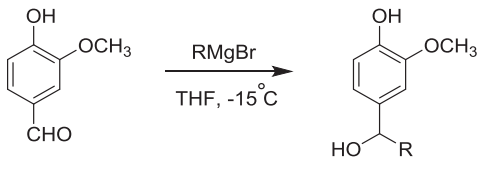
Un certain nombre de molécules de type (II) ont été préparées (Schéma 16).

Schéma 16. Structure génerale des composés de type (II)



Ils ont été préparés par les mêmes approches que précédemment, comme indiqué dans le Schéma 17.

Schéma 17. Préparation d'une série representative des composés de type (II)



25: R= nC_5H_{11}; 45 % yield

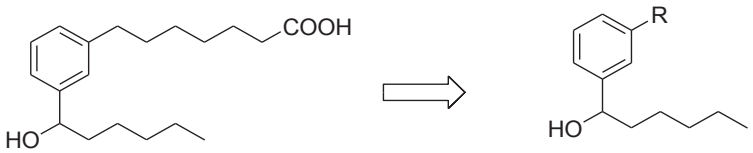
26: R= nC_4H_9 ; 52 % yield

27: R= nC_9H_{19}; 54 % yield

28: R=  ; 78 % yield

Une seconde série de molécules a été synthétisée comme indiquée dans le tableau 2.

Tableau 2. Seconde série de composés de type (II).

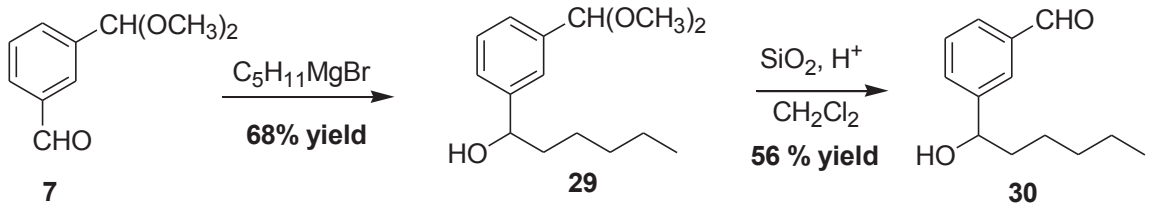


Analogue B

Composé	R
31	COOH
32	CH_2OH
33	CH=N-OH
34	CH_2-NH_2
37	*(E)* CH=CH-CO_2H

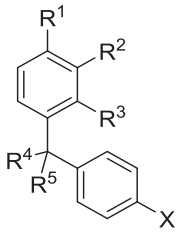
Leur synthèse part d'un intermédiaire clé, l'aldéhyde **30** (Schéma 18). Elle emploie ensuite des réactions très classiques de la fonction aldéhyde.

Schéma 18. Synthèse de l'aldehyde intermediaire **30.**



L'ensemble des molécules préparées dans la série (I) est résumé dans le Tableau 3 alors que celles de la série (II) sont mentionnées dans le Tableau 4.

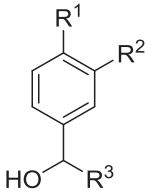
Tableau 3. Molécules de type (I) préparées.



Type (I)

Molecule	R^1	R^2	R^3	R^4	R^5	X
3	H	*(E)* $CHCHCO_2H$	H	OH	H	H
6	H	H	*(E)* $CHCHCO_2H$	OH	H	H
10	H	CO_2H	H	OH	H	H
15	H	H	CO_2H	OH	H	H
17	H	CHNOH	H	OH	H	H
18	OH	OCH_3	H	OH	H	H
19	OH	OCH_3	H	OH	H	F
20	OH	OCH_3	H	OH	CH_3	H
21	OH	OCH_3	H	CH_2	-	H
22	H	OH	H	OH	H	H
24	OCH_3	OCH_3	H	OH	H	H

Tableau 4. Molécules de type (II) préparées.



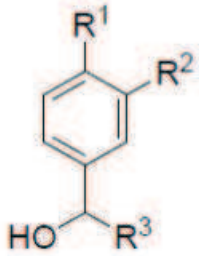
Type (II)

Molecule	R^1	R^2	R^3
25	OH	OCH_3	C_5H_{11}
26	OH	OCH_3	C_4H_9
27	OH	OCH_3	C_9H_{19}
28	OH	OCH_3	C_5H_9
31	H	CO_2H	C_5H_{11}
33	H	CHNOH	C_5H_{11}
34	H	CH_2NH_2	C_5H_{11}
37	H	$CHCHCO_2H$	C_5H_{11}

Toutes ces molécules ont été soumises aux tests biologiques d'inhibition de l'agrégation plaquettaire. *Ces tests ont été réalisés par M^{elle} Taghreed Hirz (étudiante de Master 2) dans le groupe du Dr. Aida HABIB à l'Université Américaine de Beyrouth (AUB).*

Les résultats des composés de la série (II) sur l'agrégation plaquettaire sont donnés dans le tableau 1B suivant:

Tableau 1B. Effet des molécules de type (II) sur l'agrégation plaquettaire

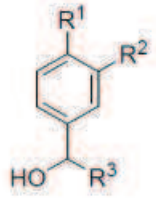
Structure	Compound	R^1	R^2	R^3	Plt aggregation $IC_{50} \pm$ S.E.M (μM) [a]
	33	H	C=NOH	nC_5H_{11}	No inhibition
	31	-	COOH	nC_5H_{11}	No inhibition
	25	OH	OCH_3	nC_5H_{11}	7.5 ± 0.8
	26	OH	OCH_3	nC_4H_9	14.2 ± 5.7
	27	OH	OCH_3	nC_9H_{19}	97.6 ± 83.5
	28	OH	OCH_3		41.2 ± 0.7

[b] n=3-4 in all experiments

On remarque que les composés **25** et **26**, avec des chaînes latérales de tailles moyennes, présentent une activité biologique significative, même si elle reste inférieure à celle de l'ibuprofène (IC_{50} : 0.5 ± 0.11 μM).

Les composés de la série (I) ont également été testés et les résultats sont résumés dans le tableau 2B:

Tableau 2B. Effet des molécules de type (I) sur l'agrégation plaquettaire.

Structure	Compound	R^1	R^2	R^3	R^4	Plt aggregation $IC_{50} \pm S.E.M$ (μM)[b]
	**18**	OH	OCH_3	Ph	H	8.5 ± 1.2
	19	OH	OCH_3	a	H	13.4 ± 0.5
	20	OH	OCH_3	Ph	CH_3	11.3 ± 4.8
	24	OCH_3	OCH_3	Ph	H	No inhibition

a= 4-fluorophenyl; [b] n=3-4 in all experiments

Les composés **18**, **19** et **20** présentent une activité significative, contrairement au dérivé **24**. Ceci indique que le phénol en position R^1 doit jouer un rôle important dans cette activité.

Des tests complémentaires ont été réalisés avec les cinq composés actifs sur la cyclooxygénase humaine (COX 1). Ils ont montré que ces dérivés inhibaient de manière significative la synthèse de la PGE_2 dans ces conditions (Tableau 3B).

Tableau 3B. Effet des molécules synthétisées sur l'activité de la cyclooxygenase-1 humaine.

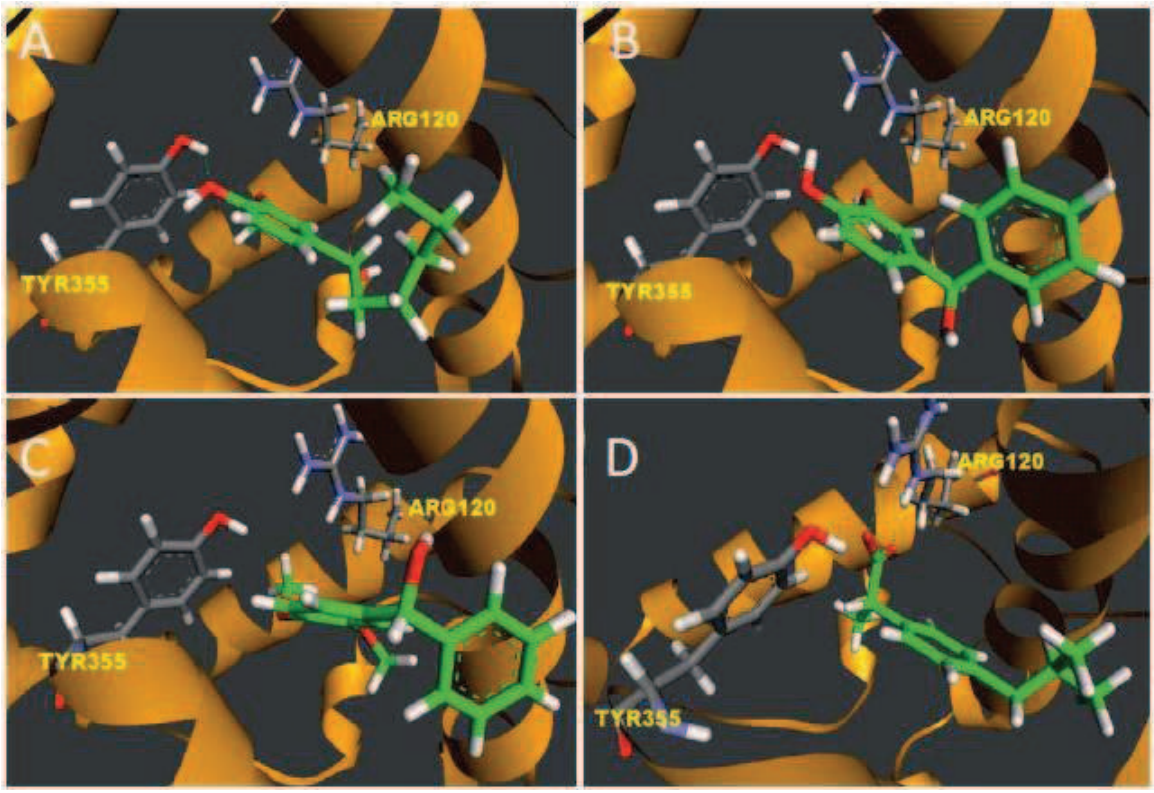
Compound	COX-1 activity $IC_{50} \pm S.E.M$ (μM)[a]
25	2.2 ± 0.7
26	12.1 ± 2.3
18	1.3 ± 0.5
19	6.5 ± 0.2
20	8.1 ± 1.7

[a] n=3-4 in all experiments

Une autre série de tests a montré qu'aucun de ces composés n'agissait sur le récepteur du thromboxane A2. Il est donc très probable que leur action passe par l'inhibition de la formation du thromboxane.

En parallèle, des études de modélisation moléculaire ont été réalisées par *Mr. Nehme El Hachem from American University of Beirut (AUB).* Les résultats obtenus sur des molécules représentatives (A à D) sont donnés dans la figure 7B. Ils sont globalement en accord avec les résultats biologiques obtenus et permettent de rationaliser, au moins en partie, le rôle joué par le phénol en position R^1.

Figure 7B. Résultats de modélisation moléculaire sur les principales molécules étudiées.



A: composé **18** (actif)

B: composé **25** (actif)

C: composé **24** (inactif)

D: ibuprofène (actif)

Chapitre 2 Eléments bibliographiques essentiels sur la synthèse et la chimie des composés possédant des motifs CF_2H ou CF_2R.

1 Introduction

Plus de 120 ans après la découverte du fluor par H. Moissan en 1866, la chimie des composés organofluorés joue un rôle extrêmement important dans de nombreux domaines, allant des matériaux à la chimie bioorganique et à la chimie médicinale. Il est bien connu en effet que l'introduction de fluor dans les molécules organiques en modifie considérablement les propriétés physiques, chimiques et biologiques. On considère qu'environ 20% des médicaments et 30-40% des produits commercialisés en agrochimie contiennent au moins un atome de fluor.

D'assez nombreuses approches ont été décrites pour la préparation de composés à motifs CF_2H ou CF_2R. Nous présenterons ici un résumé des travaux qui nous semblent les plus significatifs.

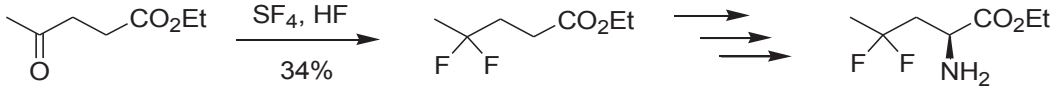
I- Préparation des molécules *gem*-difluorées

D'une manière générale, la préparation de ce type de molécules se fait par deux voies complémentaires. La première implique l'utilisation de réactions de fluoration (nucléophile ou électrophile) des molécules cibles, alors que la seconde approche est basée sur l'utilisation de « building blocks » déjà fluorés.

II-1 Approche par *gem*-difluoration directe

Plusieurs familles de réactifs permettent la fluoration d'un carbonyle en CF_2R. Les plus connus sont SF_4 et ses dérivés. Un exemple représentatif de l'emploi de SF_4 est donné dans le Schéma 1.

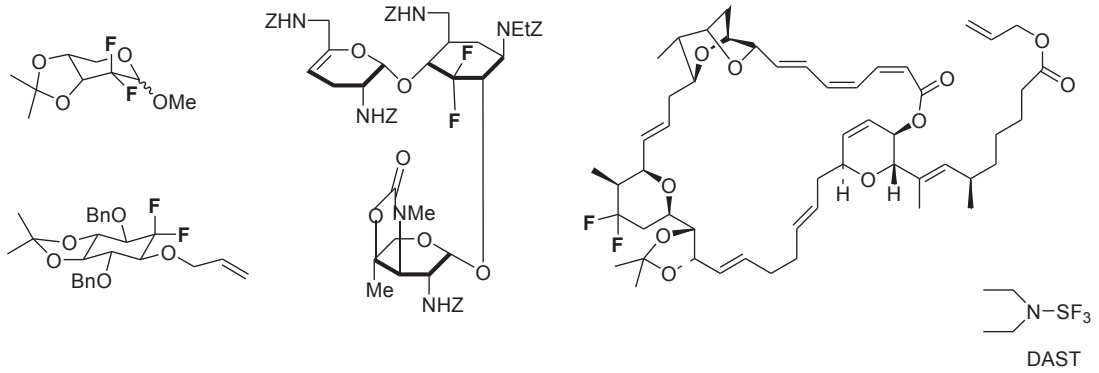
Schéma 1. Fluoration avec SF_4.



L'un des problèmes majeurs de SF_4 est sa toxicité et donc des composés dérivés ont été préparés, dont le DAST (diethylaminosulsurtrifluorure) qui s'est révélé très

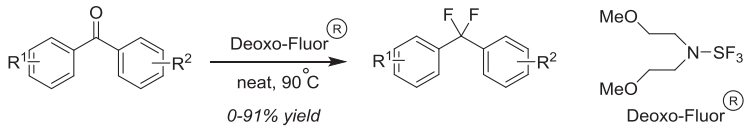
intéressant. Le Schéma 3 montre des exemples représentatifs de synthèse de composés gem-difluorés avec le DAST.

Schéma 3. Exemples de composés *gem*-difluorés préparés par fluoration au DAST.



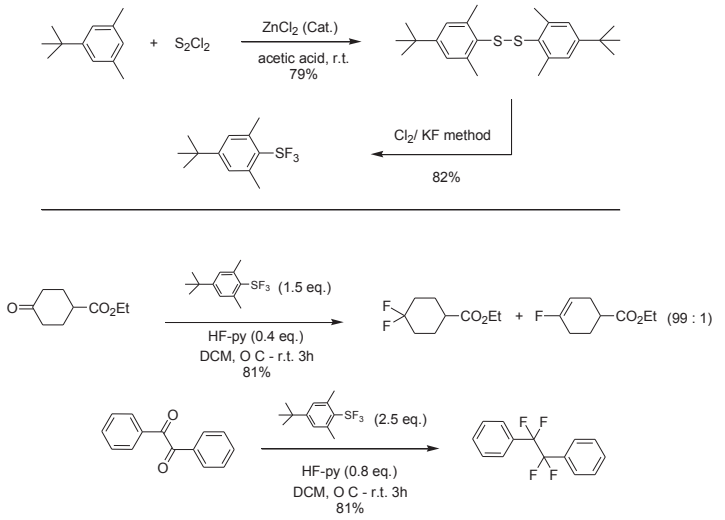
D'autres composés comme des α-cétoesters, α-cétophosphonates, etc, ont été préparés. Cependant le DAST a des limitations en termes de stabilité chimique et surtout thermique (décomposition, éventuellement violente, au dessus de 60°C). D'autres dérivés plus stables ont donc été préparés et utilisés, comme le Deoxo-Fluor® (Schéma 9).

Schéma 9. Fluoration de cétones bisaryliques avec le Deoxo-Fluor®.



Récemment, Umemoto a décrit la synthèse et l'utilisation d'un autre réactif intéressant (Schéma 10).

Schéma 10. Synthèse et utilisations du 4-*tert*-butyl-2,6-dimethylphenylsulfurtrifluorure.

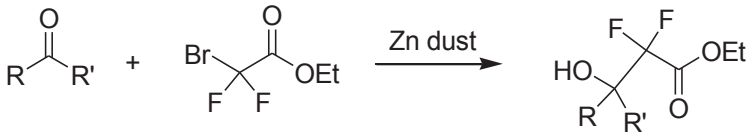


II-2 Utilisation de "building blocks" *gem*-difluorés.

L'autre approche consiste à utiliser des intermédiaires clés déjà fluorés. Différentes méthodes ont été utilisées pour la préparation de ces composés. Nous citerons les principales.

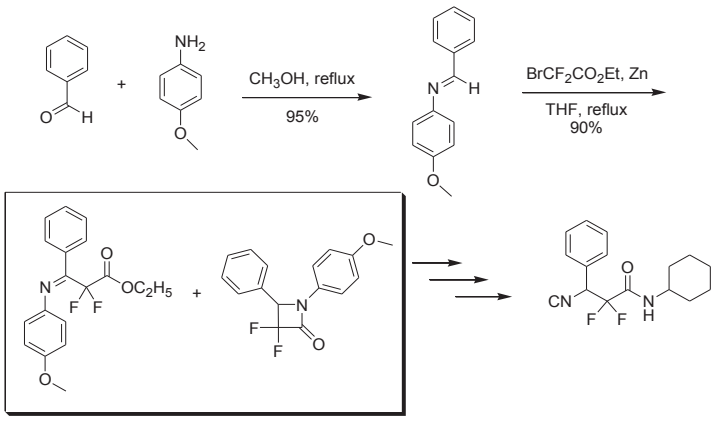
La réaction de Reformatsky est une des bonnes voies d'accès à des difluorés (Schéma 11)

Schéma 11. Réaction de Reformatsky pour accéder aux composés difluoréss.



Elle a été utilisée, par exemple, pour préparer un isonitrile difluoré qui a été employé ensuite dans des réactions multicomposants. (Schéma 13).

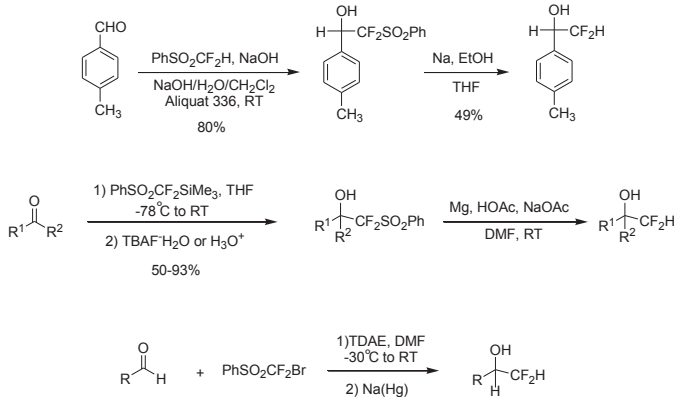
Schéma 13. Synthèse du *N*-cyclohexyl-2,2-difluoro-3-phenylpropanamide.



Des composés *gem*-difluoromethylés peuvent aussi être obtenus par addition nucléophile à partir de réactifs organo-cadmiens, zinciques et cuivreux difluoromethylés.

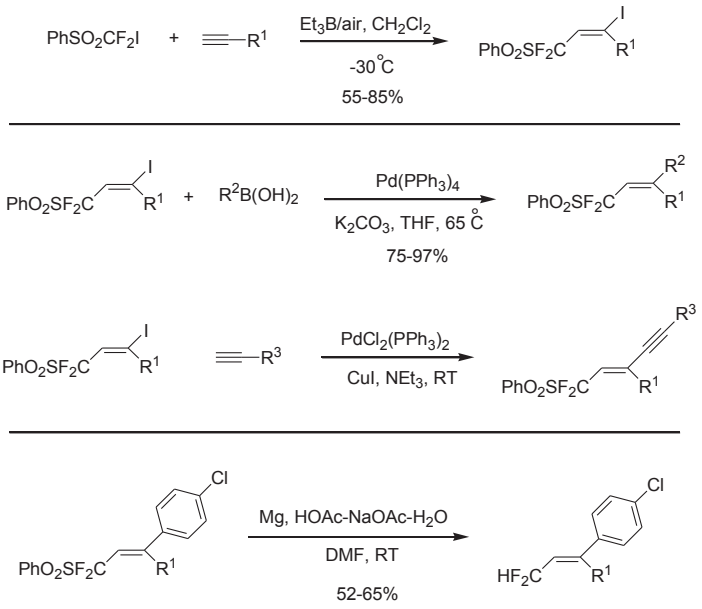
Par ailleurs, plusieurs composés phenylsulfonyldifluorés ($PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$, $PhSO_2CF_2Br$) ont été décrits comme agents de difluorométhylation nucléophile (Schéma 16).

Schéma 16. Exemples représentatifs d'utilisation de $PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$ et $PhSO_2CF_2Br$.



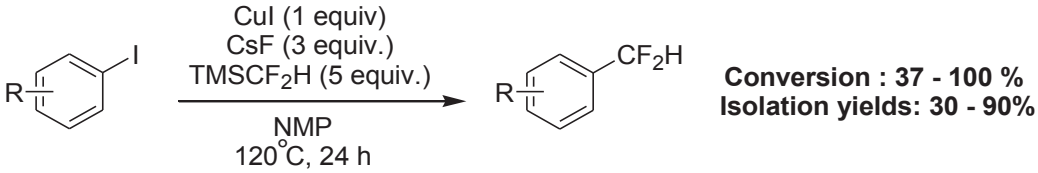
Il faut mentionner aussi l'obtention de difluorés vinyliques iodés et leur emploi dans des réactions de couplage au palladium (Schéma 17).

Schéma 17. Préparation et utilisation d'intermédiaires difluoro-vinyliques iodés.



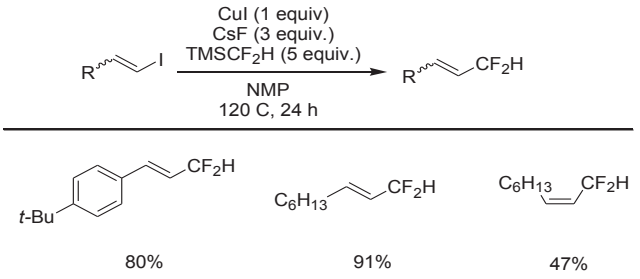
Hartwig a décrit récemment une méthode de synthèse de difluorométhylarenes par couplage au cuivre d'iodobenzènes avec $TMSCF_2H$ (Schéma 20).

Schéma 20. Difluorométhylation de iodés aromatiques avec $TMSCF_2H$



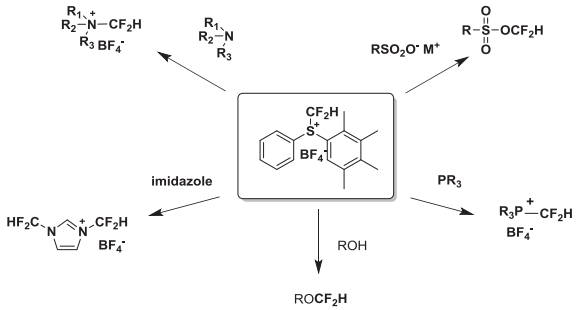
Cette jolie réaction marche aussi avec les dérivés vinyliques (Schéma 21).

Schéma 21. Difluorométhylation de dérivés iodés vinyliques avec $TMSCF_2H$

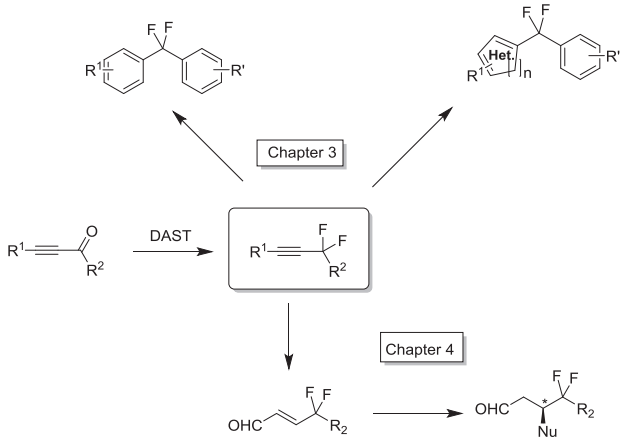


Prakash a décrit récemment un nouveau réactif de type sulfonium pour l'introduction de "CF_2H^+" (Schéma 22).

Schéma 22. Un nouveau réactif pour l'introduction du motif CF_2H



Compte tenu du très grand intérêt en synthèse des molécules contenant les groupes CF_2H et CF_2R-, il nous semble important de développer de nouvelles stratégies et/ou méthodologies pour la préparation de cette famille de composés. Ceci est donc notre objectif dans la seconde partie de cette thèse, et ceci en partant d'intermédiaires *gem*-difluoropropargyliques facilement accessibles.



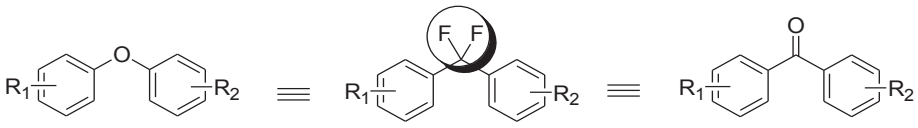
Dans le chapitre 3 nous montrerons comment ces scaffolds peuvent être facilement utilisés pour préparer des dérivés bisaryliques avec un linker CF_2, ainsi que leurs analogues mixtes aryl-heteroaryles. Ensuite, dans le chaptitre 4 nous développerons pour la première fois des réactions d'organocatalyse asymétrique pour obtenir des aldéhydes optiquement actifs avec un groupe CF_2 en position β.

Chapitre 3 Développement d'une stratégie originale pour la synthèse de composés biaryliques ou mixtes aryliques/hétéroayliques liés par un connecteur de type CF_2

1 Introduction

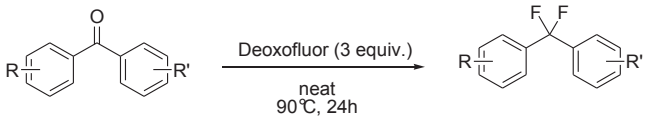
Le motif éther diarylique se retrouve fréquemment dans la chimie des produits naturels et il est souvent utilisé en chimie bioorganique et en chimie médicinale. Il en est de même de la structure benzophénone. Comme le motif CF_2 est considéré comme un bioisostère, aussi bien de l'oxygène que de la fonction carbonyle, il parait très intéressant de mettre au point des nouvelles méthodes d'accès aux composés *gem*-difluorés bisaryliques (Schéma 1) ainsi que de leurs analogues hétéroaromatiques.

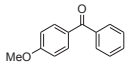
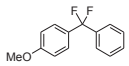
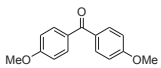
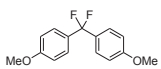
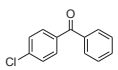
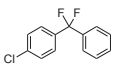
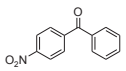
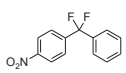
Schema 1. Ethers diaryliques, benzophenones et dérivés *gem*-difluoro-bisaryliques.



La *gem*-difluoration des benzophénones avec le DAST, et même avec le Deoxo-Fluor® présente de sévères limitations comme indiqué dans le Tableau 1.

Tableau 1. *gem*–difluoration de benzophenones avec le Deoxo-Fluor®



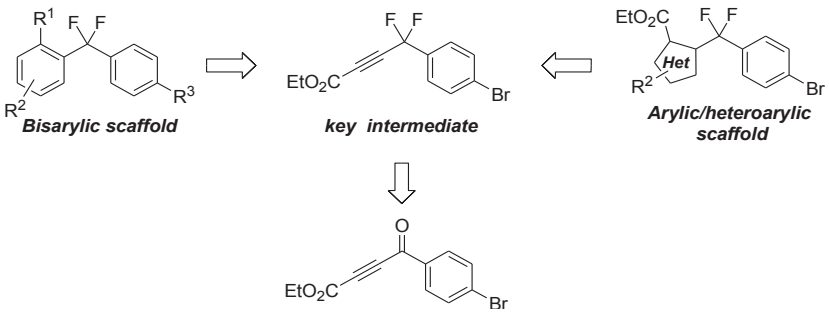
Substrate	Product	Yield (%)	Substrate	Product	Yield (%)
		63			27
		20			0
		64			91

En effet elle ne fonctionne bien qu'avec des systèmes attracteurs d'électrons sur au moins un des noyaux aromatiques. Pour les autres systèmes, des stratégies alternatives

passant par des dérivés soufrés (thiocétones ou thioacétals) doivent être mises en œuvre.

Il nous a donc paru intéressant de rechercher une méthode alternative permettant d'accéder facilement à une grande variété de composés de ce type. *Notre nouvelle stratégie envisage de construire les composés aromatiques à partir d'intermédiaires clés de type gem-difluoropropargyliques* (Schéma 3). Ces derniers sont faciles d'accès et ils doivent permettre également de préparer des composés mixtes en utilisant des réactions de cycloaddition dipolaire 1,3 ou de cyclocondensation.

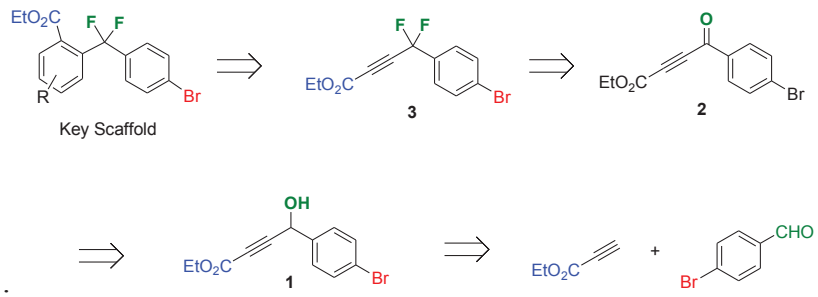
Schéma 3. Une nouvelle stratégie pour la synthèse de composés *gem*-difluorés bisaryliques et de dérivés mixtes aryl/heteroaryliques.



II- Rétrosynthèse du scaffold bisarylique

La rétrosynthèse de notre intermédiaire clé est donnée dans le Schéma 4. On notera le choix du *p*-bromobenzaldéhyde d'une part et du propiolate d'éthyle d'autre part : ceci nous permettra d'avoir deux points de démarrage (ester et brome) pour réaliser de la diversification moléculaire sur ces structures.

Schéma 4. Rétrosynthèse pour l'obtention du scaffold clé.

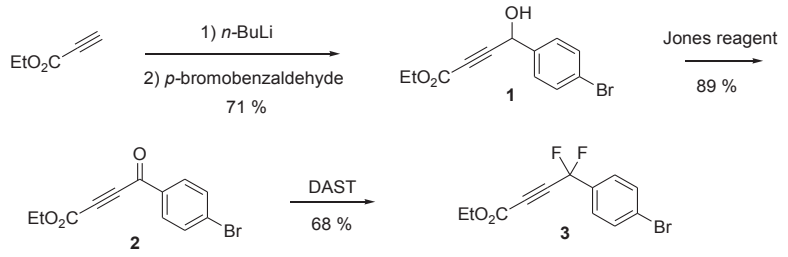


III- Résultats et discussion

1) Synthèse de l'intermédiaire clé 3.

La synthèse de cet intermédiaire *gem*-difluoré **3** est indiquée dans le Schéma 5.

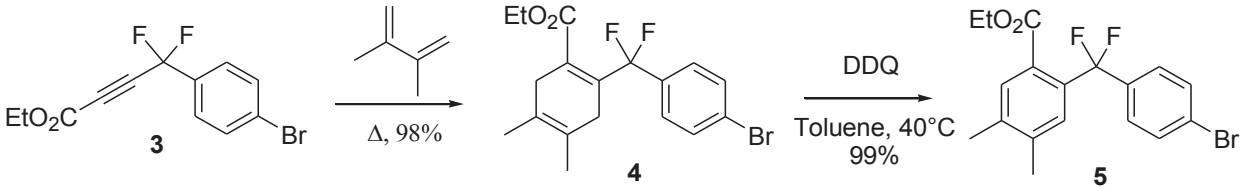
Schéma 5. Synthèse de l'intermédiaire **3**.



2) Synthèse du premier scaffold clé 6.

Dans le Schéma 6 on présente la synthèse, en deux étapes, du dérivé bisarylique 5

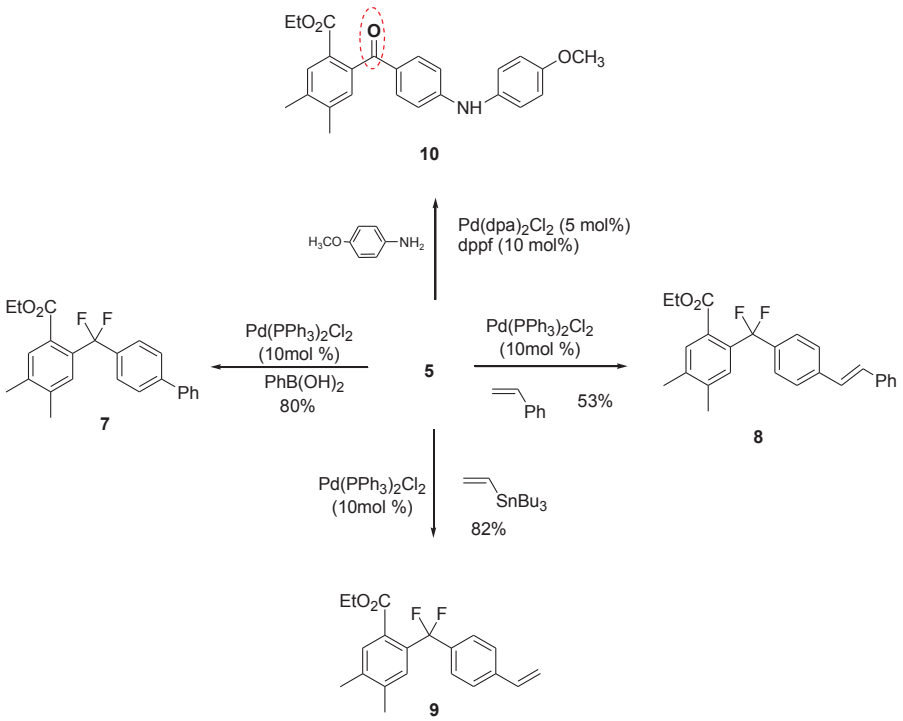
Schéma 6. Synthèse d'un exemple représentatif de scaffold clé, le composé **5**.



3) Synthèse d'une première chimiothèque ciblée utilisant des réactions de couplage au palladium.

En partant de l'intermédiaire 5, on a pu réaliser différents couplages au palladium (Schéma 8). Les couplages de Suzuki-Miyaura, Stille et Heck ont donné de bons résultats : les produits **7**, **8** et **9** sont obtenus avec des rendements de 80, 82 et 53 % respectivement. Par contre le couplage de type Buchwald-Hartwig a conduit à un dérivé **10** ayant perdu ses atomes de fluor.

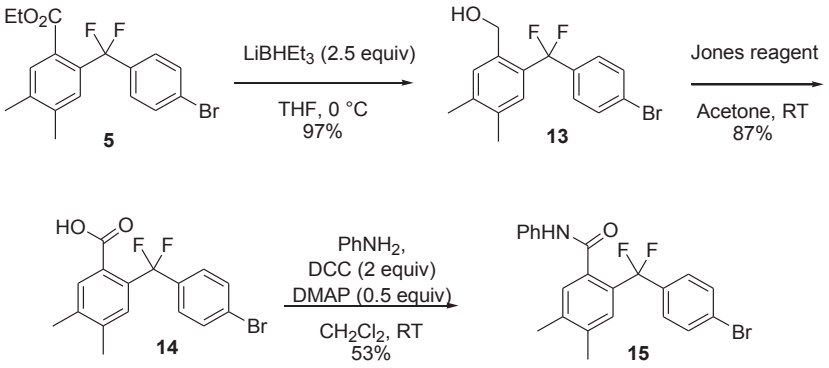
Schéma 8. Réactions de couplage au palladium sur l'aromatique **5**.



4) Synthèse d'une seconde chimiothèque en utilisant le groupe ester de 5.

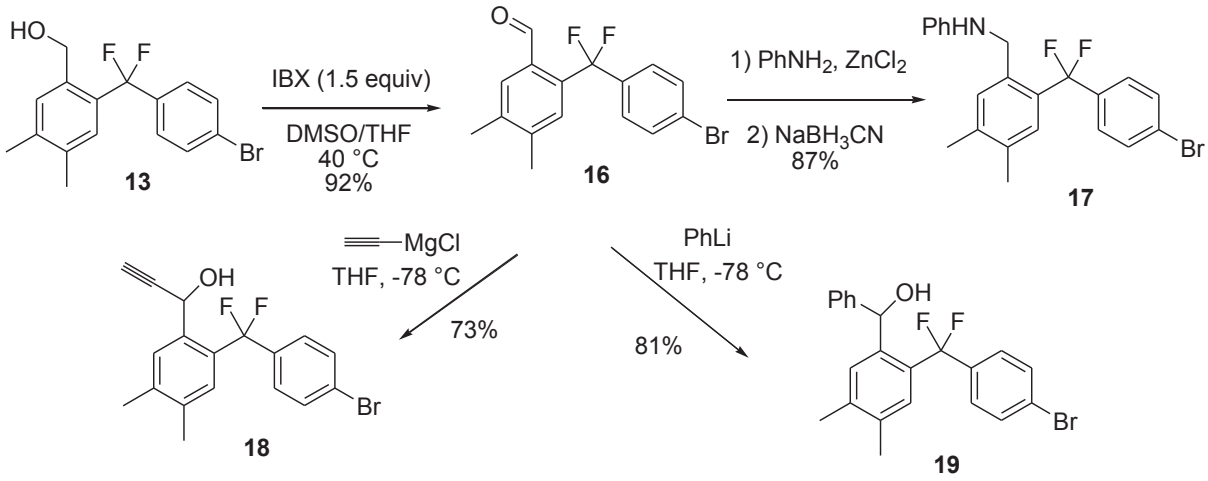
Après avoir utilisé le brome, il était intéressant de montrer aussi la possibilité d'utiliser la fonction ester pour augmenter la diversité moléculaire autour de ce squelette. Dans une première étape, on a réussi à réduire l'ester puis obtenir l'acide correspondant et de préparer un amide modèle (Schéma 13).

Schéma 13. Réduction de l'ester puis oxydation en acide et synthèse d'un amide.



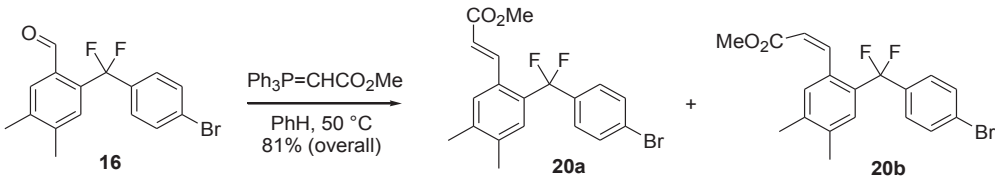
Ensuite cet alcool **13** a été oxydé en aldéhyde **16**, qui a lui-même été employé pour préparer l'amine **17** puis les alcools **18** et **19** (Schéma 14).

Schéma 14. Oxydation en aldéhyde puis utilisations de **16**



Enfin, un exemple de réaction de Wittig a aussi été réalisé conduisant au mélange 8/1 des alcènes **20a** et **20b** qui ont été séparés par chromatographie et caractérisés (Schéma 17).

Schéma 17. Réaction de Wittig à partir de l'aldehyde **16**.

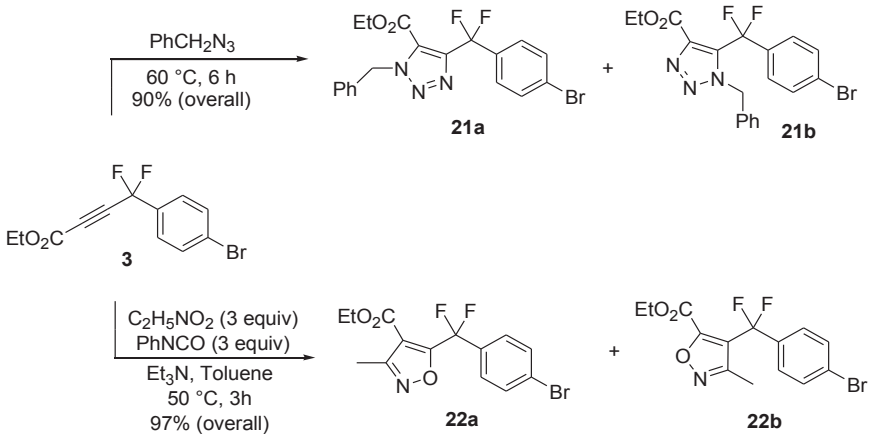


e) Synthèse de composés mixtes aryliques/hétéroaryliques à connecteur *gem*-difluoré.

Après avoir démontré l'utilisation des intermédiaires fluorés propargyliques pour la synthèse de motifs de type benzophénones, il restait à montrer leur emploi pour la synthèse de composés mixtes aryliques/hétéroaromatiques. Pour celà, nous avons employé deux exemples de réaction de cycloaddition dipolaire 1,3. Dans le premier, la réaction du benzylazide a conduit aux triazoles **21a** et **21b**. Dans le second, une

réaction d'un oxyde de nitrile a permis d'obtenir les isoxazoles **22a** et **22b** (Schéma 18). Dans les deux cas, la régiosélectivité de la cycloaddition a été démontrée par une analyse détaillée des données de RMN

Schéma 18. Synthèse de dérivés mixtes aromatique-hétéroaromatique *gem*-difluorés **21** et **22**.



En conclusion, cette nouvelle stratégie parait extrêmement prometteuse pour la synthèse d'une grande variété de composés aromatique/aromatique ou aromatique/hétéroaromatique avec un motif CF_2 comme connecteur.

Chapitre 4 Développement de l'organocatalyse asymétrique sur des énals portant un motif CF_2R en position allylique

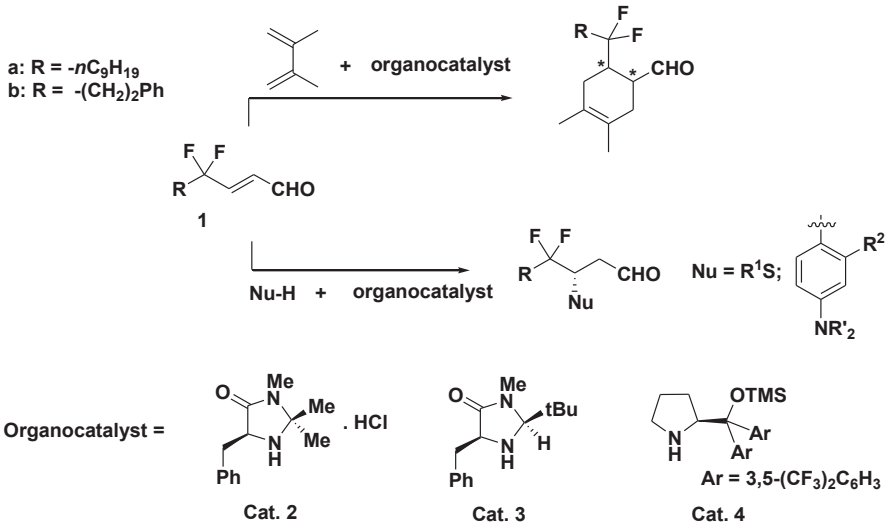
1 Introduction

La nécessité d'utiliser des composés optiquement purs, notamment dans le domaine du médicament, a été un moteur essentiel dans le développent de la catalyse asymétrique en général et plus récemment de l'organocatalyse. Ceci s'applique aussi naturellement dans le domaine de la chimie des composés fluorés. Dans ce chapitre 4 nous avons d'abord résumé les données essentielles sur l'organocatalyse et rappelé les résultats, encore relativement limités, décrits dans la littérature pour l'obtention de composés fluorés via cette stratégie.

II- Objectifs de notre recherche

Ceux-ci sont résumés dans le Schéma 13: après une sélection du, (ou des), catalyseur(s) les plus appropriés, et optimisation des conditions de réaction, nous souhaitons réaliser en partant des *gem*-difluoroenals **1** des cycloadditions de Diels-Alder énantioselectives ainsi que des additions conjugées 1,4 de thiols ou d'anilines.

Schéma 13. Nos objectifs de recherche: cycloaddition de Diels-Alder et additions conjugées 1,4 asymétriques sur les *gem*-difluoroenals **1**.

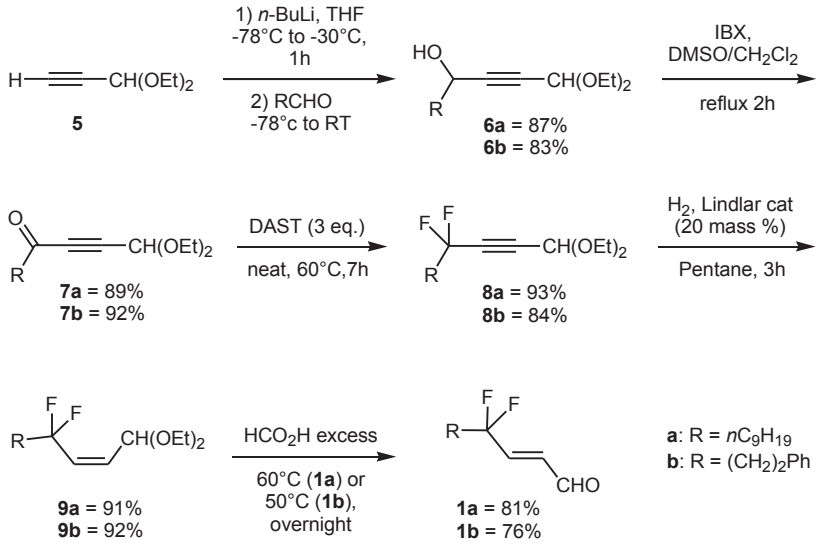


III- Résultats et discussion

III-1) Synthèse des *gem*-difluoroenals 1

Ces composés ont été préparés avec de bons rendements, comme indiqué dans le Schéma 14.

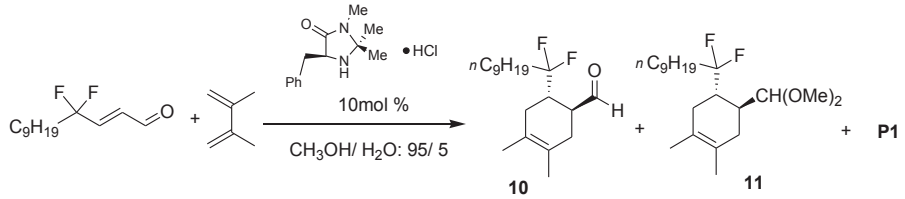
Schéma 14. Synthèse des *gem*-difluoroenals **1a** et **1b.**



III-2) Cycloadditions de Diels-Alder

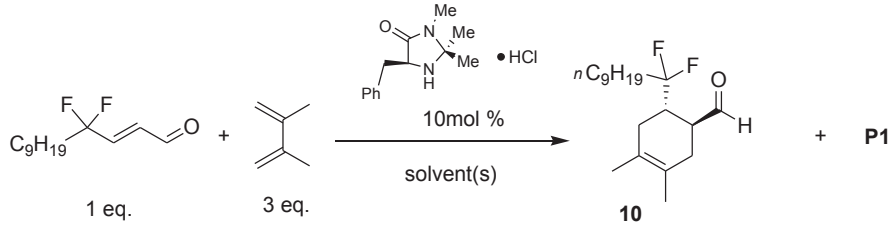
Pour cette étude, **1a** a été choisi comme modèle. L'adduit racémique qui sert de référence a été obtenu avec un rendement de 85% par chauffage de **1a** avec un excès de dimétylbutadiène. Pour ce qui est de l'organocatalyse asymétrique, les résultats se sont avérés plutôt décevants. Avec le catalyseur de Mac Millan et dans un mélange méthanol-eau le produit recherché **10** est obtenu en mélange avec l'acétal **11** et un produit secondaire P1 (Schéma 16).

Schéma 16. Cycloaddition de Diels-Alder organocatalysée dans un mélange methanol/eau.



En utilisant d'autres solvants (acétonitrile notamment) on empêche l'acétalisation mais on a toujours la formation du produit secondaire P1 (Tableau 2). Dans le meilleur des cas on obtient l'adduit recherché avec un ee modeste (76%) et en mélange avec le produit secondaire.

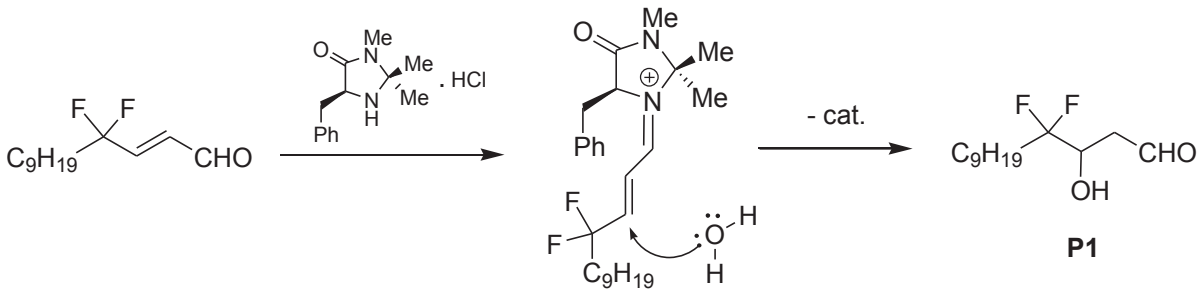
Tableau 2. Essais de cycloadditions de Diels-Alder asymétriques organocatalysées.



Entry	H_2O	Solvent	Temp./time	Conv. (%)	Adduct/side product	ee (%)
1	-	CH_3CN/H_2O:95/5	30 °C/60h	80	1/1	76
2	-	CH_3CN/H_2O:95/5	0 °C/40h	90	0/1	nd
3	0.1eq.	DMF	0 °C/40h	53	0/1	nd
4	0.1eq	CH_3CN	0 °C/40h	30	1/3	nd

Des études complémentaires ont été réalisées, nous conduisant à proposer que **P1** soit simplement le produit d'addition de l'eau sur l'iminium dérivé de notre énal **1a**, espèce qui est certainement très électrophile (Schéma 17) ;

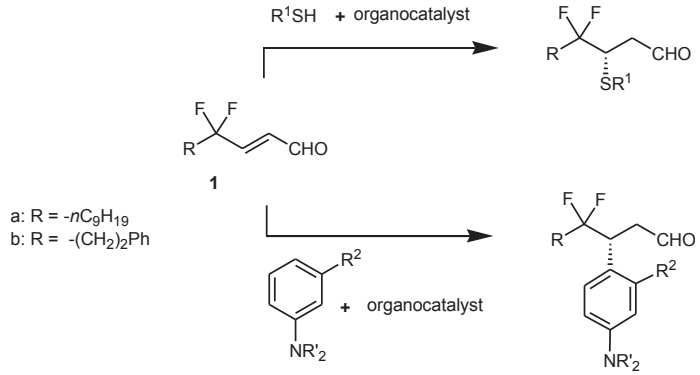
Schéma 17. Addition d'eau sur l'intermédiaire iminium et structure proposée pour **P1**.



III-3) Réactions asymétriques organocatalysées d'addition 1,4 sur les énals 1

Dans cette partie, deux types d'additions 1,4 ont été étudiées: a) l'addition conjuguée de thiols (sulfa-Michael SMA); b) l'addition conjuguée d'anilines, comme indiqué dans le Schéma 18.

Schéma 18. Additions 1,4 asymétriques et organocatalysées sur les *gem*-difluoroénals **1a** et **1b**.



III-3.1) Sélection du catalyseur et optimisation des conditions de réaction

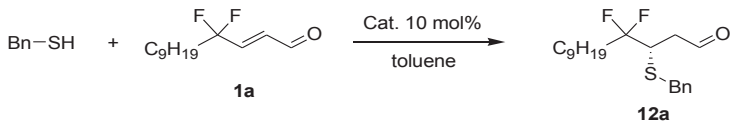
Pour développer l'utilisation de ces énals, il a fallu d'abord choisir le meilleur catalyseur et définir de bonnes conditions de réaction. Ceci a nécessité un travail important dont l'essentiel est résumé dans le tableau 4. Cette étude a montré :

a. que les catalyseurs de Mac Millan (imidazolidinones **2** et **3**) n'étaient pas appropriés pour cette réaction,

b. que, par contre, le catalyseur de Jørgensen (diarylprolinol **4**) était particulièrement performant puisqu'il peut conduire à des ee's allant jusqu'à 98%,

c. que les conditions optimisées impliquaient l'addition d'eau et d'acide benzoique à hauteur de 10% molaire chacun.

Tableau 4. Addition asymétrique 1,4 organocatalysée du benzylthiol sur **1a** avec les catalyseurs **2, 3** et **4**.

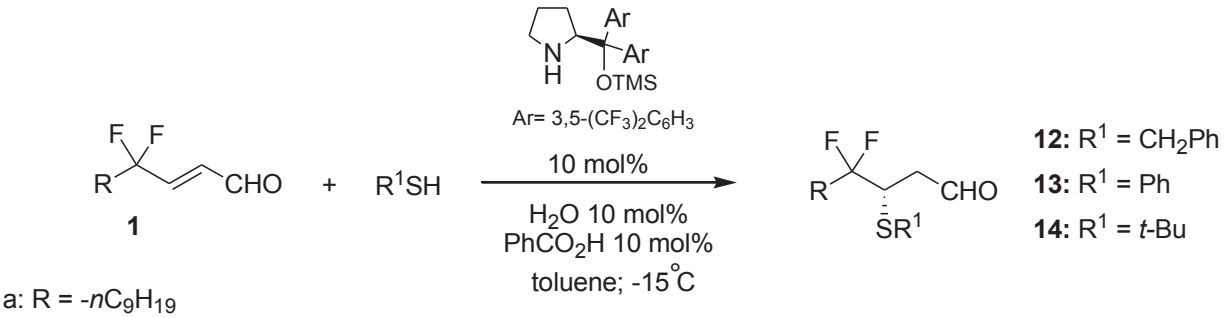


Entry	Cat	H_2O	Temp [a]	Time (hr)	**12a** conv. (%)	**12a** ee (%)[c]
1	**2**	-	R. T.	24	87	20
2	**2**	0.1eq	R. T.	24	92	26
3	**2**	0.1eq	-15°C	46	<5	nd
4	**2**	0.1eq	0°C	44	71	14
5	-	0.1eq	0°C	44	46	0
6[b]	**3**	-	-15°C	48	49	16
7[b]	**3**	0.1eq	-15°C	24	47	26
8	-	0.1eq	-15°C	46	0/0	-
9	**4**	-	-15°C	16	40	35
10[b]	**4**	-	-15°C	16	100	96
11[b]	**4**	0.1	-15°C	16	100	98

III-3.2. Additions organocatalysées (SMA) de différents thiols sur 1a and 1b

Après avoir défini ces paramètres essentiels, l'addition conjuguée a été étendue à d'autres thiols, comme résumé dans le tableau 5.

Tableau 5. Addition de différents thiols sur les énals **1.**



Entry	Enal	R^1	Time (h)	**No**/Conv./yield (%)	ee (%)
1	**1a**	CH_2Ph	16	**12a**/100/98	98
2	**1a**	Ph	21	**13a**/92/88	95
3	**1a**	*t*-Bu	40	**14a**/76/71	94
4	**1b**	CH_2Ph	16	**12b**/100/94	96

III-3.3) Addition 1,4 organocatalysée d'anilines sur les énals 1a and 1b

Après l'addition des thiols, nous nous sommes tournés vers la réaction d'anilines (schéma 20)

Schéma 20. Addition de différentes anilines aux énals **1**.

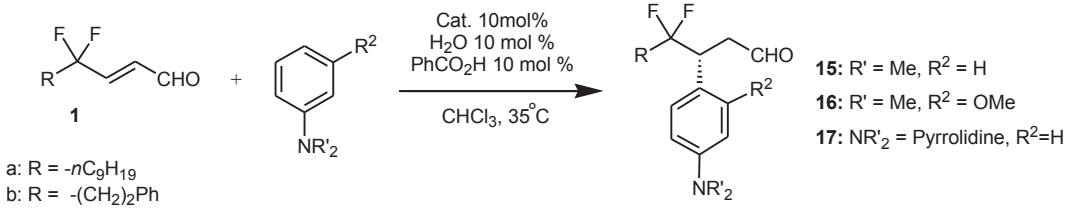


Tableau 6. Addition 1,4 asymétrique organocatalysée d'anilines sur les énals **1a** and **1b**.

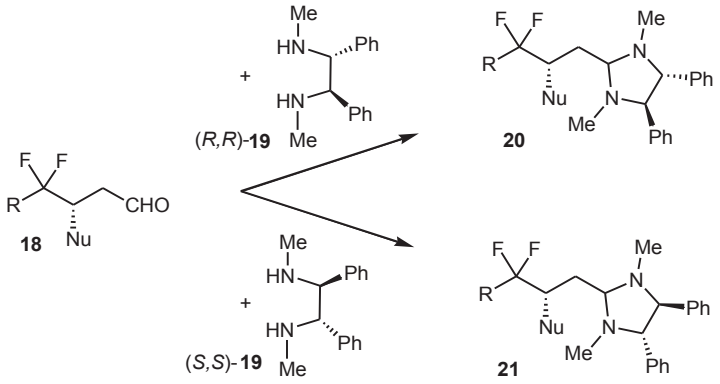
Entry	Cat	Enal	R'	R^2	Time (h)	**No**/Conv/yield (%)	ee (%)[c]
1	**-**	**1a**	Me	H	48	**15a**/0/-	-
2[b,d]	**2**	**1a**	Me	H	26	**15a**/90/nd	42
3	**3**	**1a**	Me	H	48	**15a**/38/nd	98
4[b]	**4**	**1a**	Me	H	48	**15a**/58/nd	94
5	**4**	1a	Me	H	48	**15a**/82/77	98
6	**4**	1a	Me	OMe	24	**16a**/95/87	98
7	**4**	1a	[a]	H	51	**17a**/53/40	87
8	**4**	1b	Me	OMe	24	**16b**/88/84	98

Les principaux résultats sont résumés dans le Tableau 6 : là encore le catalyseur de Jørgensen (4) s'est révélé le plus performant permettant d'obtenir les adduits recherchés avec des ee's allant jusqu'à 98%.

III-4) Méthode de détermination des excès énantiomériques

Un point important à noter concerne la méthode que nous avons utilisée pour établir les excès énantiomériques dans nos réactions. Elle est résumée dans le Schéma 24.

Schéma 24. Méthode RMN utilisée pour mesurer les ee's sur les adduits 1,4.



La condensation d'un aldéhyde énantiopur **18** avec une diamine chirale pure telle que (*R,R*)-**19** donne uniquement le composé **20**. La même réaction réalisée avec le mélange racémique de (*R,R*)-**19** et (*S,S*)-**19** va donner un mélange 1:1 de **20** et **21** qui auront des signaux bien séparés en RMN, notamment ^{19}F. Donc en partant des produits bruts de réaction, les condensations avec la diamine racémique vont donner le mélange des deux imidazolidines facilement caractérisés en RMN. La condensation avec la diamine énantiopure va donner les diastéréoisomères dans un ratio (de) qui va se transférer directement dans le ee de l'aldéhyde de départ. Outre sa grande simplicité, un avantage majeur de cette méthode est qu'elle est réalisée directement sur le produit brut de réaction, sans aucune étape de purification (ou de transformation chimique) susceptible de fausser les résultats.

III-5) Rôle des atomes de fluor dans les additions 1,4 asymétriques organocatalysées

Un dernier point intéressant à étudier concernait le rôle éventuel des atomes de fluor sur ces réactions d'additions 1,4 asymétriques organocatalysées. Pour ça, nous avons comparé les réactions des énals fluorés et non fluorés (Schéma 25 et Tableau 8).

Schéma 25. Réactivité comparée entre le *gem*-difluoroenal **1a** et son analogue hydrogéné **1aH** dans des additions 1,4 asymétriques organocatalysées représentatives.

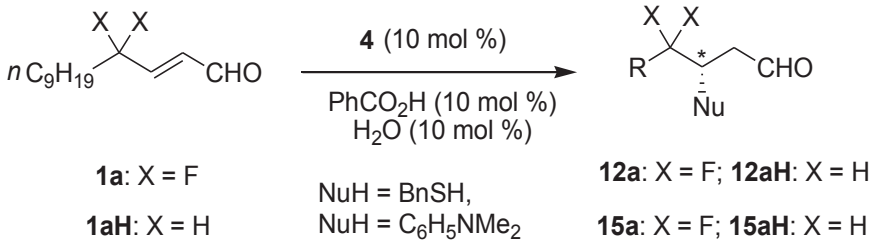


Tableau 8. Comparaison d'additions 1,4 asymétriques organocatalysées sur le *gem*-difluoro enal **1a** et son analogue non-fluoré **1aH**.

Entry	enal	NuH	Time (h)	No/Conv./yield (%)	ee[c] (%
1[a]	**1a**	BnSH	16	**12a**/100/98	98
2[a]	**1aH**	BnSH	16	**12aH**/44/40	82
3[b]	**1a**	$C_6H_5NMe_2$	48	**15a**/82/78	98
4[b]	**1aH**	$C_6H_5NMe_2$	48	**15aH**/0/0	Nd

Ces résultats montrent très bien que les deux atomes de fluor augmentent la réactivité des énals et permettent également d'obtenir de meilleurs ee's. Ces résultats peuvent s'expliquer sur la base du mécanisme couramment employé pour ces organocatalyses asymétriques.

En conclusion, nous avons démontré pour la première fois la possibilité de réaliser des additions 1,4 organocatalysées sur des énals portant une chaine CF_2R. Compte tenu du grand nombre de réactions d'organocatalyse envisageables et de la variété de composés organofluorés chiraux accessibles par ces approches, nous pensons qu'elles seront d'un apport intéressant en chimie du fluor.

Ce travail a donné lieu à trois publications, parues ou sous presse:

- A. Khalaf, D. Grée, H. Abdallah, N. Jaber, A. Hachem, R. Grée - New flexible strategy for the synthesis of gem-difluoro-bisarylic derivatives and heterocyclic analogues.
Tetrahedron, **2011**, *67*, 3881-3886.

- Taghreed Hirz, Ali Khalaf , Nehme El-Hachem, Hassan Abdallah, Christophe Créminon, René Grée, Aïda Habib, Ali Hachem and Eva Hamade - New analogues of 13-hydroxy-octadecadienoic acid and 12-hydroxyeicosatetraenoic block thromboxane-dependent aggregation of human blood platelets.
Chemistry Central Journal, **2012**, 6, 152, doi:10.1186/1752-153X-6-152

- Ali Khalaf, Danielle Grée, Hassan Abdallah, Nada Jaber, Ali Hachem and René Grée - Asymmetric Organocatalytic 1,4-Addition Reactions Starting from Enals with *gem*-difluoroalkyl Side Chains
Eur. J. Org. Chem., **2013**, sous presse DOI: 10.1002/ejoc.201201427.

GENERAL INTRODUCTION

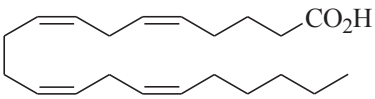
General introduction

The research work performed during this PhD thesis covers two different aspects: the first is dealing with medicinal chemistry and it is related to the search for simple and efficient compounds active as inhibitors of the COX-1 enzyme. The second is related to new developments in synthetic methodologies to be used in fluorine chemistry.

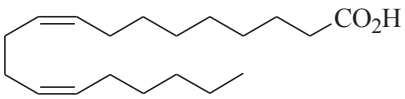
Part I Medicinal chemistry.

Mechanisms of inflammation and platelets aggregation are highly depending on metabolites of Arachidonic acid (AA) and Linoleic acid (LA) (Figure 1).

Figure 1. Arachidonic and linoleic acids.



Arachidonic acid (AA)

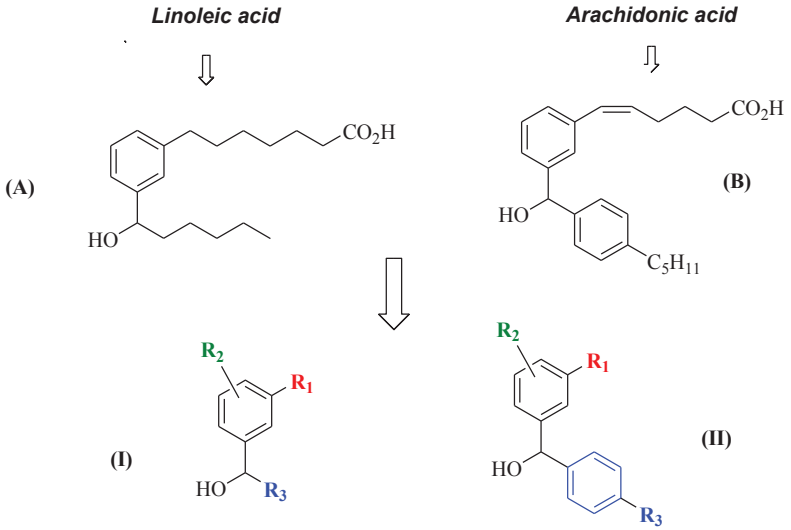


Acide Linoleic (AL)

Following the general principles of medicinal chemistry, large number of analogues designed starting from such metabolites were prepared and reported in literature. For example, more rigid and stable analogues (A) and (B) of 12-HETE and 13-HODE were obtained after stabilization of these metabolites by aromatization.

Starting from these two molecules, by simplification and then insertion of new functional groups on benzene ring(s), we have designed a series of new type-(I) and type-(II) compounds (Figure 2). In chapter I we will describe the preparation of these molecules.

Figure 2. Simplified analogues of A and B.



Extensive biological studies of these compounds have been performed at the American University of Beirut. They are also reported in Chapter 1. They show that five of our analogues are endowed with significant anti-platelet aggregation and anti-COX-1 activity. Moreover, type (II) compounds have more interesting biological activity. We hope that these results will be of much use in the design and preparation of new simple and efficient COX-1 inhibitors.

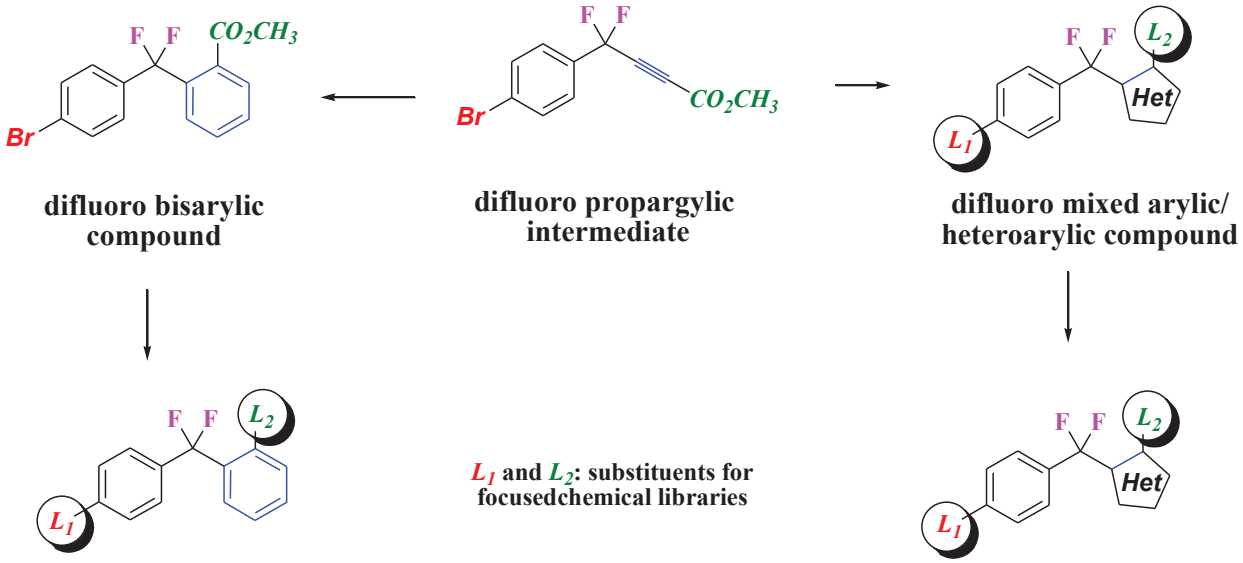
Part II Fluorine Chemistry

On the other hand, it is well known that introduction of fluorine atom(s) in organic molecules strongly modifies their physical, chemical and biological properties. This explains why fluorinated compounds are extensively studied and used in different areas such as: pharmaceuticals, agrochemicals and polymers, to name a few.

Based on this, in chapter III, we became interested in a novel methodology towards the synthesis of *gem*-difluoro bisarylic compounds, by using as key intermediates the easily accessible *gem*-difluoro propargylic derivatives (Scheme 1). This new approach will also allow the preparation

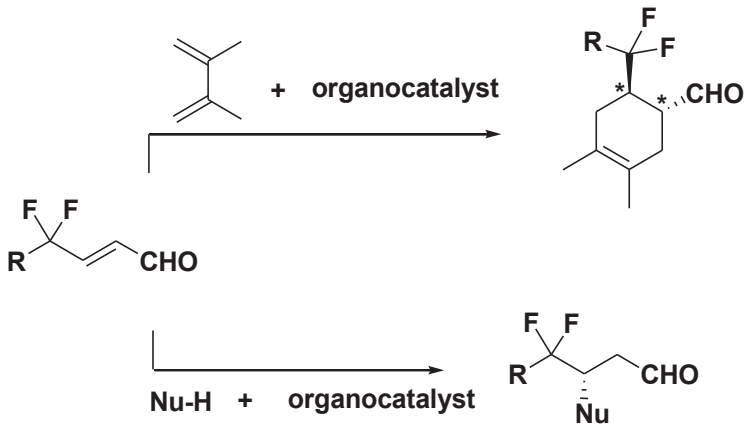
of mixed aryl/heteroaryl systems with CF_2 as a linker. Finally, this strategy will allow us to prepare focused chemical libraries around such skeletons.

Scheme 1. A new strategy for the synthesis of *gem*-difluoro-bisarylic compounds.



Finally, taking into account the importance of *gem*-difluoro molecules and optically active compounds in medicinal chemistry, in chapter IV, we studied the asymmetric organocatalytic Diels-Alder cycloaddition and 1,4-conjugated additions to *gem*-difluoro enals (Scheme 2).

Scheme 2. Asymmetric organocatalytic additions to *gem*-difluoro enals.



Asymmetric Diels-Alder reactions have not been very successful. On the contrary, after appropriate selection of the organocatalyst and optimization of the reaction conditions, we have demonstrated that 1,4 additions of thiols and anilines can be performed in good yields with excellent ee's.

We hope that these new methodologies will be helpful in the design and the preparation of new fluorinated intermediates to be of much use, especially in bioorganic and medicinal chemistry.

CHAPTER I

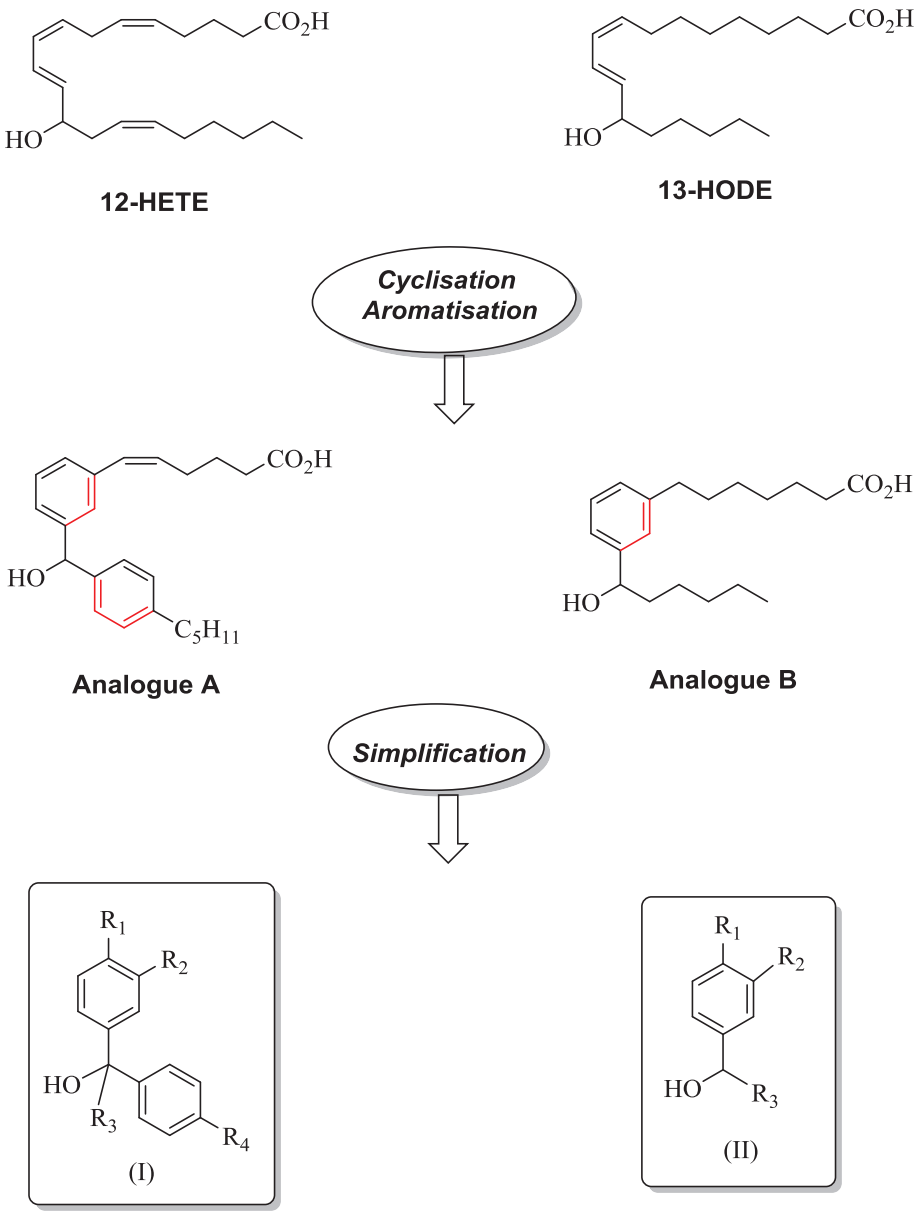
SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW COMPOUNDS WITH ANTI PLATELETS AGGREGATION ACTIVITY

I- Introduction:

12-hydroxy-5*Z*,8*Z*,10*E*,14*Z*-eicosatetraenoic acid (12-HETE) and 13-hydroxy-9*Z*,11*E*-octadecadienoic acid (13-HODE) are biologically active compounds derived from the metabolism of arachidonic acid and linoleic acid through the action of 12-lipoxygenase and 15-lipoxygenase, respectively. These metabolites were shown to have anti-platelet effects mainly through inhibition of collagen and thromboxane-dependent aggregation for 12-HETE,[1,2] 13-hydroperoxy-9Z,11*E*-octadecadienoic acid (13-HPODE)[3] and 13-HODE.[4] This later metabolite was also shown to decrease the adherence of platelets to endothelial cells.[5]

The mechanisms by which these anti-platelet molecules affect platelet activation and aggregation involve inhibition of thromboxane synthesis or blocking of its receptors, ADP, thrombin and collagen receptors as well as blocking of glycoprotein-dependent binding of extracellular matrix and fibrinogen.[6, 7] Thromboxane (TX) A2 is formed in blood platelets from arachidonic acid through the action of cyclooxygenase-1 (COX-1) and TX synthase. It acts on G-protein coupled receptors triggering platelet activation and aggregation.[8] COXs are membrane proteins that form homodimers.[9] X-Ray structure revealed a membrane protein with an active site in the interior globular part of the protein and a long non-polar channel as binding site for arachidonic acid and non-steroidal anti-inflammatory drugs (NSAIDS).[10, 11] Arachidonic acid and acidic NSAIDS were shown to interact with Arg 120 and Tyr 355 of the active site, where hydrogen bonds are involved in the interaction with the hydroxyl of Tyr 355 and carboxylate interaction with the amino residue of Arg 120.[12,13] It has been reported previously by A. Hachem et al. that stabilized analogues of 12-HETE (analogue A) and 13-HODE (analogue B), have inhibitory effects on thromboxane–dependent platelet aggregation.[14a] Starting from these analogues, we have designed two types of new compounds (I) and (II) (Scheme 1). These derivatives have been prepared and their effects on aggregation of human blood platelet in response to arachidonic acid or collagen and on cyclooxygenase-1 activity in cells overexpressing the recombinant human COX-1 have been tested.

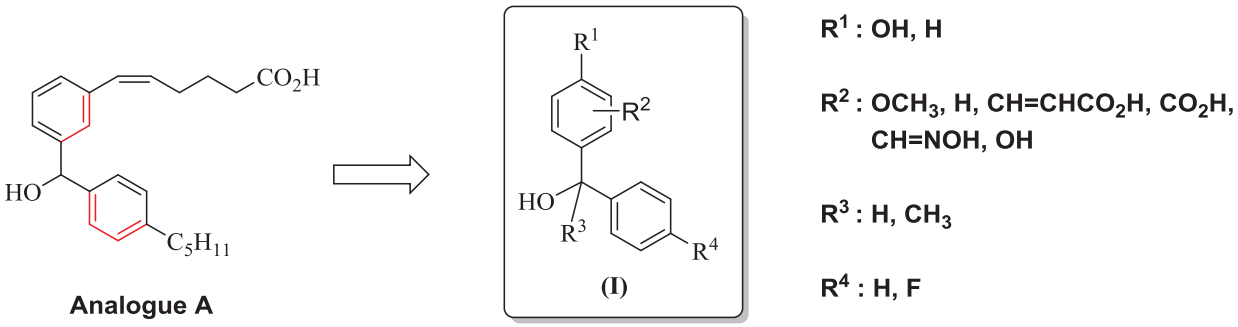
Scheme 1. Simplified analogues of 12-HETE and 13-HODE.



II- Synthesis of type (I)

Starting from analogue A, several molecules of type (I) were prepared (Scheme 2).

Scheme 2. General structure of type (I) molecules

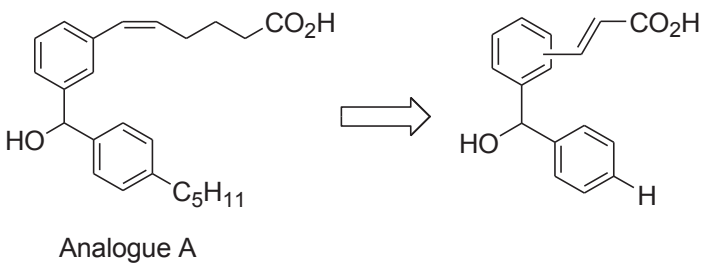


The preparation of this type of compounds involved classical Grignard additions, convenient functionalizations and palladium catalyzed coupling reactions.

1) Synthesis of carboxylic acid analogues of A type

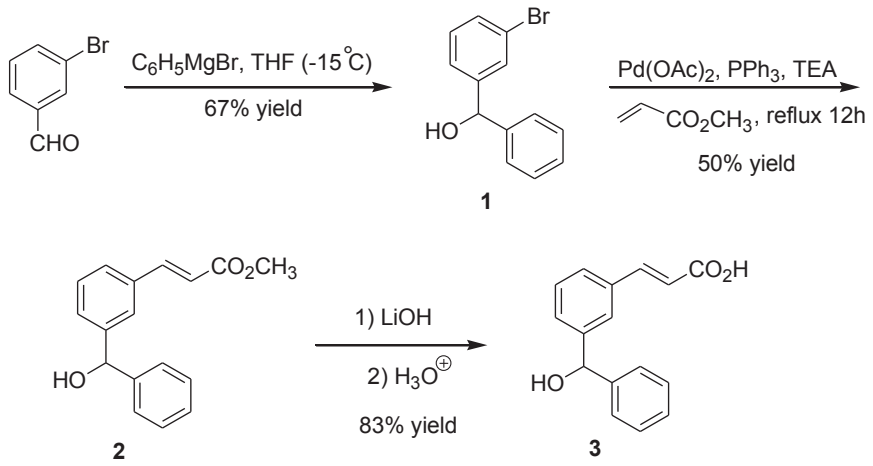
Starting from basic structure A, several carboxylic acids were prepared. The first two compounds were prepared by shortening the lipophilic chain and preserving this functional group. Moreover, the *n*-C_5H_{11} alkyl group was replaced by a hydrogen atom (Scheme 3).

Scheme 3. General structure of prepared acids **3** and **6**.



The synthesis of *meta*-substituted compound **3** is summarized in scheme 4.

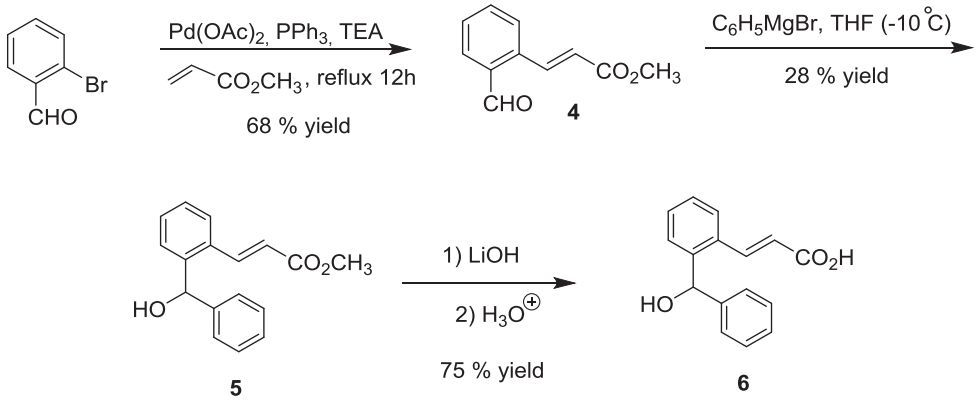
Scheme 4. Synthesis of *meta*-carboxylic acid **3**.



Addition of phenyl magnesium bromide to 3-bromobenzaldehyde afforded the bisarylic alcohol **1** in 67% yield. By Heck reaction[15] with methyl acrylate, the ester **2** was obtained in 50% yield. Saponification of **2**, followed by acidification led to the formation of the target acid **3** in 83 % yield.

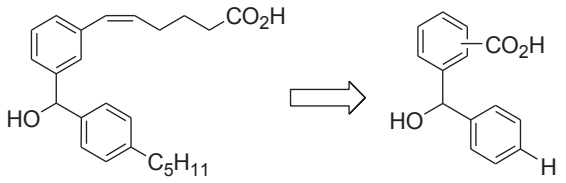
In order to check the importance of the of carbon chain bearing the carboxyl group, compound **6** was synthesized, where the chain of the carboxyl group was at *ortho* position. Starting from *o*-bromobenzaldehyde, by Heck reaction,[15] intermediate **4** was obtained in 68 % yield. Addition of phenyl magnesium bromide to **4** yielded alcohol **5** in 28 % yield. Saponification of **5** using LiOH afforded the *ortho*-substituted acid **6** in 75 % yield (Scheme 5).

Scheme 5. Synthesis of *ortho*-substituted carboxylic acid **6.**



Three other acid analogues were prepared based on structure A, where the carboxyl group is directly attached to the phenyl group. Also the *n*-C_5H_{11} alkyl group was replaced by hydrogen or fluorine atom (Scheme 6).

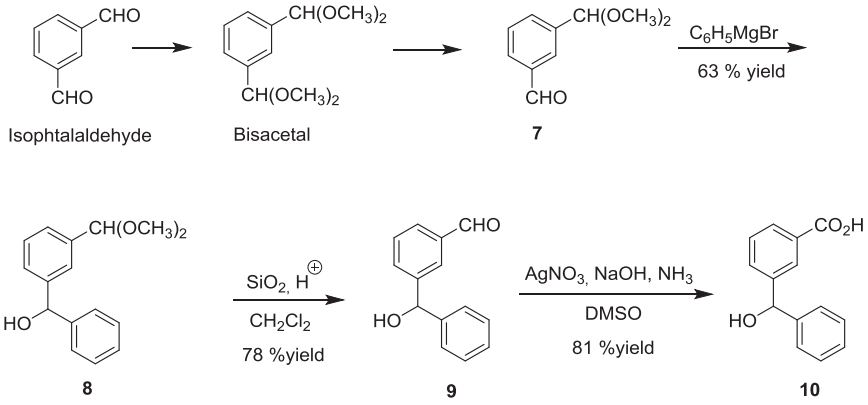
Scheme 6. General structure of acids **10** and **15**.



Analogue A

The synthesis of the *meta*-acid is summarized in scheme 7. The commercially available isophtalaldehyde is the precursor of this acid. Based on literature,[14b] the differentiation between the two aldehyde groups can't be achieved directly, but through corresponding bisacetal (Scheme 7).

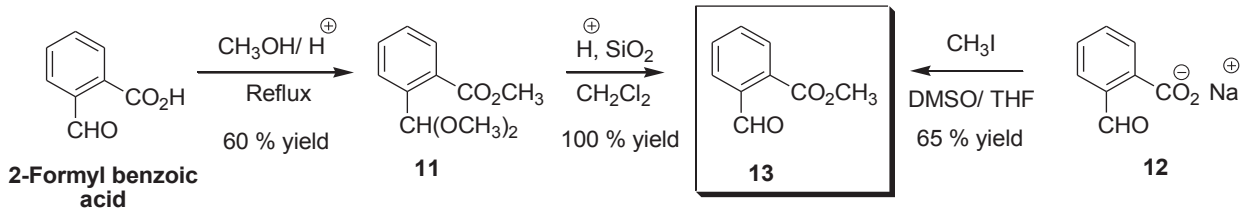
Scheme 7. Synthesis of *meta*-carboxylic acid **10.**



Addition of phenyl magnesium bromide to the mono-aldehyde **7** led to alcohol **8** in 63 % yield. Deacetalization of **8**, followed by oxidation afforded the target **10**.

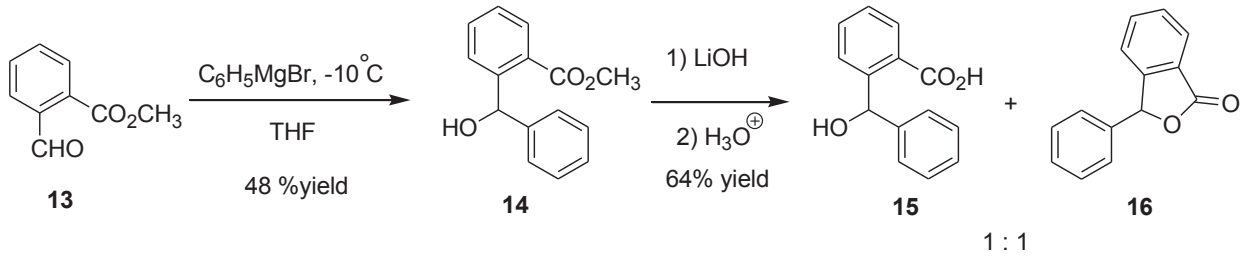
In order to study the effect of the position of carboxyl group, *ortho*-carboxylic acid **15** was also prepared. The first step in this synthesis was the preparation of ester aldehyde **13** starting from the commercially available 2-formylbenzoic acid. Compound **13** was prepared, in two different ways, as shown in scheme 8.

Scheme 8. Preparation of the ester aldehyde intermediate **13.**



Addition of phenyl magnesium bromide to previous aldehyde **13** gave alcohol **14**, which by saponification of ester followed by acidification, afforded our *ortho*-substituted acid **15** (Scheme 9).

Scheme 9. Synthesis of the *ortho*-substituted acid **15.**

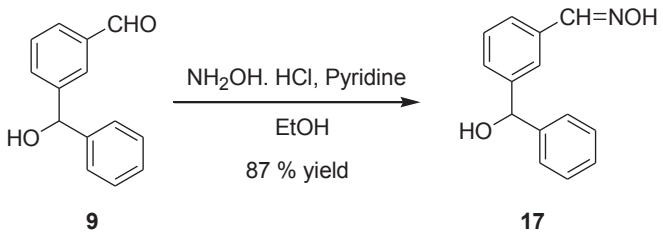


In addition to the adduct **15,** lactone **16** was observed as a side product.

2) Preparation of oxime 17.

Oximes are often found in bioactive molecules.[16] Based on that and following the same previous principles, oxime **17** was obtained in good yield by reaction of the previous aldehyde **9** with $NH_2OH.HCl$ (Scheme 10)**.**

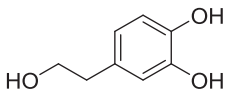
Scheme 10. Synthesis of oxime **17**.



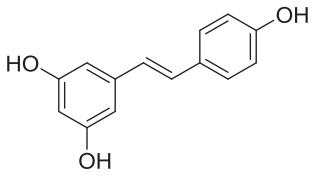
3) **Preparation of phenolic analogues**

Numerous studies show that phenolic compounds (natural and synthetic) are endowed with significant anti-platelet aggregation activity.[17] 2-(3,4-dihydroxyphenyl)ethanol (DHPE) in olive oil has been the subject of several studies and is known as a platelet aggregation inhibitor.[18]

Moreover, resveratrol which is present in red wine, and its synthetic analogues, have also been reported and their biological activities were evaluated.[19]



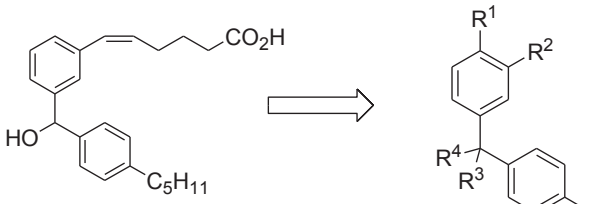
DHPE



Resveratrol

By analogy, and based on all above, several phenolic analogues were prepared (Table 1)

Table 1. Phenolic analogues of A.

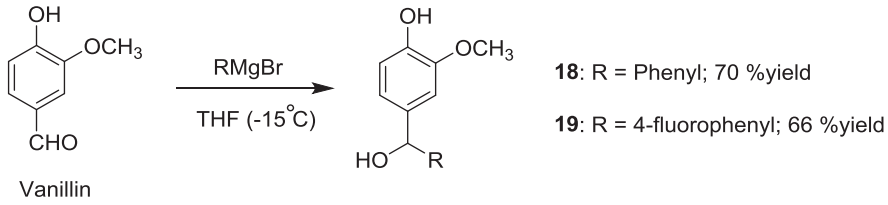


Analogue A

Compound	R_1	R_2	R_3	R_4	X
18	OH	OCH_3	OH	H	H
19	OH	OCH_3	OH	H	F
20	OH	OCH_3	OH	CH_3	H
21	OH	OCH_3	-	CH_2	H
22	H	OH	OH	H	H

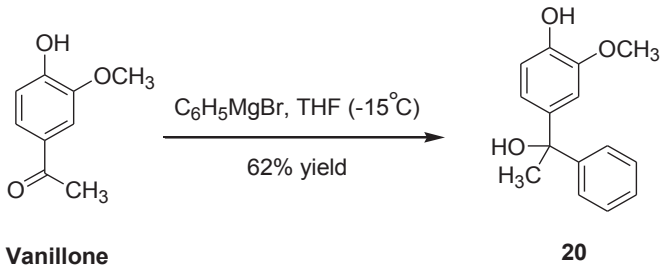
The 4-(hydroxylphenylmethyl)-2-methoxyphenol **18** and its fluorinated analogue **19** were prepared by addition of the appropriate Grignard reagent to vanillin as shown in Scheme 11.

Scheme 11. Preparation of phenol **18** and its fluorinated analogue **19.**



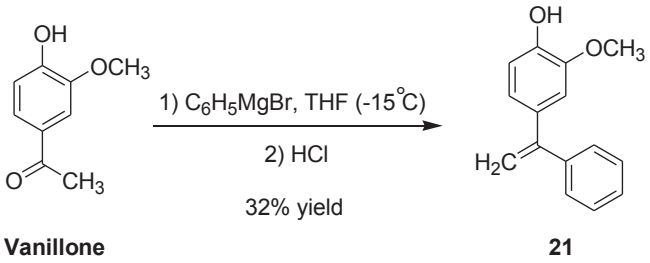
In order to study the influence of introduction of a methyl group on the lipophilic part, compound **20** was prepared directly by addition of PhMgBr to vanillone (Scheme 12).

Scheme 12. Preparation of phenol **20**.



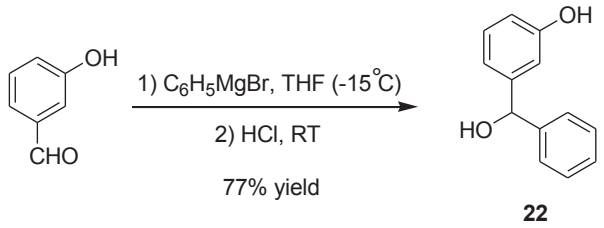
Next step was to study the role of benzylic OH in the activity in this molecule. Compound **21** was designed by replacing the CH(Me)OH group of **18** with a methylene goup. This compound was prepared by addition of phenyl magnesium bromide to vanillin, followed by hydrolysis with diluted HCl solution (Scheme 13).

Scheme 13. Preparation of compound **21**.



Following the same way, addition of phenyl magnesium bromide to the commercially available *meta*-hydroxybenzaldehyde led to the formation of phenol **22** in 77% yield. Comparing **22** with acid **10** give us the opportunity to study the effect of carboxyl group on biological activity (Scheme 14).

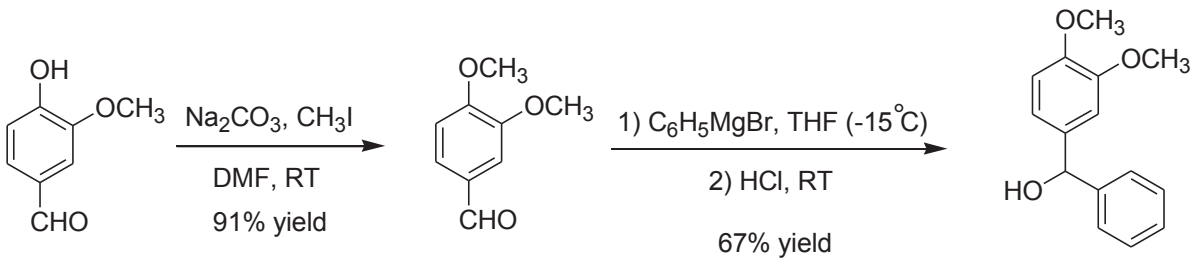
Scheme 14. Preparation of phenol **22**.



22

To continue our structure-activity relationship study, it seemed interesting to study the effect of phenolic OH. To achieve this goal compound **24** was prepared, in two steps, where the phenolic OH of **22** is replaced by a methoxy group. The synthesis of **24** is summarized in scheme15.

Scheme 15. Synthesis of protected phenol **24.**

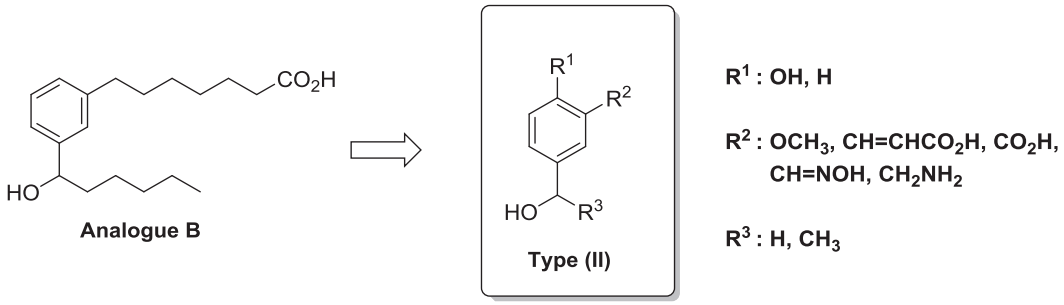


23 **24**

III- Synthesis of type (II) compounds

Based on the same principles mentioned before, several molecules of type (II) were prepared (Scheme 16).

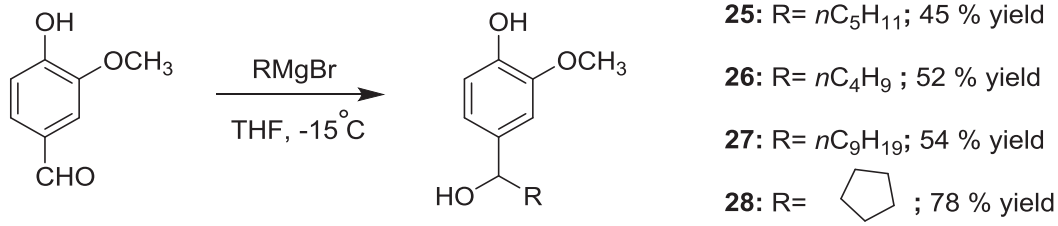
Scheme 16. General structure of type (II) compound.



As in preparation of type (I), the synthesis of these molecules involved: Grignard additions, appropriate functionalization reactions, as well as palladium catalyzed coupling reactions.

The first series of molecules of this type was prepared in order to study the influence of the lipophilic chain (R^3) on their activity. Four different compounds were prepared by addition of the appropriate alkyl magnesium bromide to vanillin, as shown in Scheme 17.

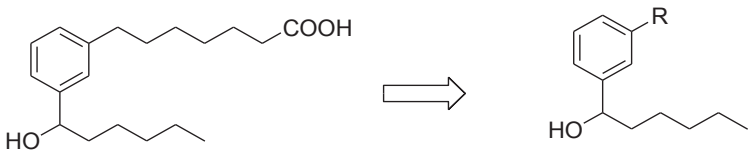
Scheme 17. Preparation of first series of type (II) compounds.



The relatively low yields obtained for compounds **25, 26** and **27** are due to the competitive reduction of the aldehyde by the Grignard reagent.

Further, a second series of type (II) compound was prepared based on the same principles as mentioned before (table 2).

Table 2. Second series of type (II) compounds.

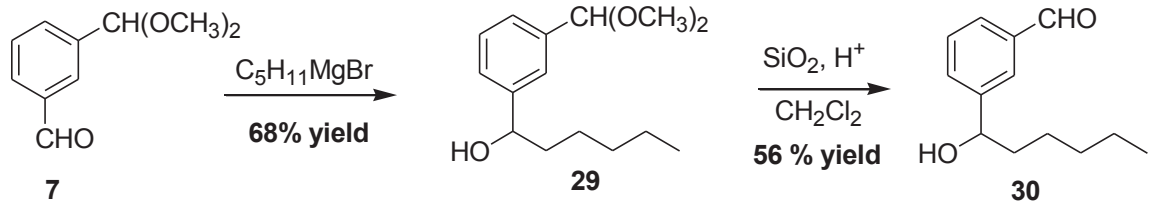


Analogue B

Compound	R
31	COOH
32	CH_2OH
33	CH=N-OH
34	CH_2-NH_2
37	*(E)* CH=CH-CO_2H

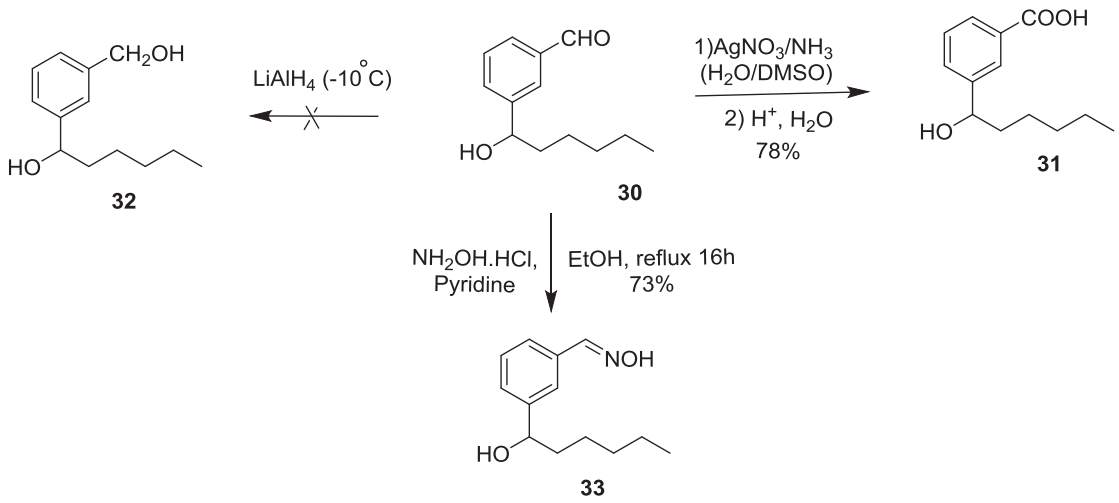
Compounds **30**, **31** and **32** were prepared starting from the same intermediate aldehyde **30**, which was prepared by Grignard addition to the aldehyde-acetal **7**, followed by deacetalization as shown in scheme 18.

Scheme 18. Synthesis of aldehyde intermediate **30.**



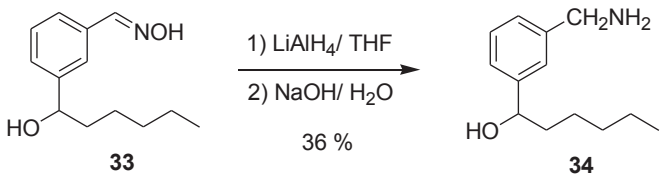
Starting from aldehyde **30**, oxidation using ammoniacal silver nitrate afforded acid **31** in 78% yield. On the other hand, $LiAlH_4$ reduction at -15 °C led to destruction of **30**. However, condensation with hydroxylamine, gave oxime **33** in 73 % yield (Scheme 19).

Scheme 19. Functionalization of aldehyde **30.**



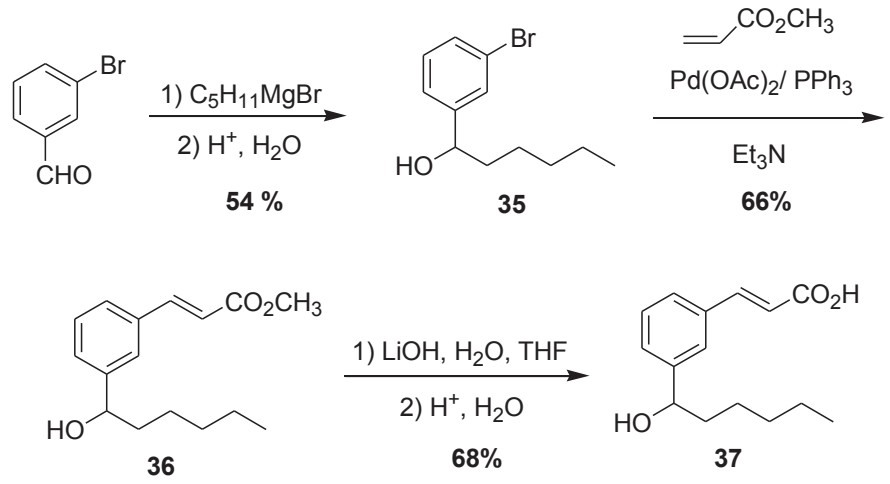
Amine **34** was obtained in low yield (36%) after reduction of oxime **33** using $LiAlH_4$ as shown in scheme 20.

Scheme 20. Reduction of oxime **33.**



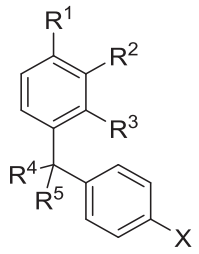
Compound **37** was prepared starting from the precursor *meta*bromobenzaldehyde. Addition of pentyl magnesium bromide gave alcohol **35** in 54% yield. Coupling of **35** with methyl acrylate led to the formation of ester **36** in 66% yield. Saponification of **36** afforded the acid target **37** in 68% yield (Scheme 21).

Scheme 21. Synthesis of acid **37.**



As a result, and based on analogues A and B, 20 new molecules of type (I) and type (II) were prepared using simple chemical reactions (Table 3 and Table 4).

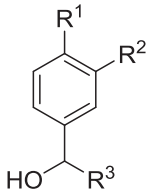
Table 3. Prepared molecules of type (I).



Type (I)

Molecule	R^1	R^2	R^3	R^4	R^5	X
3	H	*(E)* $CHCHCO_2H$	H	OH	H	H
6	H	H	*(E)* $CHCHCO_2H$	OH	H	H
10	H	CO_2H	H	OH	H	H
15	H	H	CO_2H	OH	H	H
17	H	CHNOH	H	OH	H	H
18	OH	OCH_3	H	OH	H	H
19	OH	OCH_3	H	OH	H	F
20	OH	OCH_3	H	OH	CH_3	H
21	OH	OCH_3	H	CH_2	-	H
22	H	OH	H	OH	H	H
24	OCH_3	OCH_3	H	OH	H	H

Table 4. Prepared molecules of type (II).



Type (II)

Molecule	R^1	R^2	R^3
25	OH	OCH_3	C_5H_{11}
26	OH	OCH_3	C_4H_9
27	OH	OCH_3	C_9H_{19}
28	OH	OCH_3	C_5H_9
31	H	CO_2H	C_5H_{11}
33	H	CHNOH	C_5H_{11}
34	H	CH_2NH_2	C_5H_{11}
37	H	$CHCHCO_2H$	C_5H_{11}

All these molecules were biologically evaluated as platelet aggregation inhibitors, and structure-activity study was also performed.

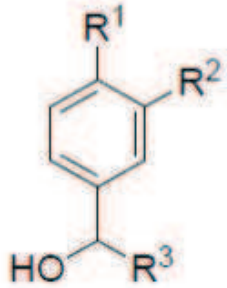
IV-Biological evaluation

These studies have been performed by Taghreed Hirz (Master 2 student) in the group of Dr. Aida HABIB at the American University of Beirut (AUB). They are reported here to give a view, as complete as possible, on the results of our joint program.

a) Effect on platelet aggregation

The capacity of these compounds to block platelet aggregation triggered by arachidonic acid was evaluated. The role of the hydrophilic chain on the inhibitory activity profile of these compounds was tested. Compounds **31** and **33** had a shorter hydrophilic carbonic chain compared to analogue A and showed no inhibitory effect on arachidonic acid-dependent platelet aggregation. The addition of substituents on the aromatic ring was also evaluated. Compound **25** with a hydroxyl at R^1 and a methoxy at R^2 was potent with an IC_{50} of 7.5 ± 0.8 µM, mean ± S.E.M. (Table 1). Shortening the hydrophobic hydrocarbon chain at position R^3 in compound **26** showed an IC_{50} of 14.2 ± 5.7 (n=4) (Table 1) and the dose-response effect on platelet aggregation by arachidonic acid was less clear. However, increasing the length of the hydrocarbon chain located at R^3 to *n*-C_9H_{19} in compound **27** or replacing it with a cyclopentane group in compound **28** resulted in the loss of the inhibitory activity platelet agregation (Table 1).

Table 1. Effect of type (II) molecules on platelet agregation

Structure	Compound	R^1	R^2	R^3	Plt aggregation IC_{50} ± S.E.M (µM) [a]
	33	H	C=NOH	nC_5H_{11}	No inhibition
	31	-	COOH	nC_5H_{11}	No inhibition
	25	OH	OCH_3	nC_5H_{11}	7.5 ± 0.8
	26	OH	OCH_3	nC_4H_9	14.2 ± 5.7
	27	OH	OCH_3	nC_9H_{19}	97.6 ± 83.5
	28	OH	OCH_3		41.2 ± 0.7

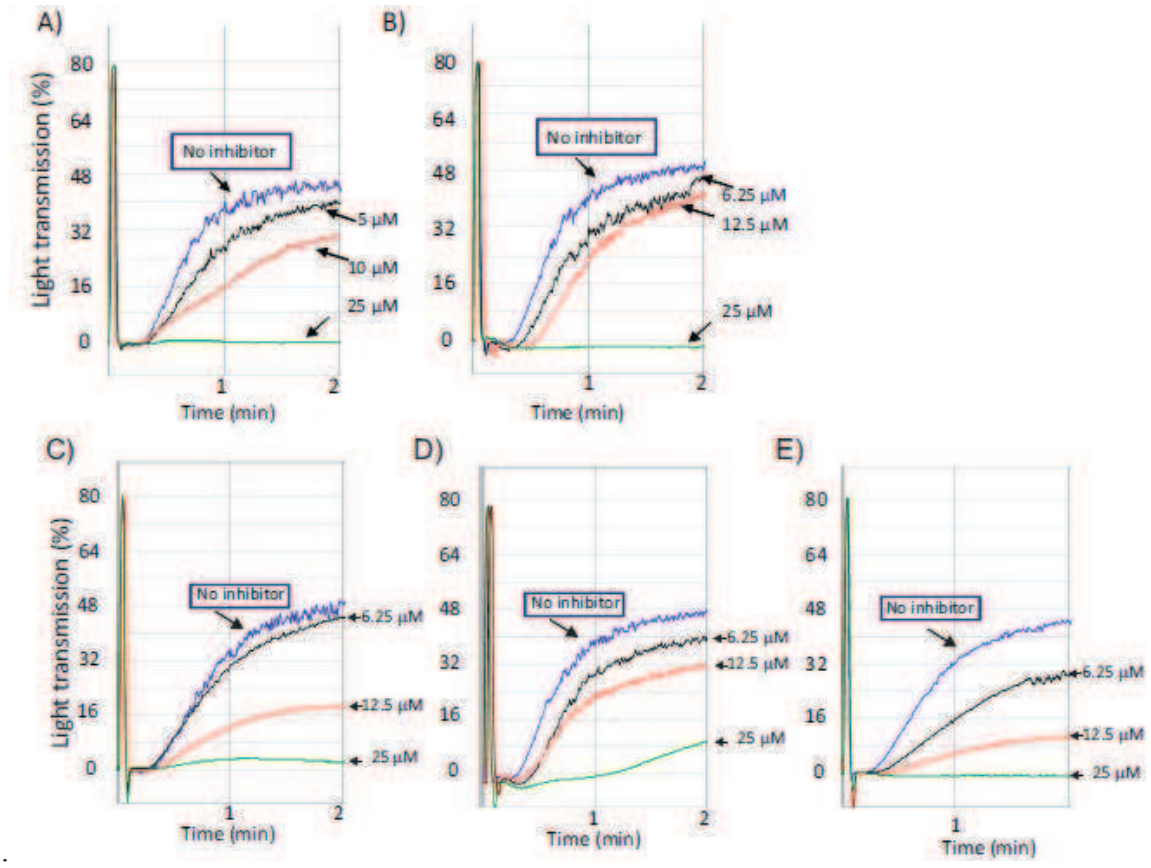
[b] n=3-4 in all experiments

Figure 1A and 1B illustrates the aggregation curves of compounds **25** and **26**, respectively and figure 2A illustrates the IC_{50} curve fitting of compounds of type II. Ibuprofen was used as a reference for the inhibition of platelet aggregation (Figure 2A) and as expected, it showed inhibition of platelet aggregation with an IC_{50} of 0.5 ± 0.11 µM (n=3)**.** These data suggest that

the OH group at position R^1 and a medium size length (n-C_5H_{11}) of the hydrophobic chain are important for the inhibitory effect of the compounds of type II.

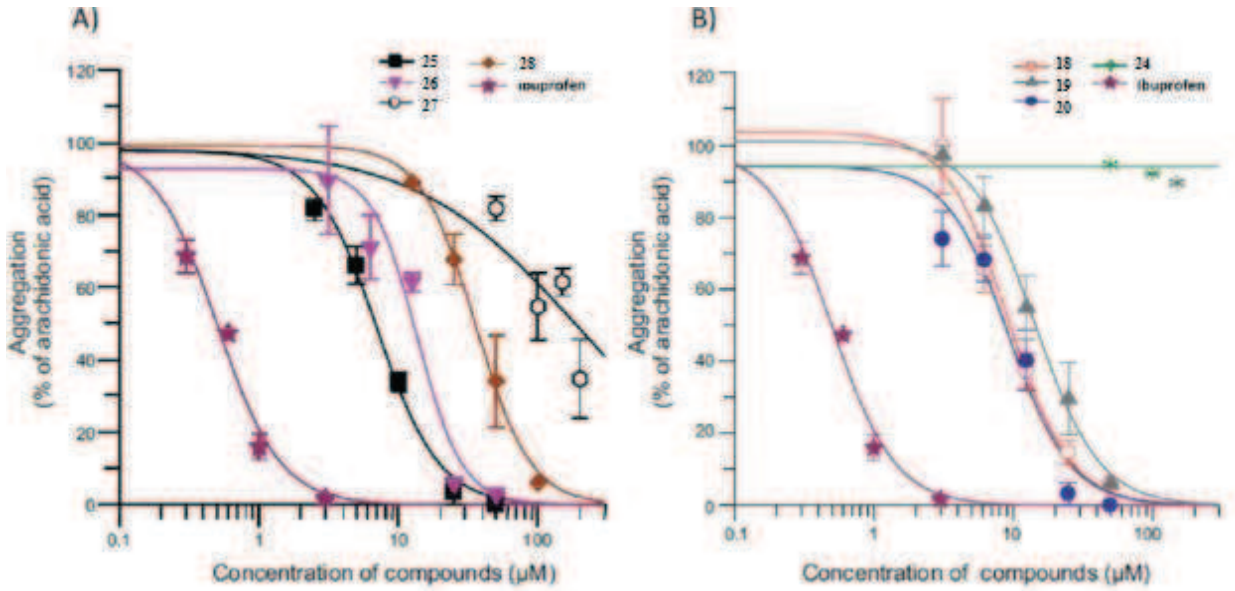
The compounds of type I were also tested (Table 2). Compounds **18** and **19** exhibit significant inhibitory activities (Figure 1C and 1D, respectively), although compound **19** exhibit a more linear dose-response inhibition of the platelet aggregation (Figure 1D). Introduction of a methyl group on the carbinol centre (R^3 group) did not change the inhibitory effect since compound **20** exhibits also the same range of inhibition with a similar linear dose-response inhibition (Figure 1E).

Figure 1. Biological activity of type (I) compounds.



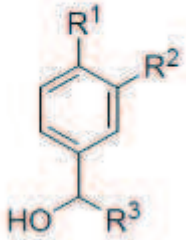
On the contrary, replacing the hydroxyl group by a methyl substituent, like in compound **10**, completely abolished the inhibitory activity (Figure 2B).

Figure 2. Comparison between biological activity of Type (I)/Type (II) compounds and Ibuprofen.



These results support a role of the OH group in position R^1. The IC_{50} of type I compounds were also compared with Ibuprofen (Table 2 and figure 2B).

Table 2. Effect of type (I) molecules on platelet aggregation.

Structure	Compound	R^1	R^2	R^3	R^4	Plt aggregation IC_{50} ± S.E.M (μM)[b]
	**18**	OH	OCH_3	Ph	H	8.5 ± 1.2
	19	OH	OCH_3	a	H	13.4 ± 0.5
	20	OH	OCH_3	Ph	CH_3	11.3 ± 4.8
	24	OCH_3	OCH_3	Ph	H	No inhibition

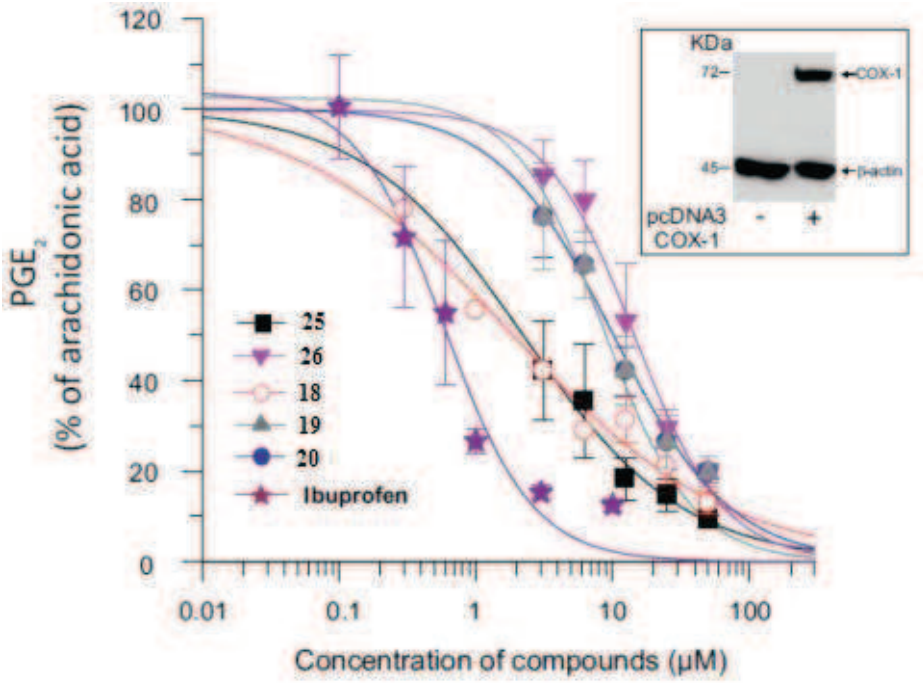
a= 4-fluorophenyl; [b] n=3-4 in all experiments

From these results it is possible to conclude that, for type II molecules, the hydroxyl group at R^1 position is critical for the inhibitory effect and that the length of the R^3 hydrocarbon chain is appropriate between 4 and 5 carbons, as described for compounds **25** and **26**, respectively. The type I compounds **18** and **24** are the most appropriate inhibitory compounds of this group with a hydroxyl group at R^1 and a methoxy group at R^2 position.

Effect on human COX-1 overexpressed in COS-7 cells

Next it was verified that these compounds, **18**, **19**, **20**, **25** and **26** which block platelet aggregation affect directly COX-1. For that purpose, COS-7 cells overexpressing human COX-1 were used. Figure 3 (insert) shows COX-1 protein overexpressed in COS-7 cells in comparison to non-transfected cells. In these cells which express only COX-1, arachidonic acid is metabolized into prostaglandin (PG)H_2 which will consequently breakdown into PGE_2.

Figure 3. Effect of the synthesized molecules on COX-1.



Measurement of PGE_2 under these conditions will reflect COX-1 activity.[20] The IC_{50} values for the inhibition of COX-1 by the five different compounds are summarized in table 3 and the fitting curves are presented in figure 4 along with the result of ibuprofen (IC_{50} was 0.5 ± 0.07

μM, Mean ± S.E.M., n=3). All five compounds showed a significant inhibition of the synthesis of PGE_2 in the COS-7 overexpressing human COX-1.

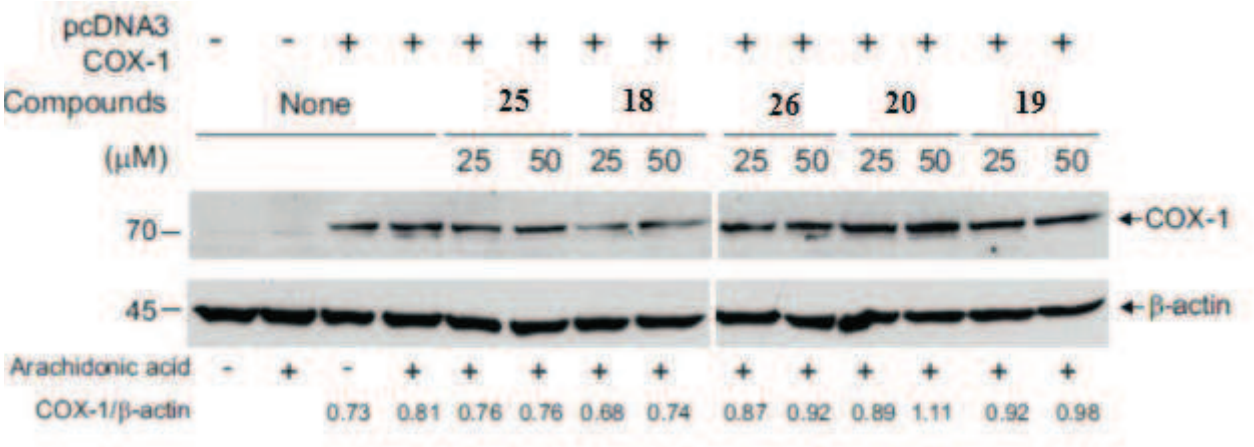
Table 3. Effect of the synthesized molecules on cyclooxygenase-1 activity.

Compound	COX-1 activity IC_{50} ± S.E.M (μM)[a]
25	2.2 ± 0.7
26	12.1 ± 2.3
18	1.3 ± 0.5
19	6.5 ± 0.2
20	8.1 ± 1.7

[a] n=3-4 in all experiments

No toxicity was observed with 25 and 50 μM of these compounds using WST-1 viability assay. Compounds **25**, **26**, **18**, **19** and **20** showed an average of 120-130 % of viability when compared to untreated cells, supporting the absence of toxicity of these compounds in the cell assay for COX-1. Moreover, the COX-1 expression in COS-7 cells was not modified after treatment with the different molecules compared to untreated cells and to arachidonic acid treated cells, as shown by western blot analysis (Figure 4).

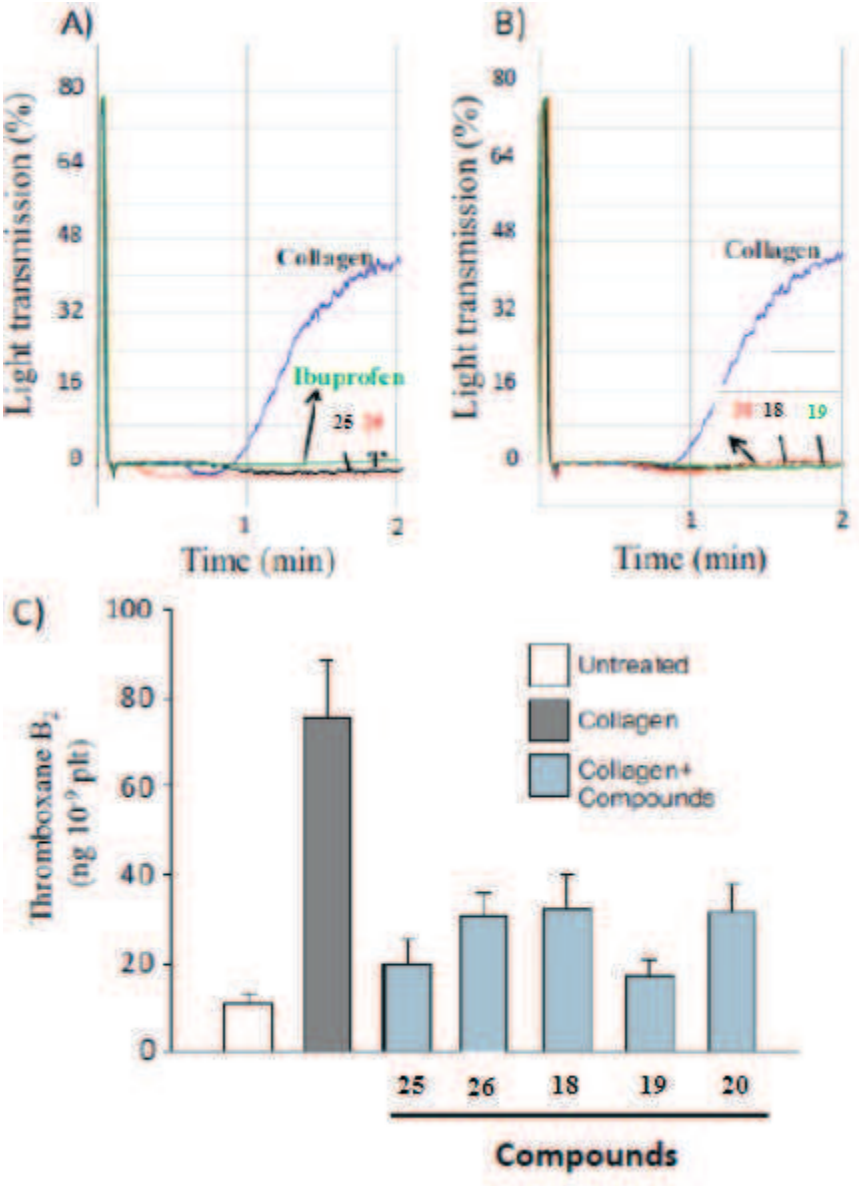
Figure 4. Effect of type (I) and type (II) compounds on COX-1.



Effect on collagen- and thromboxane receptor - dependent platelet aggregation

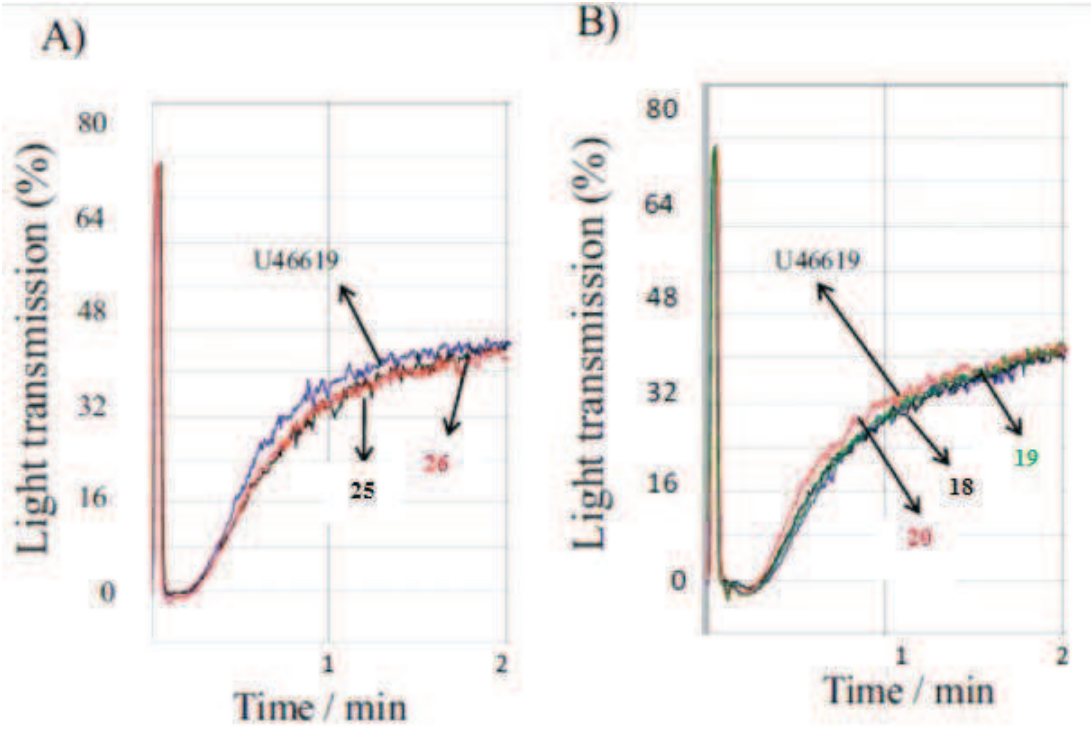
The effect of the inhibitory compounds was tested in the presence of collagen, a more physiologically platelet agonist than arachidonic acid. Low concentration of collagen is described to bind receptors linked to phospholipase A_2 activation and arachidonic acid release.[21] In experimental conditions, platelet aggregation induced by 0.5 μg/ml, a low collagen concentration, was strongly inhibited by 25 μM Ibuprofen (Figure 6A). Compounds **25** and **26** of type (II) series (Figure 5A) and compounds **18**, **19** and **20** of type (I) series (Figure 5B) blocked platelet aggregation induced by collagen. The effect of these compounds was also evaluated on collagen-dependent TX synthesis. TX concentration was increased 6-7 fold by collagen treatment as compared to untreated cells. The tested compounds strongly blocked collagen-dependent TX synthesis (Figure 5C).

Figure 5. Effect on collagen- and thromboxane.



None of the compounds **25**, **26**, **18**, **19** and **20** were able to act on the thromboxane receptor-dependent platelet aggregation in response to 1 μM of U46619, an agonist of the thromboxane receptor (Figure 6).

Figure 6. Action on thromboxane receptor**.**



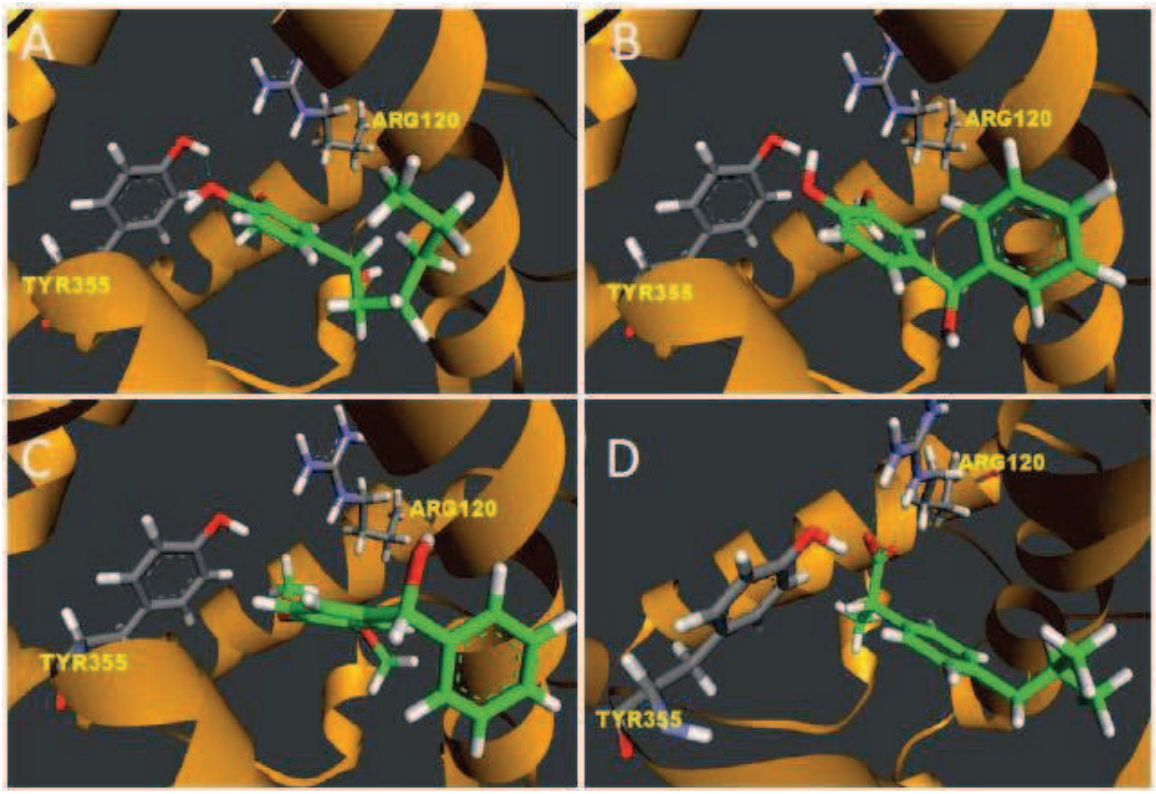
Overall, these results, along with the effect on arachidonic acid-dependent platelet aggregation and on human recombinant COX-1, support that these new molecules affect platelet aggregation via inhibition of TX formation.

Modeling analysis

Finally modeling analysis of some of the inhibitors was carried out by *Mr. Nehme El-Hachem from American University of Beirut (AUB).* Ovine COX-1, available in data base was used to examine how these compounds dock the active site of the enzyme and to determine the amino acids of the active site of the enzyme involved in the interaction with the compounds. Ibuprofen was first docked into COX-1 and, in agreement with literature, the carboxyl group of ibuprofen showed three hydrogen bonds, two with Arg 120 (guanidine $-NH_2$ group) and one with Tyr 355 (p-OH group) (Figure 7D). A root square mean deviation value of 1.2 Å was calculated between the best pose and the experimental coordinates of Ibuprofen. Compounds **18** and **25** were docked

nearby Tyr 355 and Arg 120. Both compounds exhibited hydrogen bond between phenol and Tyr 355 (Figure 7A and 7B). The binding scores of compounds **18** and **25** were -6.8 kcal/mol and -7.7 kcal/mol (-6.5 kcal/mol, and -7.6 kcal/mol for the *S*-enantiomers), respectively. These scores were comparable to Ibuprofen (-8 kcal/mol). On the other hand, compound **24** which does not affect platelet aggregation (Fig 2B) did not interact with Tyr 355 (Figure 7C) although its binding score was -7.2 kcal/mol (-6.8 kcal/mol for the *S*-enantiomer).

Figure 7. Modeling analysis of the synthesized molecules.



Also, it is important to mention that compound **24** showed many docking poses that were far from the original binding site of Ibuprofen. Furthermore, rofecoxib, a selective COX-2 inhibitor was docked and it was observed that the average RMSD between the best reported pose for rofecoxib and the native compound ibuprofen was 7 angstroms; although it docking score was -7.2 kcal/mol (data not shown). It is well known that scoring functions yield high rates of false positives especially when the docked structures are very similar. Future experiments with enriched libraries of inactive compounds may improve docking and scoring performance. As a conclusion it appears that Autodock succeeded in docking and scoring correctly active ligands **18**

and **25**. It is very probable that the hydroxyl group at R^1 is important for the interaction and the structure activity relationship of these compounds. Blocking this –OH interfered with the biological activity of these inhibitors.

Conclusion

We first designed series of new aromatic compounds based on the structure of the analogues of polyunsaturated fatty acid metabolites, 12-HETE and 13-HODE, reported earlier.[11] These new compounds have important structural differences with the initial molecules A and B. Five compounds were shown to have anti-platelet effects on arachidonic acid- and collagen-induced platelet aggregation. These compounds mediate their effects via blockade of COX and not by acting as antagonist of the TX receptor. Our results support a role of the phenol group in the inhibitory effect of these compounds, shown also by the docking observation of the molecules in the human recombinant COX-1. The addition of OH at R^1 conferred additional properties and fitting in COX-1. There is a direct interaction of the compounds with COX-1 as revealed by the structure-activity relationship data, which showed an important role for the phenol in position R^1, most likely related to hydrogen bonding with the Tyr 355 of COX-1. In conclusion, the compounds originally designed based on the structures of analogues of 12-HETE and 13-HODE show an important role for the phenol group on the anti-platelet and anti-COX-1 activities. These molecules, although structurally different from the HETE and HODE compounds, have anti-platelet effect and anti-COX activities and will help to design more potent analogues.

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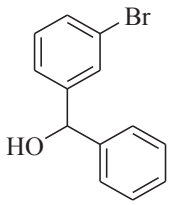
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EXPERIMENTAL PART

(3-Bromophenyl)phenylmethanol (1)



$C_{13}H_{11}BrO$
M = 263.13 g.mol^{-1}

Representative procedure for Grignard addition. Synthesis of alcohol 1:

Magnesium turnings (0.17 g, 7.08 mmol) in a reflux apparatus, equipped with a magnetic bar, dried and cooled under nitrogen were immersed in dry THF (10ml). A small iodine crystal was added and the mixture stirred and refluxed under nitrogen till iodine color disappeared. Bromobenzene (0.74 ml, 7.08 mmol) in dry THF (10 ml) was added dropwise. The reaction mixture was then stirred at reflux for 30 min, before being cooled to room temperature. The prepared C_6H_5MgBr was added dropwise, under nitrogen, to *p*-bromobenzaldehyde (1.00 g, 5.41 mmol) in dry THF (10 ml) at -15 °C. The reaction mixture was stirred under nitrogen for 1 hour, while the temperature was rising slowly to room temperature. The mixture was treated with a saturated NH_4Cl solution, extracted by ethyl acetate (3 x 30 ml), dried over $MgSO_4$, and concentrated in vacuo.

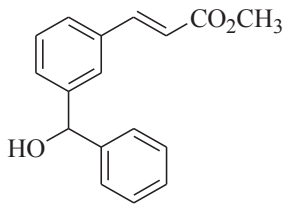
Alcohol **1** was isolated after chromatography on silica gel as colorless oil (0.95 g, 67 %yield); R_f = 0.28. (Ethyl acetate/Hexane: 10/90).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 3.1 (s, 1H, OH), 5.42 (s, 1H), 7.41-6.92 (m, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 75.5, 1227, 126.7, 127.6, 128.6, 128.73, 129.58, 130.1, 130.60, 143.2, 146.1.

MS: Found m/z = 263

3-[3-(Hydroxyphenylmethyl)phenyl]acrylic acid methyl ester (2)



$C_{17}H_{16}O_3$

M = 268.31 g.mol^{-1}

The alcohol **1 (**400 mg, 1.52 mmol)**,** triphenylphosphine (14 mg, 5.53 x 10^{-2} mmol), palladium (II) acetate (6.1 mg, 2.76 x 10^{-2} mmol), methyl acrylate (0.3 ml, 2.2 eq.) and triethylamine (5ml) have been added in a 50 ml round bottom flask, and the mixture was stirred and refluxed under nitrogen for 12 hours.

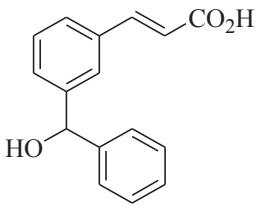
The mixture was acidified using diluted HCl, extracted by CH_2Cl_2 3 (5 x ml), dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo.

Ester **2** was isolated after chromatography on silica gel as white crystals (200 mg, 49 % yield); Melting point: 82-84 °C; R_f = 0.18 (Ethyl acetate/petroleum ether: 15/85).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ ppm 3.60 (s, 3H), 5.61 (s, 1H), 6.24 (d, 1H, *J*= 15.3 Hz), 7.08-7.25 (m, 8H), 7.37 (s, 1H), 7.48 (d, 1H, *J* = 15.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 51.8, 75.7, 117.8, 126.3, 126.6, 127.1, 127.7, 128.6, 128.7, 129.0, 134.4, 143.7, 144.9, 145.0, 167.6.

3-[3-(Hydroxyphenylmethyl) phenyl] acrylic acid (3)



$C_{16}H_{14}O_3$

M = 254.28 g.mol^{-1}

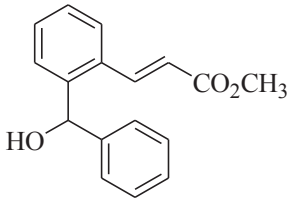
Ester **2** (100 mg, 0.37 mmol) in THF (9 ml) and LiOH (9 ml, 2M in H_2O) has been introduced into a 50 ml round bottom flask. The mixture was stirred, at room temperature, for 15 hours before being acidified using dilute HCl, extracted by CH_2Cl_2 (3 x 5 ml), dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo.

The product **3** was isolated after chromatography on silica gel (78 mg, 83% yield) as white crystals; R_f= 0.12 (Ethyl acetate/petroleum ether: 50/50).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ ppm 5.61 (s, 1H), 6.31 (d, 1H, *J* = 15.3 Hz), 7.09-7.26 (m, 9H), 7.72 (d, 1H, *J* = 15.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 74.5, 117.7, 126.2, 126.5, 127.1, 127.8, 128.5, 128.7, 129.0, 134.2, 145.6, 146.7, 171.8.

3-[2-(Hydroxyphenylmethyl)phenyl]acrylic acid methyl ester (5)



$C_{17}H_{16}O_3$
M = 268.31 g.mol^{-1}

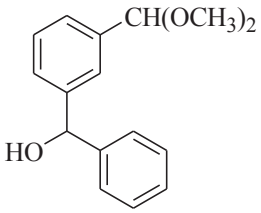
Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (3.42 mmol, 1.3 equiv) was added to 3-(2-formylphenyl) acrylic acid methyl ester (0.5 g, 2.63 mmol) in THF (10 ml).

Alcohol **5** was isolated after chromatography on silica gel as a colorless oil (200 mg, 28% yield); R_f= 0.24 (Ethyl acetate/Hexane: 20/80).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 3.71 (s, 3H), 6.04 (s, 1H), 6.16 (d, 1H, *J*= 15.2 Hz), 7.01-7.42 (m, 9H), 7.93 (d, 1H, *J*= 15.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 51.8, 72.7, 119.6, 126.9, 127.39, 127.59, 127.66, 128.50, 130.17, 132.65, 142.39, 142.65, 142.97, 142.97, 167.37.

Preparation of (3-Dimethoxymethylphenyl)phenylmethanol (8)



$C_{16}H_{18}O_3$
M = 258.31 g.mol^{-1}

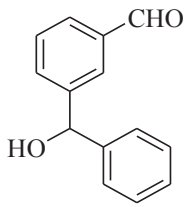
Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (1.3 equiv) was added to 3-(2-formylphenyl) acrylic acid methyl ester (0.5 g, 2.63 mmol) in THF (10 ml).

After purification by flash chromatography on silica gel, alcohol **8** was isolated as a colorless oil (220mg, 63% yield); R_f= 0.3 (Ethyl acetate/Hexane: 25/75).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 3.25 (s, 6H), 5.46 (s, 1H), 5.83 (s, 1H), 7.12-7.28 (m, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 47.7, 76.0, 109.6, 125.2, 125.8, 127.4, 128.2, 128.9, 129.2, 137.5, 142.8, 144.2.

Preparation of 3-(Hydroxyphenylmethyl)benzaldehyde (9)



$C_{14}H_{12}O_2$
M = 212.24 g.mol^{-1}

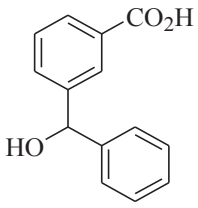
Silica gel (1 g) and CH_2Cl_2 (5 ml) were added into a 50ml round bottom flask. 2-3drops of sulfuric acid (2.5%) have been added and the mixture was stirred to become homogenous. To them, acetal **8** (220 mg, 0.85 mmol) dissolved in CH_2Cl_2 (5 ml) was added and the mixture was stirred, at room temperature, for two hours. After filtration on büchner, the solution was dried with anhydrous sodium sulfate, filtrated and evaporated under vacuum.

After purification by flash chromatography on silica gel, compound **9** was obtained as a colorless oil (140 mg, 78% yield); R_f= 0.3 (Ethyl acetate/Hexane: 25/75).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.61 (s, 1H), 5.79 (s, 1H), 7.13-7.19 (m, 5H), 7.38-7.76 (m, 4H), 9.92 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 77.6, 126.2, 127.3, 128.4, 129.0, 129.5, 129.6, 134.3, 137.2, 143.0, 143.5, 190.2.

Preparation of 3-(Hydroxyphenylmethyl)benzoic acid (10)



$C_{14}H_{12}O_3$
M = 228.24 g.mol^{-1}

Silver nitrate (0.4 g) and sodium hydroxide (0.4 g) were dissolved in water. Upon mixing them together, precipitates were formed, and then ammonia was added until all precipitates disappeared. This mixture was then added to a 50 ml round bottom flask containing aldehyde **9** (80 mg, 0.38 mmol) dissolved in DMSO (1 ml). After that, the mixture was stirred, at room temperature, for two hours.

After acidification using dilute HCl, extraction by CH_2Cl_2 (3 x 10 ml), the solution was dried with anhydrous sodium sulfate, filtrated and evaporated under vacuum.

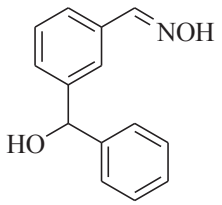
After purification by flash chromatography on silica gel, acid **10** was obtained as white crystals (70 mg, 81% yield); R_f = 0.13 (Ethyl acetate/petroleum ether: 50/50).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.25 (s, 1H), 5.81 (s, 1H), 7.13-7.21 (m, 5H), 7.41-8.08 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 78.1, 126.2, 127.4, 128.4, 128.9, 129.1, 130.2, 131.1, 133.4, 142.9, 143.2, 172.3.

MS: Found m/z : 228.

Preparation of 3-(Hydroxyphenylmethyl)benzaldehyde oxime (17)



$C_{14}H_{13}NO_2$
M = 227.26 g.mol^{-1}

Aldehyde **9** (140 mg, 0.66 mmol), NH_2-OH.HCl (80 mg, 1.16 mmol), pyridine (0.4 ml) and ethanol (10 ml) have been introduced into a 50ml round bottom flask, and the solution refluxed for 16 hours. The mixture was acidified using dilute HCl, extracted by CH_2Cl_2 (3 x 5 ml), dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo.

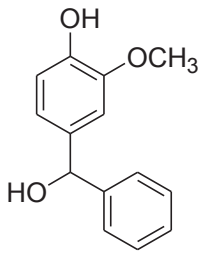
Oxime **17** was isolated after flash chromatography on silica gel as a colorless oil (130 mg, 87%); R_f= 0.15 (Ethyl acetate/Hexane: 20/80).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 1.95 (s, 1H), 5.7 (s, 1H), 7.12-7.54 (m, 9H), 8.00 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 75.9, 125.1, 126.2, 126.6, 127.7, 128.3, 128.6, 129.0, 132.05, 143.4, 144.5, 150.2.

MS: Found m/z = 227.

Preparation of 4-(Hydroxyphenylmethyl)-2-methoxyphenol (18)



$C_{14}H_{14}O_3$
M = 230.26 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (7.57 mmol, 2.3 equiv) was added to vanillin (0.5 g, 3.29 mmol) in THF (10 ml).

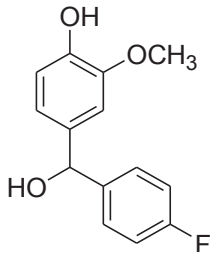
After purification by flash chromatography on silica gel, compound **18** was obtained as white crystals (0.50 g, 70 %yield); Melting point: 91-93 °C; R_f= 0.23 (Ethyl acetate/Hexane: 35/65).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.45 (s, 1H), 3.7 (s, 3H), 5.65 (s, 1H), 6.61- 6.82 (m, 3H), 7.1-7.3 (m, 5H).

^{13}C NMR ($CDCl_3$, 75 MHz,): δ ppm 55.9, 76.0, 109.3, 114.2, 119.7, 126.4, 127.4, 128.4, 136.1, 144.0, 145.1, 146.7,

MS: Found m/z: 230.

4-[(4-fluoro-phenyl)-hydroxy-methyl]-2-methoxy-phenol (19)



$C_{14}H_{13}FO_3$
M = 248.25 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** *p*-F-C_6H_5MgBr (7.57 mmol, 2.3 equiv) was added to vanillin (0.5 g, 3.29 mmol) in THF (10 ml).

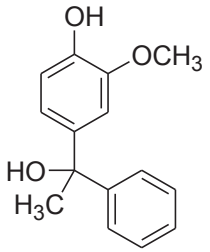
After purification by flash chromatography on silica gel, compound **18** was obtained as white crystals (0.53 g, 35% yield); Melting point: 106-108 °C R_f= 0.39 (Ethyl acetate/Hexane: 35/65).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 3.80 (s, 3H), 4.87 (d, 1H, *J*= 3.9 Hz), 5.77 (d, 1H, *J*= 3.8 Hz); 6.79 (d, 1H, *J*= 8.1 Hz); 6.84 (d, 1H, *J*= 8.1 Hz); 7.04-7.10 (m, 3H); 7.43-7.48 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 56.2, 75.38, 110.9, 115.4 (d, 2C, *J* = 21.3 Hz), 115.5, 120.2, 129.1 (d, 2C, *J* = 8.0 Hz), 137.8, 142.8 (d, 1C, *J* = 3.0 Hz), 146.6, 148.2, 162.6 (d, 1C, *J* = 242.6 Hz).

MS: Found m/z: 248.

4-(1-hydroxy-1-phenyl-ethyl)-2-methoxy-phenol (20)



$C_{15}H_{16}O_3$
M = 244.29 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (6.92 mmol, 2.3 equiv) was added to vanillone (0.5 g, 3.01 mmol) in THF (10 ml).

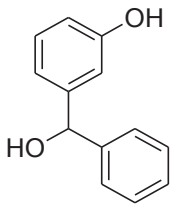
After purification by flash chromatography on silica gel, phenol **20** was obtained as white crystals (0.46 g, 62 % yield); Melting point: 119-121 °C; R_f = 0.23 (Ethyl acetate/Hexane: 35/65).

^{1}H NMR (d_6-acetone, 300 MHz): δ, ppm 1.92 (s, 3H), 3.19 (s, 1H), 3.77 (s, 3H), 4.60 (s, 1H), 6.78 (d, 1H, *J*= 8.3 Hz), 6.91 (dd, 1H, *J*= 2.1 , 8.3 Hz), 7.13 (d, 1H, *J*= 2.1 Hz), 7.15-7.21 (m, 1H), 7.26-7.31 (m, 2H), 7.48-7.52 (m, 2H).

^{13}C NMR (d_6-acetone, 75 MHz): δ, ppm 31.5, 56.3, 75.9, 110.9, 115.0, 119.5, 126.7, 127.0, 128.6, 141.9, 146.0, 147.8, 150.7.

MS: Found: m/z =244.

Preparation of 3-(hydroxyphenylmethyl) phenol (22)



$C_{13}H_{12}O_2$
M = 200.23 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (9.43 mmol, 2.3 equiv) was added to *meta*-hydroxybenzaldehyde (0.5 g, 4.1 mmol) in THF (10 ml).

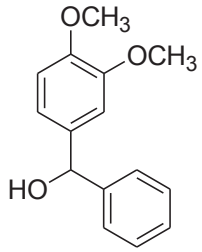
After purification by flash chromatography on silica gel, phenol **22** was obtained as white crystals (0.63 g, 77 % yield); Melting point: 159-161 °C; R_f= 0.1 (Ethyl acetate/Hexane: 20/80).

^{1}H NMR (d_6-acetone, 300 MHz): δ ppm 1.8 (s, 1H), 4.65 (s, 1H), 5.6 (s, 1H), 6.5-7.3 (m, 9H).

^{13}C NMR (d_6-acetone, 75 MHz): δ ppm 76.1, 114.3, 114.7, 118.6, 127.4, 127.7, 128.9, 129.9, 146.4, 148.0, 158.2.

MS: Found m/z = 200.

(3,4-dimethoxy-phenyl)-phenyl-methanol (24)



$C_{15}H_{16}O_3$
M = 244.29 g.mol^{-1}

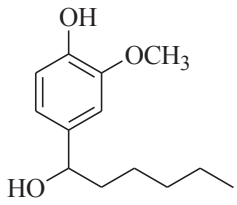
Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (0.39 mmol, 1.3 equiv) was added to 3,4-dimethoxy benzaldehyde (0.3 g, 1.81 mmol) in THF (5 ml).

After purification by flash chromatography on silica gel, phenol **24** was obtained as white crystals (0.3 g, 67 % yield); Melting point: 95-97°C; R_f= 0.28 (Ethyl acetate/Hexane: 20/80).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 3.76 (s, 3H), 3.78 (s, 3H), 5.71 (s, 1H), 6.74-6.85 (m, 3H), 7.18-7.29 (m, 5H),

^{13}C NMR (d_6-acetone, 75 MHz): δ ppm 55.8, 75.9, 109.8, 110.9, 119.0, 119.3, 126.4, 127.5, 127.7, 128.2, 128.5, 136.6, 143.9, 148.4, 149.0.

4-(1-Hydroxy-hexyl)-2-methoxy-phenol (25)



$C_{13}H_{20}O_3$
M = 224.30 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** C_6H_5MgBr (0.39 mmol, 2.3 equiv.) was added to vanillin (0.5 g, 3.29 mmol) in THF (10 ml).

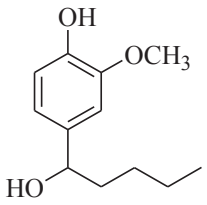
After purification by flash chromatography on silica gel, compound **25** was obtained as white crystals (0.32 g, 45 % yield); Melting point: 97-99 °C; R_f= 0.22 (Ethyl acetate/Hexane: 15/85).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 0.79 (t, 3H, *J*= 6.1 Hz), 1.20-1.36 (m, 6H), 1.53-1.62 (m, 1H), 1.64-1.72 (m, 1H), 3.80 (s, 3H), 4.49 (t, 1H, *J*= 6.7 Hz), 5.65 (s, 1H), 6.67-6.81 (m, 3H).

^{13}C NMR (d_6-acetone, 75 MHz): δ, ppm 14.0, 22.6, 25.6, 31.7, 39.0, 55.9, 74.7, 108.4, 114.1, 119.0, 137.0, 145.0, 146.6.

MS: Found m/z: 224.

4-(1-hydroxy-pentyl)-2-methoxy-phenol (26)



$C_{12}H_{18}O_3$
M = 210.27 g.mol^{-1}

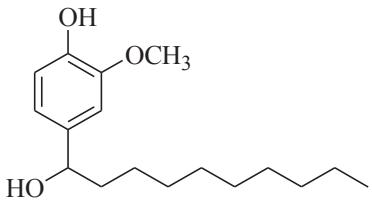
Following the same procedure as for the preparation of alcohol **1,** C_4H_9MgBr (7.57 mmol, 2.3 equiv.) was added to vanillin (0.5 g, 3.29 mmol) in THF (10 ml).

After purification by flash chromatography on silica gel, compound **26** was obtained as white crystals (0.36 g, 52 % yield); R_f= 0.22 (Ethyl acetate/Hexane: 15/85).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 0.79 (t, 3H, *J*= 6.1 Hz), 1.20-1.36 (m, 4H), 1.53-1.62 (m, 1H), 1.64-1.72 (m, 1H), 3.80 (s, 3H), 4.49 (t, 1H, *J*= 6.7 Hz), 5.65 (s, 1H), 6.67-6.81 (m, 3H).

^{13}C NMR (d_6-acetone, 75 MHz): δ, ppm 14.0, 22.6, 31.7, 39.2, 56.0, 74.7, 108.4, 114.1, 118.7, 136.8, 145.0, 146.4.

4-(1hydroxy-decyl)-2-methoxy-phenol (27)



$C_{17}H_{28}O_3$
M = 280.40 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** $C_9H_{11}MgBr$ (7.57 mmol, 2.3 equiv.) was added to vanillin (0.5 g, 3.29 mmol) in THF (10 ml).

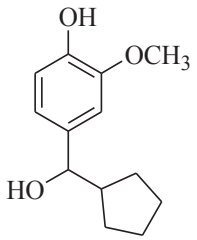
After purification by flash chromatography on silica gel, compound **27** was obtained as a colorless oil (0.50 g, 54 % yield); R_f= 0.10 (Ethyl acetate/Hexane: 15/85).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 0.77 (t, 3H, *J*= 6.9 Hz), 1.09-1.21 (m, 14H), 1.37-1.46 (m, 1H), 1.61-1.74 (m, 1H), 3.80 (s, 3H), 3.86 (dd, *J*= 5.7, 7.7 Hz), 5.68 (s, 1H), 6.58 (dd, 1H, *J*= 1.8 Hz, 8.0 Hz), 6.76 (d, 1H, *J*= 1.8 Hz), 6.78 (d, 1H, *J*= 8.0Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 14.1, 22.7, 26.2, 29.3, 29.5, 29.6, 31.9, 38.9, 55.8, 78.2, 109.0, 113.9, 120.3, 135.2, 144.9, 146.7.

MS: Found m/z = 280.

4-(cyclopentyl-hydroxy-methyl)-2-methoxy-phenol (28)



$C_{13}H_{18}O_3$
M = 222.28 g.mol^{-1}

Following the same procedure as for the preparation of alcohol **1,** $C_9H_{11}MgBr$ (7.57 mmol, 2.3 equiv.) was added to vanillin (0.5 g, 3.29 mmol) in THF (10 ml).

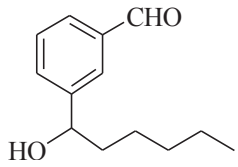
After purification by flash chromatography on silica gel, compound **28** was obtained as white crystals (0.57 g, 78 % yield); Melting point: 99-101 °C; R_f= 0.20 (Ethyl acetate/Hexane: 15/85).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.45-2.01 (m, 9H), 3.83 (s, 3H), 4.25 (d, 1H, *J*= 11.4 Hz), 5.51 (s, 1H), 6.73 (dd, 1H, *J*= 1.8, 8.1 Hz), 6.80 (d, 1H, *J*= 8.1 Hz), 6.83 (d, 1H, *J*= 1.8 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm: 25.4, 25.6, 29.5, 29.8, 47.6, 55.9, 79.2, 108.8, 114.0, 119.5, 136.6, 145.0, 146.6.

MS: Found m/z: 222.

3-(1-hydroxy-hexyl)-benzaldehyde (30)



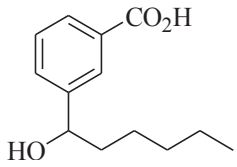
$C_{13}H_{18}O_2$
M = 206.28 g.mol^{-1}

Following the same procedure of preparation of aldehyde **9**, hydrolysis was performed starting from the known acetal **29** (0.4 g, 1.59 mmol) and aldehyde **30** was obtained as a colorless oil (183 mg, 56 %yield); R_f= 0.31 (Ethylacetate/Hexane: 20/80).

^{1}H RMN ($CDCl_3$, 300 MHz): δ ppm 0.79 (t, 3H, *J*= 6.51 Hz), 1.31-1.53 (m, 6H), 1.61-1.72 (m, 2H), 2.12 (s,1H), 4.50 (t, 1H, *J*= 7.2 Hz) 7.31-7.84 (m,4 H), 9.93 (s,1H).

^{13}C RMN ($CDCl_3$, 300 MHz,): δ ppm 14.0, 22.5, 25.3, 31.6, 39.2, 74.0, 127.0, 128.9, 129.1, 132.1, 136.5 146.1, 192.5.

3-(1-hydroxy-hexyl)-benzoic acid (31)



$C_{13}H_{18}O_3$
M = 222.28 g.mol^{-1}

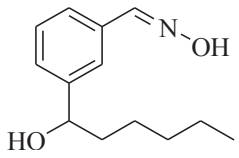
Following the same procedure as for the preparation of acid **10**, starting from aldehyde **30** (150 mg, 0.73 mmol), acid **31** was obtained as white crystals (125 mg, 78 %yield); Melting point: 108-110 °C; R_f= 0.21 (Ethylacetate/Hexane: 30/70).

^{1}H NMR (d_6-acetone, 300 MHz): δ ppm 0.73 (t, 3H, *J* = 7.1 Hz), 1.10-1.39 (m, 6H), 1.49-1.67 (m, 2H), 4.61 (dd, 1H, *J*= 5.7, 7.2 Hz), 7.29-7.34 (m, 1H), 7.47-7.51 (m, 1H); 7.77 (td, 1H, *J*= 1.6, 7.7 Hz), 7.93 (t, 1H, *J*= 1.6 Hz).

^{13}C NMR (d_6-acetone, 75 MHz): δ ppm 14.2, 21.1, 23.3, 32.3, 40.4, 75.6, 127.7, 128.2, 130.1, 131.3, 135.5, 145.3, 170.6.

MS: Found m/z = 222.

3-(1-Hydroxy-hexyl)-benzaldehyde oxime (33)



$C_{13}H_{19}NO_2$
M = 221.30 g.mol^{-1}

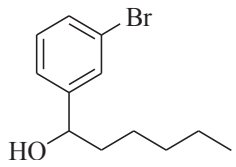
Following the same procedure as for the preparation of oxime **17**, starting from aldehyde **30** (100 mg, 0.49 mmol), oxime **33** was isolated as white crystals (78mg, 73 % yield); Melting point: 80-82 °C; R_f= 0.25 (Ethylacetate/Hexane: 20/80).

^{1}H RMN ($CDCl_3$, 300 MHz): δ ppm 0.78 (t, 3H, *J*= 6.4 Hz), 1.12-1.35 (m , 6 H), 1.54-1.70 (m , 2 H), 3.82 (bs, 1 H) OH, 4.57 (dd, 1H, *J*= 6.2, 7.0 Hz), 7.17-7.34 (m, 3H), 7.44 (s, 1H), 8.01 (s, 1 H), 9.14 (bs, 1 H) OH.

^{13}C RMN ($CDCl_3$, 300 MHz,): δ ppm 15.3, 22.5, 24.4, 34.6, 40.2, 75.6, 126.3, 128.6, 129.4, 130.7, 132.9, 137.5, 150.4.

MS: Found m/z = 221

1-(3-bromophenyl)hexan-1-ol (35)



$C_{12}H_{17}BrO$

M = 257.17 g.mol^{-1}

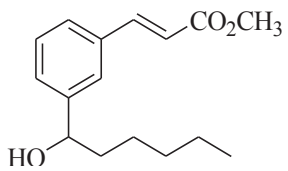
Following the general procedure indicated for the preparation of alcohol **1**, $C_5H_{11}MgBr$ (7.03 mmol, 1.3equiv.) was added to *meta*-bromobenzaldehyde (1 g, 5.41 mmol) in THF (10 ml).

After purification by flash chromatography on silica gel, compound **35** was obtained as a colorless oil (0.75 g, 54 % yield); R_f= 0.37 (Ethyl acetate/Hexane: 10/90).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 0,96 (t, 3H, *J*= 7.1 Hz), 1.31-1.52 (m, 6H), 1.58-1.72 (m, 2H), 4.52 (t, 1H, *J*= 7.3 Hz), 7.02-7.51(m, 4H).

^{13}C **NMR ($CDCl_3$, 75 MHz):** 14.0, 22.6, 25.4, 31.7, 39.1, 73.9, 122.5, 124.5, 129.0, 130.0, 130.4, 147.13

3-[3-(1-Hydroxy-hexyl)-phenyl]-acrylic acid methyl ester (36)



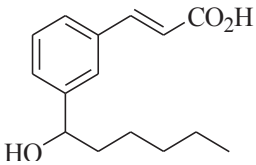
$C_{16}H_{22}O_3$
M = 262.34 g.mol^{-1}

Following the same procedure as for the preparation of ester **2**, starting from **35** (0.5 g, 1.95 mmol), ester **36** was isolated (0.34 g, 66 %yield); R_f= 0.24 (Ethyl acetate/Hexane: 10/90).

^{1}H NMR ($CDCl_3$, 300 MHz): 0.81 (t, 3H, *J*= 7.1 Hz), 1.12-1.52 (m, 6H), 1.61-1.80 (m, 2H), 3.83 (s, 3H), 4.52 (t, 1H, *J*= 7.2 Hz), 6.34 (d, 1H, *J*= 15.2 Hz), 7.21-7.46 (m, 4H), 7.52 (d, 1H, *J*= 15.2 Hz).

^{13}C **NMR ($CDCl_3$, 75 MHz):** 14.0, 22.5, 25.4, 31.7, 39.1, 51.7, 74.1, 117.7, 125.6, 127.1, 128.9, 129.9, 134.3, 145.0, 146.0, 167.5.

3-[3-(1-Hydroxy-hexyl)-phenyl]-acrylic acid (37)



$C_{15}H_{20}O_3$
M = 248.32 g.mol^{-1}

Following the same procedure as for the preparation of acid **3**, starting from ester **36** (0.3 g, 1.15 mmol), acid **37** was isolated (0.19 g, 68 %yield); R_f= 0.15 (Ethyl acetate/Hexane: 50/50).

^{1}H NMR ($CDCl_3$, 300 MHz): 0.81 (t, 3H, *J*= 6.8 Hz), 1.12-1.45 (m, 6H), 1.60-1.85 (m, 2H), 4.58 (t, 1H, *J*= 7.21 Hz), 6.52 (d, 1H, *J*= 15.32 Hz), 7.10-7.51 (m, 4H), 7.75 (d, 1H, *J*= 15.32 Hz), 11.10 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): 14.0, 22.6, 25.4, 29.7, 31.7, 39.0, 74.3, 117.6, 126.0, 127.4, 128.4, 129.0, 134.2, 145.6, 146.7, 17.3.

MS: Found m/z = 248.

Biological studies

METHODS

General

COS-7 cells were obtained from the American Type Culture Collection (ATCC, Massas, VA). Ibuprofen was from EMD-Calbiochem (San Diego, CA). Arachidonic acid and BSA were from Sigma-Aldrich (St Louis, MO). Collagen was from Chrono-Log Corp (Havertown, PA). PGE_2 and TXB_2 reagents were from Cayman Chemicals (Ann Arbor, MI). WST-1 viability assay and FuGENE® 6 transfection reagent were from Roche Applied Science**.** All drugs were dissolved in DMSO and final concentration did not exceed 0.2 %. Vehicle corresponding to 0.2 % DMSO was added in controls and arachidonic treated cells or platelets. All other chemicals and electrophoresis reagents were of high pure grade and were obtained from Amresco (Solon, OH) and BioRad (Hercules, CA).

Blood collection, platelet preparation and analysis

Venous blood was obtained from healthy volunteers who had not ingested any drugs for the last 14 days after informed consent in accordance with the Institutional Review Board (IRB) of the American University of Beirut (Approval # BioCh.AH.03). Washed platelets were prepared as described previously. Briefly, 20 ml of peripheral blood was withdrawn on ACD-C (1 volume for 9 volumes of blood) and centrifuged at 120 g for 15 min at room temperature (RT) to obtain platelet-rich plasma. Platelet-rich plasma was further centrifuged at 1,200 g for 15 min at RT, and the platelet pellet obtained was washed by Tyrode buffer solution containing 0.1 μM of PGE_1 and further centrifuged at 1,200 g for 15 min at RT. The pellet was resuspended in Hanks buffer, pH 7.4 containing 1 mg/ml of bovine serum albumin. Aggregation of washed-platelets was determined using light transmittance aggregometry (Chrono-Log Corp.). 400 μl of platelets (0.4×10^9plt/ml) were preincubated for 1 min at 37 ^{0}C in the absence or presence of inhibitors prior to the addition of 25 μM of arachidonic acid, which was controlled as optimal in our conditions. In some experiments, platelets were triggered with 1 μM U46619, a TX receptor agonist, or 0.5 μg/ml collagen, a concentration we checked in our conditions to induce COX-dependent platelet aggregation. TXB_2 was measured in the supernatant by enzyme immunoassay.

Overexpression of human recombinant COX-1 in COS-7 cells and COX-1 activity

COS-7 cells were grown using DMEM-medium containing 10% fetal bovine serum (FBS). Cells were transfected in suspension with pcDNA3-COX-1 plasmid using FuGENE® 6 transfection reagent (Roche Applied Science) at a ratio of 3:1 (FuGENE:DNA, v/w) and then cultured in DMEM media + serum in 12-well plates. For COX-1 activity, cells were incubated 48 hours post transfection in the absence or presence of different concentrations of compounds **22, 23**, **29** and **30** or Ibuprofen in Hanks buffer, pH 7.4, containing 1mg/ml BSA for 30 minutes prior to the addition of 25 μM arachidonic acid for 30 minutes. PGE_2 was measured in the supernatants by enzyme immunoassay. Cells were washed twice with PBS and lysed in scrapped with lammeli buffer. COX-1 protein was determined by western blot as previously described. [21] Briefly, SDS polyacrylamide electrophoresis was performed using 8% gels followed by protein transfer using a semi-dry transferred. Immunoblot analysis was performed using selective monoclonal antibody anti COX-1 (COX-111) (1/1000) and a monoclonal antibody anti-β-actin (1/2000). The effect of 25 and 50 μM of compounds **18, 19**, **25** and **26** on cell viability of COS-7 cells overexpressing COX-1 was evaluated using WST-1 assay and showed an absence of toxicity of these compounds.

Data analysis

Aggregation data were expressed after defining the slope for each aggregation curve, which better reflects the rate of the platelet reaction, using the Born's method. Curve fitting and calculation of the IC_{50} values were done using Grafit 7 software (Erithacus software, Staines, UK). Results of TXB_2 and PGE_2 measurement were expressed as the mean ± S.E.M. for at least 3 independent experiments and statistical analysis was performed using SigmaPlot (Systat Software Inc., San Jose, CA). Autoradiograms obtained from western blot analyses were scanned using Epson 1680 pro scanner and densitometric analysis was performed using Scion NIH software.

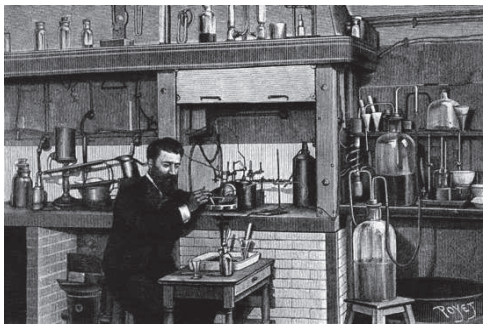
Target selection and preparation

The 3D structure of the ovine COX-1 complexed with ibuprofen (PDBID: 1EQG) was selected for docking simulations. Water and other heteratoms were removed from the structure. Chain A was retained including ibuprofen and heme group. Hydrogen atoms were added, atom typing and partial charges were assigned using AMBER forcefield. The coordinates of the binding site were extracted using the co-crystallized ligand, Ibuprofen. Docking and scoring. Low energy conformations of the chemical compounds were generated using Catalyst (Accelrys, Inc.). The (R)- enantiomers of compounds **18, 19** and **25** were selected, docking simulations were carried out using Autodock 4.2, each docking simulation was achieved with 10 docking runs with 150 individuals using the Lamarckian genetic algorithm implemented in Autodock and 250000 energy evaluations. The binding energies were estimated from a new free-energy scoring function based on the AMBER forcefield, an updated charge-based desolvation term and improved models of the unbound state. The best poses were analyzed and visualized with Disovery Studio visualizer (Accelrys, Inc.).

CHAPTER II

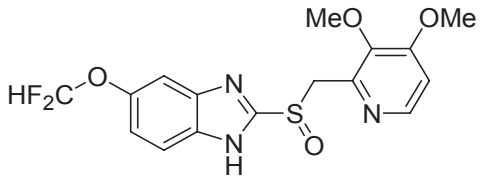
ESSENTIAL BIBLIOGRAPHIC ELEMENTS FOR THE SYNTHESIS AND THE CHEMISTRY OF COMPOUNDS WITH CF_2H AND CF_2R MOIETIES

I- Introduction

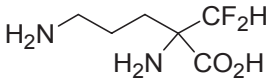


Over a century after the discovery of F_2 by Henri Moissan in 1886,[1] the impact of fluorine chemistry in life sciences became very high (around 20% of all pharmaceuticals and 30-40% of all agrochemicals on the market contain fluorine).[2] It is known that introduction of fluorine in organic molecules strongly modifies their physical, chemical and biological activities.[3] For that, and due to its wide applications in different important fields such as agriculture, medicinal and material sciences, organofluorinated chemicals has attracted high attention in the last decades.[4] Compared to trifluoromethyl compounds, the chemistry of *gem*-difluorinated molecules is less studied,[5] even though CF_2-containing derivatives may exhibit interesting biological activity. In fact, the *gem*-difluoromethylene moiety is considered as a bioisostere both of oxygen and of a carbonyl group.[6] Further, it has been proved that a difluoromethyl group (CF_2H) can act as a more lipophilic hydrogen bond donor than typical donors such as OH and NHR. This makes it as an interesting group in designing bioactive molecules,[7] and several drugs bearing CF_2 units have been prepared such as the ones indicated in Figure 1.[8]

Figure 1. Representative examples of drugs containing CF_2 group.



Pantoprazole



Eflornithine (DFMO)

Many approaches have been described for the preparation of *gem*-difluorocompounds as described in review articles.[9] In this part we will present only a selection of the most representative methods used in this context.

II-Preparation of *gem*-difluoromolecules

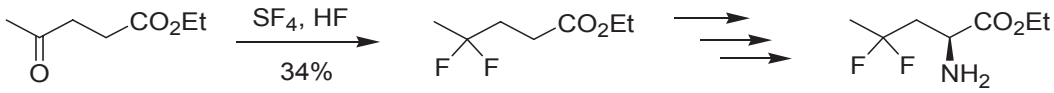
In general, the preparation of *gem*-difluoromolecules falls broadly into two classes. The first involves direct fluorination reactions, either nucleophilic or electrophilic, while the second draws from the use of fluorinated building blocks.[10]

II-1 Direct *gem*-difluorination

One of the most common and successful strategies in the preparation of *gem*-difluoro molecules is the transformation of CO to CF_2, in which aldehydes and ketones react with several fluorinating agents. Diethylaminosulfur trifluoride (DAST) is considered as the most classical representative of these agents. Selenium tetrafluoride[11] and molybdenum hexafluoride[12] have been used on a number of simple systems. In addition to their mildness, their hazards during their preparation and use, as well as toxicity problems, limited their applications and this gives more advantages to the DAST chemistry.

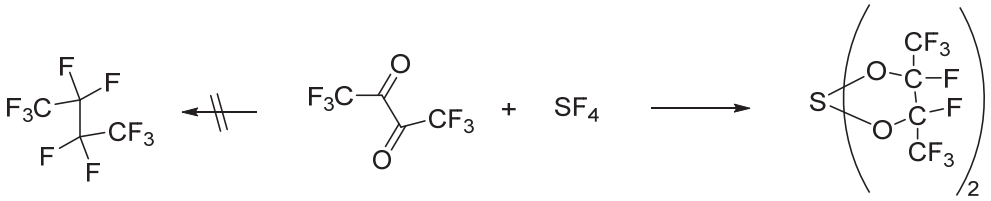
Sulfur tetrafluoride, which is a gaseous reagent, has received high attention as a fluorinating agent.[13] It was successfully used also in selective *gem*-difluorination reactions (Scheme 1).[14]

Scheme 1. Fluorination using sulfur tetrafluoride.



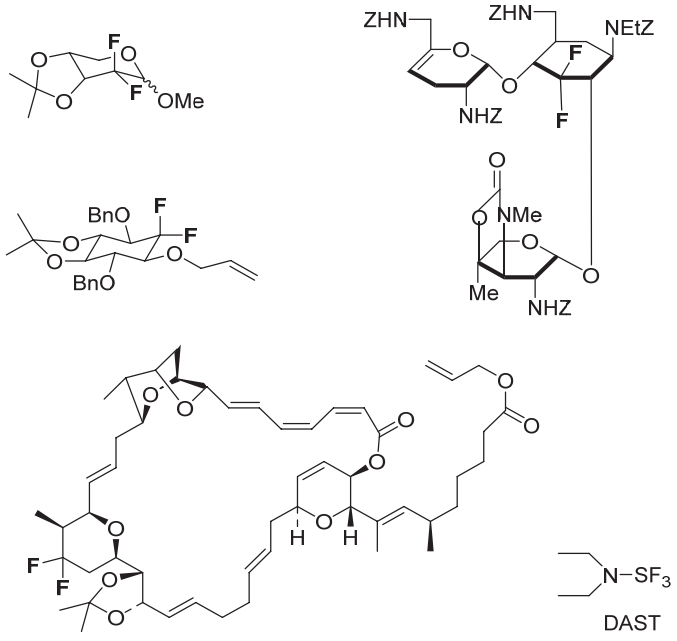
However, SF_4 is a toxic gas, and many transformations involving it require elevated temperatures,[15] which makes its handling very difficult, and need special apparatus. Further, the presence of excess HF is considered as a drawback, since it leads to side reactions (Scheme 2).[16]

Scheme 2. Unexpected reaction of sulfurtetrafluoride with α-dicarbonyl compounds.



To overcome these problems several dialkylaminosulfurtrifluorides were prepared.[17] In 1975, Middleton has reported DAST as an efficient fluorinating agent.[18] DAST was successfully applied across a wide range of aldehydes and ketones.[19] One of the earliest studies about the efficiency of DAST was done by Cross,[14b] who reported DAST as a good *gem*-difluorination reagent in complex systems and several reports later supported Cross results. Many difluoro compounds were obtained from ketone precursors by DAST fluorination (Scheme 3).[20]

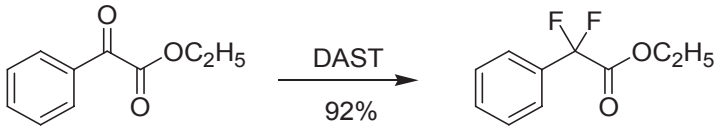
Scheme 3. Representative *gem*-difluoro compounds prepared by DAST fluorination.[21]



In addition to its mildness and its easy handle, compared to SF_4, DAST is more selective and fluorinate a wider range of carbonyl compounds. In 1980, Middleton reported a high yield one-

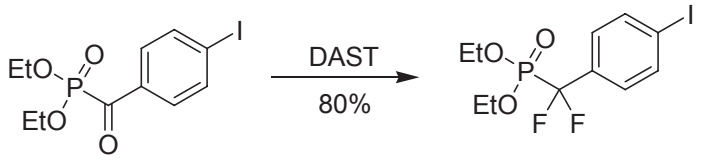
step method for preparing esters of *α,α*-difluoroacetic acids by the selective replacement of the *α*-oxo group of α-oxoarylacetates with two fluorine atoms, using DAST (Scheme 4).[22]

Scheme 4. Fluorination of α-ketoesters using DAST.



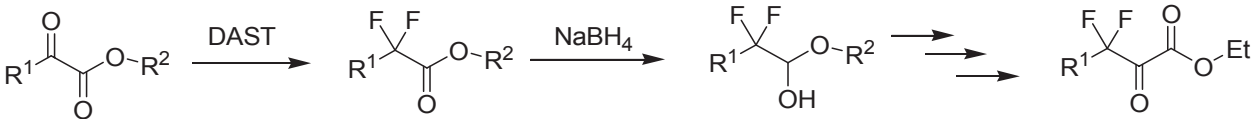
Further, DAST has shown an efficient CO/CF_2 transformation of α-ketophosphonates to *α,α*-difluorophosphonates (Scheme 5).[23]

Scheme 5. Extension of DAST fluorination toward ketophosphonates.



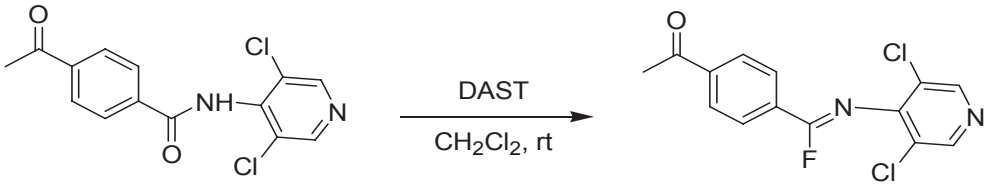
Parisi has extended the synthesis of *α,α*-difluoroesters toward synthesis of *β,β*-difluoroesters (Scheme 6).[24]

Scheme 6. Synthesis of of *β,β*-difluoroesters.



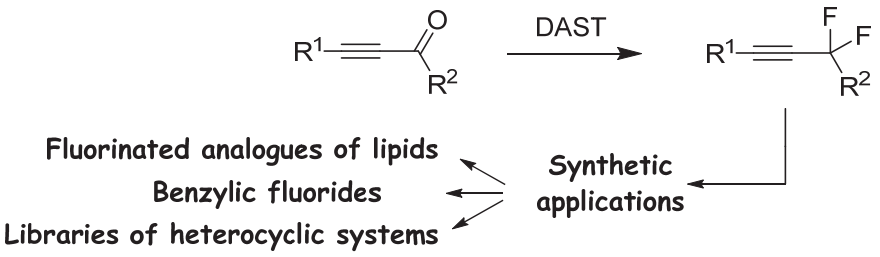
DAST has shown an interesting selectivity and reactivity toward fluorination of aldehydes and ketones over an ester group.[25] However, unexpected products were isolated while fluorinating some special kinds of carbonyls (Scheme 7). During this fluorination, instead of the difluoro target molecule, a fluoroimine was isolated in good yield.

Scheme 7. DAST fluorination side product.



During last the years, our lab has developed the synthesis of *gem*-difluoropropargylic molecules since they appeared as highly versatile intermediates in organic synthesis (Scheme 8).[26] Due to the presence of propargylic system,[27] the carbonyl group is efficiently transformed into CF_2 using DAST. Then, corresponding *gem*-difluoro intermediates have been applied in several areas of research, either for linear derivatives (analogues of lipids) or for carbo- or heterocyclic series.

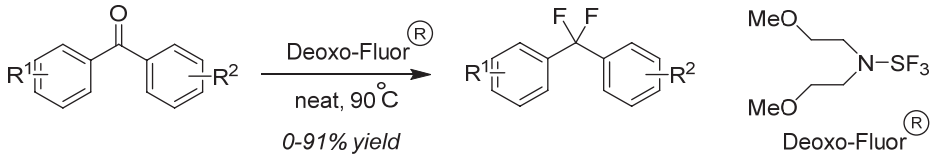
Scheme 8. Preparation and examples of synthetic applications of *gem*-difluoropropargylic compounds.



However, serious drawbacks of DAST should be noted: its thermal instability above 60 °C and it's water sensitivity induce special handling and shipping restrictions.[28] Moreover, some ketones such as non-enolizable ketones, are difficult to fluorinate by DAST.[29] For that, investigations to find new fluorinating agents have been performed.

Deoxo-Fluor®,[30] which is thermally more stable than DAST, was prepared and used in fluorination reactions, especially those which need harsh conditions such as fluorination of bisarylic ketones (Scheme 9).[31]

Scheme 9. Fluorination of bisarylic ketones using Deoxo-Fluor®.

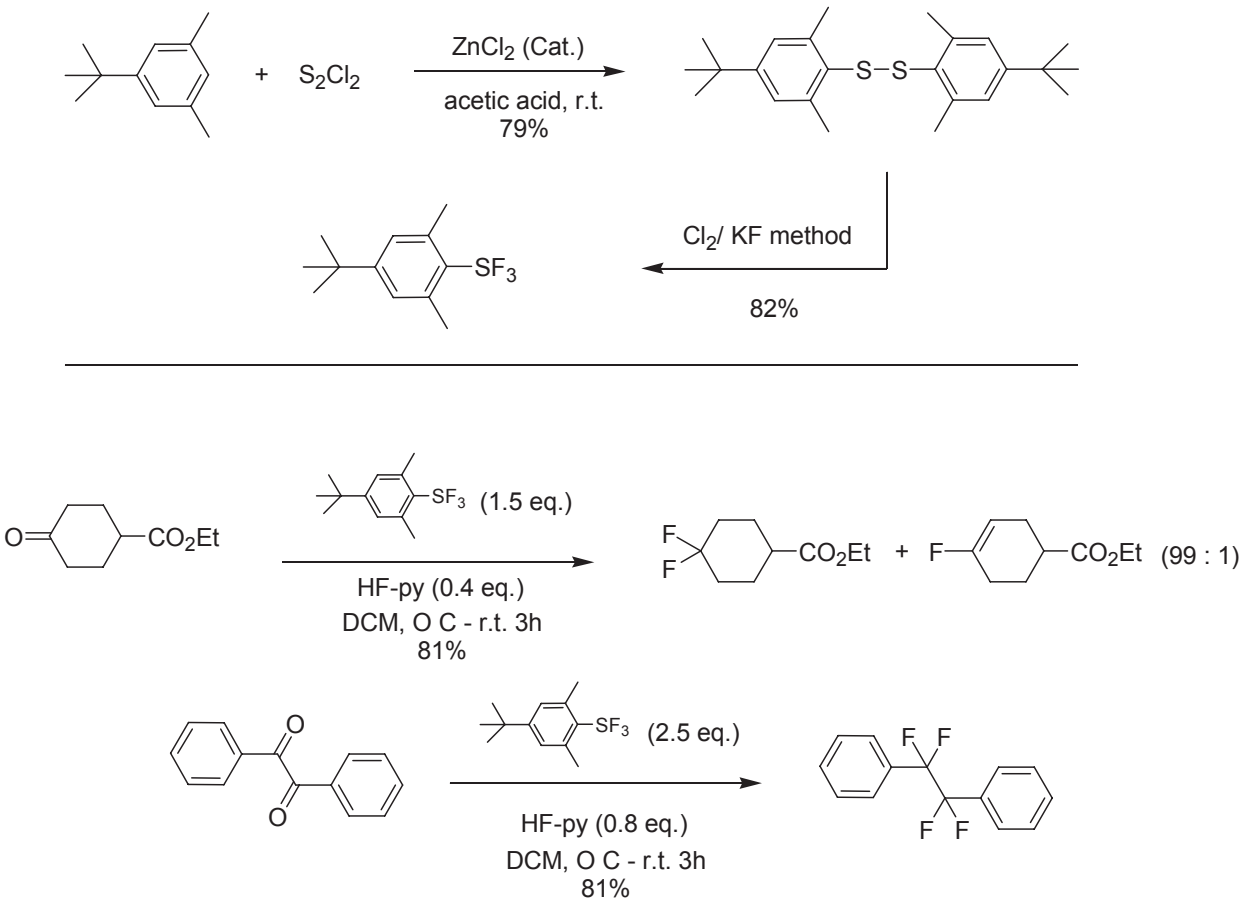


As discussed in the next chapter, the fluorination of such ketones was found to be highly sensitive to the nature and position of the substituents of the arylic systems. The synthesis of the desired *gem*-difluorinated adducts was occurring between 0 to 91 % yield: lower yields were obtained with donating groups, while withdrawing groups afforded higher yields.

In addition, Umemoto *et al* [32] reported more recently 4-*tert*-butyl-2,6-dimethyl phenylsulfurtrifluoride as a new deoxofluorinating agent. This reagent is characterized by its high thermal stability, unexpected resistance to water, high fluorinating capability and extensive potential application.

In addition to performing the conversion of aldehydes and ketones, even the non-enolizable ones, to CF_2 groups this reagent efficiently converts also thiocarbonyls to CF_2 groups (Scheme 10).

Scheme 10. Synthesis of 4-*tert*-butyl-2,6-dimethylphenylsulfurtrifluoride and representative examples of its use as a deoxofluorinating agent.



Recently, the same group reported the use of arylsulfurchlorotetrafluorides in deoxo- and dethioxo-fluorinations.[33] Phenylsulfurchlorotetrafluoride itself is not the fluorinating agent. Treating the tetrafluoride compound with a reducer generates *in situ* the phenylsulfurtrifluoride which reacts with the substrates to afford the difluorinated adducts in high yields (Table 1).

Table 1. Fluorination with $PhSF_3$ prepared *in situ* from $PhSF_4Cl$.[33]



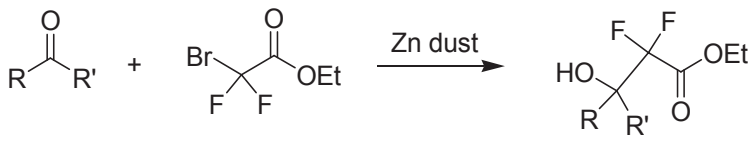
Trial	Reducer	Substrate	Product	Yield (%)
1	Pyridine	PhCHO	$PhCF_2H$	87
2	Pyridine	$PhCOCH_3$	$PhCF_2CH_3$	75
3	Pyridine	n-$C_{10}H_{21}COCH_3$	n-$C_{10}H_{21}CF_2CH_3$	86
4	Pyridine	Cyclohexanone	1,1-diF-cyclohexane	94
5	Pyridine	PhCOCOPh	$PhCF_2CF_2Ph$	95
6	ArSSAr	PhCH[-S$(CH_2)_3$S -]	$PhCF_2H$	99
7	ArSSAr	PhC(=S)OCH_3	$PhCF_2OCH_3$	98

II-2 Use of *gem*-difluorinated building blocks.

Using already fluorinated building blocks is considered as a very efficient way to prepare *gem*-difluoro compounds.[10] Different types of reactions have been developed for the introduction of the CF_2R or CF_2H moieties.

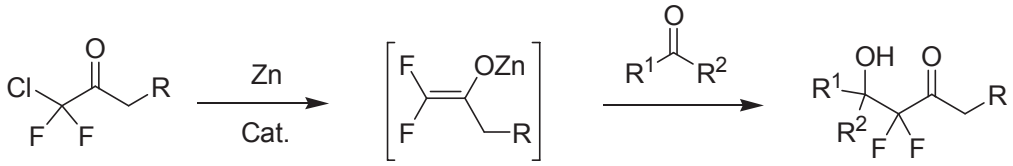
Reformatsky reaction of halodifluoroacetates and halodifluoroketones is an old efficient approach of using difluorinated building blocks.[12] In 1984, the preparation of difluorohydroxyesters has been reported by Fried, in which a Reformatsky reaction of a bromodifluoroester with aldehydes and ketones was performed (Scheme 11). [34]

Scheme 11. Reformatsky reaction using bromodifluoro compounds.



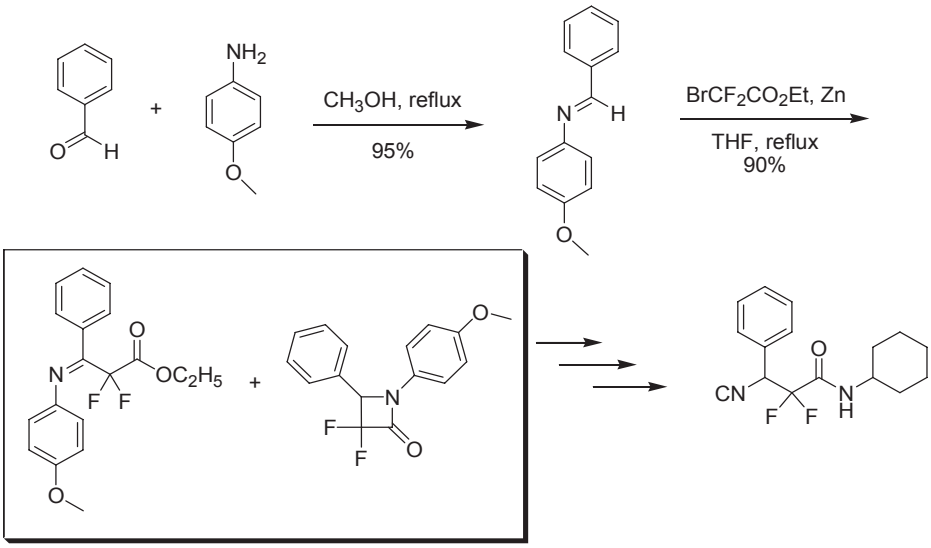
Moreover, the synthesis of hydroxydifluoro ketones has been reported by reacting chlorodifluoromethyl ketone with carbonyl compounds. The reaction was mediated by zinc and catalyzed by copper chloride or silver acetate (Scheme 12).[35]

Scheme 12. Reformatsky reaction of chlorodifluoro compounds.



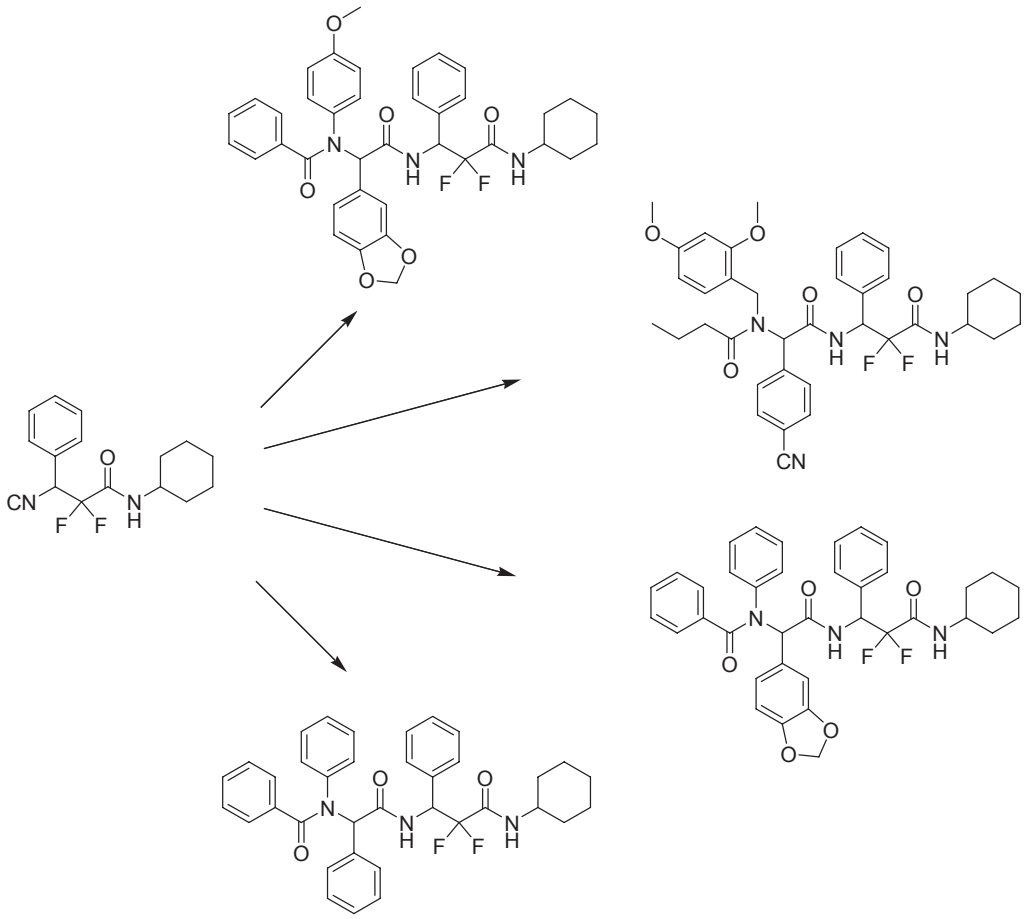
In 2009, N. Liu et al. have reported a new efficient method for the synthesis of a novel *gem*-difluoromethylene-containing isocyanides, which can be used as a building block for the synthesis of difluorinated pseudopeptides via Ugi reaction.[36] The *gem*-difluoromethyl group was inserted via a Reformatsky-type reaction and the difluoro adducts have been obtained in excellent yields (Scheme 13).

Scheme 13. Synthesis of *N*-cyclohexyl-2,2-difluoro-3-phenylpropanamide.



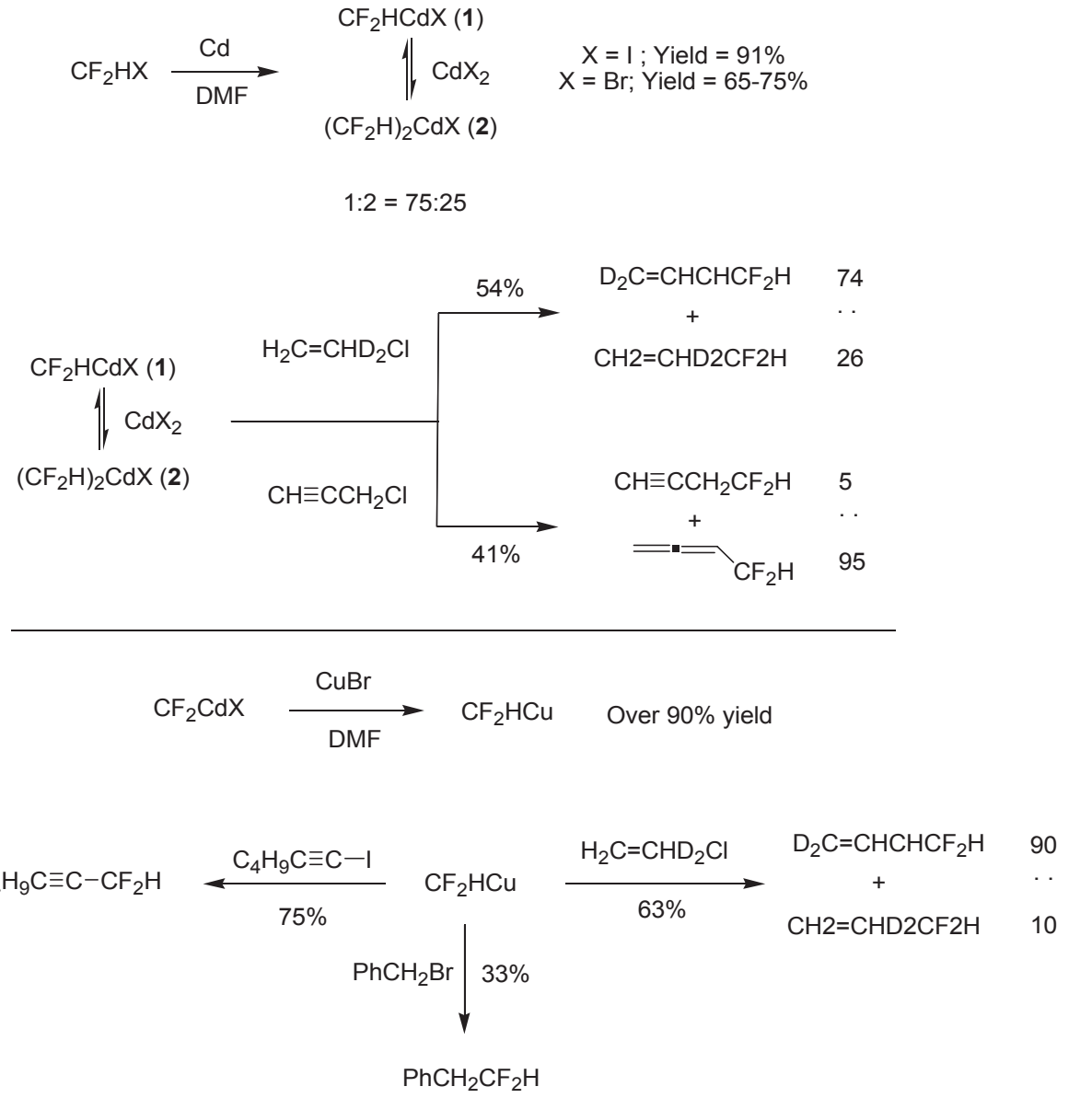
The unique character of isocyanides is that they can react readily with both nucleophiles and electrophiles at the same carbon atom. Due to this exceptional reactivity, isocyanides are very often used in multicomponent reactions (Scheme 14). [37]

Scheme 14. Several examples of α,α-difluoromethylene analogues of β-aminoacids starting from an isocyanide intermediate.



In addition, *gem*-difluoromethyl compounds could be obtained by nucleophilic additions of difluoromethyl cadmium, zinc and copper reagents. In contrary to the difluoromethyllithium (CF_2HLi) and the difluoromethyl Grignard reagent (CF_2HMgX), those organometallic reagents have been successfully prepared and used as difluoro-nucleophilic reagents (Scheme 15).[38] It is useful to mention that the reactivity of the organozinc reagent is significantly less than that of corresponding cadmium and copper reagents.[38c]

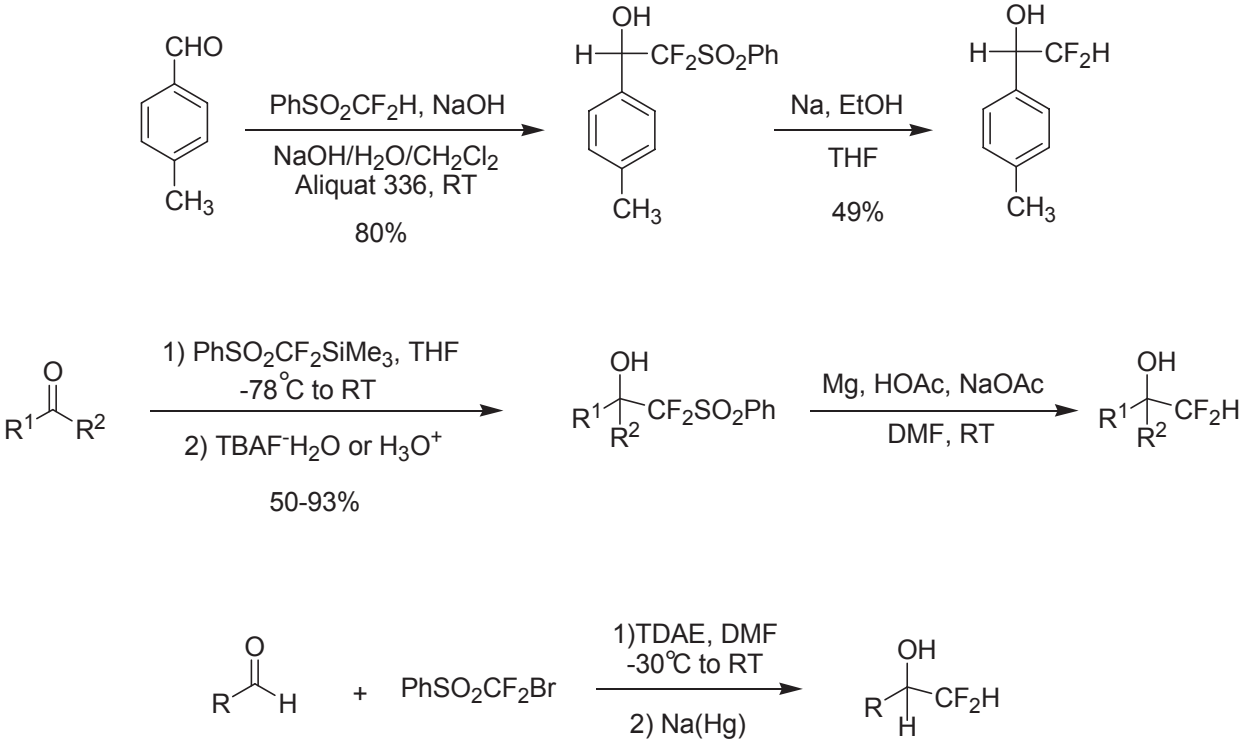
Scheme 15. Preparation and examples of synthetic applications of difluoro-cadmium and copper reagents.



It should be pointed out that, due to the less free ionic character of carbon-metal bonds in these organometallic reagents, they do not react with other classical electrophiles such as aldehydes, ketones and imines.[39]

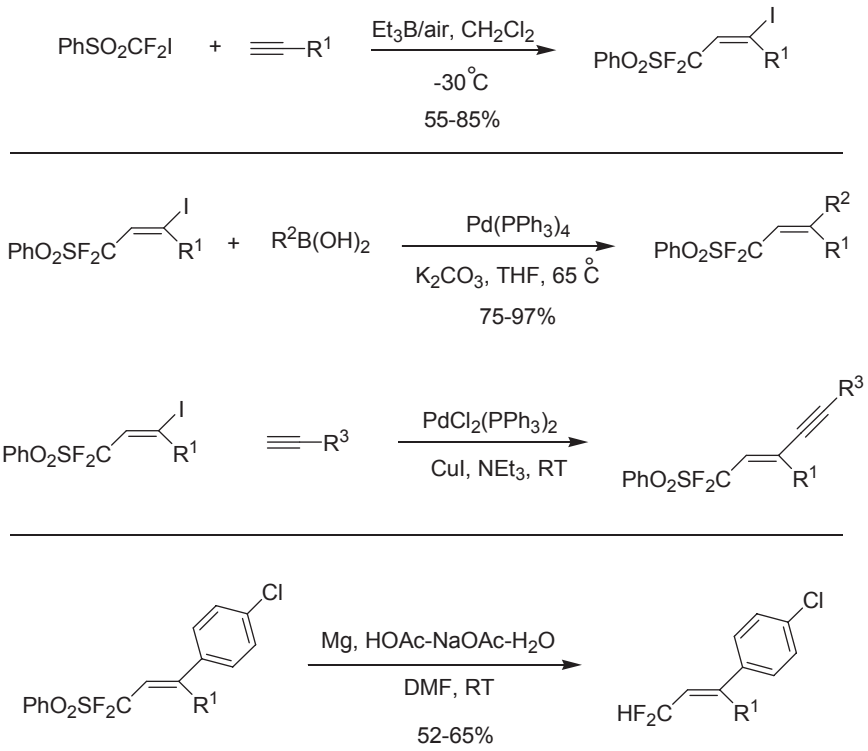
While continuing the effort to develop difluoromethylation methodologies, several phenylsulfonyldifluoro compounds ($PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$, $PhSO_2CF_2Br$) were reported as nucleophilic difluoromethylation reagents (Scheme 16).[40]

Scheme 16. Representative examples for the use of $PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$ and $PhSO_2CF_2Br$ as nucleophilic difluoromethylation reagents.



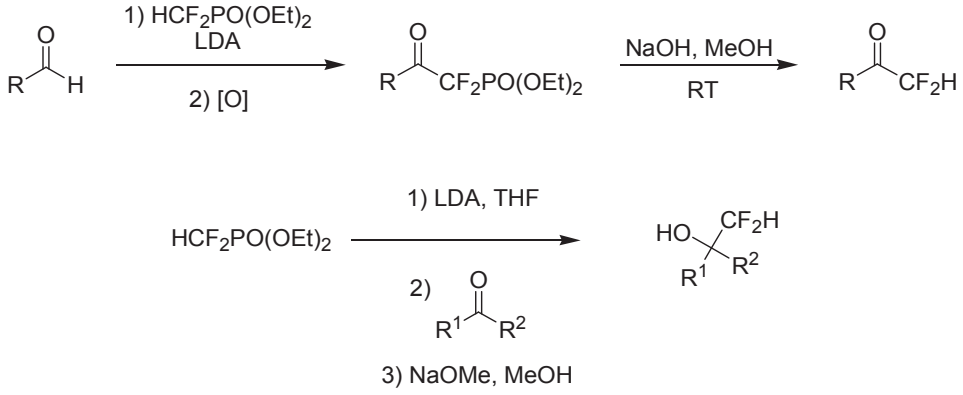
In 2009, *Y.Li et al* reported a stereoselective free radical (phenylsulfonyl)difluoromethylation of terminal alkynes starting from iododifluoromethylphenylsulfone ($PhSO_2CF_2I$) and using Et_3B/air as an initiator.[41] The difluoro-alkenes with vinylic iodides could be further subjected to Suzuki and Sonogashira coupling reactions. This makes them as useful precursors for the preparation of many CF_2-substituted alkenes (Scheme 17).

Scheme 17. Preparation of difluoro-vinylic iodide intermediates and their use in Suzuki and Sonogashira coupling reactions.



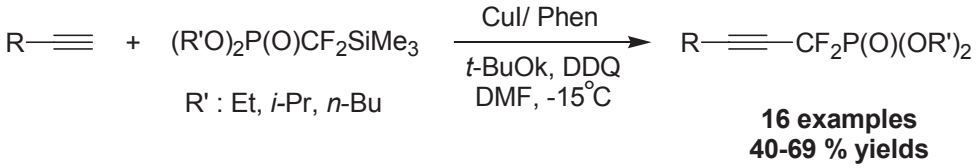
Similar to difluoromethylphenylsulfone ($PhSO_2CF_2H$), the diethyl difluoromethylphosphonate [$HCF_2PO(OEt)_2$] is considered as a useful difluoromethylation reagent.[42] In 1996, Piettrev et al. reported the difluoromethylation of aldehydes using $HCF_2PO(OEt)_2$.[43] More recently, this reaction was successfully extended to ketones (Scheme 18). [44]

Scheme 18. Difluoromethylation of aldehydes and ketones using [$HCF_2PO(OEt)_2$].



Further, copper-mediated oxidative cross-coupling reactions of terminal alkynes with readily available α-silyldifluoromethylphosphonates under mild conditions have been developed.[45] This method allows for an efficient synthesis of a series of synthetically useful α,α-difluoropropargylphosphonates with excellent functional group compatibility (Scheme 19).

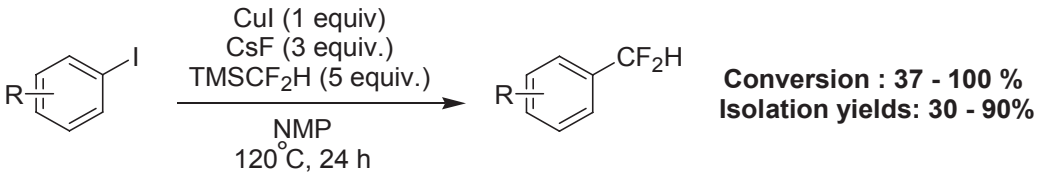
Scheme 19. Copper-mediated oxidative cross-coupling reactions.



Generally, difluorophosphonates can be prepared by direct electrophilic fluorination of phosphonate carbanions[46] or DAST-promoted nucleophilic fluorination of α-oxophosphonates.[47] The addition of a phosphonodifluoromethyl radical onto alkenes, alkynes, and unsaturated ketones has also been developed.[48] Furthermore, the nucleophilic displacement,[49] nucleophilic addition, or transition metal-mediated cross-coupling reaction of metalated difluoromethylphosphonates ($(EtO)_2P(O)CF_2M$; M = Li, ZnBr, MgCl, CdBr) have been extensively investigated.

Hartwig recently reported a straightforward method for the cross-coupling of aryl and vinyl iodides with a difluoromethyl group, generated from readily available reagents, to form difluoromethylarenes and difluoromethyl-substituted alkenes.[50] The reaction of electron-neutral, electron-rich, and sterically hindered aryl and vinyl iodides with the combination of CuI, CsF and $TMSCF_2H$ leads to the formation of difluoromethyl-substituted products in high yield with good functional group compatibility. This reaction type was suitable for the conversion of a range of aryl iodides to difluoromethylarenes (Scheme 20).

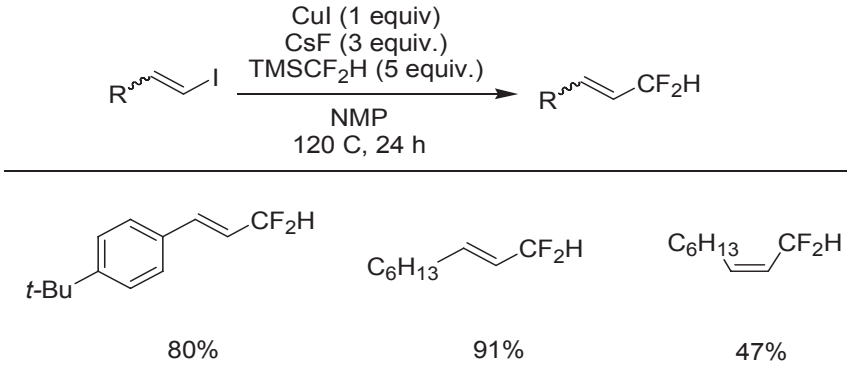
Scheme 20. Difluoromethylation of aryl iodides with $TMSCF_2H$ mediated by copper iodide.



The volatility of difluoromethylarenes and the similar polarity of the difluoromethylarene to side products made the yields of isolated material lower than the yields determined by NMR spectroscopy in some cases.

This difluoromethylation protocol was also suitable for the difluoromethylation of vinyl iodides to prepare allylic difluorinated alkenes. This family of products has been prepared also earlier by the reaction of sulfur tetrafluoride or aminosulfurtrifluorides with α-ß unsaturated aldehydes. However, formation of products from allylic substitution and rearrangements of reaction intermediates occur in these systems, resulting in a mixture of isomers.[51] Further, the cross-coupling of vinyl iodides with $TMSCF_2H$ avoids the use of hazardous sulfur fluoride reagents and reactive, electrophilic, *α,β*-unsaturated aldehydes (Scheme 21).

Scheme 21. Difluoromethylation of vinyl iodides with $TMSCF_2H$, mediated by copper iodide.

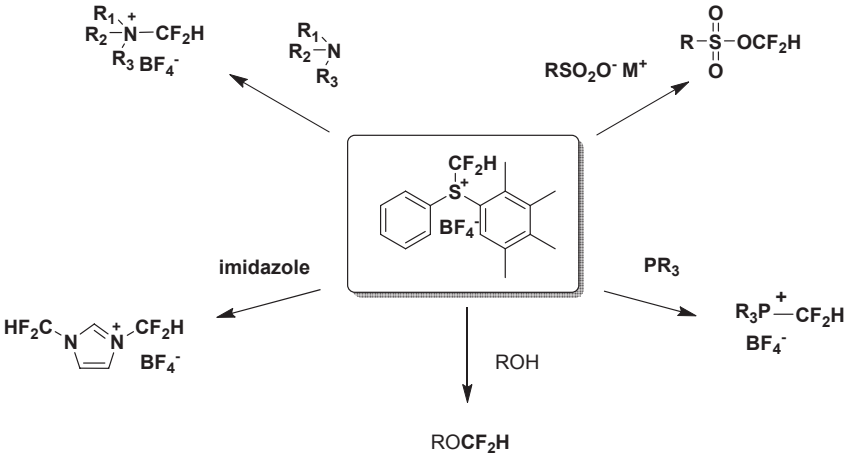


Cis- and *trans*-vinyl iodides, as well as styrenyl iodides, reacted in good yield to give a single stereoisomer of the coupled product.

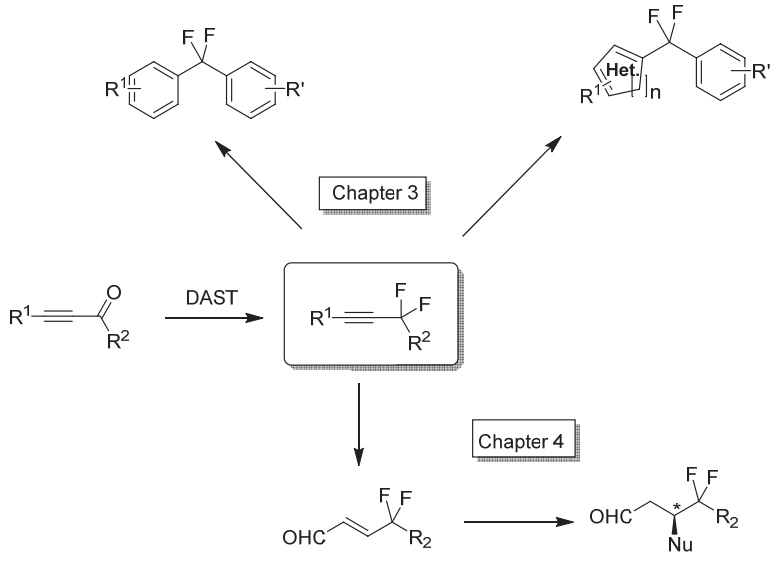
Few years ago, Prakash reported a new sulfonium reagent for the introduction of "CF_2H^+",[52] and this reagent allowed an efficient introduction of difluoromethyl group to different types of

molecules (Scheme 22). It was also successfully applied to acids, amines, phosphines and malonates.[52b]

Scheme 22. New reagents for introduction CF_2H group



Due to this high interest in the synthesis of CF_2H and CF_2R-containing molecules, it seemed important to develop new strategies/methodologies for the preparation of this kind of molecules. This was our target in the second part of this thesis, starting from easily accessible *gem*-difluoropropargylic intermediates. In chapter 3 we will demonstrate how these versatile scaffolds can be used to prepare bisarylic derivatives with a CF_2 linker, as well as corresponding mixed aryl-heteroaryl compounds. Then, in Chapter 4 we will develop asymmetric organocatalytic reactions towards optically active aldehydes with a CF_2 group in β-position.



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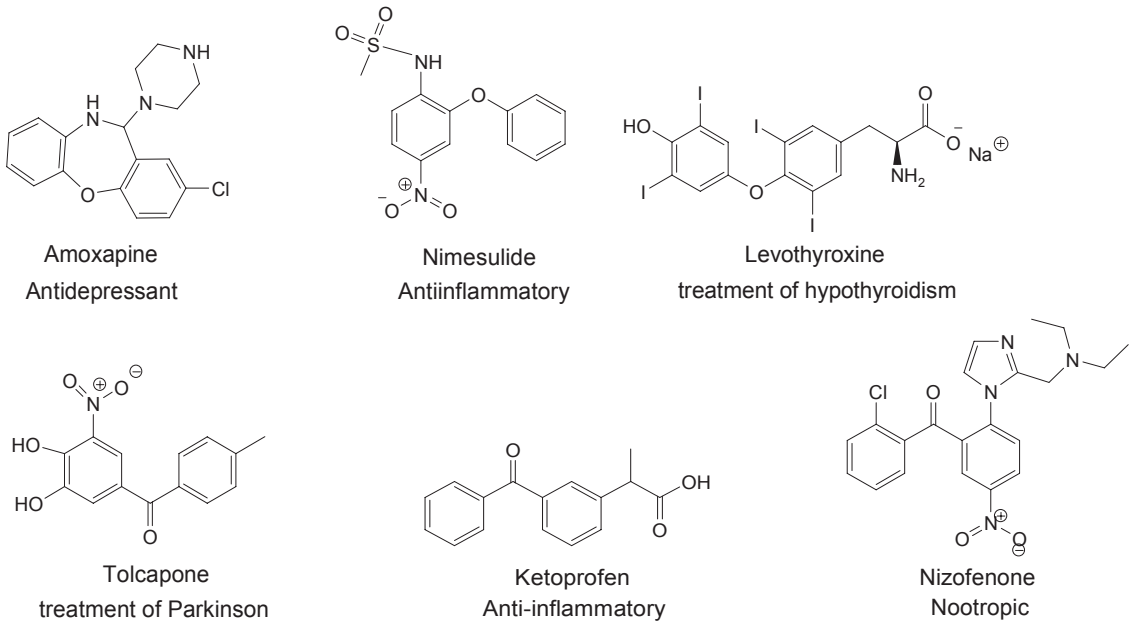
CHAPTER III

DEVELOPMENT OF A NOVEL STRATEGY FOR THE SYNTHESIS OF BISARYLIC COMPOUNDS OR MIXED ARYLIC/HETEROARYLIC COMPOUNDS WITH A CF_2 LINKER

I- Introduction

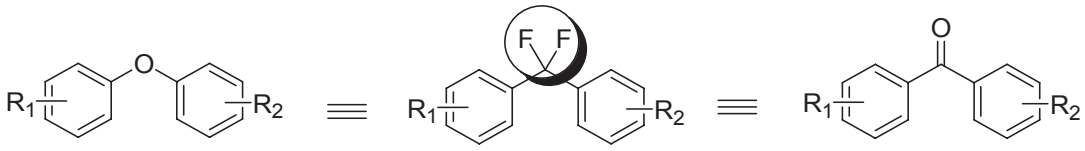
Diaryl ethers are recognized as important moieties since they are key parts of many natural products,[1] and also very often used in bioorganic and medicinal chemistry.[2] Similarly, diaryl ketones are frequently found in the core structures of natural products and/or drugs[3] (Figure 1).

Fig. 1 Selected examples of diaryl ethers and diaryl ketones and their medical applications.



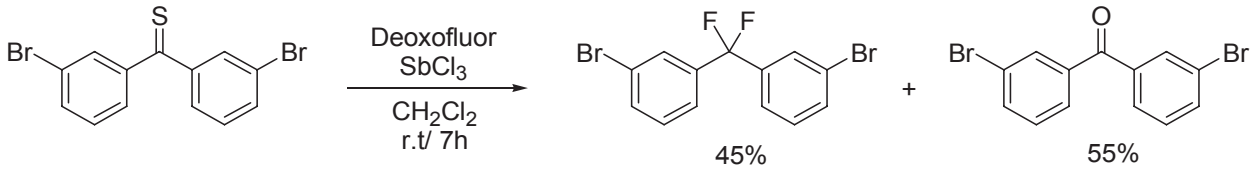
On the other hand, since CF_2 is usually considered as a bioisostere of the oxygen atom, as well as of a carbonyl group[5], therefore it would be of much interest to have an easy access to *gem*-difluoro-bisarylic derivatives (Scheme 1).

Scheme 1. Diaryl ethers, benzophenones and *gem*-difluoro-bisarylic derivatives.



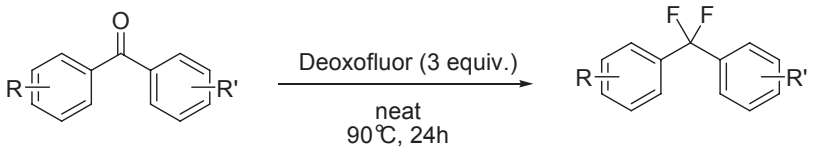
However, carbonyl groups of substituted benzophenones are relatively unreactive under classical fluorination conditions. The direct fluorination of such benzophenones, in the presence of hydrogen fluoride catalyst, has been reported,[6] but it required harsh conditions (180 °C) and pressure equipment. Thus, for the *gem*-difluorination of benzophenones, two step synthetic pathways have been developed. They involve first preparation of derivatives from the carbonyl precursors (such as thioketones or thioacetals), which need to be isolated, and then fluorination reactions of these intermediates. A typical example is given in scheme 2.[7]

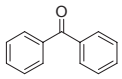
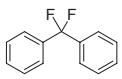
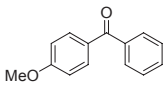
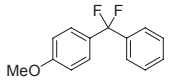
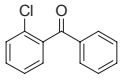
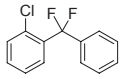
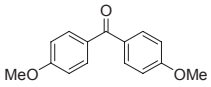
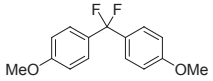
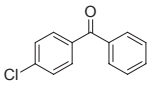
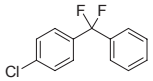
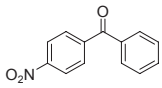
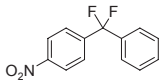
Scheme 2. *gem*-difluorination of benzophenone-derived thioketone.



In addition, direct fluorination of benzophenones using nucleophilic fluorinating agents, such as Deoxofluor®, has important limitations since it is very sensitive to the nature of substituents on the aromatic systems [8] (Table 1).

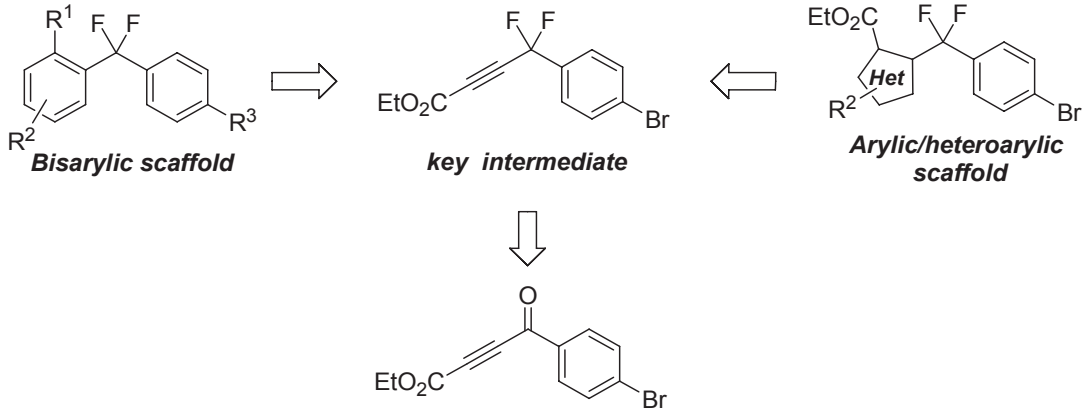
Table 1. *gem*–difluorination of benzophenones with Deoxofluor®



Substrate	Product	Yield (%)	Substrate	Product	Yield (%)
		63			27
		20			0
		64			91

Therefore it appeared of much interest to develop new strategies to access such attractive molecules. *Towards this goal, our design was to build the aromatic rings starting from a propargylic gem-difluoride as a key intermediate (Scheme 3).*

Scheme 3. A new synthetic strategy towards *gem*-difluoro-bisarylic derivatives and mixed aryl/heteroaryl systems.

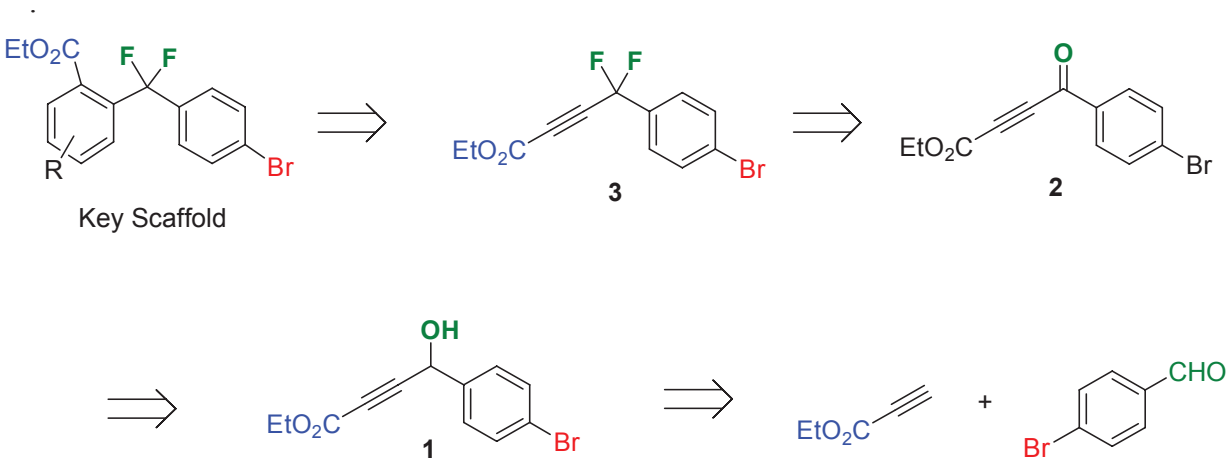


This new approach takes advantage of the easy access and the good reactivity of such fluorinated intermediates [9,10] and further, should allow the preparation of many other carbo- and heterocycles through various types of cycloaddition reactions. Moreover, the presence of ester and bromine should allow the preparation of designed chemical libraries of new fluorinated molecules.

II- Retrosynthetic study of the bisarylic scaffold

The retrosynthesis of the bisarylic scaffold is reported in Scheme 4. It should be obtained by a Diels-Alder-aromatisation sequence, starting from the propargylic *gem*-difluoro intermediate **3**. This one could be prepared by fluorination of highly electrophilic alkyne **2**. The synthesis of latter derivative should involve a two step sequence starting from ethyl propiolate and *p*-bromobenzaldehyde.

Scheme 4. Retrosynthesis of the key scaffold.



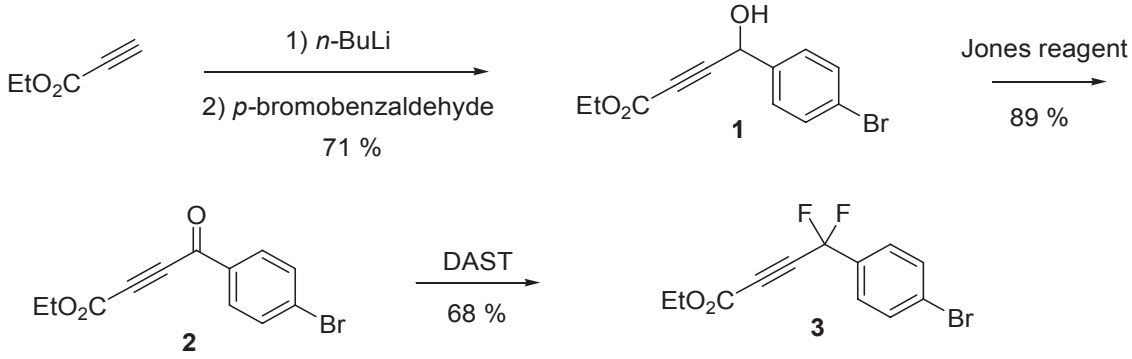
The main advantage of this retrosynthesis is the versatility, since by classical Diels-Alder-aromatization sequences, different diaryl compounds with different substituents and/or functional groups could be prepared from **3**. Moreover, arylic/heteroarylic compounds could be prepared by 1,3-dipolar cycloadditions on this intermediate.

III- Results and Discussion

1) Synthesis of the key *gem*-difluoro intermediate 3.

The synthesis of the key *gem*-difluoro intermediate **3** is reported in Scheme 5. Metallation of ethylpropiolate at strictly controlled temperature (≤ -80°C),[11] followed by trapping with *p*-bromobenzaldehyde and then by TMSCl, afforded propargylic alcohol **1** in 71% yield. Oxidation with Jones reagent gave ketone **2** in 89% yield. Due to the presence of the propargylic system[12] and the ester function, this ketone reacted efficiently with diethylaminosulfurtrifluoride (DAST) to afford **3** in 68% yield. Therefore this new *gem*-difluoropropargylic key intermediate was obtained in three steps and 43% overall yield from ethylpropiolate (Scheme 5).

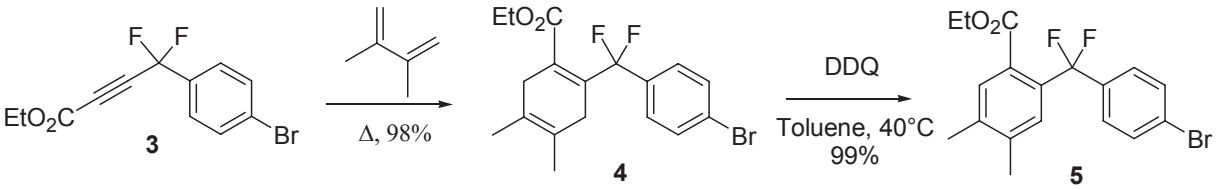
Scheme 5. Synthesis of *gem*-difluoro intermediate **3**.



2) Synthesis of the key scaffold

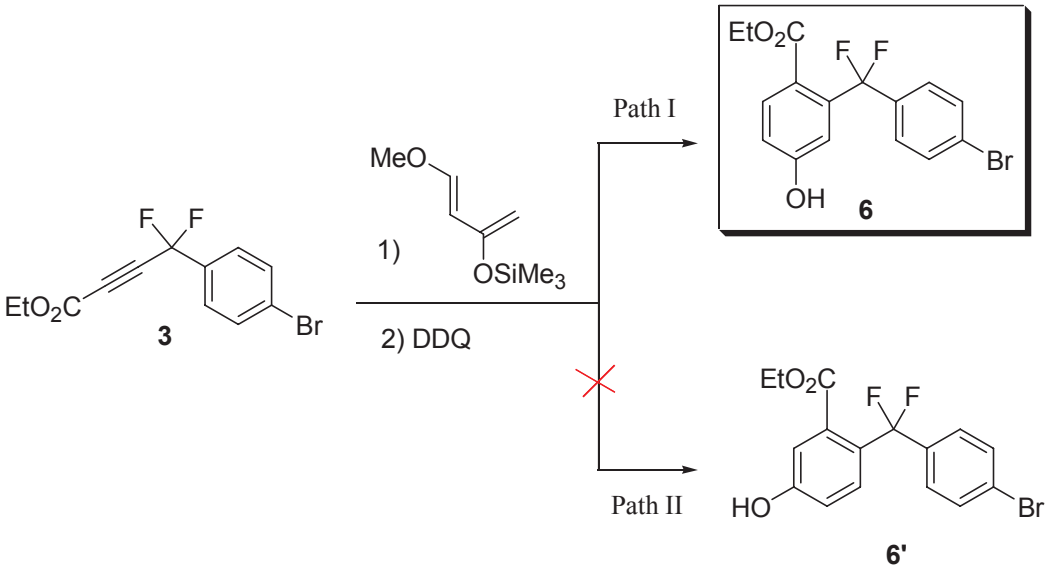
Starting from **3** two representative examples of the bisarylic scaffold have been obtained by a classical Diels-Alder-aromatisation sequence. Reaction with excess dimethylbutadiene (10 equiv.) at reflux gave **4**, which by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-mediated aromatisation afforded the first *gem*-difluoro-bisaryl derivative **5** in 96% overall yield (Scheme 6).

Scheme 6. Synthesis of a representative example of the key scaffold **5**.



On the other hand, reaction with Danishefsky's diene (3 equiv.),[13] followed by DDQ aromatisation, gave the second *gem*-difluorobisarylic molecule **6** in 83% overall yield without formation of the second regioisomer **6'**(Scheme 7).

Scheme 7. Possible products of cycloaddition with Danishefsky's diene.

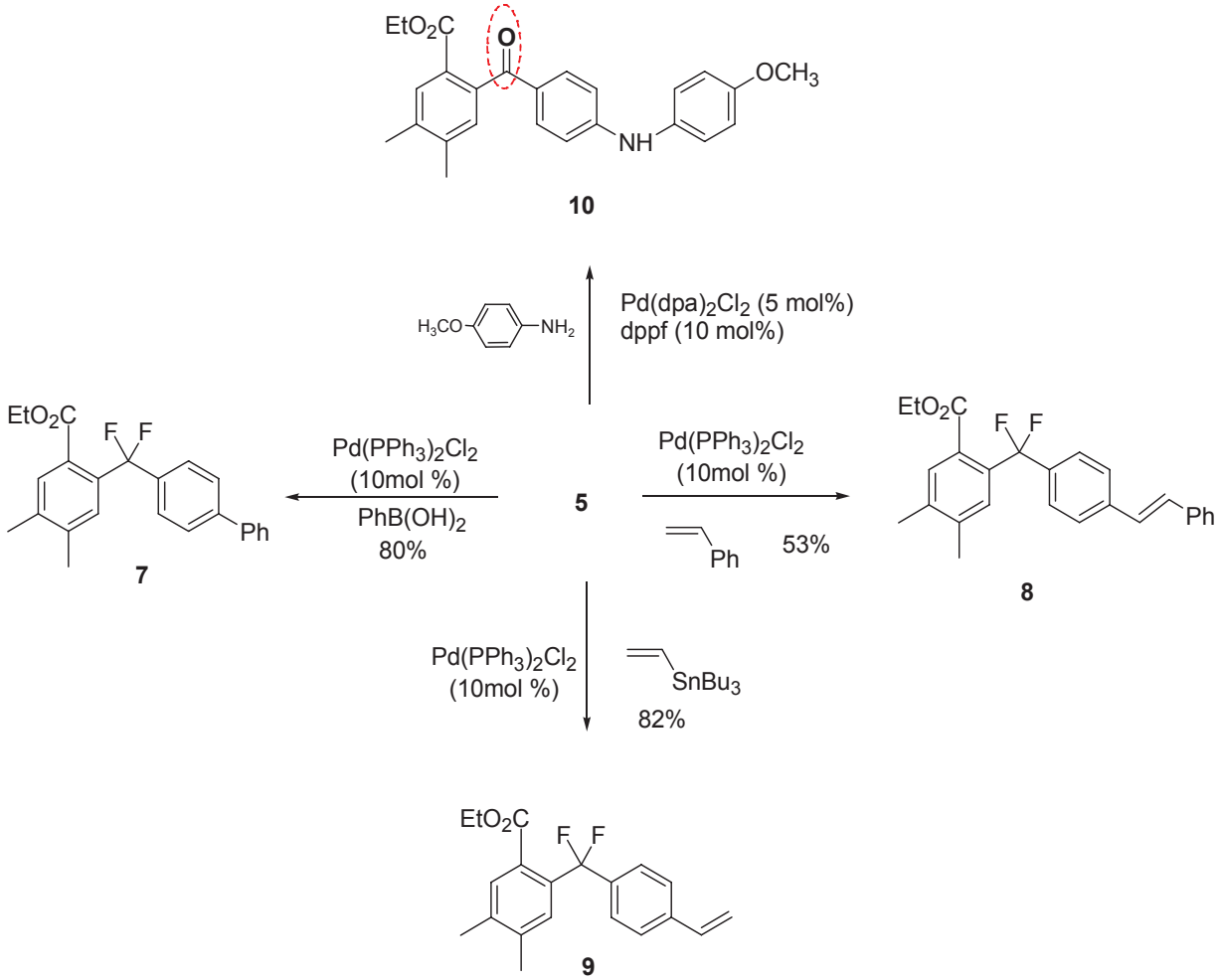


The regioselectivity was established by NMR analysis: ^{13}C NMR showed a singlet at 125.5 ppm, which is typical for <u>C</u>OH at *meta*-position to CF_2, since <u>C</u>OH at *para*-position appears as a triplet (J = 2.3 Hz), thus this cycloaddition takes place through path I where **6** is the obtained product.

3) Synthesis of first chemical library using palladium-catalyzed reactions

Starting from the key scaffold **5**, and due to the presence of bromine group, four different palladium-catalyzed reactions were performed as indicated in scheme 8. First a Suzuki-Miyaura coupling,[14] with phenylboronic acid, afforded biphenyl-type compound **7** in 80% yield. Then a Heck reaction,[15] gave the stilbene-type product **8** in 53% yield while a Stille cross coupling,[16] afforded the styrene-type derivative **9** in 82% yield.

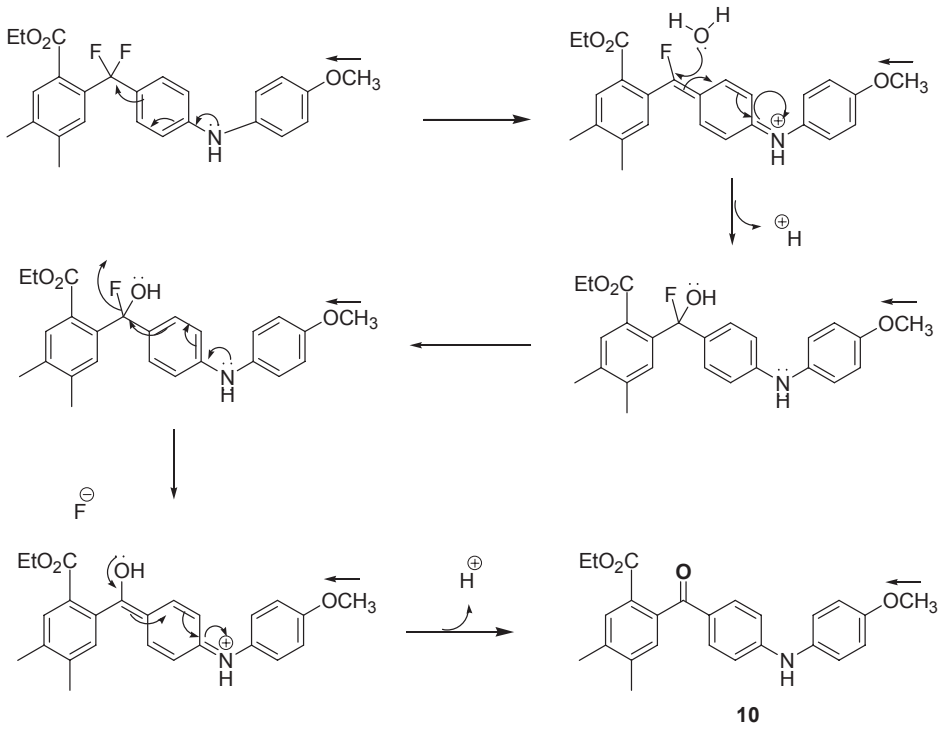
Scheme 8. Palladium-catalyzed reactions on aromatic **5**.



Unfortunately, Buchwald-Hartwig coupling [17] with *p*-anisidine afforded a non-fluorinated compound **10**. In order to understand the formation of this compound, the same reaction under

identical conditions, except the catalyst, was performed again and the starting material was recovered without any loss of fluorine. This indicates that the loss of fluorine should occur after the coupling of *p*-anisidine to **5.** Due to the high electrondonating effect of this anisidine, the benzylic C-F bond becomes more labile, and thus fluorine atom could be easily substituted by the oxygen atom of water as shown in scheme 9.

Scheme 9. Mechanistic proposal for loss of fluorine atoms after Buchwald-Hartwig coupling.



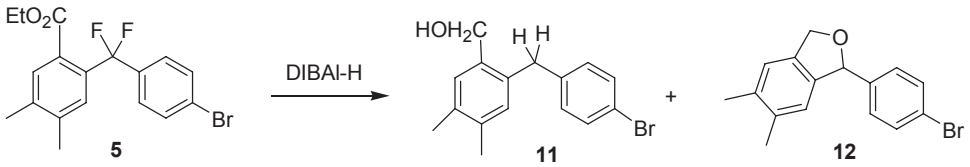
These data prove that bromine atom can be of much use to build some chemical libraries around this fluorinated bisarylic-type skeleton.[18] We could validate the concept with three important examples of different Pd-catalyzed reactions and some more work will be required to establish appropriate reaction conditions for the last Buchwald-Hartwig coupling.

4) Synthesis of second chemical library by using the ester group of 5

After showing the feasibility of using the bromine atom in the synthesis of a first type of chemical library, [18] it was of interest to examine the possibility of using the ester group as a second point of molecular diversity. Since saponification of ester group in compound **5** was unsuccessful under various conditions, reduction of ester followed by oxidation was our strategy to obtain the desired acid. Lithium aluminium hydride ($LiAlH_4$) seemed to be a possible choice for reduction.[19] Unfortunately, the result of such a reduction, under several conditions, was not clean and complex mixtures were obtained. Diisobutylaluminium hydride (DIBAl-H) [20] was our

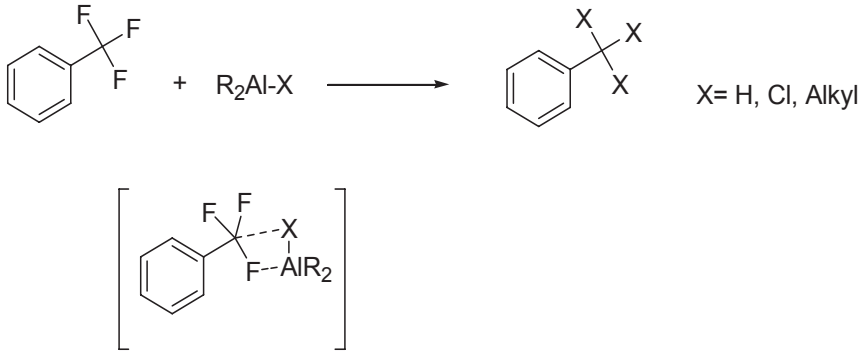
second choice, but this reduction afforded the two non fluorinated compounds **11** and **12** (Scheme 10).

Scheme 10. Reduction of intermediate **5** by DIBAl-H.



The carbon–fluorine bond is commonly regarded as a very strong single bond and stable against a variety of reagents, not only due to their high bonding energy, but also due to the shielding of carbon by the non-bonding electrons of F.[21] It was reported that C-F bond of benzotrifluorides can be converted into a C-H bond by organoaluminium reagents [22] and this should explain the formation of **11** (Scheme 11).

Scheme 11. Cleavage of benzylic C-F bonds using organoaluminium reagents.



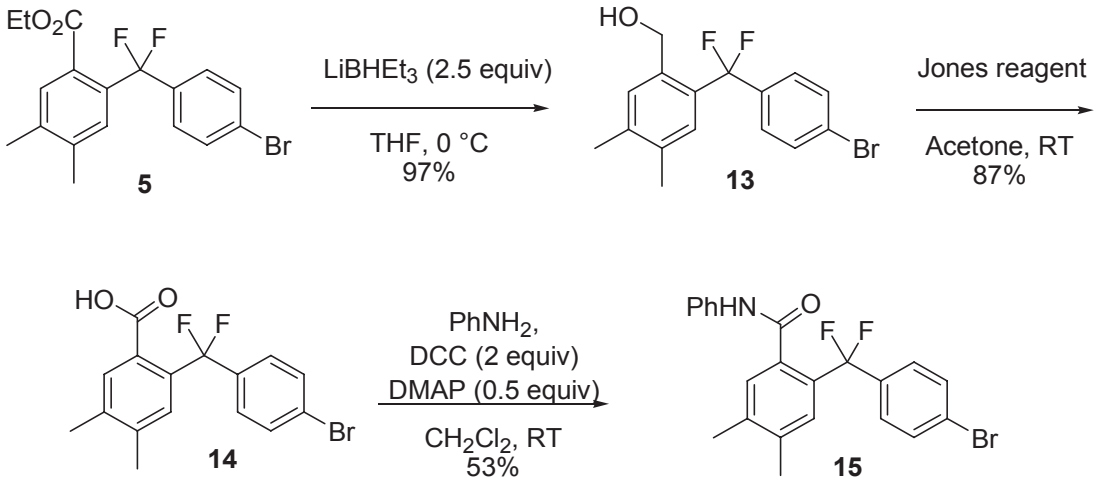
Moreover, in 2003, J. Hu has reported a C-F Bond cleavage by an intramolecular S_N2 reaction of alkyl fluorides with *O*-nucleophiles (Scheme 12). [23] A similar process could explain the formation of compound **12** in our reaction.

Scheme 12. C-F bond cleavage by intramolecular S_N2 reaction.



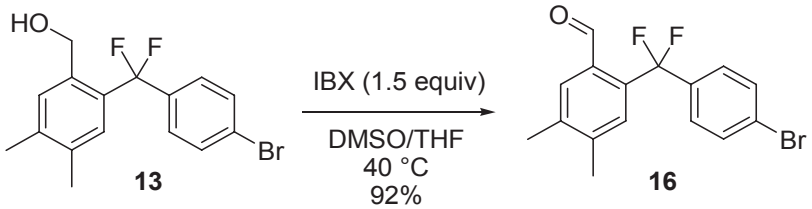
However, ester **5** was successfully reduced in a clean reaction, using organoborane reducing agents. Reduction using Lithium tri-sec-*butyl*(hydrido)borate (L-Selectride) and Lithium triethylborohydride (Superhydride®) afforded the adduct **13** in 71 and 97 % yield respectively. Oxidation of **13** with Jones reagent gave the desired carboxylic acid **14** in 87 % yield. A classical coupling reaction with DCC and DMAP and aniline afforded the amide **15** in 52% yield (Scheme 13).

Scheme 13. Reduction of ester followed by oxidation to acid and synthesis of amide.



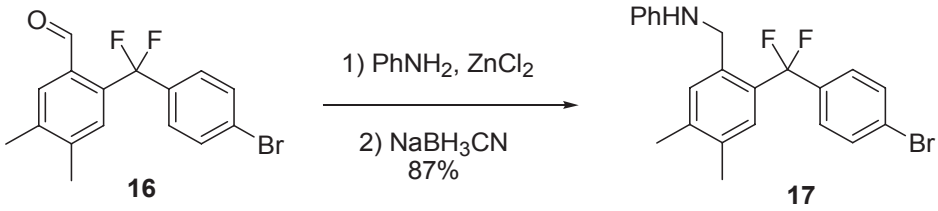
Further, oxidation of alcohol **13** by 2-iodoxybenzoic acid (IBX) afforded, in 92% yield, the aldehyde **16** as shown in scheme 14.

Scheme 14. Oxidation of alcohol **13** to aldehyde **16**.



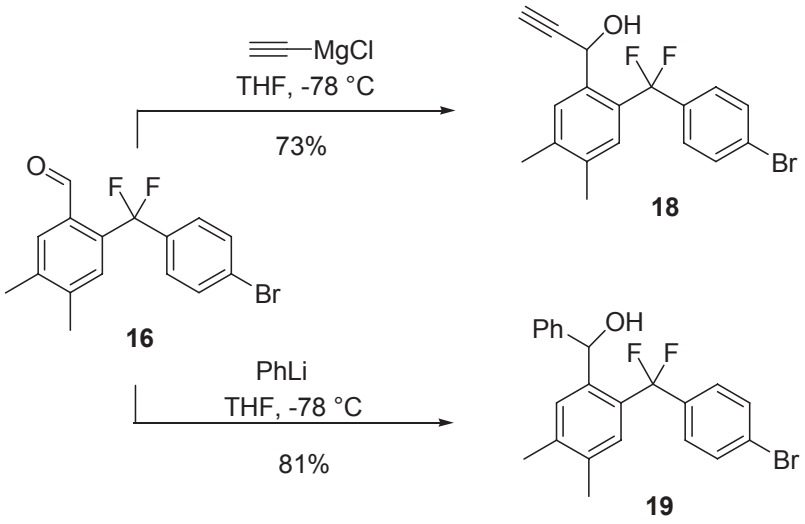
This aldehyde was considered as a versatile intermediate for the preparation of many molecules. First, reductive amination with aniline gave amino derivative **17** in 87% yield (Scheme 15).

Scheme 15. Reductive amination of aldehyde **16**.



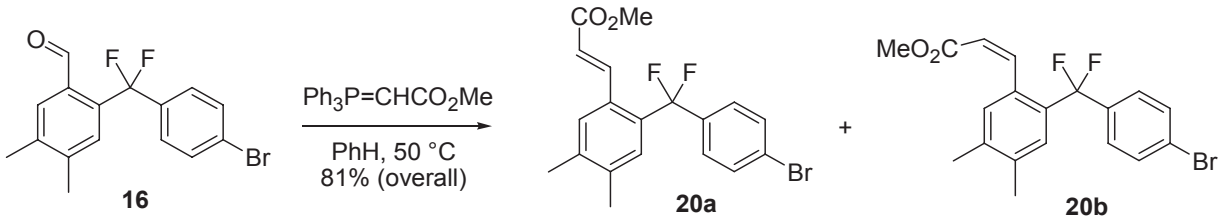
On the other hand, two representative examples of alcohols were prepared by reaction with alcynyl Grignard and phenyl lithium. The adducts **18** and **19** were obtained in 73% and 81% yields respectively (Scheme 16).

Scheme 16. Addition of an organolithium and an organomagnesium reagent.



Finally, a Wittig reaction with carbomethoxymethylenetriphenylphosphorane gave the alkenes **20a** and **20b**, as a 8:1 mixture, in 81% overall yield. These isomers were separated by silica gel chromatography (Scheme 17).

Scheme 17. Wittig reaction of aldehyde **16**.



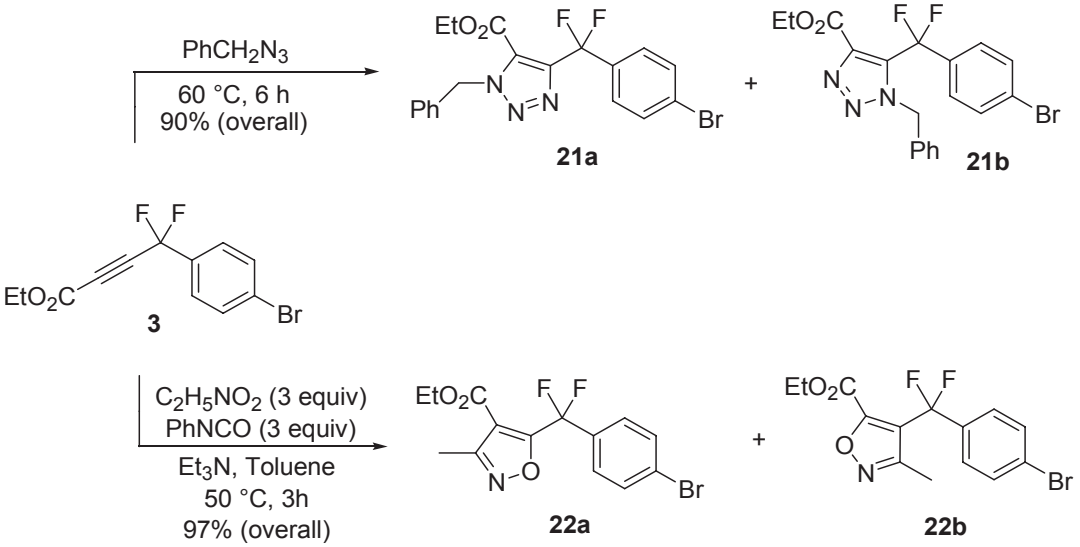
These last results demonstrate that the ester group is a useful second point to extend molecular diversity on these key *gem*-difluorobisarylic intermediates.

All together our data establish that both the bromine and the ester function can be used to introduce new groups and/or functions and therefore such scaffolds are of much interest regarding the preparation of chemical libraries of new fluorinated compounds for biological studies.

5) Synthesis of arylic/heteroarylic *gem*-difluoro compounds

After proving the efficiency of our route in the synthesis of *gem*-difluoro bisarylic compounds, and the successful extension towards focused chemical libraries, the next step was to demonstrate the possibility of using the same propargylic intermediate **3** for the preparation of mixed aromatic/heteroaromatic derivatives with a CF_2 group as a linker. This was performed on two representative examples of 1,3 dipolar cycloadditions (Scheme 18): reaction of **3** with benzyl azide afforded in 90% overall yield a 1:2 mixture of triazoles **21a** and **21b**, separated by silica gel chromatography. The regioselectivity was established on the basis of ^{13}C NMR data: for **21b** there is a small J_{CF} coupling constant (4.5 Hz) between the carbon of the CH_2Ph group with the two fluorine atoms, coupling which do not exist for **21a**. On the other hand, nitrile oxide cycloaddition, using nitroethane under Mukaiyama's conditions,[24] gave an unseparable (2:1) mixture of isoxazoles **22a** and **22b** in 97% overall yield. The regioselectivity of the cycloaddition was also established by NMR: for **22b** there is a small J_{HF} coupling constant (1.9 Hz) between the two fluorine atoms and the protons of the CH_3 group; further, there is also a small J_{CF} coupling constant (3.1 Hz) with the carbon of this CH_3. Such coupling constants are not present in **22a**.

Scheme 18. Synthesis of mixed *gem*-difluoro aromatic-heteroaromatic derivatives **21** and **22**.



As in the *gem*-difluorobisarylic scaffold, and due to the presence of the two sites of diversity (ester and bromine), these arylic/heteroarylic analogues could be of much use for the preparation of novel chemical libraries in the same way as demonstrated with previous bisarylic systems.

IV-Conclusion

This study confirms the versatility of propargylic fluorides in the synthesis of useful fluorinated building blocks. A functionalized *gem*-difluoropropargylic intermediate **3,** with a CF_2Ar group, has been prepared for the first time. Through cycloadditions, it afforded versatile scaffolds which could be developed in many different ways. In particular intermediates of this type could easily generate chemical librairies of new bisarylic or mixed aromatic/heteroaromatic molecules with a CF_2 linker. It seems to us that these new structures could be of much interest in bioorganic and medicinal chemistry.

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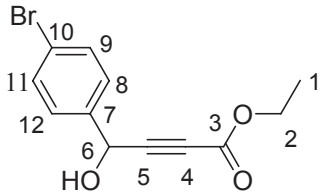
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EXPERIMENTAL PART

4-(4-Bromophenyl)-4-hydroxybut-2-ynoicacid ethyl ester (1)



$C_{12}H_{11}BrO_3$
M = 283.12 g.mol^{-1}

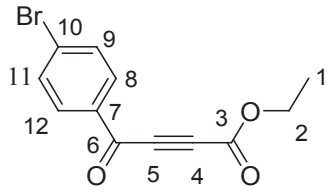
To a solution of ethylpropiolate (2.1 mL, 0.02 mmol) in anhydrous THF (25 mL) cooled at -90 °C, was added, dropwise under nitrogen, a solution of n-BuLi in hexanes (15.3 mL, 1.6 M, 1.2 equiv). The mixture was stirred for 30 min at t < -80 °C before dropwise addition, of *p*-bromobenzaldehyde (4.26 g,1.2 equiv) in anhydrous THF (15 mL). After 20 min additional stirring at the same temperature, TMSCl (6.1 mL, 2.5 equiv) was added dropwise. The reaction mixture was stirred for additional 90 min at t< -80 °C and then in an ice bath for additional 1 h. The mixture was treated with a saturated NH_4Cl solution, extracted by ether (3 x 80 mL). The combined organic phases were washed with water, dried over MgSO4 and concentrated in vacuo. After purification by chromatography on silica gel, using as eluent a 15/85 ether/pentane mixture, compound 1 was obtained as a yellow oil (4.08 g, 71% yield). R_f= 0.16 (Et2O/pentane, 2/8).

^{1}H NMR ($CDCl_3$, 300MHz): δ, ppm 1.29 (t, 3H, H_1, *J*= 7.1 Hz) , 4.22 (q, 2H, H_2, *J*= 7.1 Hz), 5.50 (s, 1H, H_6), 7.47- 7.49 (m, 2H, $H_{8\ and\ 12}$), 7.50 - 7.52 (m, 2H, $H_{9\ and\ 11}$).

^{13}C NMR ($CDCl_3$, 75MHz): δ, ppm 13.9 (1C, C_1), 62.4 (1C, C2), 63.4 (1C, C6), 77.9 (1C, C4), 85.7 (1C, C_5), 122.8 (1C, C_{10}), 128.3 (2C, $C_{8\ and\ 12}$), 131.8 (2C, $C_{9\ and\ 11}$), 137.5 (1C, C_7), 153.3 (1C, C_3).

HRMS (ESI) calcd for $C_{12}H_{11}O_3\ ^{79}BrNa$:$[M + Na]^+$: m/z 304.9789. Found: m/z 304.9792 (1 ppm).

4-(4-Bromophenyl)-4-oxo-but-2-ynoicacid ethylester (2)



$C_{12}H_9BrO_3$
M = 281.10 g.mol^{-1}

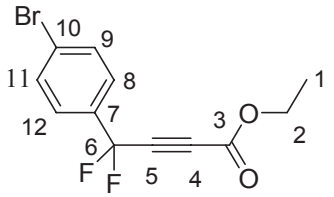
To alcohol **1** (2.78 g, 9.82 mmol) in acetone (30 mL) was added dropwise under magnetic stirring at room temperature, a concentrated (5.4 M) solution of Jones reagent until disappearance of the starting material (TLC analysis). After addition of isopropanol (5 equiv), the reaction mixture was filtered and the residues were washed with ether. The combined organic phases were dried over MgSO4, filtered and concentrated in vacuo. After purification by flash chromatography on silica gel ketone **2** was obtained as yellow crystals. Mp: 32-34 °C. (2.48 g, 89% yield). R_f= 0.26 (Et2O/pentane, 2/98).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.36 (t, 3H, H_1, *J*=7.1 Hz), 4.34 (q, 2H, H_2, *J*= 7.1Hz), 7.63 – 7.68 (m, 2H, $H_{(8 \text{ and } 12) \text{ or } (9 \text{ and } 11)}$), 7.93 – 7.98 (m, 2H, $H_{(8 \text{ and } H12) \text{ or } (9 \text{ and } 11)}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.9 (1C, C_1), 63.1 (1C, C_2), 79.2 (1C, $C_{4 \text{ or } 5}$), 80.8 (1C, $C_{4 \text{ or } 5}$), 130.8 (1C, C_{10}), 130.9(2C, $C_{(8 \text{ and } C12) \text{ or } (9 \text{ and } 11)}$), 132.2 (2C, $C_{(8 \text{ and } C12) \text{ or } (9 \text{ and } 11)}$), 134.3 (1C, C_7), 152.0 (1C, C_3), 175.0 (1C, C_6).

HRMS (ESI) calcd for $C_{12}H_9O_3$ ^{79}BrNa: $[M + Na]^+$: m/z 302.9633. Found: m/z = 302.9636 (1 ppm).

4-(4-Bromophenyl)-4,4-difluorobut-2-ynoicacid ethylester (3)



$C_{12}H_9BrF_2O_2$
M = 303.10 g.mol^{-1}

To propargylic ketone **2** (2.18 g, 7.76 mmol) were added three drops of 95% ethanol and DAST (8.14 mL, 8 equiv). The reaction mixture was stirred at 65 °C for 8 h. After coming back to room temperature, pentane (50 mL)was added, followed by slow addition of a 1% HCl solution. The organic layerswere separated,washed with water (3 x 5 mL), dried over MgSO4 and concentrated under vacuum at 300 mbar pressure. After purification by chromatography on silica gel, ester **3** was obtained as a colourless oil (1.6 g, 68% yield). R_f = 0.46 (Et2O/pentane, 2/98).

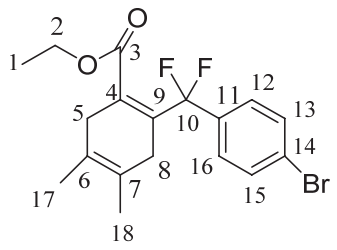
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.34 (t, 3H, H_1, *J*= 7.1Hz), 4.29 (q, 2H, H_2, *J*= 7.1Hz), 7.50- 7.53 (m, 2H, $H_{8 \text{ and } 12}$), 7.60- 7.63 (m, 2H, $H_{9 \text{ and } 11}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.9 (1C, C_1), 63.1 (1C, C_2), 76.3 (t, 1C, C_5, *J*= 43.9 Hz), 78.7 (t, 1C, C_4, *J*= 5.9 Hz), 111.1 (t, 1C, C_6, *J*= 235.5 Hz), 126.0 (t, 1C, C_{10}, *J*= 2.3 Hz), 126.9 (t, 2C, $C_{8 \text{ and } 12}$, *J*= 4.8 Hz), 132.1 (2C, $C_{9 \text{ and } 11}$), 133.4 (t, 1C, C_7, *J*= 27.5 Hz), 151.7 (t, 1C, C_3, *J*= 2.3 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm -79.69 (s).

HRMS (ESI) calcd for $C_{12}H_9O_2F_2$ ^{79}BrNa: $[M + Na]^+$: m/z 324.9652. Found: m/z = 324.9652 (0 ppm).

2-[(4-Bromophenyl)-difluoromethyl]-5-methylcyclohexa-1,4-dienecarboxylicacid ethylester (4)



$C_{18}H_{19}BrF_2O_2$
M = 385.24 g.mol^{-1}

The difluoro-propargylic ester **3** (1.75 g, 1 equiv) and 3,4-dimethylbutadiene (6.5 mL, 10 equiv) were refluxed neat at 80 °C overnight. After purification by flash chromatography on silica gel, cyclohexadiene **4** was isolated as a colorless oil (2.18 g, 98 % yield). R_f = 0.68 (Et_2O/pentane, 4/96).

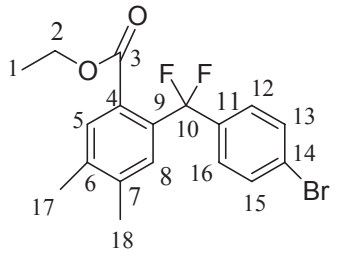
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.25 (t, 3H, H_1, *J*= 7.1 Hz), 1.58 (s, 3H, $H_{17 \text{ or } 18}$), 1.64 (s, 3H, $H_{17 \text{ or } 18}$), 2.53 (t, 2H, $H_{5 \text{ or } 8}$, *J*= 7.7 Hz), 2.92 (t, 2H, $H_{5 \text{ or } 8}$, *J* = 7.1 Hz), 4.20 (q, 2H, H_2, *J*= 7.1 Hz), 7.49- 7.57 (m, 4H, $H_{12\text{-}16}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.9 (1C, C_1), 17.7 (1C, $C_{17 \text{ or } 18}$), 18.0 (1C, $C_{17 \text{ or } 18}$), 31.61 (t, 1C, C8, *J*= 3.2 Hz), 35.5 (1C, C_5), 61.1 (1C, C_2), 120.06 (t, 1C, C_{10}, *J*= 243.5 Hz), 121.2, 121.6 (2C, $C_{6 \text{ and } 7}$), 124.5 (t, 1C, C_{14}, *J*= 2.3 Hz), 127.6 (t, 2C, $C_{12 \text{ and } 16}$, *J*= 5.6 Hz), 128.5 (t, 1C, C_9, *J*= 25.6 Hz), 130.1 (t, 1C, C_4, *J*= 4.7 Hz), 131.6 (2C, $C_{13 \text{ and } 15}$), 134.7 (t, 1C, C_{11}, *J*= 28.5 Hz), 169.9 (t, 1C, C_3, *J*= 0.9 Hz).

^{19}F ($CDCl_3$, 282 MHz): δ, ppm -92.41-(s).

HRMS (ESI). Calcd for $C_{18}H_{19}O_2F_2{}^{79}BrNa$ [M+Na]+: *m/z* 407.0434. Found: *m/z* 407.0435 (0 ppm).

2-[(4-Bromophenyl)difluoromethyl]-4,5-dimethylbenzoicacid ethylester (5)



$C_{18}H_{17}BrF_2O_2$
M = 383.23 g.mol^{-1}

A solution of the cyclohexadiene **4** (790 mg, 1 equiv) and DDQ (559 mg, 1.2 equiv) in toluene (2 mL) was stirred at 40 ^{0}C for 2 h. The reaction mixture was filtered on silica gel and the residues were washed ether. The organic phase was concentrated in vacuo and the product **5** was isolated by flash chromatography on silica as yellow crystals (776 mg, 99% yield). Mp: 83-85 °C. R_f = 0.60 (Et_2O/pentane, 4/96).

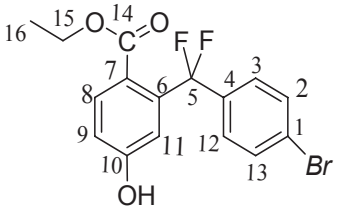
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.10 (t, 3H, H_1, *J*= 7.1 Hz), 2.33 (s, 3H, $H_{17 \text{ or } 18}$), 2.34 (s, 3H, $H_{17 \text{ or } 18}$), 4.12 (q, 2H, H_2, *J*= 7.1 Hz), 7.33-7.36 (m, 2H, $H_{12 \text{ and } 16}$), 7.42 (s, 1H, $H_{8 \text{ or } 5}$), 7.46 (s, 1H, $H_{8 \text{ or } 5}$), 7.49-7.53 (m, 2H, $H_{13 \text{ and } 15}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.7 (1C, C_1), 19.4 (1C, $C_{17 \text{ or } 18}$), 19.8 (1C, $C_{17 \text{ or } 18}$), 61.2 (1C, C_2), 120.3 (t, 1C, C_{10}, *J*= 241.5 Hz), 124.2 (t, 1C, C_{14}, *J*= 2.5 Hz), 127.9 (t, 2C, $C_{12 \text{ and } 16}$, *J*= 4.9 Hz), 128.5 (t, 1C, C_8, *J*= 7.7 Hz), 129.0 (t, 1C, C_4, *J*= 3.4 Hz), 130.8 (1C, C_5), 131.2 (2C, $C_{13 \text{ and } 15}$), 131.8 (t, 1C, $C_{9 \text{ or } 11}$, *J*= 26.8 Hz), 137.1 (t, 1C, $C_{9 \text{ or } 11}$, *J*= 28.5 Hz), 139.0 (t, 1C, $C_{6 \text{ or } 7}$, *J*= 1.5 Hz), 139.7 (1C, $C_{6 \text{ or } 7}$), 197.9 (1C, C_3).

^{19}F NMR ($CDCl_3$, 282 MHz): δ, ppm -81.93 (s).

HRMS (ESI). Calcd for $C_{18}H_{17}O_2F_2{}^{79}BrNa$ [M+Na]+: *m/z* 405.02778. Found: *m/z* 405.0278 (0 ppm).

2-[(4-Bromo-phenyl)-difluoro-methyl]-4-hydroxy-benzoic acid ethyl ester (6)



$C_{16}H_{13}BrF_2O_3$
M = 371.17 g.mol^{-1}

A mixture of difluoro-propargylic ester **3** (100 mg, 0.33 mmol) and Danishefsky's diene (0.19 mL, 3 equiv), was stirred neat overnight at 70 ^{0}C. After addition of DDQ (90 mg, 1.2 equiv) and toluene (1mL), the mixture was stirred for 3 h at 40 ^{0}C. Then the reaction mixture was filtered and the residues were washed with ether. The combined organic phases were concentrated in vacuo. After purification by flash chromatography on silica gel, the product **6** was isolated as yellow crystals (101 mg, 83% yield). Mp: 130-132 ^{0}C. R_f = 0.34 (Et_2O/pentane, 30/70).

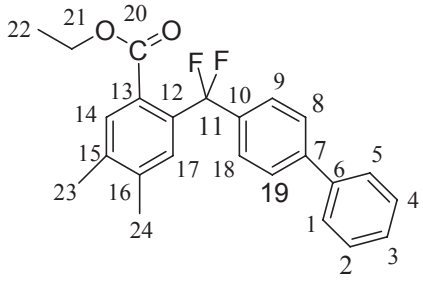
^{1}H NMR (d_6 acetone, 300 MHz): δ, ppm 1.06 (t, 3H, H_{16}, *J*= 7.1 Hz), 3.19 (bs, 1H, OH), 4.05 (q, 2H, H_{15}, *J*= 7.1 Hz), 7.08 (dd, 1H, H_9, *J* = 2.49, 8.49 Hz), 7.25 (d, 1H, H_{11}, *J*= 2.5 Hz), 7.42-7.45 (m, 2H, $H_{3 \text{ and } 12}$), 7.63-7.66 (m, 2H, $H_{2 \text{ and } 13}$), 7.70 (d, 1H, H_8, *J*= 8.5 Hz).

^{13}C NMR (d_6 acetone, 75 MHz): δ, ppm 15.0 (1C, C_{16}), 62.4 (1C, C_{15}), 116.2 (t, 1C, C_{11}, *J*= 8.7 Hz), 118.6 (t, 1C, C_9, *J*= 1.3 Hz), 122.1 (t, 1C, C_5, *J*= 241.0 Hz), 124.4 (t, 1C, C_7, *J*= 3.3 Hz), 125.5 (t, 1C, C_1, *J*= 2.5 Hz), 129.9 (t, 2C, $C_{3 \text{ and } 12}$, *J*= 5.0 Hz), 133.1 (2C, $C_{2 \text{ and } 13}$), 134.4 (1C, C8), 138.4 (t, 1C, C_6, *J*= 26.8 Hz), 139.0 (t, 1C, C_4, *J*= 28.0 Hz), 161.6 (s, 1C, C_{10}), 168.3 (1C, C_{14}).

^{19}F NMR (d_6 acetone), 282 MHz): δ, ppm -82.73 (s).

HRMS (ESI). Calcd for $C_{16}H_{13}O_3F_2{}^{79}BrNa$: [M+Na]+: *m/z* 392.9914. Found: *m/z* 392.9911 (1 ppm).

2-(Biphenyl-4-yl-difluoro-methyl)-4,5-dimethyl-benzoic acid ethyl ester (7)



$C_{24}H_{22}F_2O_2$
M = 380.43 g.mol^{-1}

A solution of bromo-ester **5** (150 mg, 0.39 mmol), phenylboronic acid (96 mg, 2 equiv), palladium dichlorobis triphenylphosphine (14 mg, 5 mol %) and potassium carbonate (108 mg, 2 equiv) in a 5/1 mixture of dioxane and water (3 mL) was stirred at 90 ^{0}C for 22 h. After addition of $MgSO_4$ and filtration, the residues were washed with ether and the solution concentrated in vacuo. After purification by chromatography on silica gel, the product **7** was isolated as white crystals (120 mg, 80% yield). Mp: 79-81 ^{0}C. R_f = 0.27 (Et_2O/pentane, 5/95).

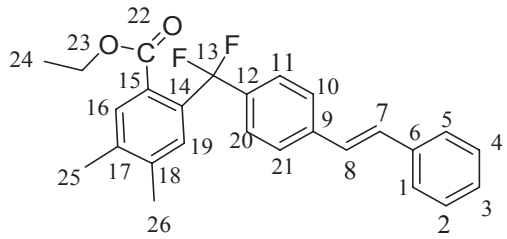
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.09 (t, 3H, H_{22}, *J*= 7.2 Hz), 2.35 (s, 3H, $H_{23\ or\ 24}$), 4.14 (q, 2H, H_{21}, *J*= 7.2 Hz), 7.34-7.63 (m, 11H, aromatic).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.6 (1C, C_{22}). 19.4 (1C, $C_{23\ or\ 24}$), 19.9 (1C, $C_{23\ or\ 24}$), 61.2 (1C, C_{21}), 120.8 (t, 1C, C_{11}, *J*= 240.9 Hz), 126.6 (t, 2C, $C_{9\ and\ 18}$, *J*= 4.9 Hz), 126.8, 127.2, 127.7, 128.6 (t, 1C, C_{17}, *J*= 7.5 Hz), 128.8 (2C, aromatic), 129.2 (t, 1C, C_{13}, *J*= 3.3 Hz), 130 (1C, C_{14}), 132.3 (t, 1C, $C_{10\ or\ 12}$, *J*= 27.1 Hz), 136.9 (t, 1C, $C_{10\ or\ 12}$, *J*= 28.1 Hz), 138.8 (t, 1C, $C_{15\ or\ C16}$, *J*= 1.5 Hz), 139.5 (1C, $C_{15\ or\ 16}$), 140.3 (1C, C_6), 142.6 (t, 1C, C_7, *J*=2.0 Hz), 168.2 (1C, C_{20}).

^{19}F NMR ($CDCl_3$, 282 MHz): δ, ppm -81.43 (s).

HRMS (ESI). Calcd for $C_{24}H_{22}O_2F_2Na$: [M+Na]+: *m/z* 403.1485. Found: *m/z* 403.1483 (1 ppm).

2-[Difluoro-(4-styryl-phenyl)-methyl]-4,5-dimethyl-benzoic acid ethyl ester (8)



$C_{26}H_{24}F_2O_2$
M = 406.46 g.mol^{-1}

DMF (2 mL) was first degazed by bubbling argon. Then were added successively: bromo-compound **5** (100 mg, 0.26 mmol), palladium dichlorobis triphenylphosphine (9 mg, 5 mol %), potassium carbonate (72 mg, 2 equiv) and styrene (0.15 mL, 5 equiv). The reaction mixture was stirred under argon at 120 ^{0}C for 3 days. After addition of ether (25 mL) the reaction mixture was washed with water (3 x 5 mL), the aqueous phase was extracted with ether (3 x 2 mL). The combined organic phases were dried ($MgSO_4$) filtered and concentated in vacuo. After purification by chromatography on silica gel the product **8** was isolated as white crystals (56 mg, 53% yield). Mp: 73-75 ^{0}C. R_f = 0.29 (Et_2O/pentane, 1/9).

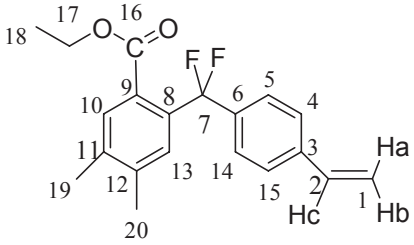
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.10 (t, 3H, H24, J=7.15Hz), 2.34 (s, 3H, $H_{25 \text{ or } 26}$), 2.35 (s, 3H, $H_{25 \text{ or } 26}$), 4.13 (q, 2H, H23, J=7.15Hz), 16.42 (d, 1H, $H_{7 \text{ or } 8}$, *J*=16.4 Hz), 7.16 (d, 1H, $H_{7 \text{ or } 8}$, *J*=16.4 Hz), 7.27-7.54 (m, 11H, aromatic).

^{13}C NMR ($CDCl_3$, 100 MHz): δ, ppm 13.7 (1C, C_{24}), 19.3 (1C, $C_{25 \text{ or } 26}$), 19.8 (1C, $C_{25 \text{ or } 26}$), 61.2 (1C, C_{23}), 120.7 (t, 1C, C_{13}, *J*= 240.9 Hz), 126.1 (2C, $C_{10 \text{ and } 21}$), 126.5 (t, 2C, $C_{11 \text{ and } 20}$, *J*= 5.0 Hz), 126.6 (2C, $C_{1 \text{ and } 5}$), 127.7 (1C, $C_{7 \text{ or } 8}$), 127.9 (1C, C_3), 128.6 (t, 1C, C_{19}, *J*= 7.6 Hz), 128.7 (2C, $C_{2 \text{ and } 4}$), 129.3 (t, 1C, C_{15}, *J*=3.2 Hz), 130.0 (1C, $C_{7 \text{ or } 8}$), 130.6 (1C, C_{16}), 132.3 (t, 1C, $C_{12 \text{ or } 14}$, *J*= 27.1 Hz), 136.9 (1C, C_6), 137.0 (t, 1C, $C_{12 \text{ or } C14}$, *J*= 28.0 Hz), 138.7 (bs, 1C), 138.8 (t, 1C, aromatic, *J*= 2.0 Hz), 139.5 (1C,aromatic), 168.2 (1C, C22).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -81.47 (s).

HRMS (ESI). Calcd for $C_{26}H_{24}O_2F_2Na$: [M+Na]+: *m/z* 429.1642. Found: *m/z* 429.1638 (1 ppm).

2-[Difluoro-(4-vinyl-phenyl)-methyl]-4,5-dimethyl benzoic acid ethyl ester (9)



$C_{20}H_{20}F_2O_2$
M = 330.37 g.mol^{-1}

A solution of bromo-ester **5** (100 mg, 0.26 mmol), vinyltributylstannane (0.15 mL, 2 equiv), palladium dichlorobis triphenylphosphine (18 mg, 10 mol %) in dioxane (2 mL), was stirred under argon, at 90 ^{0}C for 24 h. After filtration, the residues were washed with Et_2O and the solution was concentrated in vacuo. After purification by chromatography on silica gel the product **9** was isolated as white crystals (71 mg, 82% yield). Mp: 62-64 °C. R_f = 0.26 (Et_2O/pentane, 5/95).

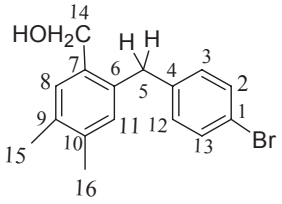
^{1}H NMR (d$_6$ DMSO, 300 MHz): δ, ppm 1.08 (t, 3H, H_{18}, *J*= 7.1 Hz), 2.32 (s, 3H, $H_{19 \text{ or } 20}$), 2.33 (s, 3H, $H_{19 \text{ or } 20}$), 4.10 (q, 2H, H_{17}, *J*= 7.1 Hz), 5.30 (d, 1H, H_b, *J*= 10.9 Hz), 5.8 (d, 1H, H_a, *J*= 17.6 Hz), 6.72 (dd, 1H, H_c, *J*= 10.9, 17.6 Hz), 7.42-7.44 (m, 6H, aromatic).

^{13}C NMR (d$_6$ DMSO, 75 MHz): δ, ppm 13.6 (1C, C_{18}), 19.4 (1C, $C_{19 \text{ or } 20}$), 19.9 (1C, $C_{19 \text{ or } 20}$), 61.2 (1C, C_{17}), 115.2 (1C, C_1), 120.7 (t, 1C, C_7, *J*= 240.8 Hz), 125.8 (s, 2C, $C_{4 \text{ and } 15}$), 126.4 (t, 2C, $C_{5 \text{ and } 14}$, *J*= 5.0 Hz), 128.6 (t, 1C, C_{13}, *J*= 7.6 Hz), 129.2 (t, 1C, C_9, *J*=3.3 Hz), 130.6 (s, 1C, C_{10}), 132.6 (t, 1C, $C_{6 \text{ or } 8}$, *J*= 27.1 Hz), 136.1 (s, 1C, C_2), 137.3 (t, 1C, $C_{6 \text{ or } 8}$, *J*= 27.9 Hz), 138.8 (t, 1C, $C_{\mathbf{11} \text{ or } 12}$, *J*= 1.4 Hz), 138.9 (t, 1C, C_3, *J*= 2.1 Hz), 139.5 (s, 1C, $C_{11 \text{ or } \mathbf{12}}$), 168.2 (s, 1C, C_{16}).

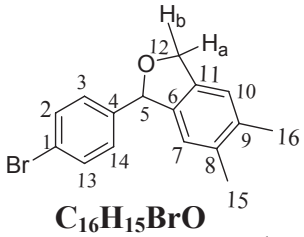
^{19}F NMR (d$_6$ DMSO, 282 MHz): δ, ppm -81.63 (s).

HRMS (ESI). Calcd for $C_{20}H_{20}O_2F_2Na$: [M+Na]+: *m/z* 353.1329. Found: *m/z* 353.1328 (0 ppm).

Synthesis of the non-expected products [2-(4-Bromo-benzyl)-4,5-dimethyl-phenyl]-methanol (11) and 1-(4-Bromo-phenyl)-5,6-dimethyl-1,3-dihydro-isobenzofuran (12)



$C_{16}H_{17}BrO$
M = 305.21 g.mol^{-1}



$C_{16}H_{15}BrO$
M = 303.19 g.mol^{-1}

DIBAL-H (1.6 ml, 1M, 4eq), was put under nitrogen and cooled in (ice-salt) mixture before the addition of ester (4) (150mg, 0.39mmol) in 1ml anhydrous DCM was performed. The cooled mixture was stirred under nitrogen for 90 min. TLC showed the completion of reaction, but the presence of two different products. Reaction was quenched with saturated aqueous solution of potassium sodium tartrate. The aqueous and organic phases were separated, the aqueous layer was extracted with Et_2O, the organic fractions were collected together, dried over $MgSO_4$, filtrated and concentrated using rotary evaporation. After flash chromatography products **20** and **21** were isolated as white crystals. Compound **11** melting point: 71-73°C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm 2.23 (s, 3H, $H_{15 \text{ or } 16}$), 2.25 (s, 3H, $H_{15 \text{ or } 16}$), 3.98 (s, 2H, H_5), 4.56 (s, 2H, H_{14}), 6.91 (s, 1H, $H_{8 \text{ or } 11}$), 7.00-7.02 (m, 2H, $H_{3 \text{ and } 12}$), 7.15 (s, 1H, $H_{8 \text{ or }} 11$), 7.37-7.39 (m, 2H, $H_{2 \text{ and } 13}$).

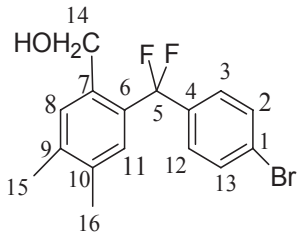
^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 19.2, 19.4 (2C, C15 and C16), 37.4 (1C, C5, 63.1 (1C, C14**)** 119.8 (s, 1C, C1), 130.2 (1C, $C_{8 \text{ or } 11}$), 130.3 (2C, C3 and C12), 131.5 (2C, C2 and C13), 132.0 (1C, $C_{8 \text{ or } 11}$), 135.1, 135.4, 136.0, 136.5, 140.0 (5C, aromatic).

Spectral analysis of compound 12

^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm 2.21 (s, 3H, $H_{15 \text{ or } 16}$), 2.27 (s, 3H, $H_{15 \text{ or } 16}$), 5.14 (d, 1H, H_a or H_b, J= 11.8 Hz), 5.27 (dd, H_a or H_b, J= 12.0, 2.5 Hz), 6.06 (s, 1H, H_5), 6.76, 7.06 (s, 2H, $H_{7 \text{ and } 10}$), 7.19-7.22 (m, 2H, $H_{3 \text{ and } 14}$), 7.46-7.48 (m, 2H, $H_{2 \text{ and } 13}$).

^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 19.8 (1C, $C_{15 \text{ or } 16}$), 19.9 (1C, $C_{15 \text{ or } 16}$), 73.2 (1C, C12), 85.4 (1C, C_5), 121.8 (1C, C_1), 121.9 (1C, $C_{7 \text{ or } 10}$), 122.9 (1C, $C_{7 \text{ or } 10}$), 136.1, 136.4, 136.6, 139.3, 141.7.

{2-[(4-Bromophenyl)difluoromethyl]-4,5-dimethylphenyl}methanol (13)



$C_{16}H_{15}BrF_2O$
M = 341.19 g.mol^{-1}

To the ester **5** (276 mg, 0.72 mmol) in anhydrous THF (3 mL) was added, dropwise under magnetic stirring and under N_2 at 0°C, a 1M solution of $LiEt_3BH$ in THF (1.8 mL, 2.5 equiv). At the end of the addition the reaction mixture was stirred at room temperature for 30 min and then quenched by addition of a saturated NH_4Cl solution and 2 drops of 2N HCl. The organic phase was separated, washed with a saturated Na_2CO_3 solution, while the aqueous phase was extracted by diethyl ether. The organic fractions were collected, dried over $MgSO_4$, and concentrated in vacuo. After purification by flash chromatography on silica gel the alcohol **10** was isolated as white crystals (238 mg, 97% yield). Mp: 85-87 °C. R_f = 0.27 (Et_2O/pentane, 15/85).

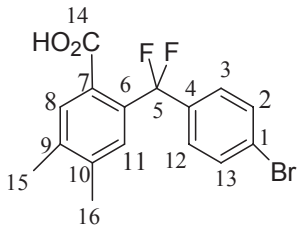
^{1}H NMR (d_6 acetone, 300 MHz): δ, ppm 2.30 (s, 3H, $H_{15 \text{ or } 16}$), 2.32 (s, 3H, $H_{15 \text{ or } 16}$), 4.14 (t, 1H, OH, J= 5.7 Hz), 4.50 (d, 2H, H_{14}, *J*= 5.6 Hz), 7.32 (s, 1H, $H_{8 \text{ or } 11}$), 7.42-7.43 (m, 2H, $H_{3 \text{ and } 12}$), 7.56 (s, 1H, $H_{8 \text{ or } 11}$), 7.65-7.69 (m, 2H, $H_{2 \text{ and } 13}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 19.4 (1C, $C_{15 \text{ or } 16}$), 19.5 (1C, $C_{15 \text{ or } 16}$), 62.0 (t, 1C, C_{14}, *J*= 3.4 Hz), 121.3 (t, 1C, C_5, *J*= 241.1 Hz), 124.6 (t, 1C, C_1, *J*= 2.5 Hz), 127.7-127.9 (m, 3C, $C_{3,\ 11 \text{ and } 12}$), 130.6 (t, 1C, $C_{6 \text{ or } 4}$, *J*= 26.3 Hz), 130.1 (1C, C_{11}), 131.7 (2C, $C_{2 \text{ and } 13}$), 135 (1C, $C_{9 \text{ or } \mathbf{10}}$), 136.2 (t, 1C, C_7, *J*= 2.1 Hz), 136.5 (t, 1C, $C_{4 \text{ or } 6}$, *J*= 28.8 Hz), 139.5 (t, 1C, $C_{\mathbf{9} \text{ or } 10}$, *J*= 1.6 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz): δ, ppm -83.13 (s).

HRMS (ESI). Calcd for $C_{16}H_{15}OF_2{}^{79}BrNa$ [M+Na]+: *m/z* 363.0172. Found *m/z* 363.0172 (0 ppm).

2-[(4-Bromophenyl)-difluoromethyl]-4,5-dimethylbenzoic acid (14)



$C_{16}H_{13}BrF_2O_2$
M = 355.17 g.mol^{-1}

To a solution of alcohol **13** (100 mg, 0.26 mmol) in acetone (1 mL) was added dropwise at room temperature, a concentrated (5.4M) solution of Jones reagent was added until TLC showed the completion of reaction. Then isopropanol (5 equiv) was added to the reaction mixture which was filtered and the residues were washed with ether. The combined organic phases was dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography on silica gel, the acid **14** was isolated as white crystals (81 mg, 87% yield). Mp: 188-190 °C.

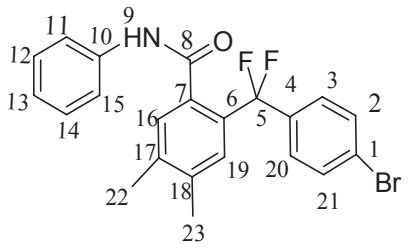
^{1}H NMR (d_6 DMSO, 300 MHz): δ, ppm 2.28 (s, 3H, $H_{15 \text{ or } 16}$), 2.30 (s, 3H, $H_{15 \text{ or } 16}$), 7.38-7.42 (m, 2H, $H_{3 \text{ and } 12}$), 7.46 (s, 1H, $H_{8 \text{ or } 11}$), 7.48 (s, 1H, $H_{8 \text{ or } 11}$), 7.63-7.66 (m, 2H, $H_{2 \text{ and } 13}$).

^{13}C NMR (d_6 DMSO, 75 MHz): δ, ppm 18.8 (1C, $C_{15 \text{ or } 16}$), 19.2 (1C, $C_{15 \text{ or } 16}$), 120.4 (t, 1C, C_5, *J*= 241.5 Hz), 123.4 (t, 1C, C_1, *J*= 2.3 Hz), 127.6 (t, 1C, C_{11}, *J*=7.7 Hz), 127.8 (t, 2C, $C_{3 \text{ and } 12}$, *J*= 5.0 Hz), 129.6 (t, 1C, C_7, *J*= 3.3 Hz), 130.0 (1C, C_8), 130.7 (t, 1C, $C_{4 \text{ or } 6}$, *J*= 27.0 Hz), 131.2 (2C, $C_{2 \text{ and } 13}$), 136.6 (t, 1C, $C_{4 \text{ or } 6}$, *J*= 28.6 Hz), 139.0 (t, 1C, $C_{9 \text{ or } 10}$, *J*= 1.3 Hz), 139.2 (1C, $C_{9 \text{ or } 10}$), 168.6 (1C, C_{14}).

^{19}F NMR (d_6 DMSO, 282 MHz): δ, ppm -76.81 (s).

HRMS (ESI). Calcd for $C_{16}H_{13}O_2F_2{}^{79}BrNa$: [M+Na]+: *m/z* 376.9965. Found: *m/z* 376.9966 (0 ppm).

2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-*N*-phenyl-benzamide (15)



$C_{22}H_{18}BrF_2NO$
M = 430.29 g.mol^{-1}

A solution of carboxylic acid **14** (37 mg, 0.10 mmol), DCC (25 mg, 2 equiv), DMAP (11 mg, 0.5 equiv) and aniline (12 µL, 1.2 equiv) was stirred in CH_2Cl_2, at room temperature during 5 h. After addition of a 1% HCl solution, the aqueous and organic phases were separated. The organic phase was washed twice with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by silica gel flash chromatography, the amide **15** was isolated as white crystals. (24 mg, 53% yield). Mp: 171-173 ^{0}C. R_f = 0.32 (Et_2O/pentane, 25/75).

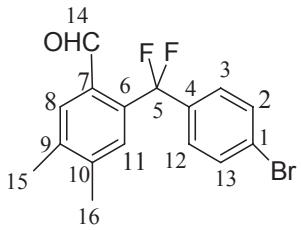
^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 2.33 (s, 6H, $H_{22 \text{ and } 23}$), 7.10-7.15 (m, 1H, H_{13}), 7.29- 7.47 (m, 9H, 8 aromatic and H_9), 7.48-7.49 (m, 2H, $H_{2 \text{ and } 21}$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ, ppm 19.4 (1C, $C_{22 \text{ or } 23}$), 19.8 (1C, $C_{22 \text{ or } 23}$), 119.8 (2C, $C_{11 \text{ and } 15}$), 120.6 (t, 1C, C_5, J= 242.3 Hz), 124.5 (1C, C_{13}), 124.6 (t, 1C, C_1, J= 2.4 Hz), 127.8 (t, 2C, $C_{3 \text{ and } 20}$, J= 5.4 Hz), 128.2 (t, 1C, C_{19}, J= 7.0 Hz), 129.0 (2C, $C_{12 \text{ and } C14}$), 129.8 (1C, C_{16}), 130.8 (t, 1C, C_6, J= 27.2 Hz), 131.5 (2C, $C_{2 \text{ and } 21}$), 133.5 (t, 1C, C_7, J= 3.3 Hz), 136.2 (t, 1C, C_4, J= 28.3 Hz), 137.6 (1C, $C_{10 \text{ or } 17}$), 138.8 (1C, $C_{10 \text{ or } 17}$), 139.5 (t, 1C, C_{18}, J= 1.7 Hz), 166.9 (1C, C_8).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -83.08 (s).

HRMS (ESI). Calcd for $C_{22}H_{18}NOF_2{}^{79}BrNa$: [M+Na]+: *m/z* 452.0438. Found: *m/z* 452.0440 (1 ppm).

{2-[(4-Bromophenyl)difluoromethyl]-4,5-dimethylbenzaldehyde (16)



$C_{16}H_{13}BrF_2O$
M = 339.17 g.mol^{-1}

To a solution of IBX (252 mg, 0.90 mmol, 1.5 equiv) in DMSO (3 mL), was added a solution of alcohol **13** (205 mg, 0.60 mmol) in THF (2 mL) and the reaction mixture was stirred at 40 ^{0}C for 1 h. After coming back to room temperature, ice cold water (10 mL) was added. The reaction mixture was filtered and the solid residue washed with ether (10mL). The organic phase was separated and washed with water while the aqueous phase was extracted with diethylether (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. After purification by flash chromatography on silica gel, the aldehyde **16** was isolated as white crystals (190 mg, 92% yield). Mp: 78-80 ^{0}C. R_f = 0.33 (Et_2O/pentane, 2/98).

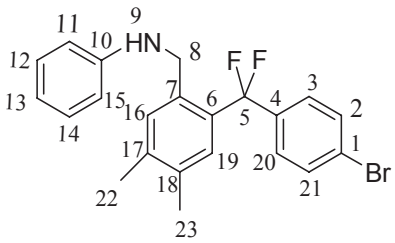
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 2.36 (s, 6H, $H_{15 \text{ and } 16}$), 7.30-7.35 (m, 2H, $H_{3 \text{ and } 12}$), 7.37 (s, 1H, $H_{8 \text{ or } \mathbf{11}}$), 7.54-7.60 (m, 2H, $H_{2 \text{ and } 13}$), 7.84 (s, 1H, $H_{\mathbf{8} \text{ or } 11}$), 10.14 (t, 1H, H_{14}, *J*= 2.0 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 19.5 (1C, $C_{15 \text{ or } 16}$), 20.3 (1C, $C_{15 \text{ or } 16}$), 120.5 (t, 1C, C_5, *J*= 242.0 Hz), 125.1 (t, 1C, C_1, *J*= 2.4 Hz), 127.7 (t, 2C, $C_{3 \text{ and } 12}$, *J*= 5.0Hz), 128.2 (t, 1C, C_{11}, *J*= 7.9 Hz), 130.1 (1C, C_8), 131.6 (t, 1C, C_7, *J*= 1.9 Hz), 131.9 (2C, $C_{2 \text{ and } C13}$), 134.9 (t, 1C, $C_{4 \text{ or } 6}$, *J*= 27.6 Hz), 136.6 (t, 1C, $C_{4 \text{ or } 6}$, *J*= 28.1 Hz), 139.8 (t, 1C, $C_{\mathbf{9} \text{ or } 10}$, *J*= 1.5 Hz), 143.2 (1C, $C_{9 \text{ or } \mathbf{10}}$), 190.3 (t, 1C, C_{14}, *J*= 3.7 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -78.62 (s).

HRMS (ESI). Calcd for $C_{16}H_{13}OF_2{}^{79}BrNa$ [M+Na]+: *m/z* 361.0015. Found: *m/z* 361.0020 (1 ppm).

{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-benzyl}-phenyl-amine (17)



$C_{23}H_{24}BrF_2N$
M = 432.34 g.mol^{-1}

A solution of aldehyde **16** (60 mg, 0.18 mmol), aniline (20 µL, 1.2 equiv) and a 1M solution of zinc chloride (0.23 mL, 1.3 equiv) in THF was stirred at room temperature for 3 h before addition of ethanol (0.5 mL) and sodium cyanoborohydride (33 mg, 3 equiv). The reaction mixture was stirred at room temperature overnight and then quenched by addition of water. The inorganic precipitate was filtered and washed with ethanol. The combined organic phases were concentrated in vacuo. The crude product was dissolved in ethyl acetate, filtered to remove the remaining inorganic solids, and concentrated in vacuo. After purification by flash chromatography on silica gel, the amine **17** was isolated as white crystals (64 mg, 87% yield). Mp: 114-116 °C. R_f = 0.37 (Et_2O/pentane, 4/96).

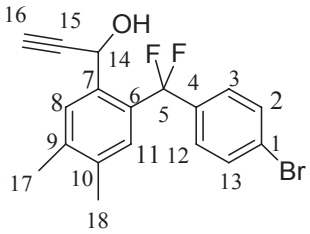
^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 2.28 (s, 3H, $H_{22 \text{ or } 23}$), 2.32 (s, 3H, $H_{22 \text{ or } 23}$), 3.86 (bs, 1H, H_9), 6.40-6.43 (m, 2H, $H_{11 \text{ and } 15}$), 6.68-6.72 (m, 1H, H_{13}), 7.10-7.14 (m, 2H, $H_{12 \text{ and } 14}$), 7.34 (s, 1H, $H_{16 \text{ or } 19}$), 7.35-7.37 (m, 2H, $H_{3 \text{ and } 20}$), 7.39 (s, 1H, $H_{16 \text{ or } 19}$), 7.52-7.56 (m, 2H, $H_{2 \text{ and } 21}$)

^{13}C NMR ($CDCl_3$, 100 MHz): δ, ppm 19.5 (1C, $C_{22 \text{ or } 23}$), 19.7 19.5 (1C, $C_{22 \text{ or } 23}$), 45.2 (t, 1C, C_8, *J*= 3.2 Hz), 112.8 (2C, $_{C11 \text{ and } C15}$), 117.5 (1C, C_{13}), 121.2 (t, 1C, C_5, *J*= 241.8 Hz), 124.6 (t, 1C, C_1, *J*= 2.5 Hz), 127.9 (t, 2C, $C_{3 \text{ and } 20}$, *J*= 5.1 Hz), 127.9 (t, 1C, C_{19}, *J*= 8.1 Hz), 129.2 (2C, $C_{12 \text{ and } 14}$), 130.7 (1C, C_{16}), 131.3 (t, 1C, C_6, *J*= 26.1 Hz), 131.7 (2C, $C_{2 \text{ and } 21}$), 134.8 (t, 1C, C_7, *J*= 2.3 Hz), 135.4 (1C, C_{17}), 136.6 (t, 1C, C_4, *J*= 28.6 Hz), 139.4 (t, 1C, C_{18}, *J*= 1.6 Hz), 147.9 (1C, C_{10})

^{19}F NMR ($CDCl_3$, 376 MHz) δ, ppm: -84.64 (s).

HRMS (ESI). Calcd for $C_{22}H_{20}NF_2{}^{79}BrNa$: [M+Na]+: *m/z* 438.0645. Found: *m/z* 438.0646 (0 ppm).

1-{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-prop-2-yn-1-ol (18)



$C_{18}H_{15}BrF_2O$
M = 365.21 g.mol^{-1}

To a solution of aldehyde **16** (48 mg, 0.14 mmol) in anhydrous THF (1mL) was added dropwise at 0 °C under nitrogen, a 0.5 M solution of ethynyl magnesium bromide in THF (0.34 mL, 0.17 mM, 1.2 equiv). The reaction mixture was stirred for 3 h, at 0°C, before quenching by addition of a saturated NH_4Cl solution. After extraction with diethyl ether, the combined organic phases were washed with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by chromatography on silica gel, the product **18** was isolated as white crystals (38 mg, 73% yield). Mp: 83-85 °C. *Rf* = 0.23 (Et_2O/pentane, 20/80).

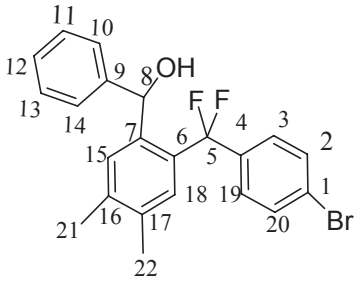
^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 2.17 (d, 1H, OH, *J*= 4.2 Hz), 2.29 (s, 3H, $H_{17 \text{ or } 18}$), 2.34 (s, 3H, $H_{17 \text{ or } 18}$), 2.53 (d, 1H, H_{16}, *J*=2.2 Hz), 5.58 (dd, 1H, H_{14}, J= 2.2, 4.2 Hz), 7.24 (s, 1H, $H_{8 \text{ or } 11}$), 7.32-7.34 (m, 2H, $H_{3 \text{ and } 12}$), 7.54-7.56 (m, 2H, $H_{2 \text{ and } 13}$), 7.72 (s, 1H, $H_{8 \text{ or } 11}$).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ, ppm 19.5 (1C, C17 or C18), 19.6 (1C, C17 or C18), 60.4 (t, 1C, C_{14}, *J*= 3.7 Hz), 74.2 (1C, C_{16}), 83.5 (1C, C_{15}), 121.0 (t, 1C, C_5, J= 241.0 Hz), 124.9 (t, 1C, C_1, *J*= 2.4 Hz), 127.8 (t, 1C, C11, J= 7.74Hz), 127.9 (t, 2C, $C_{3 \text{ and } C12}$, *J*= 5.0 Hz), 130.2 (t, 1C, C_6, *J*= 26.2 Hz), 130.3 (1C, C_8), 131.7 (2C, $C_{2 \text{ and } 13}$), 136.1 (t, 1C, C_7, *J*= 2.0 Hz), 136.3 (t, 1C, C_4, *J*= 28.5 Hz), 137.2 (1C, $C_{9 \text{ or } \mathbf{10}}$), 140.1 (t, 1C, $C_{\mathbf{9} \text{ or } 10}$), *J*= 1.6 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz): δ, ppm -81.67 (d, J= 268.6 Hz), -80.629 (d, J= 268.5 Hz), (AB system).

HRMS (ESI). Calcd for $C_{18}H_{15}OF_2{}^{79}BrNa$: [M+Na]+: m/z 387.0172. Found: m/z 387.0175 (1 ppm).

{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-phenyl-methanol (19)



$C_{22}H_{19}BrF_2O$
M = 417.29 g.mol^{-1}

To a solution of aldehyde **16** (50 mg, 0.15 mmol) in anhydrous THF (1mL) was added, dropwise under magnetic stirring and under nitrogen at -70 ^{0}C, a 1.5-1.7 M solution of phenyl lithium in a 70:3à mixture of cyclohexane and ether (0.11 ml, 1.2 equiv). The mixture was stirred for 2 h at this temperature, before quenching by addition of a saturated NH_4Cl solution. After extraction with diethyl ether, the combined organic phases were washed with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by silica gel chromatography, the alcohol **19** was isolated as white crystals (50 mg, 81% yield). Mp: 85-87 °C. R_f = 0.38 (Et_2O/pentane, 20/80).

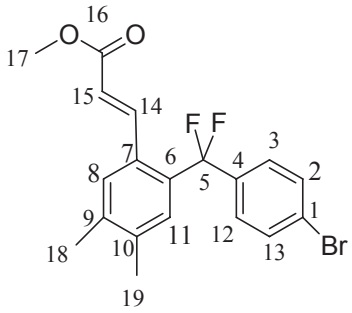
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 2.06 (s, 1H, OH), 2.26 (s, 3H, $H_{21 \text{ or } 22}$), 2.31 (s, 3H, $H_{21 \text{ or } 22}$), 6.03 (s, 1H, H_8), 7.19-7.39 (m, 9H, aromatic), 7.53-7.56 (m, 2H, $H_{2 \text{ and } 20}$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 19.5 (1C, $C_{21 \text{ or } C22}$), 19.7 (1C, $C_{21 \text{ or } C22}$), 70.6 (t, 1C, C_8, *J*= 2.8 Hz), 121.1 (t, 1C, C_5, *J*= 241.4 Hz), 124.7 (t, 1C, C_1, *J*= 2.5 Hz), 126.3 (1C, $C_{\mathbf{12} \text{ or } 15}$), 127.0 (1C, $C_{12 \text{ or } \mathbf{15}}$), 127.4 (t, 1C, C_{18}, *J*= 8.1 Hz), 127.9 (t, 2C, $C_{3 \text{ and } 19}$), 128.1 (2C, $C_{10 \text{ and } 14}$), 130.9 (2C, $C_{11 \text{ and } 13}$), 130.9 (t, 1C, C_6, *J*= 25.7 Hz), 131.7 (2C, $C_{2 \text{ and } 20}$), 136.2 (1C, C_{16}), 136.9 (t, 1C, C_4, *J*= 28.6 Hz), 139.5 (t, 1C, C_7, *J*= 2.1 Hz), 139.7 (t, 1C, C_{17}, *J*= 1.6 Hz), 143.0 (1C, C_9).

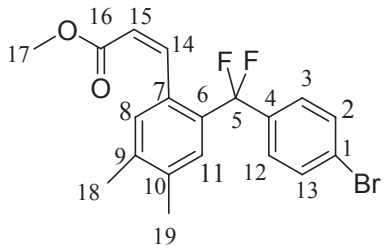
^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -82.25 (d, J_{FF}= 266.0 Hz), -79.83 (d, J_{FF}= 266.0 Hz), (AB system).

HRMS (ESI). Calcd for $C_{22}H_{19}OF_2{}^{79}BrNa$: [M+Na]+: *m/z* 439.0485. Found: *m/z* 439.0485 (0 ppm).

3-{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-(*E*)-acrylic acid methyl ester (20a) and 3-{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-(*Z*)-acrylic acid methyl ester 20b).



(20a)



(20b)

$C_{19}H_{17}BrF_2O_2$
M = 395.24 g.mol^{-1}

A solution of aldehyde **16** (50 mg, 0.15 mmol) and Ph_3PCHCO_2Me [100 mg, 2 equiv. in benzene (1mL)] was stirred at 50 ^{0}C for 6 h. The reaction mixture was filtered on a short pad of silica gel to remove large part of triphenylphosphine oxide, and the residues washed with ether and the solution concentrated in vacuo. The alkenes **20a** and **20b**, obtained in a 8:1 ratio by NMR analysis, were separated by chromatography on silica gel (47 mg, 81% combined yield).

20a: White crystals (42 mg, 72% yield). Mp: 122-124 ^{0}C. R_f = 0.49 (Et_2O/pentane, 20/80).

^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 2.31 (s, 3H, $H_{18 \text{ or } 19}$), 2.32 (s, 3H, $H_{18 \text{ or } 19}$), 3.74 (s, 3H, H_{17}), 6.19 (d, 1H, H_{15}, *J*= 15.8 Hz), 7.30-7.33 (m, 2H, $H_{3 \text{ and } 12}$), 7.38 (s, 1H, $H_{8 \text{ or } 11}$), 7.39 (s, $H_{8 \text{ or } 11}$), 7.51-7.54 (m, 2H, $H_{2 \text{ and } 13}$), 7.83 (td, 1H, H_{14}, J_{HF}= 1.9 Hz, *J*=15.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ, ppm 19.5 (1C, $C_{18 \text{ or } 19}$), 19.8 (1C, $C_{18 \text{ or } 19}$), 51.6 (1C, C_{17}), 119.5 (1C, C_{15}), 120.6 (t,1C, C_5, *J*= 242.4 Hz), 124.6 (t, 1C, C_1, *J*= 2.3 Hz), 127.8(t, 2C, $C_{3 \text{ and } 12}$, *J*= 5.1 Hz), 127.9 (t, 1C, C_{11}, *J*=7.9 Hz), 129.1 (1C, C_8), 130.6 (t, 1C, C_7, *J*= 2.5 Hz), 131.7 (2C, $C_{2 \text{ and } 13}$), 132.5 (t, 1C, $C_{4 \text{ or } 6}$, *J*= 26.0 Hz), 136.6 (t, 1C, $C_{4 \text{ or } 6}$, *J*=28.4 Hz), 138.6 (1C, $C_{9 \text{ or } 10}$), 139.3 (bs, $C_{9 \text{ or } 10}$), 142.1 (t, 1C, C_{14}, *J*= 2.6 Hz), 166.8 (1C, C_{16}).

^{19}F NMR ($CDCl_3$, 376 MHz): δ, ppm -83.867 (s).

HRMS. (ESI) Calcd for $C_{19}H_{17}O_2F_2{}^{79}BrNa$: [M+Na]+: *m/z* 411.0278. Found: *m/z* 417.0280 (1 ppm).

20b: White crystals (5 mg, 9% yield) Mp: 63-65 ^{0}C. R_f = 0.66 (Et_2O/ pentane, 20/80).

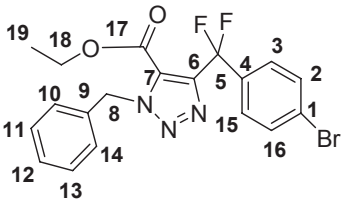
^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm 2.29 (s, 3H, $H_{9\ or\ 10}$), 2.31 (s, 3H, $H_{9\ or\ 10}$), 3.55 (s, 3H, H17), 5.78 (d, 1H, H15, *J* = 12.0 Hz), 7.04 (d, 1H, H14, *J* = 12.0 Hz), 7.08 (s, 1H, $H_{8\ or11}$), 7.29 - 7.33 (m, 2H, $H_{3\ and\ 12}$), 7.36 (s, 1H, $H_{8\ or\ 11}$), 7.47 - 7.50 (m, 2H, $H_{2\ and\ 13}$).

^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 19.5 (1C, $C_{18\ or\ 19}$), 19.7 (1C, $C_{18\ or\ 19}$), 51.1 (1C, C_{17}) 120.5 (1C, C_{15}), 120.7 (t, 1C, C_5, *J* = 241.8 Hz), 124.4 (t, 1C, C_1, *J* = 2.3 Hz), 127.3 (t, 1C, C_{11}, *J* = 7.5 Hz), 128.1 (t, 2C, $C_{3\ and\ 12}$, *J* = 5.0 Hz), 130.8 (t, 1C, $C_{4\ or\ 6}$, *J* = 25.2Hz); 131.4 (1C, $C_{2\ or\ 13}$), 131.5 (1C, $C_{2\ or\ 13}$), 132.0 (t, 1C, C_7, *J* =3.0 Hz); 136.5 (t, 1C, $C_{4\ or\ 6}$, *J* = 28.5 Hz), 136.7 (1C, C10), 138.4 (t, 1C, C_9, *J* = 1.4 Hz),143.0 (1C, C_{14}), 165.7 (1C, C_{16}).

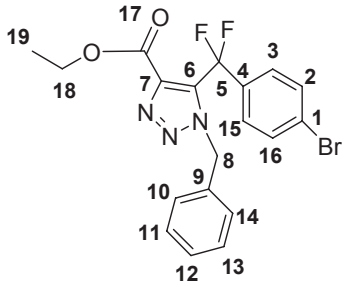
^{19}F NMR ($CDCl_3$, 376 MHz): δ, ppm - 86.03 (s).

HRMS (ESI). Calcd for $C_{19}H_{17}O_2F_2{}^{79}BrNa$: [M+Na]+: *m/z* 411.0278. Found: *m/z* 417.0276 (0 ppm).

3-Benzyl-5-[(4-bromophenyl)-difluoromehtyl]-3*H*-[1,2,3]triazole-4-carboxylicacid ethyl ester (21a) and 1-Benzyl-5-[(4-bromo-phenyl)-difluoromehtyl]-1*H*-[1,2,3]triazole-4-carboxylicacid ethyl ester (21b)



(21a)



(21b)

$C_{19}H_{16}BrF_2N_3O_2$
M = 436.25 g.mol^{-1}

The difluoro-propargylic ester **5** (195 mg, 0.64 mmol, 1 equiv) and benzylazide (0.06 mL, 1.5 equiv) were stirred, neat, at 60 ^{0}C for 6 h. The adducts **21a** and **21b**, obtained in a 1:2 ratio by NMR analysis, were separated by chromatography on silica gel (251 mg, 90% combined yield). **21a** (83 mg, 30% yield) was obtained as white crystals, Mp: 50-52 ^{0}C. R_f = 0.41 (Et_2O/pentane, 1/9).

^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.22 (t, 3H, H_{19}, *J*= 7.2 Hz), 4.27 (q, 2H, H_{18}, *J*= 7.2 Hz), 5.87 (s, 2H, H_8), 7.28 -7.36 (m, 5H, $H_{10\text{-}14}$), 7.44-7.46 (m, 2H, $H_{3 \text{ and } 15}$), 7.56-7.59 (m, 2H, $H_{2 \text{ and } 16}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.7 (1C, C_{19}), 54.1 (1C, C_8), 62.6 (1C, C_{18}), 116.3 (t, 1C, C_5, *J*= 240.9 Hz), 124.8 (t, 1C, C_1, *J*= 2.3 Hz), 126.4 (bs, 1C, C_7), 127.6 (t, 2C, $C_{3 \text{ and } 15}$, *J*= 5.6 Hz), 128.0 (2C, $C_{(11 \text{ and } 13) \text{ or } (10 \text{ and } 14)}$), 128.6 (1C, C_{12}), 128.8 (2C, $C_{(10 \text{ and } 14) \text{ or } (11 \text{ and } 13)}$), 131.5 (2C, $C_{2 \text{ and } 16}$), 134.2 (1C, C_9), 134.9 (t, 1C, C_4, *J*= 27.1 Hz), 145.4 (t, 1C, C_6, *J*= 34.4 Hz), 157.7 (1C, C_{17}).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -87.72 (s).

HRMS (ESI). Calcd for $C_{19}H_{16}N_3O_2F_2{}^{79}BrNa$: [M+Na]+: *m/z* 458.0292. Found: *m/z* 458.0288 (1 ppm).

21b (168 mg, 60% yield) was obtained as white crystals, Mp: 86-88 ^{0}C. R_f = 0.40 (Et_2O/pentane, 2/8)

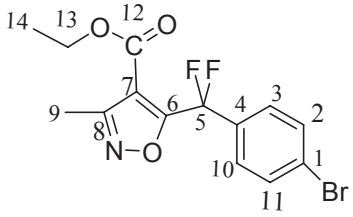
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 1.26 (t, 3H, H_{19}, *J*= 7.1 Hz), 4.27 (q, 2H, H_{18}, *J*= 7.1 Hz), 5.76 (s, 2H, H_8), 7.01-7.05 (m, 2H, $H_{3\ and\ 15}$), 7.12-7.15 (m, 2H, aromatic), 7.22- 7.31 (m, 3H,aromatic), 7.35- 7.39 (m, 2H, $H_{2\ and\ 16}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ, ppm 13.9 (1C, C_{19}), 54.9 (t, 1C, C_8, *J*= 4.5 Hz), 61.8 (1C, C_{18}), 116.7 (t, 1C, C_5, *J*= 242.7 Hz), 125 (t, 1C, C_1, *J*= 2.5 Hz),127.1 (t,2C, $C_{3\ and\ 15}$, *J*= 5.0 Hz), 127.7 (2C, $C_{(11\ and\ C13)\ or\ (10\ and\ 14)}$), 128.7 (1C, C_{12}), 128.8 (2C, $C_{(11\ and\ C13)\ or\ (10\ and\ 14)}$), 131.6 (2C, $C_{2\ and\ 16}$), 133.1 (t, 1C, C_4, *J*= 27.0 Hz), 133.8 (1C, C_9), 134.0 (t, 1C, C_6 , *J*= 34.8 Hz), 139.3 (t, 1C, C_7, *J*= 2.0 Hz), 159.6 (1C, C_{17}).

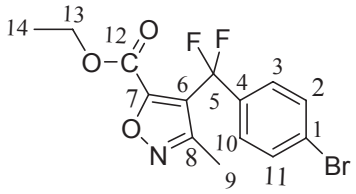
^{19}F NMR ($CDCl_3$, 282 MHz): δ, ppm -83.18 (s).

HRMS (ESI). Calcd for $C_{19}H_{16}N_3O_2F_2{}^{79}BrNa$: [M+Na]+: *m/z* 458.0292. Found: *m/z* 458.0293 (0 ppm).

5-[(4-Bromo-phenyl)-difluoro-methyl]-3-methyl-isoxazole-4-carboxylic acid ethyl ester (22a) and 4-[(4-Bromo-phenyl)- difluoro-methyl]-3-methyl-isoxazole-5-carboxylic acid ethyl ester (22b).



(22a)



(22b)

$C_{14}H_{12}BrF_2NO_3$
M = 360.15 g.mol^{-1}

A solution of fluoro-alkyne **5** (100 mg, 0.33 mmol), $C_2H_5NO_2$ (70 µL, 3 equiv), PhNCO (110 µL, 3 equiv) and 3 drops of Et_3N in toluene (5 mL) was stirred, at 50 ^{0}C during 3 h. The reaction mixture was filtered on silica gel, and concentrated in vacuo. The two isomers **19a** and **19b** were obtained as a 2:1 mixture by NMR analysis. The inseparable mixture of **19a** and **19b** was isolated as yellow oil by chromatography on silica gel (115 mg, 97% yield). The analysis of the spectral data could be done on this purified reaction mixture.

19a: R_f = 0.42 (Et_2O/pentane, 10/90).

^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 1.26 (t, 3H, H14, J=7.15Hz), 2.45 (s, 3H, H9), 4.25 (q, 2H, H_{13}, *J*= 7.1 Hz), 7.45-7.50 (m, 2H, $H_{3\ and\ 10}$), 7.57-7.60 (m, 2H, $H_{2\ and\ 11}$).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ, ppm 11.4 (1C, C_9), 13.9 (1C, C_{14}), 61.5 (1C, C_{13}), 111.2 (t, 1C, C_7, *J*= 1.4 Hz), 114.8 (t, 1C, C_5, *J*= 246.0 Hz), 125.6 (t, 1C, C_1, *J*= 2.3 Hz), 127.2 (t, 2C, $C_{3\ and\ 10}$, *J*= 5.5 Hz), 131.8 (2C, $C_{2\ and\ 11}$), 133.0 (t, 1C, C_4, *J*= 26.9 Hz), 158,8 (t, 1C, C_8, *J*= 1.2 Hz), 160.8 (t, 1C, C12, *J*= 0.7 Hz), 166.3 (t, 1C, C_6, *J*= 36.4 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -92.27 (s).

22b: R_f = 0.42 (Et_2O/pentane, 10/90).

^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 1.27 (t, 3H, H_{14}, *J*= 7.2 Hz), 2.40 (t, 3H, H_9, *J*= 1.9 Hz), 4.29 (q, 2H, H_{13}, *J*= 7.2 Hz), 7.41-7.42 (m, 2H, $H_{3 \text{ and } 10}$), 7.55-7.57 (m, 2H, $H_{2 \text{ and } 11}$).

^{13}C NMR (CDCl3, 100 MHz): δ, ppm 11.6 (t, 1C, C_9, *J*= 3.1 Hz), 13.7 (1C, C_{14}), 62.7 (1C, C_{13}), 117.3 (t, 1C, C_5, *J*= 240.2 Hz), 119.13 (t, 1C, C_6, *J*= 34.3 Hz), 125.15 (t, 1C, C_1, *J*= 2.4 Hz), 127.1 (t, 2C, $C_{3 \text{ and } 10}$, *J*= 5.4 Hz), 131.8 (1C, 2C, $C_{2 \text{ and } 11}$), 135.0 (t, 1C, C_4, *J*= 27.9 Hz), 156.1 (t, 1C, C_7, *J*= 1.2 Hz), 158.0 (t, 1C, C_8, *J*= 4.8 Hz), 160.0 (t, 1C, C_{12}, *J*= 0.9 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -83.89 (s).

HRMS (19a + 19b) (ESI): Calcd for $C_{14}H_{12}NO_3F_2{}^{79}BrNa$: [M+Na]+: *m/z* 381.9866. Found: *m/z* 381.9868 (0 ppm).

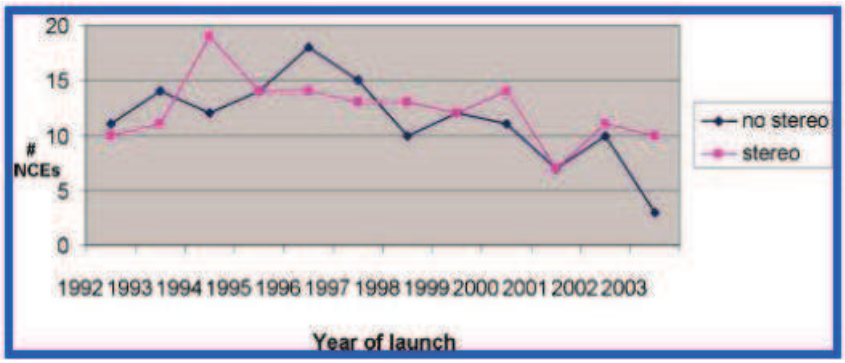
CHAPTER IV

DEVELOPMENT OF ASYMMETRIC ORGANOCATALYZED ADDITIONS TO ENALS WITH A CF_2R MOIETY IN ALLYLIC POSITION

I-Introduction

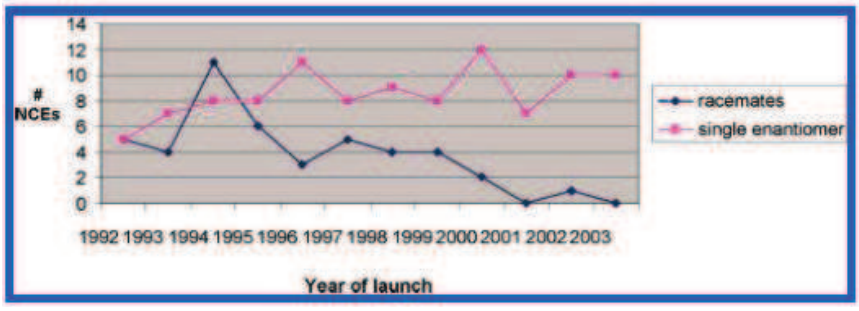
The requirement for the preparation and use of single enantiomers has been clearly identified in the last 20 years, especially in the case of bioactive molecules and "Active Pharmaceutical Ingredients".[1] This trend is easily demonstrated by considering different data from literature: in Figure 1 are indicated the number of marketed drugs per year with, or without, stereochemistry.

Figure 1. Marketed drugs with, or without, stereochemistry [1]



The second indicate the number of "New Chemical Entities" launched on the market, as single enantiomers in comparison with racemates (Figure 2). It clearly shows that nowadays, no racemate can be really considered for further development.

Figure 2. Single enantiomers versus racemates [1]



Finally, in Table 1 are considered the marketed drugs by year and type. These data confirm previous remarks, indicating that a last chiral molecule was marketed, in racemic form, in 2002.

Table 1. Marketed drugs by year and by type.[1]

type	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
nonchiral molecule	11	14	12	14	18	15	10	12	11	7	10	3
chiral, racemic	5	4	11	6	3	5	4	4	2		1	
chiral, single enantiomer	5	7	8	8	11	8	9	8	12	7	10	10
natural products and their semisynthetic derivatives	11	8	6	7	4	1	6	8	3	3	6	1
proteins, polymers, antibodies, polysaccharides	11	5	8	6	11	9	14	10	9	16	7	11
inorganic									2	1		
total	**43**	**38**	**45**	**41**	**47**	**38**	**43**	**42**	**39**	**34**	**34**	**25**

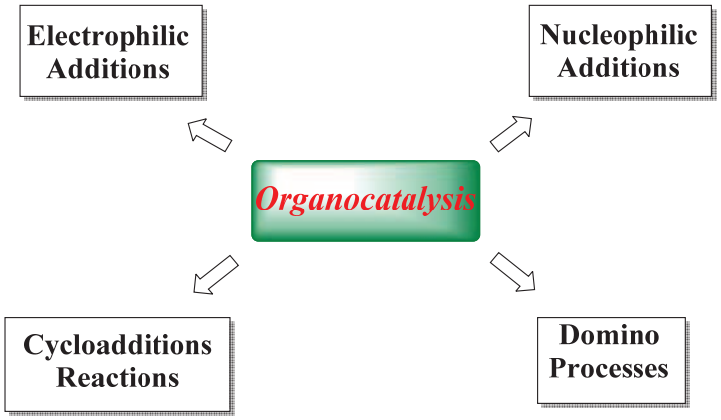
As described in a recent review article,[1] there are various scientific reasons for this trend, but extremely important is the fact that in most cases a single enantiomer is bioactive, the other one being at best inactive and in certain cases even toxic. Further, economic reasons are also important: it is costly to develop the chemical synthesis and the biological experiments on two enantiomers and the question remains, as well, on what to do with the second (unwanted) enantiomer?

All these data explain, at least in large part, the developments of asymmetric synthesis and more recently, of the asymmetric catalysis.

On the other hand, the chemistry of organofluorine compounds is a rapidly developing area of research, due to their wide range of applications in a number of important fields such as drug discovery and materials science,[2] therefore preparation of optically active molecules containing fluorine atoms is a rapidly developing topic.

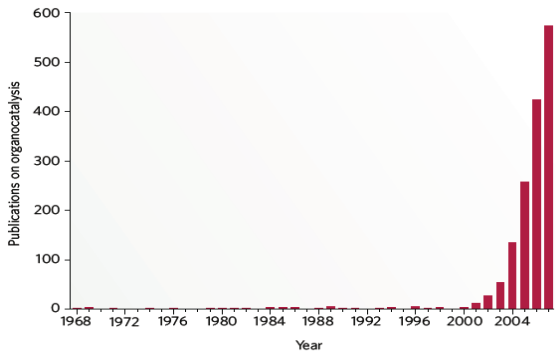
Organocatalysis, is now considered as the third pillar in the "trio of asymmetric catalysis" [3] (with the other two being biocatalysis and metal catalysis). Synthetic chemists have established a large number of very efficient and useful asymmetric synthetic protocols in many reactions types since its official birth (or rebirth) in 2000 [4] (Figure 3).

Figure 3. Use of organocatalysis in a wide range of asymmetric synthesis.



Besides its efficiency, the number of practical advantages of organocatalysis relative to macromolecular or metal catalysts, (non sensitivity to air and moisture, low cost, availability from renewable resources, and relative nontoxicity)[5] makes organocatalysis one of the most rapidly growing and competitive research areas in synthetic organic chemistry during the last decade.[6] This exponential growth is clearly represented in Figure 4 with the number of publications on this topic.

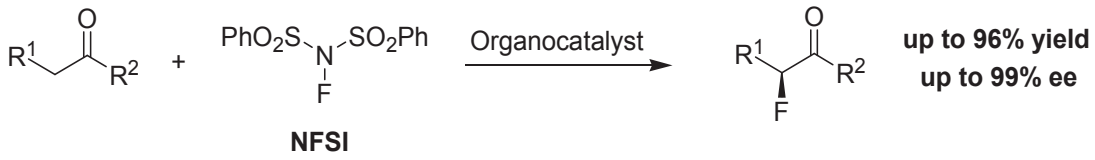
Figure 4. Quantitative evolution of organocatalysis.[7]



Therefore, the use of asymmetric organocatalysis for the preparation of optically pure fluorine containing molecules appears to be of much interest, even if relatively few examples have been published until now.

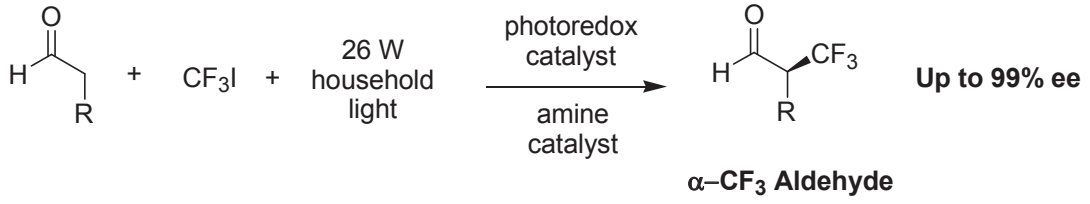
Most representative is the asymmetric monofluorination.[8] In 2005, MacMillan and co-workers reported the first enantioselective organocatalytic α-fluorination of aldehydes.[8c] Six years later, this group successfully extended the α-fluorination to cyclic ketones.[8f] The products of both fluorinations (aldehydes and ketones) were obtained in a very good yields, with excellent enantioselectivities (Scheme 1).

Scheme 1. Enantioselective α-fluorination of aldehydes and ketones.



Moreover, a trifluoromethylation reaction was reported in 2011,[9] in which enantioriched α-CF_3 aldehydes were prepared through enantioselective photoredox organocatalysis. In this report Macmillan described a new approach to asymmetric α-trifluoromethylation of aldehydes through a successful combination of enamine and organometallic photoredox catalysis (scheme 2).

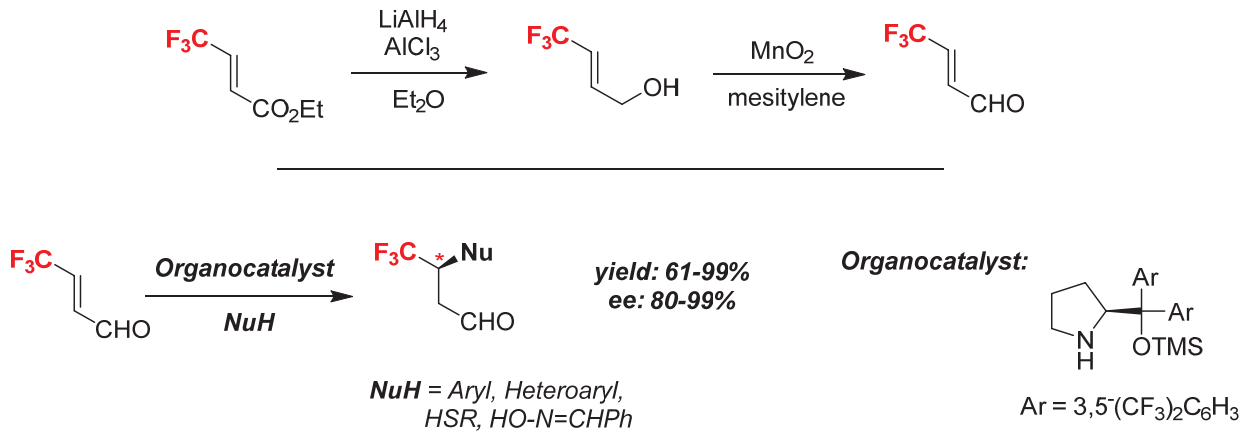
Scheme 2. Enantioselective α-trifluoromethylation of aldehydes.



In addition, several studies reported the synthesis of optically active CF_3 through asymmetric additions to trifluoromethylcrotonates or corresponding corresponding amides.[10] Very recently, an elegant study has been reported on the preparation of trifluorocrotonaldehyde and its use in

various asymmetric organocatalytic reactions.[11] After showing an efficient route for the synthesis of the fluorinated aldehyde, several organocatalytic 1,4-nucleophilic additions were performed with very good yields and ee's (Scheme 3).

Scheme 3. Synthesis and use of 4,4,4-trifluorocrotonaldehyde.



Besides purely synthetic aspects, it appears also of much interest to study the pratically unknown effect of the fluorine atoms in such organocatalytic reactions. A rare example of mechanistic-driven study is the use of fluorine-iminium *gauche* effect to control the enantioselectivity in organocatalytic epoxidation reactions.[12]

However, to the best of our knowledge, no example of asymmetric organocatalysis has been reported to date with derivatives containing *gem*-difluoromethyl, or *gem*-difluoroalkyl systems, which is the goal of our study.

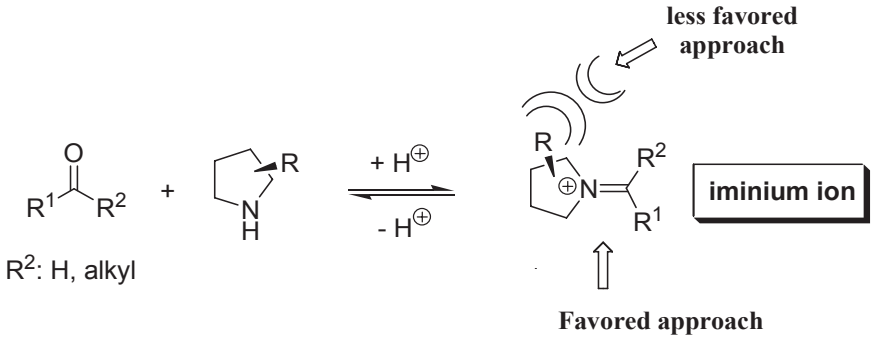
Before describing our own results, we will present briefly a few basic data on organocatalysis.

I-1) Organocatalysis

Organocatalysis, which is the use of small organic molecules as catalysts, has been known for more than a century. But organocatalysis has become, only during the past decade, a thriving area of general concepts and widely applicable asymmetric reactions.[7] This catalysis was obtained by using chiral secondary amines as rate enhancers and chiral inducers in reactions

involving aldehydes and ketones. The scheme 4 represents, in a simple manner the concept: the "activation" of the carbonyl is obtained by its transformation into more reactive iminium ions. Further, use of a chiral amine allows these reactive intermediates to have two differentiated faces and therefore preferred reactions on one or the other face should lead to asymmetric induction.

Scheme 4. Activation, with stereoinduction, of aldehydes/ketones by chiral amine.

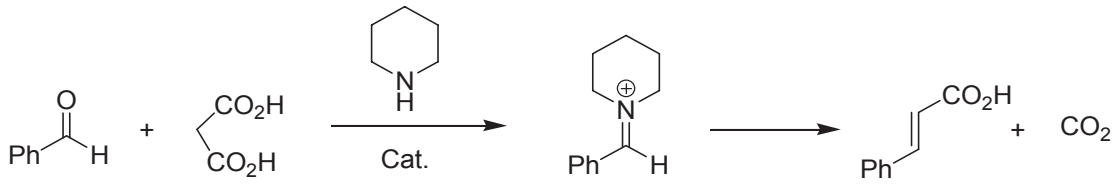


I-2) Historical development of organocatalysis (in iminium catalysis)

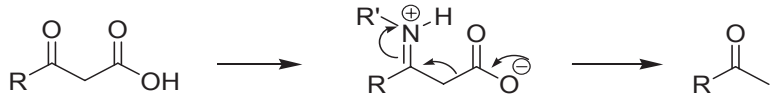
It is difficult to give a specific date for the introduction of the concept of iminium catalysis. Instead, the history of iminium catalysis is characterized by serendipitous discoveries and intervening theoretical advances. Scheme 5 (from reference 13) illustrates the key developments of the field.[13]

Scheme 5. Historical development of iminium catalysis. [13]

1894 -1898 *Knoevenagel discovers a family of iminium-catalyzed condensation reactions.*

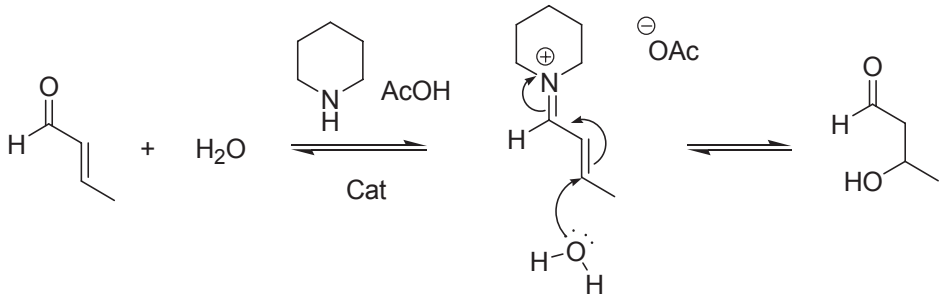


1907 *Iminium-catalyzed β-decarboxylation reactions discovered by Pollak.*

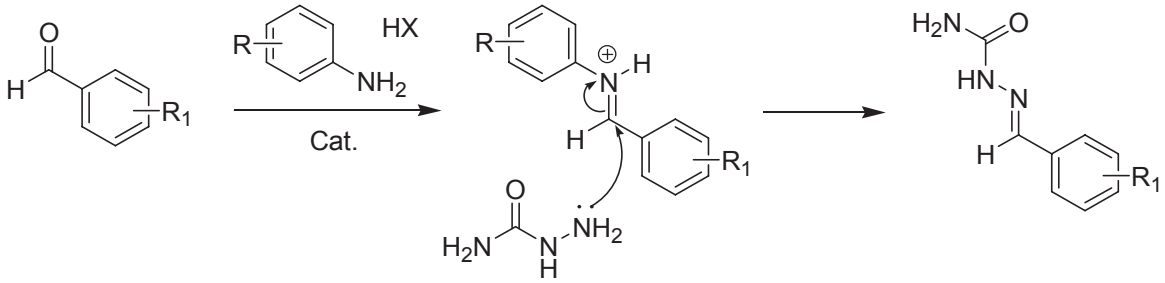


1934 *Pedersen proposes the intermediacy of iminium ions as intermediates in the decarboxylation reaction.*

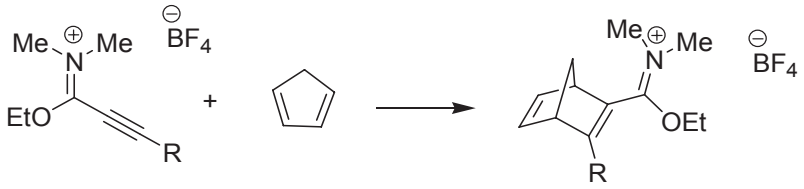
1937 *Langenbeck discovers the first iminium-catalyzed conjugated addition.*



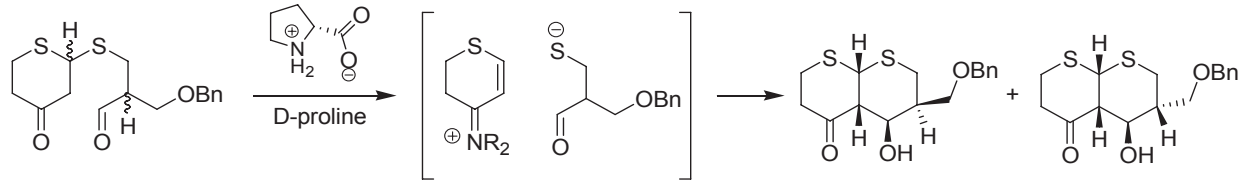
1962 *Jenks discovered aniline catalysis of semicarbazone formation.*



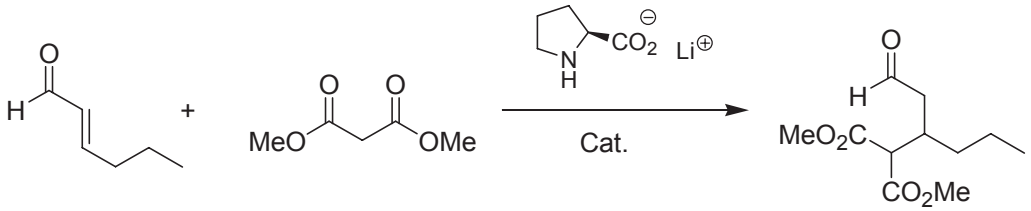
1976 *The role of iminium activation in cycloaddition is recognized by Viehe and Baum.*



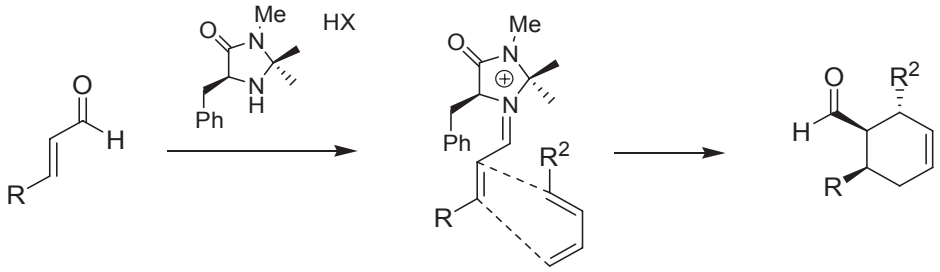
1981 *Woodward and co-workers use asymmetric proline catalysis to perform an iminium-catalyzed deracemization and intramolecular aldol reaction in the total synthesis of erythromycin.*



1991 *The first catalytic asymmetric iminium-catalyzed conjugated addition reaction is discovered by Yamaguchi.*



2000 *MacMillan reports the first asymmetric iminium-catalyzed cycloaddition reactions, and this is considered as the official birth of the modern organocatalysis.*

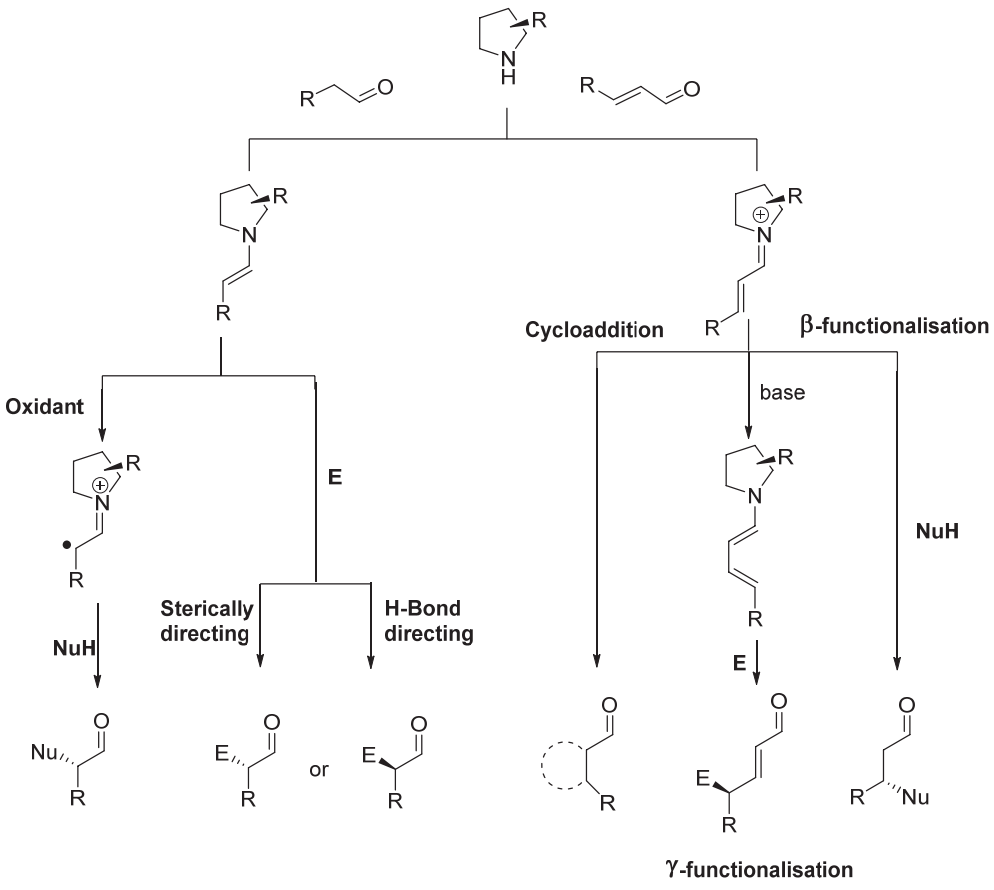


Thereafter many scientists have contributed to this emerging area. Even if it is difficult to mention all of them, it is important to notice also the contributions of B. List, C. A. Barbas III, K. A. Jørgensen, among many others.

I-3) Different types of aminocatalyzed carbonyl functionalisations.

Four distinct types of aminocatalyzed carbonyl functionalisations have been identified: two applying to aldehydes and two using α,β-unsaturated aldehydes. With respect to aldehydes, both electrophilic and nucleophilic α-functionalisations can be achieved. Both *β* and γ-functionalisations can be performed, respectively, through nucleophilic and electrophilic additions to α,β-unsaturated aldehydes.[14] Moreover, cycloadditions can be achieved also on *α,β*-unsaturated aldehydes (Scheme 6).

Scheme 6. Main aminocatalytic pathways for carbonyl functionalisations.
E = electrophile. NuH = nucleophile.

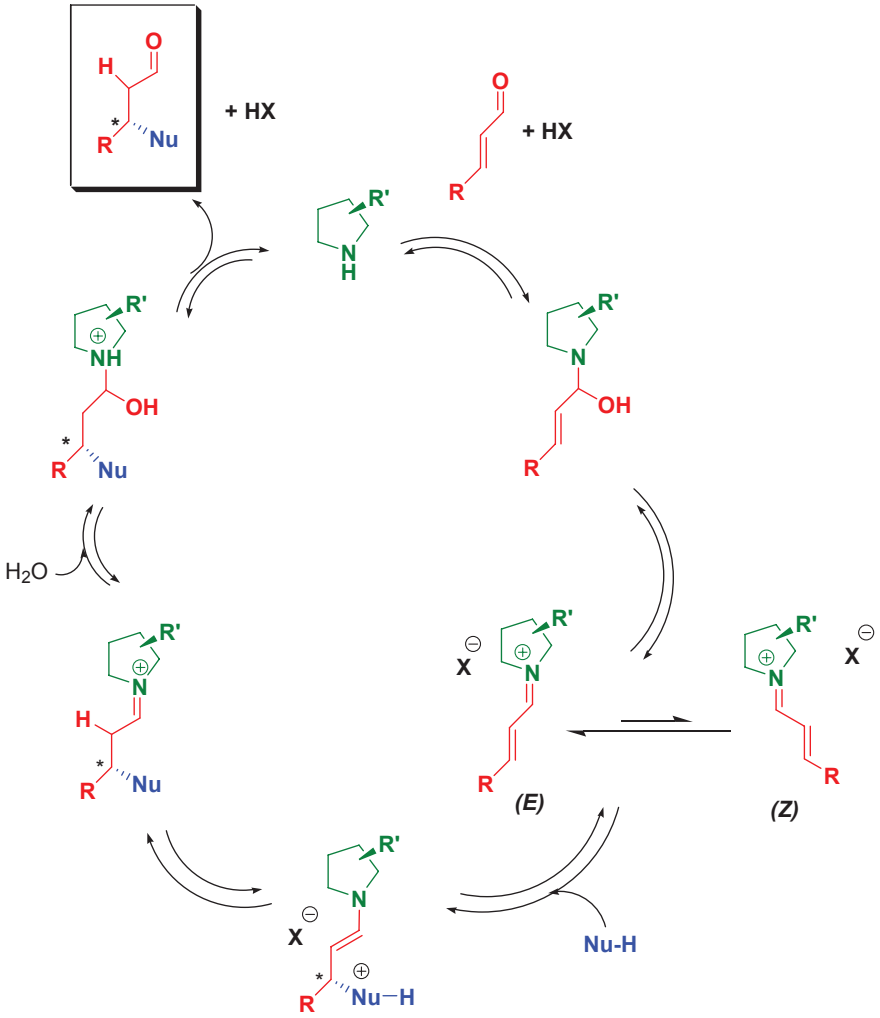


In our research we were interested in functionalisations of *α,β*-unsaturated aldehydes and therefore we will present the key basic data in this area.

I-4) Functionalisation of *α,β*-unsaturated aldehydes

The catalytic cycle of such functionalisations is reported in scheme 7. Condensation between chiral secondary amines and *α,β*-unsaturated aldehydes lead to the formation of the reactive iminium ions, which are sterically hindered from one side. Selective nucleophilic addition from less hindered side, onto the *β*-carbon atom of this ion leads to a *β*-functionalised enamine, which is protonated to give a new iminium ion. Latter derivative is hydrolyzed to release the product and the catalyst as last step in the catalytic cycle. [14]

Scheme 7. Detailed catalytic cycle of *β*-functionalisation of aldehyde (Nu = nucleophile).

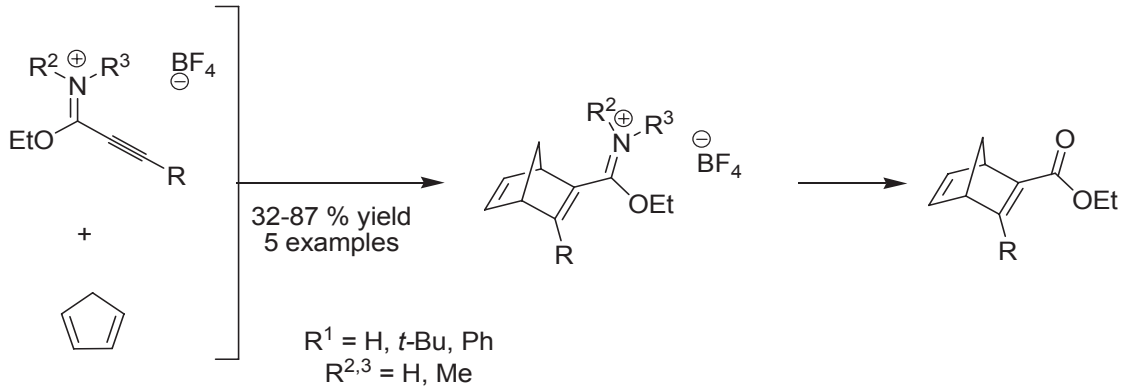


An important factor which plays a role in the efficiency of this type of reaction is the reversible formation of iminium ions from the chiral amine and *α,β*-unsaturated carbonyl compounds. Moreover, hydrolysis to the final products generally occurs smoothly and doesn't have any influence on the configuration at the chiral center generated in the previous step.[15]

I-4.1) Diels-Alder cycloaddition

As mentioned previously, the concept of iminium activation of α,β-substituted carbonyl compounds in Diels-Alder reactions was introduced by Baum and Viehe in 1976.[16] But the method reported was not catalytic, the acetylenic iminium salt had been prepared beforehand. Reactions between the prepared iminium salt and cyclopentadiene afforded cycloadducts that could be further hydrolyzed to the bicyclic esters (Scheme 8).[13,16]

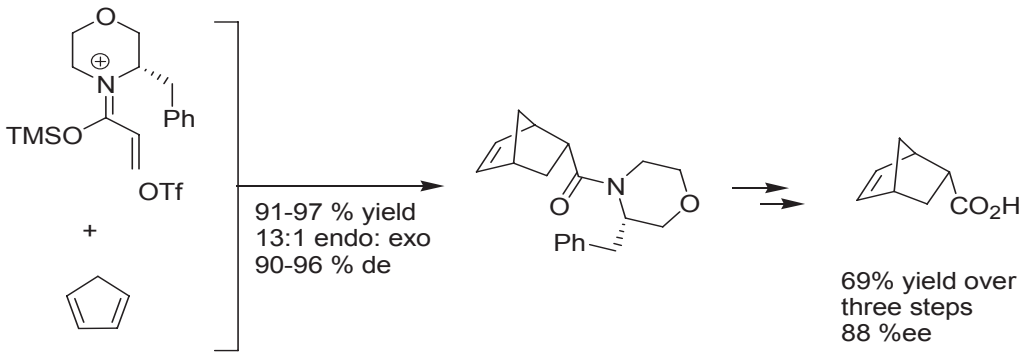
Scheme 8. Diels-Alder reactions of propargylic iminium ions. [16]



The amidium moiety was found to be more activating than any carbonyl functionality, when conjugated with the multiple bond. In addition to the Diels-Alder reactions, [3+2]-cycloadditions involving the same acetylenic iminium ethers and diethyl diazoacetate or münchnones were also reported.[13]

Jung and co-workers reported an enantioselective version of this reaction type in 1989.[17] Chiral iminium silyl triflates were prepared before, which in turn reacted with cyclopentadiene to afford the desired cycloadducts (Scheme 9).

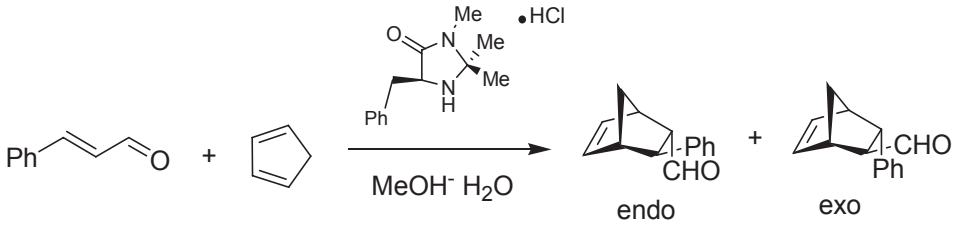
Scheme 9. Asymmetric Diels-Alder reactions of a chiral iminium salt.[17]



Good yields and stereoselectivities were obtained during cycloadditions with these auxiliaries. However, their hydrolysis proved to be difficult, requiring two separated steps which lead to

some decrease in the global yields. After that, few report were published on this type of reaction,[18] till the official birth of asymmetric organocatalysis in 2000, when MacMillan and his group reported the first highly enantioselective organocatalytic Diels-Alder reaction,[4b] using again a chiral secondary amine as a catalyst (Scheme 10).

Scheme 10. Asymmetric organocatalytic Diels-Alder cycloaddition.



The yields and ee's were excellent (>75% yield, *endo* > 90% ee, *exo* > 84% ee) and this reaction offers attractive potentialities in synthesis. However this type of reaction is still a challenge with fluorinated α-β unsaturated aldehydes.

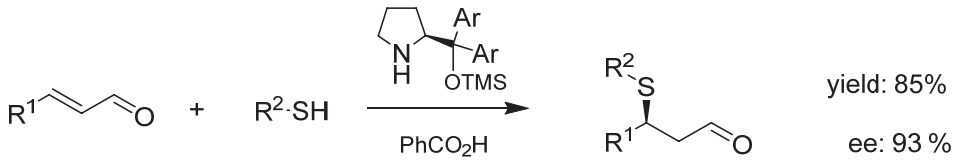
I-4.2) Asymmetric organocatalyzed 1,4-conjugated addition

Asymmetric organocatalysis has shown to be a very efficient protocol for different types of 1,4-conjugated additions.[13, 14, 19] In this work, we were interested mainly in two types of asymmetric organocatalyzed conjugated additions: i) sulfa-Michael addition (SMA); ii) aniline conjugated addition.

a. Asymmetric organocatalyzed sulfa-Michael addition

The importance of sulfur-containing and sulfur-based compounds is uncontested.[20] Many biochemical processes in nature involve sulfur, both in organic and inorganic forms.[21] Asymmetric organocatalytic SMA on *α,β*-unsaturated aldehydes can be considered as one of the most promising methods for the synthesis of sulfur-containing compounds, especially optically active ones (Scheme 11).[22]

Scheme 11. Asymmetric organocatalyzed (SMA) to *α,β*-unsaturated aldehydes.



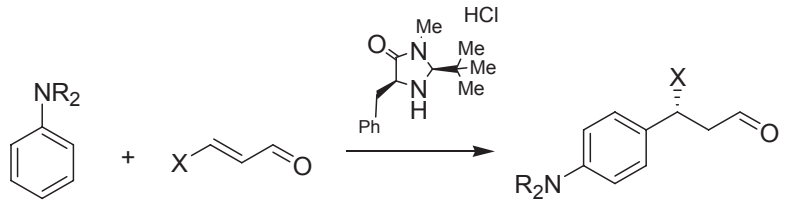
R^1 = ethyl; R^2= Bn; Ar= 3,5-$(CF_3)_2C_6H_3$

Very good results, including ee's up to 93%, have been obtained in the group of Jørgensen by using a diarylprotected prolinol auxiliary.[22] However, the study of this type of reactions on *γ*-difluoro-*α,β*-unsaturated aldehydes has not been performed previously, and the possible effect of fluorine atoms is unknown at this stage. This was considered as one of the goals of our study.

b. Aniline conjugated addition

Molecules with a stereocenter on a benzylic carbon are found in over 5000 isolated natural products.[23] Further, this stereochemical motif has also gained an important status in medicinal chemistry, due to its recurring presence among therapeutic agents (e.g. Zoloft,[24] Paxil,[25] Detrol[26]). In 2002, MacMillan described the first enantioselective organocatalytic alkylation of aniline ring (Scheme 12),[27] by reacting simple *α,β*-unsaturated aldehydes and aryl substrates in the presence of a secondary amine as catalyst.

Scheme 12. Organocatalytic conjugated addition of aniline.



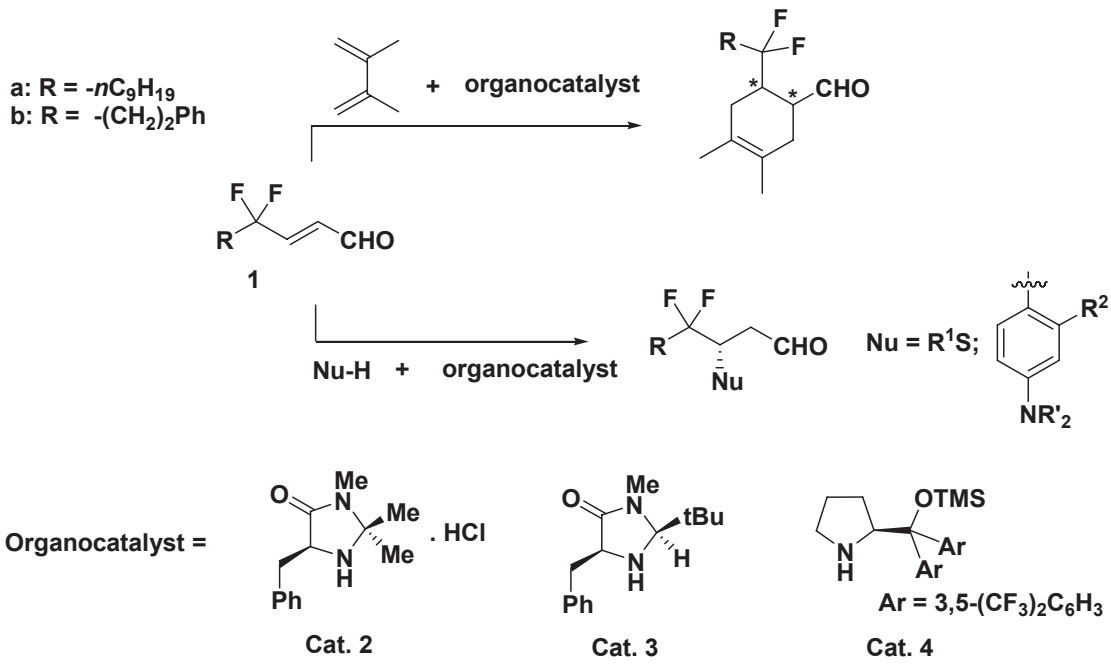
up to 99 %ee

This protocol gave effectively the desired adducts with good yields and high enantioselectivities (up to 99 %ee). In this work we will try to apply this protocol, for the first time, to *γ*-difluoro-*α,β*-unsaturated aldehydes.

II- Goals of our research

Based on previous literature data, the purpose of our work was to establish that, after proper selection of the catalysts and optimisation of the conditions, enantioselective Diels-Alder cycloadditions as well as 1,4-conjugated additions can be performed on *gem*-difluoroenals **1** (Scheme 13).

Scheme 13. Goals for Diels-Alder cycloaddition and 1,4-conjugated additions to enals **1**.



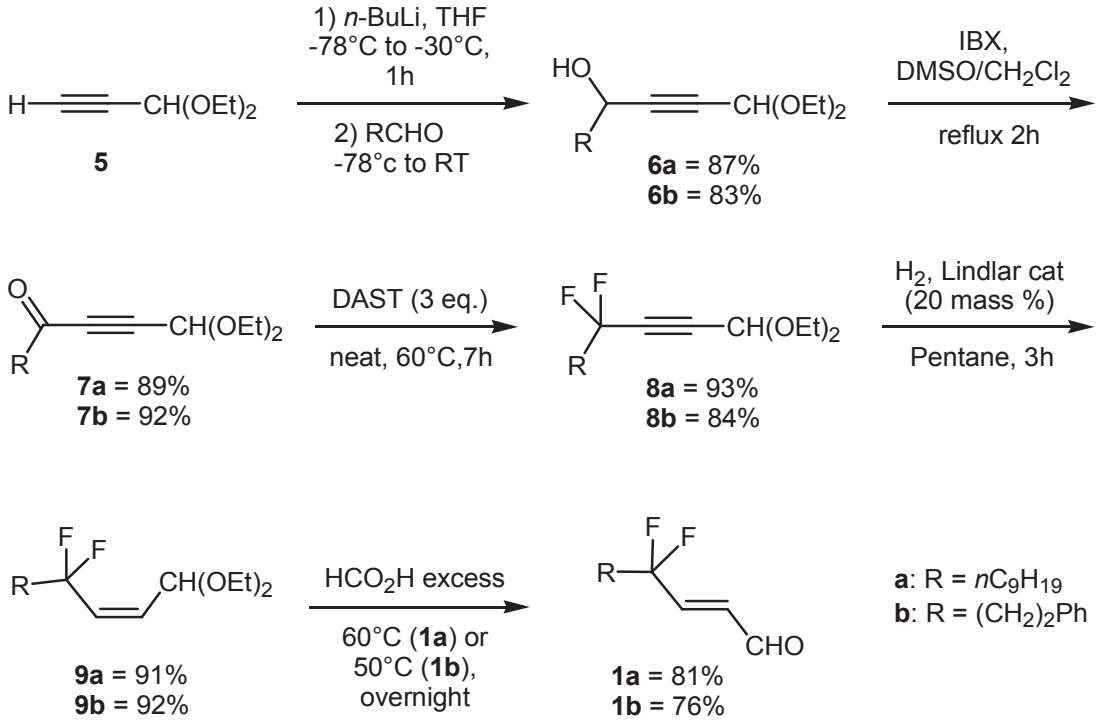
We will also evaluate the effect of the two fluorine atoms on these organocatalytic reactions, by comparison with the hydrogeno analogues.

III- Results and discussion

III-1) Synthesis of *gem*-difluoro enals 1

The *gem*-difluoroenals were prepared by a methodology that our group reported previously for the synthesis of a *gem*-difluoro-analogue of 13 HODE.[28] Metallation of acetal **5**, followed by trapping with appropriate aldehydes, afforded propargylic alcohols **6** in 83-87 % yield. Oxidation with IBX gave ketones **7** in 89-92 % yield. Due to the presence of the propargylic system,[29] these ketones reacted efficiently with diethylaminosulfurtrifluoride (DAST) to afford **8** in 84-93 % yield. Partial hydrogenation using Lindlar catalyst, followed by deacetalization with excess formic acid, gave the target *gem*-difluoroenals **1** (Scheme 14).

Scheme 14. Synthesis of *gem*-difluoro enals **1a** and **1b.**

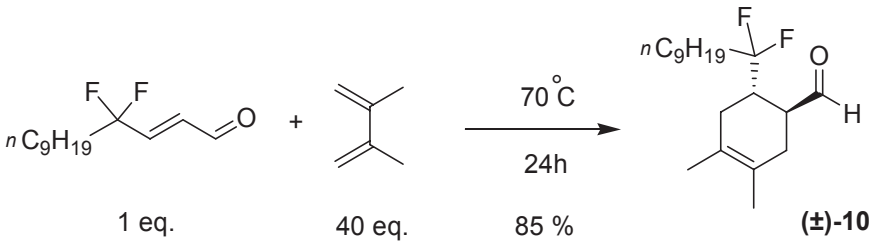


Therefore, both enals **1a** and **1b** were obtained from commercially available propioladehyde diethylacetal **5** in five steps and 53% and 45% overall yields respectively. In this synthesis only the *E* isomer of enals **1** is obtained.

III-2) Diels-Alder cycloadditions

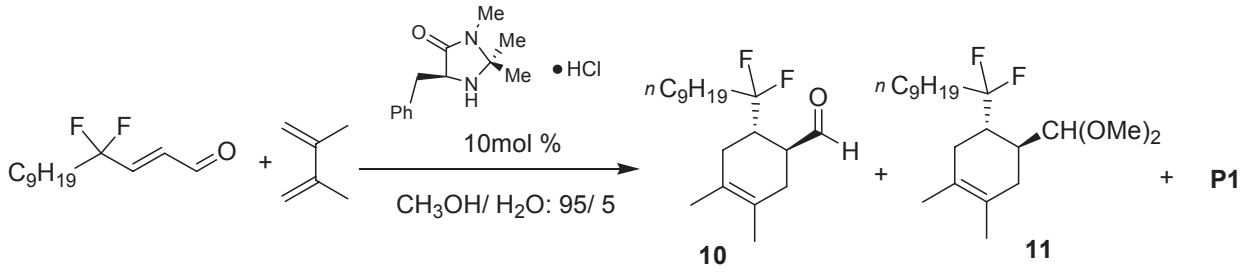
During this work **1a** was selected as a model. We started with the non-catalyzed Diels-Alder cycloaddition, and reaction of 2,3-dimethyl-1,3-butadiene in excess with **1a** gave the racemic adduct (±)-**10** in a very good yield (Scheme 15).

Scheme 15. Non-catalyzed Diels-Alder cycloaddition.



The first trial toward optically active product was done, using Mac Millan's second generation catalyst **3**, in a 95/5 mixture of methanol/water at 30 °C. At the end of the reaction three fluorinated products were obtained: the desired adduct **10**, the corresponding acetal **11** and a byproduct **P1** in a ratio 1:1:0.3 respectively (Scheme 16).

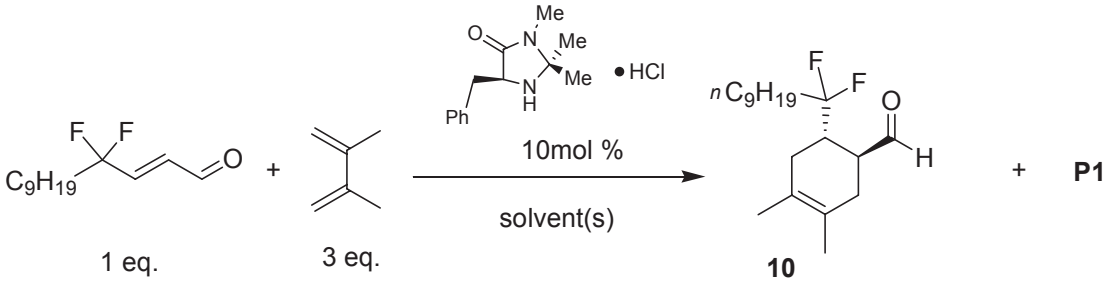
Scheme 16. Catalyzed Diels-Alder cycloaddition in methanol/water solvent



To avoid acetalization, the reaction was performed again, using acetonitrile instead of methanol. The Diels-Alder adduct was obtained with 76% ee, but the same side product **P1** again appeared (Table 2, entry 1).

Note: the NMR-based method used to establish the enantiomeric excess in our organocatalyzed reactions will be described in part III-4.

Table 2. Asymmetric organocatalyzed Diels-Alder cycloadditions.



Entry	H_2O	Solvent	Temp./time	Conv. (%)	Adduct/side product	ee (%)
1	-	CH_3CN/H_2O:95/5	30 °C/60h	80	1/1	76
2	-	CH_3CN/H_2O:95/5	0 °C/40h	90	0/1	nd
3	0.1eq.	DMF	0 °C/40h	53	0/1	nd
4	0.1eq	CH_3CN	0 °C/40h	30	1/3	nd

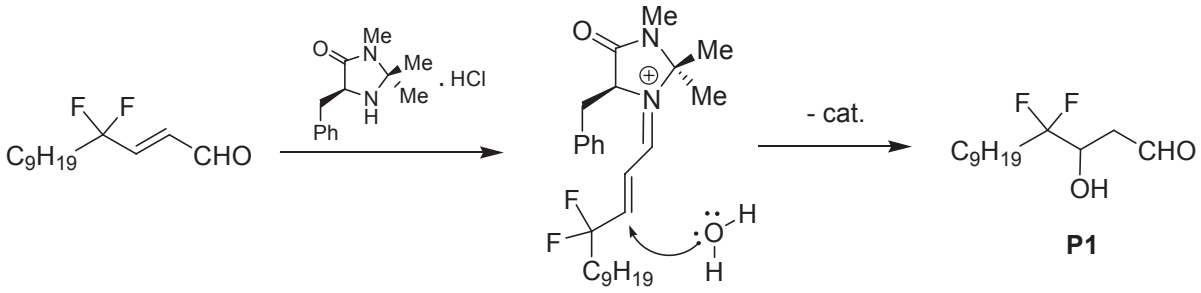
In order to improve the selectivity, the next reaction was performed at 0° C. Unfortunately, these conditions shifted the reaction totally toward formation of the side product **P1** (entry 2). Using DMF as a solvent with 0.1 eq water yielded only the side product (entry 3). On the other hand, using only acetonitrile as a solvent, with 0.1 eq. of water at 0° C, afforded the adduct and the side product **P1** in 1:3 ratio respectively (entry 4). Moreover, replacing **Cat. 2** by **Cat. 3** or **Cat. 4** (structures are in Scheme 13), while using 10 mol % benzoic acid as co-catalyst didn't lead to the formation of the desired product. In order to identify this by-product, and understand its formation, different reactions were performed without the addition of nucleophile (except H_2O) or diene, and using dichloromethane as a solvent. The results are summarized in table 3.

Table 3. Reactions of *gem*-difluoro aldehyde **1a** with water and without addition of nucleophile or diene.

Entry	RCHO	Cat. **2**	Water	Temp./time	Conv. (%)	Result
1	1 eq.	0.1 eq.	0.1eq	RT/overnight	15	P1
2	1 eq.	0.1 eq.	1 eq.	RT/overnight	50	P1
3	1 eq	0.1 eq	2 eq.	RT/overnight	73	P1

Since all our trials towards isolation of the byproduct **P1** failed, the analysis was performed using the crude mixture. First point to be noticed is that formation of **P1** is directly related to the quantity of water in the reaction medium. Moreover, ^{19}F NMR of **P1** showed an AB system with peaks obtained at -113.7, -112.8 and -110.1, -109.2. On the other hand, ^{1}H NMR showed the presence of an aldehyde group and a proton as a multiplet around 4.3 ppm, which is typical for a $CF_2C\underline{\boldsymbol{H}}OH$. In addition, ^{13}C NMR showed a triplet around 70 ppm, which is typical for a $CF_2\underline{\boldsymbol{C}}HOH$. This indicates the possible formation of an asymmetric center through a nucleophilic addition of water to the double bond. Therefore, all these results led us to propose the structure indicated below to compound **P1**. This derivative could be obtained through addition of water to the highly electrophilic double bond (Scheme 17).

Scheme 17. Addition of water to the reactive iminium salt and proposed structure for **P1**.



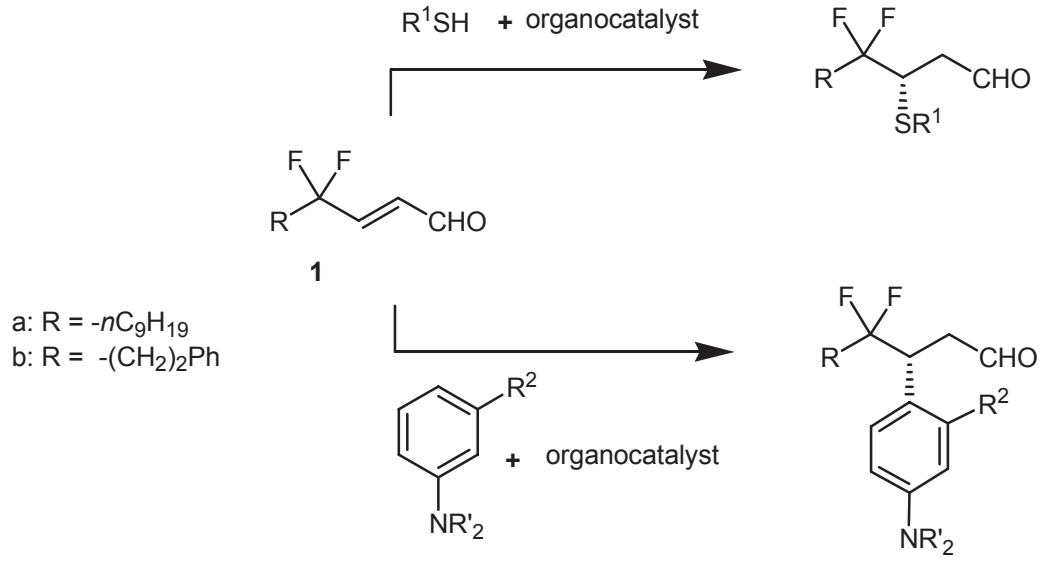
Furthermore, mass spectrum analysis of (crude) **P1** was performed. The data confirmed the proposed structure in addition to some polymer, in agreement with old reports about the non-fluorinated enals. [30]

As a conclusion, during this reaction, under the mentioned conditions, there is a competition between the Diels-Alder reaction cycloaddition and nucleophilic addition of water. Therefore we focused our attention on the organocatalyzed 1,4 additions.

III-3) Asymmetric organocatalytic 1,4-addition reactions

In this part two different types of 1,4-addition reactions were performed: a) sulfa-Michael conjugated addition (SMA); b) aniline conjugated additions, as shown in scheme 18.

Scheme 18. Asymmetric organocatalytic 1,4 additions on *gem*-difluoroenals **1a** and **1b**.

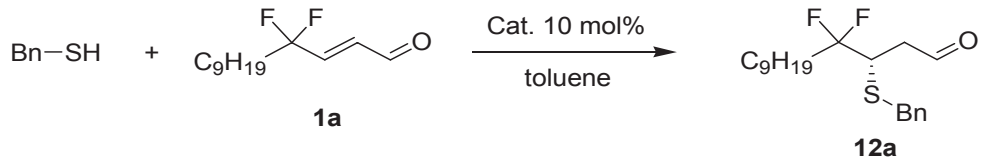


III-3.1) Selection of catalyst and optimization of the reaction conditions

To develop the use of **1** in asymmetric 1,4 additions of thiols and aniline derivatives, the first problem was the selection of the organocatalyst and the optimization of the reaction conditions. We have chosen **1a** as a model and considered three derivatives as catalysts: the two Mac Millan's imidazolidones **2** and **3**,[31] as well as Jørgensen's diarylprolinol silyl ether **4**.[32]

We have screened different reaction conditions and the results are reported in table 4. For benzylthiol addition, the hydrochloride salt catalyst **2** alone, at RT, gave good conversion but low ee (Table 4, entry 1).

Table 4. Asymmetric organocatalyzed 1,4-addition of benzylthiol on *gem*-difluoro enal **1a** by using catalysts **2, 3** and **4**.



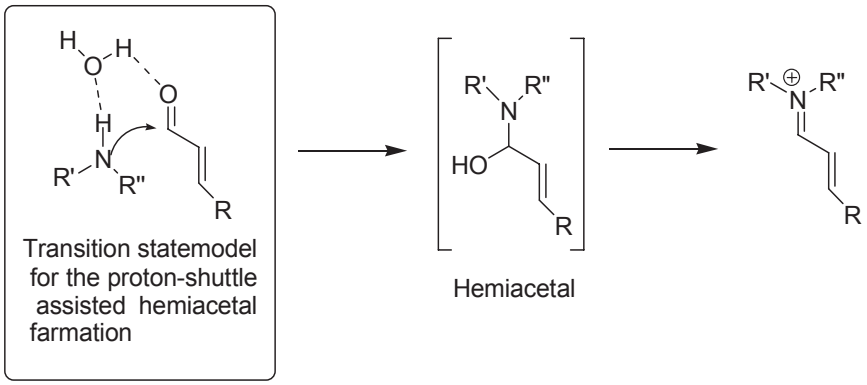
Entry	Cat	H_2O	Temp [a]	Time (hr)	**12a** conv. (%)	**12a** ee (%)[c]
1	**2**	-	R. T.	24	87	20
2	**2**	0.1eq	R. T.	24	92	26
3	**2**	0.1eq	-15°C	46	<5	nd
4	**2**	0.1eq	0°C	44	71	14
5	-	0.1eq	0°C	44	46	0
6[b]	**3**	-	-15°C	48	49	16
7[b]	**3**	0.1eq	-15°C	24	47	26
8	-	0.1eq	-15°C	46	0/0	-
9	**4**	-	-15°C	16	40	35
10[b]	**4**	-	-15°C	16	100	96
11[b]	**4**	0.1	-15°C	16	100	98

[a] reactions performed in toluene; [b] reaction performed with addition of benzoic acid at 10 mol%; [c] ee established by ^{19}F NMR on corresponding imidazolidines (see text); nd: not determined.

It is well known that water can enhance the reactivity in organocatalysis since it acts as a proton shuttle from the nitrogen atom to forming hydroxyl moiety during the catalytic cycle.[33]

Moreover, addition of water may enhance hydrolysis of enamine, which is the final step in the catalytic cycle (Scheme 19).[34]

Scheme 19. Effect of water in first and final step of catalytic cycle.[14]



For that reason, the same reaction was performed with 10 mol % water. Both reactivity and enantioselectivity were enhanced, going from 87 to 92 % conversion and from 20 to 26 % ee (entries 1 and 2). In order to improve the enantioselectivity of this addition two experiments were performed at lower temperature: at -15 °C, a very low conversion was obtained (entry 3). At 0 °C an improvement in reactivity was observed (entry 4) but the ee remained low (14 %). These results showed that catalyst **2** is not efficient for the reaction under study and this could be linked to fact that the reactive lone pair of nitrogen of this catalyst is eclipsed by the neighboring CH_3 which leads to a lower iminium ion formation efficiency.[35] This should explain the lower ee obtained at 0 °C, compared to that observed at room temperature (entries 1 and 4). At room temperature, there is a competition between the catalyzed and non-catalyzed pathways of the addition. Going to 0 °C, the rate of iminium ion formation becomes slower, without blocking the non-catalyzed pathway (entry 5). So as a result, at 0 °C, this reaction shifted more toward formation of the racemic product. Based on that, and on literature, catalyst **2** was replaced by the second generation of Mac Millan's imidazolidones **3** which was expected to be more reactive.[35,36] Catalyst **3** was tested in the presence of 0.1 eq of benzoic acid (entry 6) or with further addition of 0.1 eq. of water (entry 7). After 24 h at -15°C, conversions were only moderates and ee's remained low (16-26%). Therefore, these imidazolidine type catalysts are not appropriate for the

reaction under study. This could be due, at least in part, to the competition between catalyzed and non-catalyzed nucleophilic additions, as well as racemization process at room temperature.[37] We have performed control experiments, without any catalyst, establishing that no reaction was occurring at -15°C (entry 8) while after 44h at 0°C the conversion was 46% affording the adduct **12a** in racemic form (entry 5).

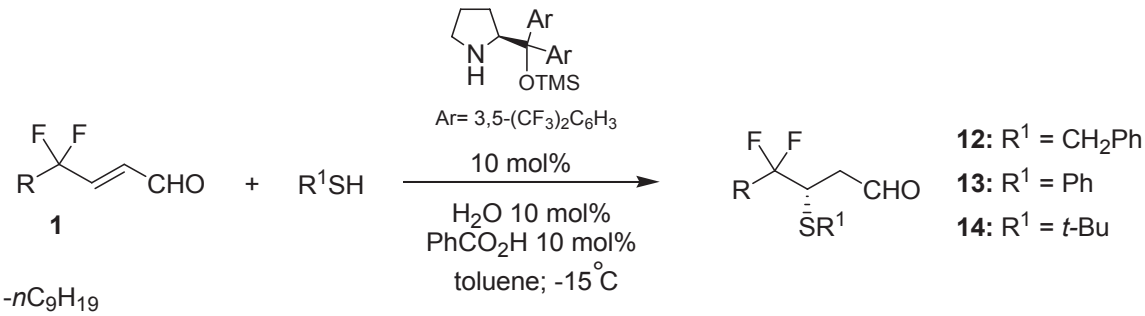
Then we considered diarylprolinol silyl ether **4** [13] and better results were obtained, as indicated in Table **4**. The reactions were performed at -15°C. The catalyst **4** alone gave low conversion (entry 9). In the presence of 0.1 eq. of benzoic acid the reaction was complete after 16 h, giving excellent ee for **12a** (entry 10). Similar results were obtained after further addition of water (0.1 eq., entry 11). This gave us the optimized reaction conditions.

III-3.2. Organocatalyzed (SMA) of different thiols to 1a and 1b

After finding the best catalyst and the optimized conditions, different organocatalyzed reactions (SMA) were performed and the products were obtained in good to excellent yields and high ee's, as shown in table 5.

As mentioned before, addition of benzylmercaptan to **1a,** under the optimized conditions, afforded the product **12a** in 98 % yield with excellent ee (entry 1). Extension of these conditions to thiophenol addition gave very good results (compound **13a**, entry 2). Similarly, *tert*-butylthiol gave good conversion to **14a** and excellent ee (entry 3). Finally, these optimized conditions were used starting with **1b**, to afford the desired adduct **12b** in excellent yield and ee (entry 4). So this catalyst is well suited for such 1,4 additions on *gem*-difluoroenals **1**, in agreement with literature results with nonfluorinated enals,[37] as well as with trifluorocrotonaldehyde.[10, 11]

Table 5. Addition of different thiols to enals **1.**

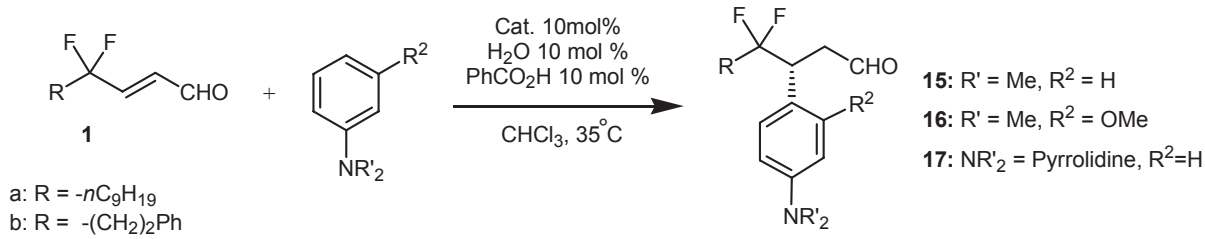


Entry	Enal	R^1	Time (h)	**No**/Conv./yield (%)	ee (%)
1	**1a**	CH_2Ph	16	**12a**/100/98	98
2	**1a**	Ph	21	**13a**/92/88	95
3	**1a**	*t*-Bu	40	**14a**/76/71	94
4	**1b**	CH_2Ph	16	**12b**/100/94	96

III-3.3) Organocatalyzed 1,4-addition of aniline to enals 1a and 1b

After establishing the efficiency of catalyst **4** in different (SMA) additions, where the products have been obtained in good to excellent yields (71-98 %) with high ee s (94-98 %), the next step was the extension to addition of aniline derivatives (Scheme 20).[38]

Scheme 20. Addition of different anilines to enals **1**.



The results of these additions are summarized in table 6. No reaction was observed without catalyst (entry 1). Then, several catalyzed aniline additions were performed under different conditions: starting from **1a** and using catalyst **2**, without addition of water and benzoic acid, the reaction gave the desired adduct **15a**, however in moderate ee (42%) (entry 2). On changing to catalyst **3**, and in the presence of benzoic acid, the addition product was obtained in lower yield but with excellent ee (98%, entry 3). On the contrary, by using the catalyst **4** with 0.1 eq. of benzoic acid and 0.1 eq. of water, at 35°C, the reactions gave good to excellent conversions and high ee's for adducts **15a**-**17a** (87 - 98%, entries 4-7). The same result was obtained in the case of adduct **16b**, starting from the second enal **1b** (entry 8).

Therefore, we have defined good reaction conditions for the addition of anilines on these gem-difluoroenals. It is noteworthy that for such fluorinated molecules, the Jørgensen's catalyst is working efficiently, while for the non fluorinated analogues the Mac Millan's catalysts proved to be best.

Table 6. Asymmetric organocatalyzed 1,4 addition of aniline derivatives on *gem*-difluoro enals **1a** and **1b**.

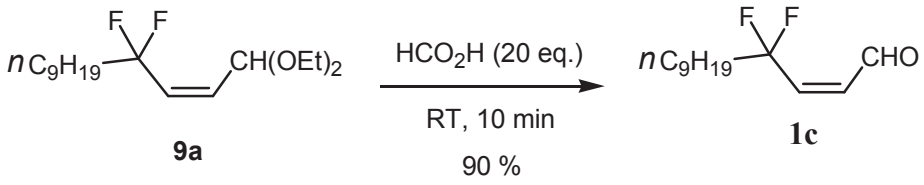
Entry	Cat	Enal	R'	R^2	Time (h)	**No**/Conv/yield (%)	ee (%)[c]
1	**-**	**1a**	Me	H	48	**15a**/0/-	-
2[b,d]	**2**	**1a**	Me	H	26	**15a**/90/nd	42
3	**3**	**1a**	Me	H	48	**15a**/38/nd	98
4[b]	**4**	**1a**	Me	H	48	**15a**/58/nd	94
5	**4**	1a	Me	H	48	**15a**/82/77	98
6	**4**	1a	Me	OMe	24	**16a**/95/87	98
7	**4**	1a	[a]	H	51	**17a**/53/40	87
8	**4**	1b	Me	OMe	24	**16b**/88/84	98

nd: yield not determined [a] NR'_2= 1-pyrrolidino; [b] reaction performed without water; [c]ee established by ^{19}F NMR on corresponding imidazolidines (see text: III-4); [d] reaction performed without benzoic acid.

III-3.4) *β*-functionalisation of *Z*-α-β-unsaturated aldehyde (1c)

After establishing the efficient *β*-functionalisation of the *E gem*-difluoroaldehydes **1**, it seemed interesting to check how this reaction works with the *Z* isomer. To achieve this goal, the *Z gem*-difluoroaldehyde **1c** was prepared as performed previously for an analogue with a *n*-C_5H_{11} chain (Scheme 21). [28]

Scheme 21. Synthesis of the *Z-gem*-difluoroenal **1c**.

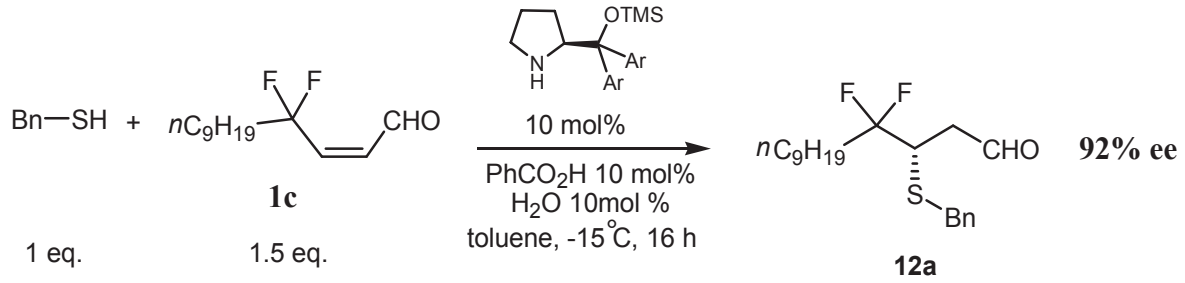


9a **1c**

Starting from **9a**, deacetalization using only 20 eq. of formic acid and with a short reaction time, afforded the target *cis*-enal **1c** in 90% yield.

Addition of benzylmercaptan to aldehyde **1c**, under the optimized conditions, afforded the same enantiomer as the one obtained previously by the addition of benzylmercaptan to the *E*-enal **1a**, but with slightly lower ee (Scheme 22). Importantly, ^{19}F NMR analysis of the crude reaction mixture showed that the remaining aldehyde was almost exclusively *E*.

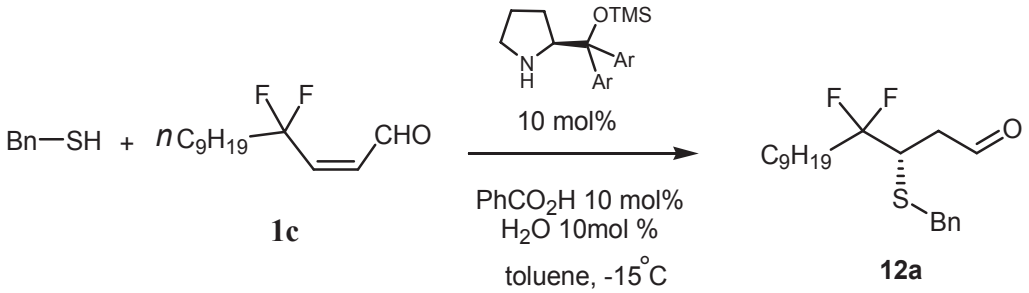
Scheme 22. Benzylmercaptan addition to the *cis*-aldehyde.



1 eq. 1.5 eq. **1c** **12a**

In order to understand these results, three different reactions have been performed, and the results are summarized in table 7.

Table 7. *E*/*Z* isomerisation during BnSH addition.



Entry	BnSH	RCHO	Cat.	*E*/*Z*[a]
1	-	30 mg	-	100/0
2	1 eq.	1.5 eq.	-	100/0
3	-	30 mg	10 mol%	2/8

[a] *E*/*Z* ratio was calculated by ^{19}F NMR of the crude mixture.

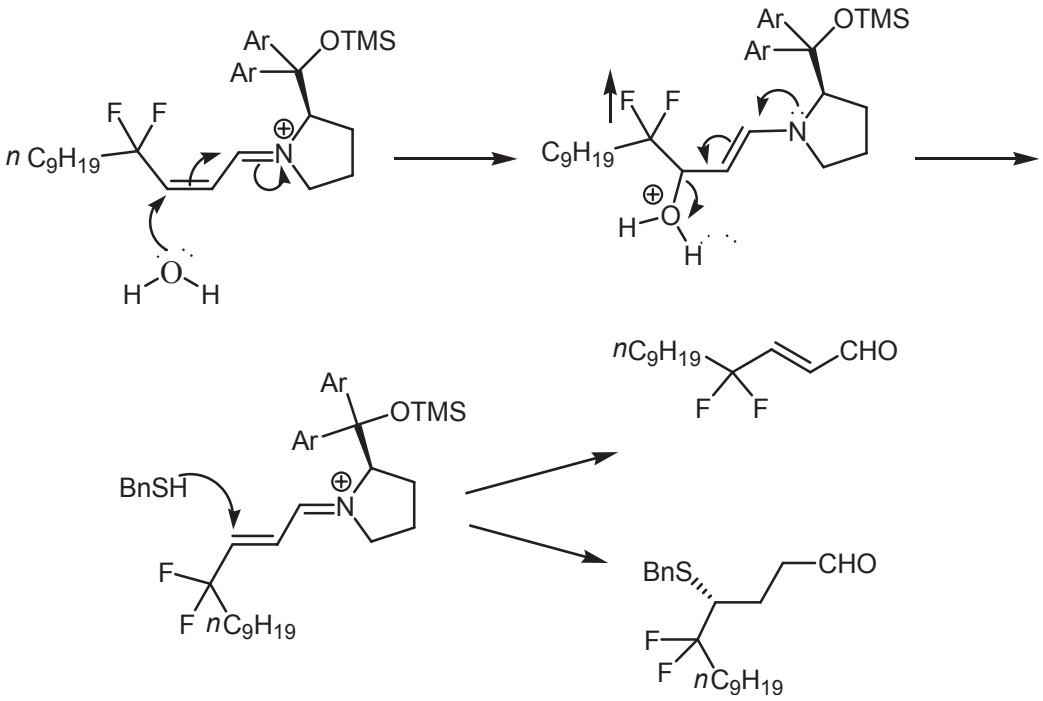
The three reactions were performed at -15 °C. After 1h, ^{19}F NMR of the crude samples showed:

- The *Z*-aldehyde in the reaction medium, without catalyst or nucleophile, didn't make any isomerization (entry 1).

- Moreover, the non-catalyzed addition reaction didn't lead to such isomerization.

- Mixing aldehyde and catalyst in the reaction medium led to 80 % isomerization. This could be explained by an addition-elimination reaction sequence of water to the highly reactive iminium intermediate, which leads to the formation of the *E*-aldehyde. This should also explain the result obtained from the addition of benzylmercaptan to the aldehyde **1c** (Scheme 23).

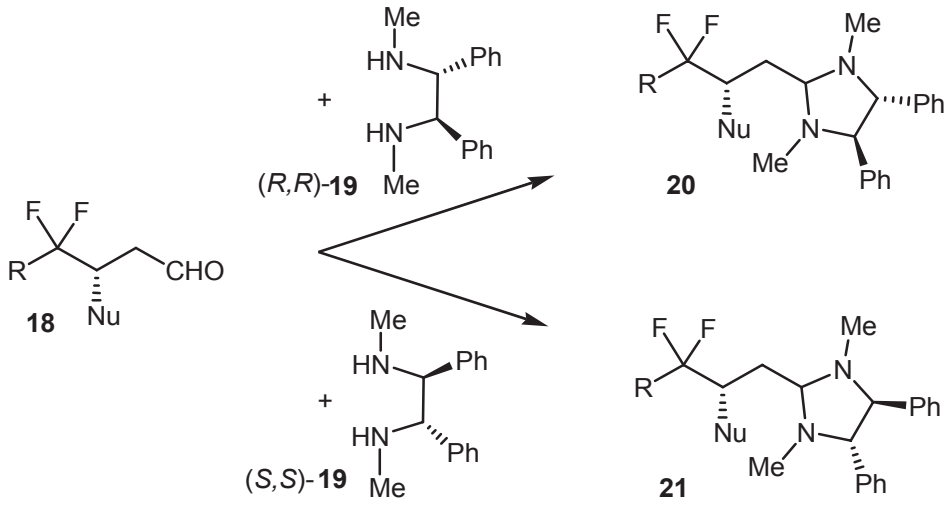
Scheme 23. *E/Z* isomerisation of aldehyde under the effect of catalyst.



III-4) Determination of the enantiomeric excess

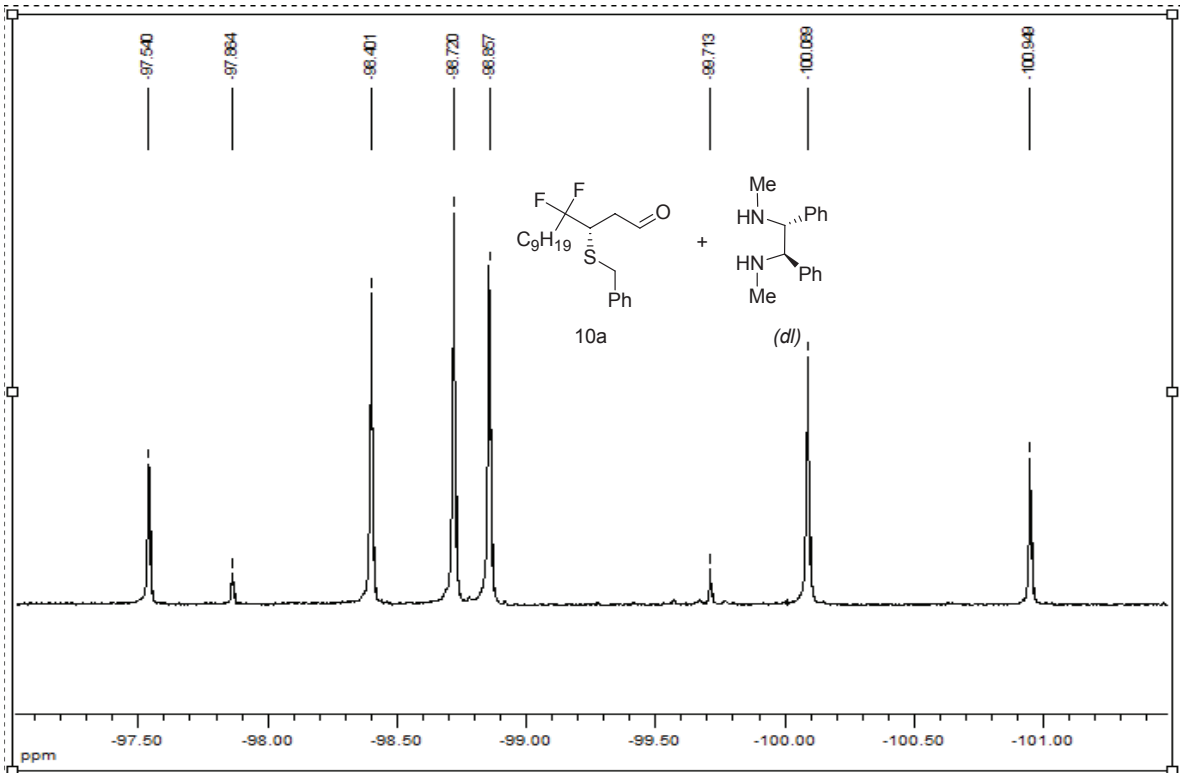
An important point to notice here is the method used for the measurement of the enantiomeric excess in our reactions (Scheme 24). Due to the presence of an aldehyde in the final product, it is possible to use diastereoisomeric imidazolidines, which are easily analyzed by NMR. Condensation of enantiopure aldehyde **18** with easily accessible enantiopure diamine (*R,R*)-**19** [39] gives a single diastereoisomer **20**. The same condensation, performed with racemic diamine, will give the mixture of **20** and **21**, with well separated signals especially in ^{19}F NMR.

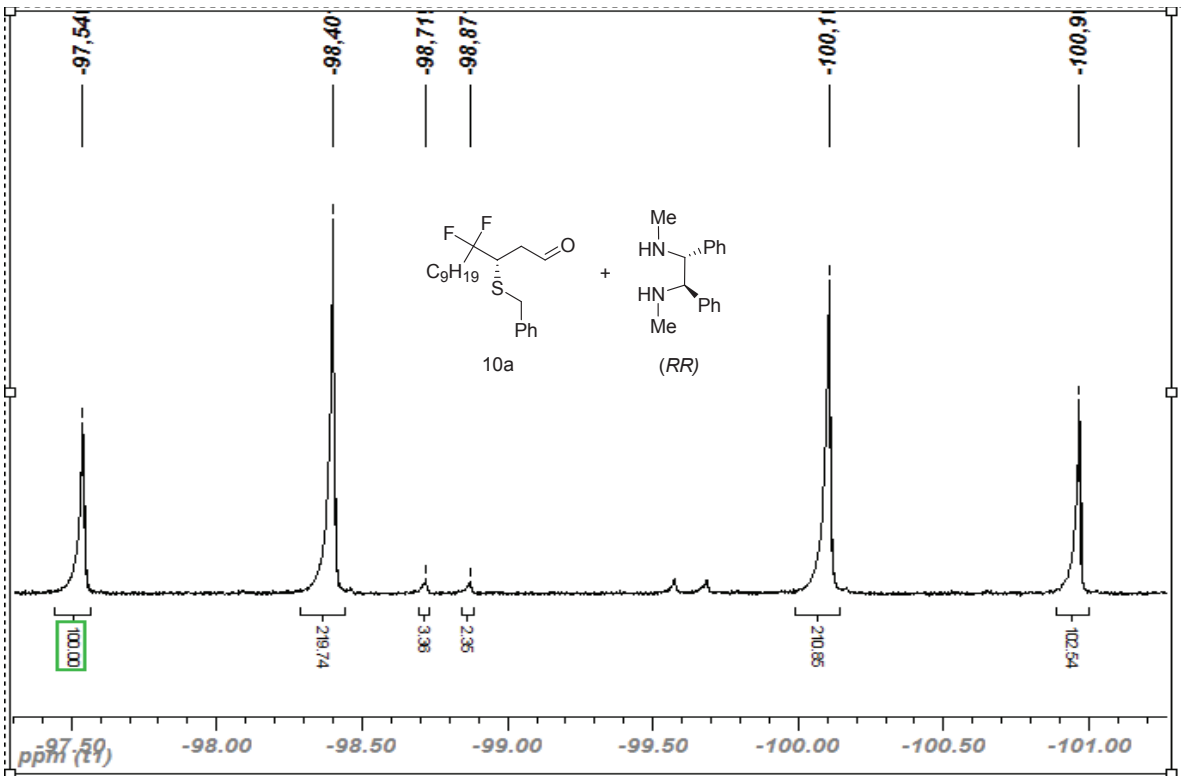
Scheme 24. NMR method used to measure the ee's on the 1,4 adducts.



Therefore, starting from the crude reaction mixtures, condensations performed with racemic diamine will give the two set of signals corresponding to the two diastereoisomers, while condensation with one enantiopure diamine gives the stereoisomers, in a ratio (de) which will transfer directly to the ee of the starting aldehyde. A key advantage of this very simple and efficient method is that it avoids any purification step (Fig. 5). [40]

Fig 5. Representative example for determination of ee using ^{19}F NMR**.**





III-5) Role of fluorine atoms in asymmetric organocatalyzed 1,4-Additions

An interesting point to be checked was the effect of the *gem*-difluoro group in the asymmetric catalytic process. To answer this question, we have compared the reactivity and selectivity of our *gem*-difluoroenal **1a** with the same derivative having two hydrogens in allylic position, in 1,4-conjugated additions (Scheme 25 and Table 8).

Scheme 25. Reactivity comparison between *gem*-difluoroenal **1a** and hydrogeno analogue **1aH** during representative asymmetric organocatalyzed 1,4 additions.

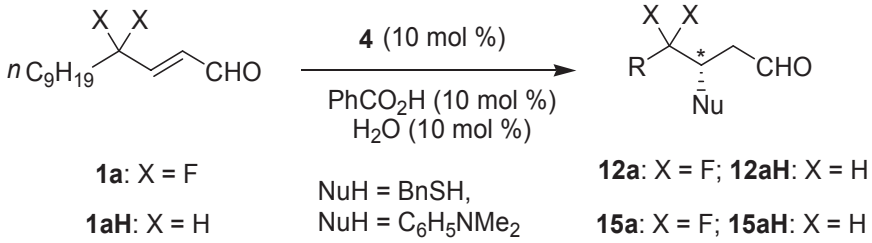


Table 8. Comparison of asymmetric organocatalyzed 1,4 addition on gem-difluoro enals **1a** and similar non-fluorinated molecules **1aH**.

Entry	enal	NuH	Time (h)	No/Conv./yield (%)	ee[c] (%)
1[a]	**1a**	BnSH	16	**12a**/100/98	98
2[a]	**1aH**	BnSH	16	**12aH**/44/40	82
3[b]	**1a**	$C_6H_5NMe_2$	48	**15a**/82/78	98
4[b]	**1aH**	$C_6H_5NMe_2$	48	**15aH**/0/0	Nd

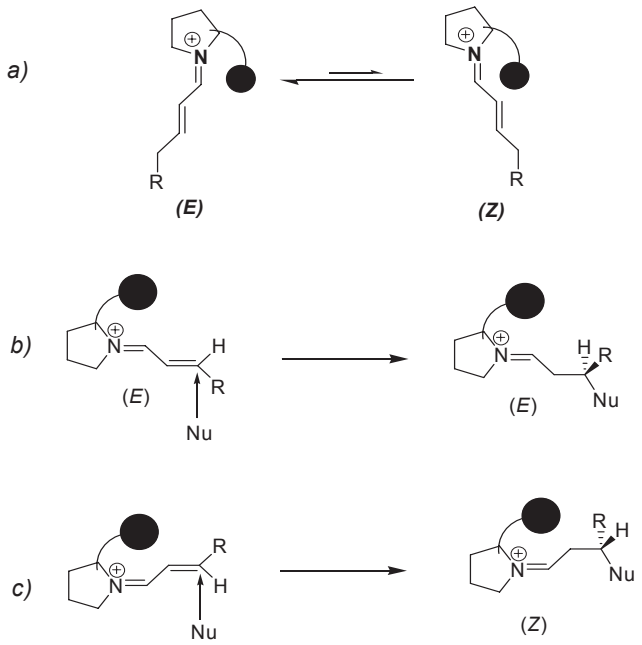
[a] Reactions performed in toluene at -15°C; [b] Reactions performed in $CHCl_3$ at 35°C; [c] ee established by ^{19}F NMR and ^{1}H NMR on corresponding imidazolidines (see text).

The results clearly indicate that the presence of the two fluorine strongly accelerate the reactions in both cases (Table 8). In BnSH addition complete conversion is observed after 16h for the fluorocompound **1a**, while for the hydrogeno analogue **1aH** conversion is only 44% (entries 1

and 2). The ee is also slightly lower in latter case (82% versus 98%). In the case of *N*,*N*-dimethylaniline (entries 3 and 4), the difference is even more striking since there is no reaction at all starting from the hydrogeno analogue, **1aH**, while addition is highly successfull with **1a**.
In depth mechanistic studies have been performed on this type of asymmetric organocatalytic reactions.[41] Based on these literature data, it is possible to propose an explanation for the effect of the **CF_2R** groups: the increase in reactivity with type **1** enals is likely connected to the electronegativity of the fluorine atoms which should increase the electrophilicity of the iminium intermediates.

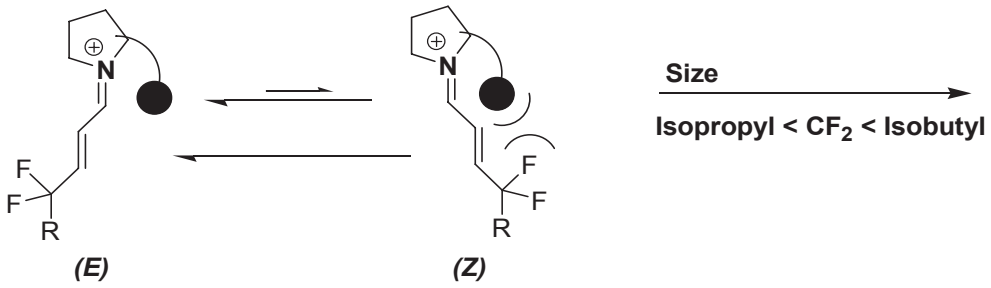
On the other hand, the larger size of F as compared to H should also increase the steric effects during these reactions and improve the enantioselectivity. In fact, during the catalytic cycle, iminium salt is formed in two geometric isomers (*Z*) and (*E*) which are in equilibrium[41, 42] (Scheme 26, *a*), and nucleophilic attack from the *anti-face* of (*E*) and (*Z*), which is the less hindered face, will lead to formation of the two different enantiomers (Scheme 27, *b* and *c*). [41] Thus, control of (*Z*)/(*E*) equilibrium has a direct effect on the enantiomeric excess of the final product.

Scheme 26. (*Z*)/(*E*) equilibrium of iminium ion and its effect on the final product.



Insertion of two fluorine atoms at *γ*-position, and due their large size [43] compared to hydrogen atoms, should increase the steric effect on the iminium intermediate and improve the enantioselectivity. This will shift the (*Z*)/(*E*) equilibrium more towards the *E* isomer and thus improves the ee (Scheme 27).

Scheme 27. Effect of fluorine atoms on (*Z*)/(*E*) equilibrium.



Furthermore, electronic effects, for instance through repulsions due to the electron pairs of fluorine, could also participate to the improved stereoselectivity of **1a** versus **1aH**.

III-6) absolute configuration

The (*S*) absolute configuration at the new stereogenic center of 1,4 adducts was attributed by analogy with previous results from literature with related enals: by using catalyst **4,** the same absolute configuration was obtained both in the series of enals with alkyl chains [8d] and enal with the CF_3 group.[11] These data are also in agreement with the mechanism proposed for these reactions.

IV- Conclusions

In conclusion, we have performed for the first time the asymmetric organocatalyzed Diels-Alder cycloaddition reaction to a *gem*-difluoroenal. The product was successfully obtained by using catalyst **2,** in a moderate yield and selectivity (76% ee). Unfortunately the reaction was not clean since there was a competition between the cycloaddition reaction and other side reactions like nucleophilic additions. Optimization of this type of reactions still needs more investigations, eventually with new catalysts and co-catalysts.

In the case of asymmetric organocatalyzed 1,4-addition reactions, *gem*-difluoroenals are excellent substrates. The desired adducts were obtained in fair to good yields and good to excellent ee's by using Jørgensen's catalyst **4**.[17] It has been established also that the CF_2R group strongly activates enals towards these organocatalytic 1,4-additions.

An interesting point to mention is that the reactivity of organocatalysts is obviously structure/reaction dependent. For instance with our derivatives, in case of Diels-Alder reactions, imidazolidinone derivative **2** is the most reactive, while it is the least one in the case of 1,4-conjugated additions, where the proline derivative **4** is the most reactive.

Further, a very simple and efficient NMR method has been used to establish the ee's, directly on the crude reaction mixtures.

Taking into account the large number of reactions which can be used in asymmetric organocatalysis, such enals could be of much interest for the preparation of various types of bioactive molecules with *gem*-difluoroalkyl side chains.

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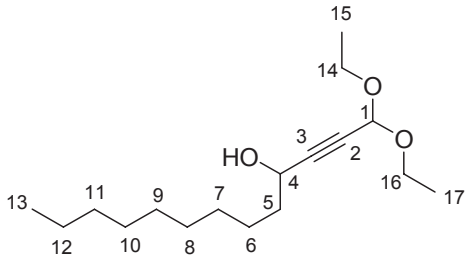
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EXPERIMENTAL PART

1,1-Diethoxy-tridec-2-yn-4-ol (6a)



$C_{17}H_{32}O_3$
M = 284.43 g.mol^{-1}

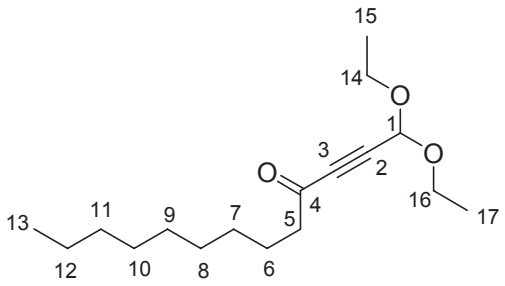
To a solution of propiolaldehyde diethyl acetal (2 g, 15.6 mmol, 1eq) in anhydrous THF (30 ml), cooled at t < -78°C,was added, dropwise under nitrogen, a solution of *n*-BuLi in hexane (10.7 ml, 1.6 M, 1.1 equiv.). The mixture was stirred at t < -30°C for 1h min., before the dropwise addition of decanal (3.23 ml, 1.1equiv.) at t < -78°C. The mixture was stirred for 2h while the temperature raised up slowly to room temperature. The mixture was treated with saturated NH_4Cl solution, extracted with ether (3 x 50 ml). The combined organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography on silica gel, compound **6a** was obtained as a colorless oil (3.86 g, 87% yield); R_f = 0.42 (Et_2O/pentane, 3/7).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 0.84 (t, 3H, H_{13}, J=6.62Hz), 1.17- 1.40 (m, 21H), 1.65-1.68 (m, 2H, H_5), 2.58 (bs, 1H, OH), 3.49-3.59 (m, 2H, H $_{14 \text{ or } 16}$), 3.64- 3.75 (m, 2H, H $_{14 \text{ or } 16}$), 4.37 (dt, 1H, H_4, J_1= 0.9Hz, J_2= 6.6Hz), 5.26 (d, 1H, H_1, J= 0.9Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.0 (1C, C13), 14.9 (2C, $C_{15 \text{ and } 17}$), 22.6, 25.0, 29.1, 29.2, 29.4, 31.8; 60.7, 60.8, 62.0 (1C, C_4), 79.8 (1C, C_2), 86.7 (1C, C_3), 91.2 (1C, C_1).

HRMS (ESI) [M+Na]+ ($C_{17}H_{32}O_3Na$): Calculated m/z = 307.22491. Found m/z = 307.2247 (1 ppm)

1,1-Diethoxy-tridec-2-yn-4-one (7a)



$C_{17}H_{30}O_3$
M = 282.42 g.mol^{-1}

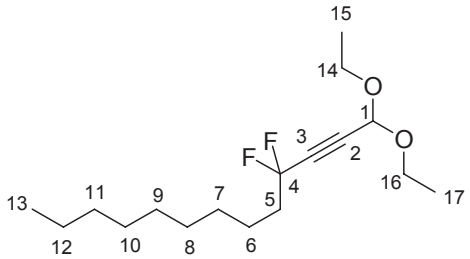
IBX (3.21 g, 1.5 equiv.) was dissolved in DMSO (15 ml) before the addition of alcohol **6a** (2.17 g, 7.64 mmol) in DCM (45 ml). The mixture was refluxed during 3 hours before TLC showed the completion of reaction. Ice-cold water was added to quench the reaction and a white suspension appeared. The reaction mixture was filtered and the layers were separated. The aqueous phase was extracted by DCM (3 x 50 ml). The combined organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum. After purification by flash chromatography on silica gel, compound **7a** was obtained as a colorless oil (1.92 g, 89% yield); R_f= 0.53 (Et_2O/pentane, 1/9).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 0.87 (t, 3H, H13, *J*= 6.6), 1.22-1.27 (m, 18H), 1.60-1.68 (m, 2H, H_6), 2.58 (t, 2H, H_5, *J*=7.4 Hz), 3.57-3.65 (m, 2H, $H_{14 \text{ or } 16}$), 3.67-3.77 (m, 2H, $H_{14 \text{ or } 16}$), 5.38 (s, 1H, H_1).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.1 (1C, C_{13}), 15.0 (2C, $C_{15 \text{ and } 17}$), 22.6, 23.8, 28.9, 29.2, 29.3, 29.4, 31.8, 45.5 (1C, C_5), 61.5 (2C, $C_{14 \text{ and } 16}$), 82.8 (1C, $C_{2 \text{ or } 3}$), 84.9 (1C, $C_{2 \text{ or } 3}$), 91.1 (1C, C_1), 187.4 (1C, C_4).

HRMS (ESI) [M+Na]+ ($C_{17}H_{30}O_3Na$): Calculated m/z = 305.20926. Found m/z = 305.2093 (0 ppm).

1,1-Diethoxy-4,4-difluoro-tridec-2-yn (8a)



$C_{17}H_{30}F_2O_2$
M = 304.42 g.mol^{-1}

To the propargylic ketone **7a** (617 mg, 2.19 mmol) were added a drop of ethanol then DAST (0.87 ml, 3 equiv.). The reaction mixture was stirred, without solvent, at 65 °C during 8h. After coming back to room temperature, the mixture was diluted by pentane (50 ml), then added slowly to a saturated Na_2CO_3 solution. The phases were separated and the organic phase was washed by distilled water (3 x 15 ml), and the aqueous layer was extracted with pentane (3 x 15 ml), the organic fractions were collected, dried over $MgSO_4$, and concentrated by rotary evaporation under a 300 mbar pressure. The product **8a** was isolated after chromatography on silica gel as a colorless oil (618 mg, 93% yield). R_f = 0.63 (Et_2O/pentane, 2/98);

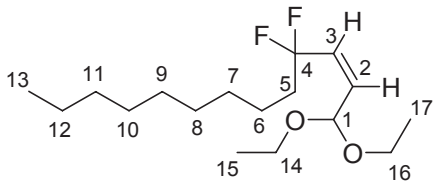
^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 0.88 (t, 3H, H_{13}, *J*= 6.8 Hz), 1.22-1.37 (m, 18H), 1.50-1.58 (m, 2H), 1.97-2.08 (m, 2H, H_5), 3.57-3.63 (m, 2H, $H_{14\ or\ 16}$), 3.64-3.76 (m, 2H, $H_{14\ or\ 16}$), 5.32 (t, 1H, H1, J_{HF} = 3.0 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 14.0 (1C, C_{13}), 15.0 (2C, $C_{15\ and\ 17}$), 22.62 (t, 1C, C6, *J*= 3.6 Hz) 22.64, 28.9, 29.2, 29.3, 29.4, 31.8, 39.1 (t, 1C, C_5, *J*= 25.6 Hz), 61.3 (2C, $C_{14\ and\ 16}$), 78.0 (t, 1C, C_3, *J*= 41.3 Hz), 82.0 (t, 1C, C_2, *J*= 6.7 Hz), 90.8 (t, 1C, C_1, *J*= 1.5 Hz), 114.6 (t, 1C, C_4, *J*= 233.3 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) : -83.72 (dt, J_1= 2.9 Hz; J_2= 15.1 Hz).

HRMS (ESI) [M+Na]+ ($C_{17}H_{30}F_2O_2Na$): Calculated m/z = 327.21116. Found m/z = 327.2111 (0 ppm).

***Z*-1,1-Diethoxy-4,4-difluoro-tridec-2-ene (9a)**



$C_{17}H_{32}F_2O_2$
M = 306.43

Alkyne **8a** (1g, 3.29 mmol) and Lindlar catalyst (0.2 g, 20% by mass) were stirred in pentane (25 ml), under hydrogen gas (1 atm). The course of reaction was monitored by TLC or ^{19}F NMR. After 1 hour, the reaction was complete, and the mixture was filtered on silica and concentrated by rotary evaporation under a 300 mbar pressure. After purification by flash chromatography on silica gel, product **9a** was obtained as a colorless oil (916 mg, 91% yield). R_f = 0.30 (Et_2O/pentane, 2/98).

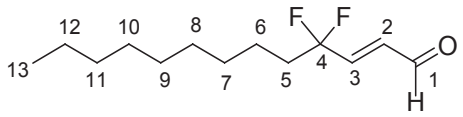
^{1}H NMR (C_6D_6, 400 MHz): δ ppm 0.90 (t, 3H, H_{13}, *J*=7.0 Hz), 1.09-1.29 (m, 18H), 1.43-1.47 (m, 2H), 1.79-1.91 (m, 2H, H_5), 3.39-3.47 (m, 2H, $H_{14\ or\ 16}$), 3.53-3.61 (m, 2H, $H_{14\ or\ 16}$), 5.38 (ddt, 1H, H_3, *J*= 0.7 Hz, *J*= 12.4 Hz, J_{HF}= 14.6 Hz); 5.56 (dd, 1H, H_1, *J*=0.7 Hz, *J*=7.6 Hz); 5.79 (tdd, 1H, H_2, J_{HF}= 1.9 Hz, *J*= 7.6 Hz, *J*= 12.4 Hz).

^{13}C NMR (C_6D_6, 75 MHz): δ ppm 14.3 (1C, C_{13}), 15.5 (2C, $C_{15\ and\ 17}$), 22.61 (t, 1C, C_6, *J*= 4.0 Hz), 23.1 29.62, 29.68, 29.73, 29.8, 32.25, 38.82 (t, 1C, C_5, *J*= 26.1 Hz), 61.44 (2C, $C_{14\ and\ 16}$), 97.44 (t, 1C, C1, *J*= 3.2 Hz), 122.62 (t, 1C, C4, *J*= 239.7 Hz), 127.17 (t, 1C, C_3, *J*= 28.4 Hz), 134.77 (t, 1C, C_2, *J*= 5.3 Hz).

^{19}F NMR (C_6D_6, 282 MHz): δ (ppm) : -91.30 (dt, J_{HF}= 14.6 Hz, *J*= 16.1 Hz).

HRMS (ESI) [M+Na]+ ($C_{17}H_{32}F_2O_2Na$): Calculated m/z = 329.22681. Found m/z = 329.2271 (0 ppm).

***E*-4,4-Difluoro-tridec-2enal (1a)**



$C_{13}H_{22}F_2O$
M = 232.31 g.mol^{-1}

To acetal **9a** (800 mg, 2.61 mmol), formic acid (19.7 ml, 200 equiv.) was added and the mixture was stirred overnight at 60°C. After cooling to room temperature, the reaction mixture was neutralized by addition of solid Na_2CO_3. Water was added and the aqueous phase was extracted with ether (3 x 100 ml). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum at a 300 mbar pressure. After flash chromatography *E*-aldehyde **1a** was obtained as a colorless oil (491 mg, 81 %yield). R_f = 0.37 (Et_2O/pentane, 4/96).

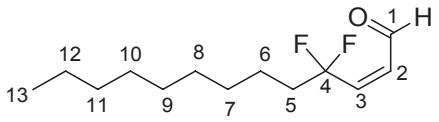
^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 0.88 (t, 3H, H_{13}, J= 6.8 Hz), 1.27-1.36 (m, 12H), 1.42-1.52 (m, 2H, H_6), 1.90-2.06 (m, 2H, H_5), 6.45 (tdd, 1H, H_2, J_{HF} = 1.9 Hz, J=7.4 Hz, J= 16.0 Hz), 6.66 (td, 1H, H_3, J_{HF} = 10.6 Hz, J= 16.0 Hz), 9.66 (td, 1H, H_1, J_{HF} = 0.9 Hz, J =7.4 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.1 (1C, C_{13}), 22.0 (t, 1C, C6, J = 4.1 Hz), 22.6, 29.14, 29.18, 29.3, 29.4, 31.8 (6C, $C_{7\text{-}12}$), 36.90 (t, 1C, C_5, J = 25.5 Hz); 120.6 (t, 1C, C_4, J = 240.0 Hz), 133.3 (t, 1C, C_2, J = 7.3 Hz), 146.3 (t, 1C, C_3, J = 28.9 Hz), 192.1 (1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz): δ ppm -98.85 (ddt, J_{HF} = 0.9 Hz, J_{HF} = 10.6 Hz, J_{HF} = 16.2 Hz).

HRMS (ESI): calculated for $C_{13}H_{22}FONa$ $[M\text{-}F]^+$: 213.1655; found 213.1655.

***Z*-4,4-Difluoro-tridec-2-enal (1c)**



$C_{13}H_{22}F_2O$
Mol. Wt: 232.31

To acetal **9a** (333 mg, 1.09 mmol), formic acid (0.82 ml, 20 equiv.) was added and the mixture stirred at room temperature for 10 minutes. The reaction mixture was neutralized by solid Na_2CO_3. Water was added and the aqueous phase was extracted by ether (3 x 30 ml). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum at 300 mbar pressure. After flash chromatography *E*-aldehyde **1c** was obtained as a colorless oil (227 mg, 90% yield). R_f = 0.37 (Et_2O/pentane, 4/96).

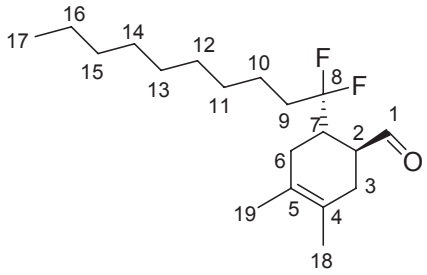
^{1}H NMR ($(CD_3)_2CO$, 400 MHz): δ ppm 0.88 (t, 3H, H_{13}, *J*= 6.9 Hz), 1.29-1.51 (m, 12H), 1.43-1.58 (m, 2H, H_6), 2.10-2.22 (m, 2H, H_5), 6.11 (tdd, 1H, H_2, J_{HF}= 2.0 Hz, *J*= 7.8 Hz, *J*= 12.2 Hz), 6.72 (dt, 1H, H_3, *J*=12.2 Hz, J_{HF}=15.9 Hz), 10.12 (td, 1H, H_1, J_{HF}=2.0 Hz, *J*=7.8 Hz).

^{13}C NMR ($(CD_3)_2CO$, 100 MHz): δ ppm 15.3 (1C, C_{13}), 23.9 (t, 1C, C_6, *J*= 4.1 Hz), 24.3, 30.8, 31.0, 31.1, 33.6, 39.7 (t, 1C, C_5, *J*= 25.4 Hz), 124.3 (t, 1C, C_4, *J*= 240.0 Hz), 135.1 (t, 1C, C_2, *J*= 4.0 Hz), 142.2 (t, 1C, C_3, *J*= 29.1 Hz), 192.6 (t, 1C, C_1, *J*= 4.6 Hz).

^{19}F NMR ($(CD_3)_2CO$, 282 MHz): δ (ppm) : -89.60 (dddt, J_{HF}=2.0 Hz, J_2=2.0 Hz, J_{HF}=15.9 Hz, J_4=16.5 Hz).

HRMS (ESI) $[M-F]^+$ ($C_{17}H_{32}F_2O_2Na$): Calculated m/z = 213.1655. Found m/z = 213.1655 (0 ppm).

6-(1,1-difluoro-decyl)-3,4dimethyl-cyclohex-3-enecarbaldehhyde (10)



$C_{19}H_{32}F_2O$
Mol. Wt.: 314.45

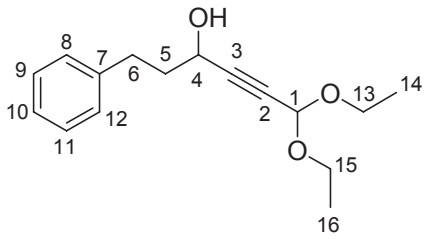
^{1}H NMR ($CDCl_3$, 400 MHz) δ, ppm 0.88 (t, 3H, H_{17}, J = 6.9 Hz); 1.22-1.33 (m, 12H, $H_{11\text{-}16}$); 1.42-1.53 (m, 2H); 1.63 (s, 3H, $H_{18 \text{ or } 19}$), 1.65 (s, 3H, $H_{18 \text{ or } 19}$), 1.74-1.89 (m, 2H); 1.97-2.09 (m, 3H); 2.19-2.26 (m, 1H); 2.44 (m, 1H, $H_{2 \text{ or } 7}$); 2.61 (m, 1H, $H_{2 \text{ or } 7}$), 9.57 (m, 1H, H_1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ, ppm 14.07(C_{17}); 18.60; 18.79 (2C, $C_{18 \text{ and } 19}$), 21.61 (dd, 1C, C_{10}, J = 3.6 Hz, J = 5.5 Hz), 22.6, 29.2, 29.37, 29.41, 30.5, 30.78 (dd, 1C, C_6, J = 3.4 Hz, J = 6.2 Hz), 31.8 (1C), 34.2 (t, 1C, C_9, J = 25.3 Hz), 41.3 (t, 1C, C_7, J = 23.8 Hz), 46.8 (t, 1C, C_2, J= 1.8 Hz); 123.24; 123.85 (2C, $C_{4 \text{ and } 5}$); 126.02 (dd, 1C, C_8, J = 243.1 Hz, J = 244.8 Hz); 202.46 (d, 1C, C_1, J = 2.4 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm): -103.61(dm, J_{FF} = 243.62 Hz); -96.23 (dm, J_{FF} = 243.6 Hz).

HRMS (ESI) $[M+Na+CH_3OH]^+$ ($C_{20}H_{36}O_2F_2Na$): Calculated m/z = 369.25811; Found m/z = 369.258 (0 ppm); **HRMS (ESI) $[M+Na]^+$ ($C_{19}H_{32}OF_2Na$):** Calculated m/z = 337.23189; Found m/z = 337.2318 (0 ppm).

6, 6-diethoxy-1-phenyl-hex-4-yn-3-ol (6b)



$C_{16}H_{22}O_3$
M = 262.34 g.mol^{-1}

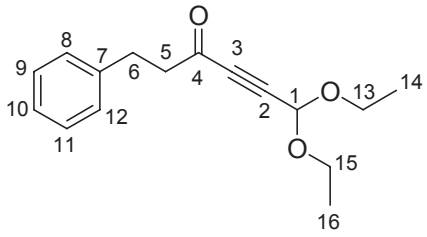
To a solution of propiolaldehyde diethyl acetal (1 g, 7.81 mmol, 1eq) in anhydrous THF (30 ml), cooled at t < -78°C,was added dropwise under nitrogen, a solution of *n*-BuLi in hexane (5.4 ml, 1.6 M, 1.1 equiv.). The mixture was stirred at t < -30°C for 1h , before the dropwise addition of 3-phenylpropanal (1.1 ml, 1.1 equiv.) at -78°C. The mixture was stirred for 2h while the temperature raised up slowly to room temperature. The mixture was treated with a saturated NH_4Cl solution, and extracted with ether (3 x 75 ml). The combined organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by chromatography on silica gel, compound **6b** was obtained as a colorless oil (1.69g, 83% yield). R_f= 0.56 (Et_2O/pentane, 4/6).

^{1}H NMR (C_6D_6, 300 MHz): δ ppm 1.18 (t, 6H, $H_{14\ and16}$, *J*= 7.1 Hz), 1.92- 2.10 (m, 2H, H_5), 2.53 (bs, 1H, OH), 2.78 (t, 2H, H_6, *J*= 7.8Hz), 3.49-3.60 (m, 2H, $H_{13or\ 15}$), 3.74- 3.84 (m, 2H, $H_{13\ or\ 15}$), 4.32 (bt, 1H, H_4, *J*= 6.1Hz), 5.39 (d, 1H, H_1, *J*= 1.3Hz), 7.07-7.22 (m, 5H, $H_{8\text{-}12}$).

^{13}C NMR (C_6D_6, 75 MHz): δ ppm 15.3 (2C, $C_{14\ and\ 16}$), 31.7 (1C, C_6), 39.6 (1C, C_5), 60.9 (2C, $C_{13\ and\ 15}$), 61.4 (1C, C_4), 80.9 (1C, C_2), 86.7 (1C, C_3), 91.9 (1C, C_1), 126.2 (1C, C_{10}), 128.7 (2C, $C_{(8\ and\ 12)\ or\ (9\ and\ 11)}$), 128.8 (2C, $C_{(8\ and\ 12)\ or\ (9\ and\ 11)}$), 141.6 (1C, C_7).

HRMS (ESI) [M+Na]$^+$ (C16H22O3Na): Calculated m/z = 285.144666. Found m/z = 285.1466 (0 ppm)

6, 6-diethoxy-1-phenyl-hex-4-yn-3-one (7b)



$C_{16}H_{20}O_3$
M = 260.33 g.mol^{-1}

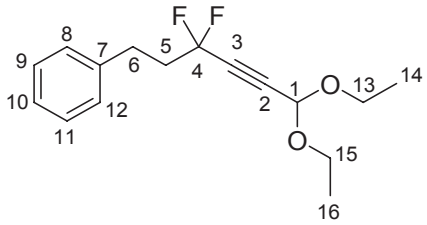
IBX (1.60 g, 1.5equiv.) was dissolved in DMSO (5 ml) before the addition of alcohol **6b** (1 g, 3.82 mmol) in DCM (10 ml). The mixture was refluxed during 3 hours before TLC showed the completion of reaction. Ice-cold water was added to quench the reaction and a white suspension appeared. The reaction mixture was filtered and the layers were separated. The aqueous phase was extracted with DCM (3 x 20 ml). The combined organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum. After purification by flash chromatography on silica gel, compound **7b** was obtained as a colorless oil (912 mg, 92 % yield). R_f= 0.35 (Et_2O/pentane, 1/9).

^{1}H NMR (C_6D_6, 300 MHz): δ ppm 1.18 (t, 6H, $H_{14 \text{ and } 16}$, *J*= 7.1 Hz), 2.83-2.93 (m, 4H, $H_{5 \text{ and } 6}$), 3.51-3.70 (m, 4H, $H_{13 \text{ and } 15}$), 5.32 (s, 1H, H_1), 7.10-7.22 (m, 5H, $H_{8\text{-}12}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.9 (2C, $C_{14 \text{ and } 16}$), 29.5 (1C, C_6), 46.9 (1C, C_5), 61.5 (2C, $C_{13 \text{ and } 15}$), 82.4 (1C, $C_{2 \text{ or } 3}$), 85.4 (1C, $C_{2 \text{ or } 3}$), 91.0 (1C, C_1), 126.3 (1C, C_{10}), 128.3 (2C, $C_{(8 \text{ and } 12) \text{ or } (9 \text{ and } 11)}$), 128.5 (2C, $C_{8 \text{ and } 12}$ or $C_{9 \text{ and } 11}$), 139.9 (1C, C_7), 186.0 (1C, C_4).

HRMS (ESI) $[M+Na]^+$ ($C_{16}H_{20}O_3Na$): Calculated m/z = 283.13101. Found m/z = 283.1310 (0 ppm).

(6,6-diethoxy-3,3-difluoro-hex-4-ynyl)-benzene (8b)



$C_{16}H_{20}F_2O_2$
M = 282.33 g.mol^{-1}

To the propargylic ketone **7b** (886 mg, 3.41 mmol) were added sequentially, two drops of ethanol and DAST (1.3 ml, 3 equiv.). The reaction mixture was stirred, without solvent, at 65 °C during 8h. After coming back to room temperature, the mixture was diluted by pentane (50 ml), then added dropwise to a Na_2CO_3 solution. The phases were separated, the organic phase was washed by distilled water (3 x 10 ml), and aqueous layer was extracted with pentane (3 x 15 ml); the organic fractions were collected, dried over $MgSO_4$, and concentrated by rotary evaporation under 300 mbar pressure. The product **8b** was isolated after flash chromatography on silica gel as a colorless oil (809 mg, 84 % yield). R_f = 0.5 (Et_2O/pentane, 6/94).

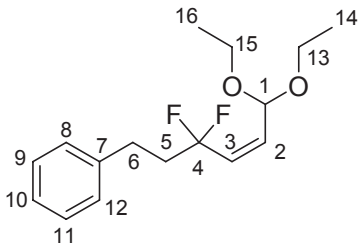
^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 1.28 (t, 6H, $H_{14 \text{ and } 16}$, J= 7.1 Hz); 2.32-2.48 (m, 2H, H_5); 2.88-2.93 (m, 2H, H_6), 3.60-3.67 (m, 2H, $H_{13 \text{ or } 14}$), 3.70-3.82 (m, 2H, $H_{13 \text{ or } 14}$), 5.36 (t, 1H, H1, J_{HF}= 3.0 Hz), 7.21-7.36 (m, 5H, $H_{8\text{-}12}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 15.0 (2C, $C_{14 \text{ and } 16}$), 29.9 (t, 1C, C_6, J= 3.9 Hz); 40.9 (t, 1C, C_5, J= 25.9 Hz), 61.4 (2C, $C_{13 \text{ and } 15}$), 77.6 (t, 1C, C_3, J= 41.1 Hz), 82.5 (t, 1C, C_2, J= 6.7 Hz), 90.8 (t, 1C, C_1, J= 1.8 Hz), 114.0 (t, 1C, C_4, J= 233.9 Hz), 126.4 (1C, C_{10}), 128.3 (2C, $C_{8 \text{ and } 12}$ or $C_{9 \text{ and } 11}$), 128.6 (2C, $C_{8 \text{ and } 12}$ or $C_{9 \text{ and } 11}$), 139.7 (1C, C7).

^{19}F NMR ($CDCl_3$, 282 MHz): δ ppm -98.85 (dt, J_{HF}= 3.0 Hz, J_2= 14.6 Hz).

HRMS (ESI) $[M+Na]^+$ ($C_{16}H_{20}F_2O_2Na$): Calculated m/z = 305.13291. Found m/z = 305.1327 (1 ppm).

***Z*-(6,6-diethoxy-3,3-difluoro-hex-4-enyl)-benzene (9b)**



$C_{16}H_{22}F_2O_2$
M = 284.34 g.mol^{-1}

To alkyne **8b** (0.5 g, 1.77 mmol) in pentane (10ml), lindlar catalyst (0.1 g, 20% by mass) was added, the mixture was stirred under hydrogen gas (1 atm.). The course of reaction was monitored by TLC or ^{19}F NMR. After 1 hour, the reaction was complete, the mixture was filtered on Celite and concentrated by rotary evaporation under a 300 mbar pressure. After purification by flash chromatography on silica gel, product **9b** was obtained as a colorless oil (457 mg, 92% yield). R_f = 0.27 (Et_2O/pentane, 6/94)

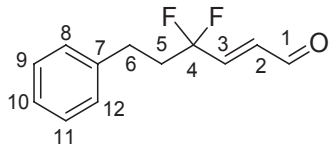
^{1}H NMR ($(CD_3)_2CO$, 400 MHz): δ ppm 1.16 (t, 6H, $H_{14\ and16}$, *J*= 7.1 Hz), 2.24-2.40 (m, 2H, H_5), 2.78-2.85 (m, 2H, H_6), 3.50-3.58 (m, 2H, $H_{13\ or\ 14}$), 3.62-3.69 (m, 2H, $H_{\ 13\ or\ 14}$), 5.39-5.41 (m, 1H), 5.74-5.87 (m, 2H), 7.17-7.33 (m, 5H, $H_{8\text{-}12}$).

^{13}C NMR ($(CD_3)_2CO$, 100 MHz): δ ppm 16.6 (2C, $C_{14\ and\ 16}$), 30.1 (t, 1C, C_6, *J*= 4.6 Hz), 41.8 (t, 1C, C_5, *J*= 26.3 Hz), 62.7 (2C, $C_{13\ and\ 15}$), 98.7 (t, 1C, C_1, *J*= 3.1 Hz), 123.8 (t, 1C, C_4, *J*= 239.6 Hz), 128.0 (1C, C_{10}), 128.4 (t, 1C, C_3, *J*= 28.17 Hz), 130.1 (2C, $C_{\ (8\ and12)\ or\ (9\ and\ 11)}$), 130.3 (2C, (2C, $C_{\ (8\ and12)\ or\ (9\ and\ 11)}$), 136.5 (t, 1C, C_2, *J*= 5.5 Hz), 142.4 (1C, C_7).

^{19}F NMR ($(CD_3)_2CO$, 282 MHz): δ ppm -92.33 (m).

HRMS (ESI) $[M+Na]^+$ ($C_{16}H_{22}F_2O_2Na$): Calculated m/z = 307.14856. Found m/z = 307.1484 (0 ppm).

***E*-4,4-difluoro-6-phenyl-hex-2-enal (1b)**



$C_{12}H_{12}F_2O$
M = 210.22 g.mol^{-1}

To acetal **9b** (1 g, 3.52 mmol), formic acid (20 ml, 150 equiv.) was added and the mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was neutralized by addition of solid Na_2CO_3. Water was added and the aqueous phase was extracted with ether (3 x 100 ml). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum at 300 mbar pressure. After flash chromatography *E*-aldehyde **1b** was obtained as a colorless oil (560 mg, 76% yield). R_f = 0.26 (Et_2O/pentane, 1/9).

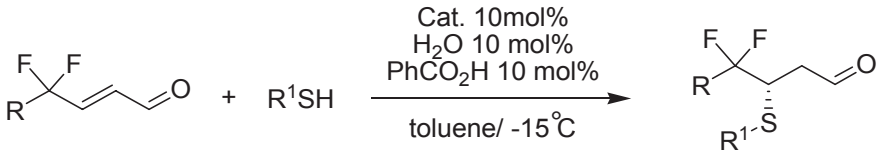
^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.14-2.30 (m, 2H, H_6), 2.71-2.76 (m, 2H, H_5), 6.36 (tdd, 1H, H_2, J_{HF}= 1.8 Hz, J= 7.3 Hz, J= 16.0 Hz), 6.54 (td, 1H, H3, J_{HF} = 10.6 Hz, J= 16.0 Hz), 7.08-7.24 (m, 5H, $H_{8\text{-}12}$), 9.51 (d, 1H, H_1, J=7.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 28.1 (t, 1C, C_6, J= 4.5 Hz), 38.6 (t, 1C, C_5, J= 25.7 Hz), 120.0 (t, 1C, C_4, J= 240.5 Hz), 126.5 (1C, C_{10}), 128.2 (2C, $C_{(8 \text{ and } 12) \text{ or } (9 \text{ and } 11)}$), 128.6 (2C, $C_{(8 \text{ and } 12) \text{ or } (9 \text{ and } 11)}$), 133.4 (t, 1C, C_2, J= 7.3 Hz), 139.6 (1C, C_7), 145.7 (t, 1C, C_3, J= 28.5 Hz), 191.9 (1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm): -99.37 (dt, J_{HF}= 10.6 Hz, J= 15.9 Hz).

HRMS (ESI) $[M+Na]^+$ ($C_{12}H_{12}F_2ONa$): Calculated m/z = 233.0754. Found m/z = 233.0752.

General procedure for the enantioselective Michael addition with thiols under optimized conditions.



Enal (0. 43 mmol, 1.5 equiv.), catalyst (17 mg, 10 mol%), benzoic acid (3.5 mg, 10 mol%) and water (57 µl, 0.5M in dioxane, 10 mol%) in toluene (1ml) were cooled at -15 °C before the dropwise addition of alkylthiol (0.29 mmol, 1 equiv.) and the reaction mixture was stirred at this temperature for 16-40h time. The course of reaction was monitored by $^{19}F/^{1}H$ NMR. The reaction mixture was directly subjected to silica gel column chromatography to give pure 1,4 addition products.

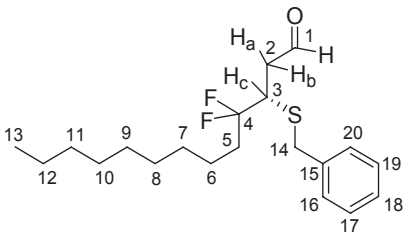
All thiols 1,4 additions have been performed starting from the same quantity (0.43 mmol.) of enals.

Determination of enantiomeric excess.

Two samples of the crude reaction mixture (0.043 mmol each) were taken in two NMR tubes containing two molecular sieves (1-2 mm size). In the first one was added the racemic diamine (20 mg, 2 equiv.), while in the second one, enantiopure diamine (20 mg, 2 equiv.) was added. The mixtures were left in $CDCl_3$ at -15 °C for 24h before recording $^{19}F/^{1}H$ NMR. The data of the first sample gives the two sets of signals of the two diastereoisomers formed, while that of the second sample gives the ratio of the two diastereoisomers (de) which is directly transformed into the (ee) of the starting aldehyde.

In the case of pure product obtained after chromatography, the same procedure was followed, by using a 1:2 molar ratio of product to chiral diamine.

3-Benzylsulfanyl-4,4-difluoro-tridecanal (12a)



$C_{20}H_{30}F_2OS$
Mol. Wt.: 356.51

Following the general procedure of thiols addition, after 16h, ^{19}F NMR showed 100% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (100 mg, 98% yield), with 98% ee; $[\alpha]^{22}_D$: = +5.1 (0.25, $CHCl_3$); R_f = 0.41 (pentane/diethyl ether = 9/1).

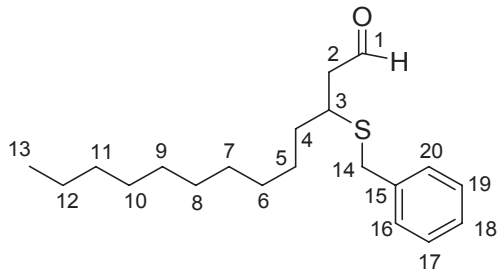
^{1}H NMR ($CDCl_3$, 400MHz): δ, ppm 0.82 (t, 3H, H13, *J*= 6.9 Hz); 1.19-1.36 (m, 14H, $H_{6\text{-}12}$); 1.78-1.91 (m, 2H, H_5); 2.61 (ddd, 1H, $H_{a\text{ or }b}$, *J*= 2.0 Hz, *J*= 9.4 Hz, *J*= 17.8 Hz), 2.82 (ddd, 1H, $H_{a\text{ or }b}$, *J*= 0.8 Hz, *J* = 4.4 Hz, *J*= 17.8 Hz); 3.27 (dddd, 1H, Hc, *J*= 4.5 Hz, J_{HF}= 7.1 Hz, *J*= 9.4 Hz, J_{HF}=19.4 Hz); 3.77 (s, 2H, H_{14}); 7.15-7.33 (m, 5H, $H_{16\text{-}20}$); 9.49 (dd, 1H, H_1, *J*= 0.8 Hz, *J*= 2.0 Hz).

13C NMR ($CDCl_3$, 100): δ, ppm 14.1 **(**1C, C_{13}), 21.5 (dd, 1C, C_6, *J*= 3.8Hz, *J*= 4.6 Hz); 22.7; 29.26; 29.28; 29.3; 29.4; 31.9; 33.7 (t, 1C, C_5, *J*= 24.6 Hz); 36.8 (1C, C_{14}); 42.9 (t, 1C, C_3, *J*= 27.2 Hz); 43.44 (dd, 1C, C_2, *J*= 1.5 Hz, *J*= 4.1 Hz); 125.7 (t, 1C, C4, *J*= 245.9 Hz)**;** 127.5 (1C, C18); 128.7 (2C, C $_{16 \text{ and } 20 \text{ or } 17 \text{ and } 19}$); 129.2 (2C, C $_{16 \text{ and } 20 \text{ or } 17 \text{ and } 19}$); 137.2 (1C, C_{15}); 198.7 (1C, C_1).

^{19}F NMR (376 and 282 MHz, $CDCl_3$): *δ* ppm -98.78 (dddd, J_{HF} =7.1, 15.7, 23.0 Hz, J_{FF} = 244.6), -101.81 (dtd, J_{HF} = 12.7, 19.4, J_{FF} = 244.6).

HRMS (ESI) [M+Na+CH_3OH]+ ($C_{21}H_{34}F_2O_2NaS$): Calculated m/z = 411.21453. Found m/z = 411.2145 (0 ppm); **HRMS (ESI) $[M+Na]^+$ ($C_{20}H_{30}F_2ONaS$):** Calculated m/z = 379.1883. Found m/z = 379.1890 (2 ppm).

3-Benzylsulfanyl-tridecanal (12aH)



$C_{20}H_{32}OS$
Mol. Wt.: 320.53

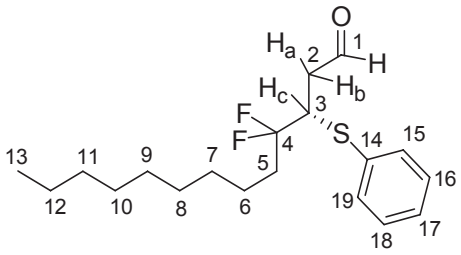
Following the general procedure of thiols addition, after 16h analysis by ^{1}H NMR showed 44% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (37 mg, 40% yield), with 82% ee; $[\alpha]^{22}_{D}$: = +1.8 (0.55, $CHCl_3$); R_f = 0.42 (pentane/diethyl ether = 85/15).

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 0.89 (t, 3H, H_{13}, *J*= 6.7 Hz), 1.40-1.24 (m, 16H), 1.60-1.52 (m, 2H), 2.57 (t, 1H, *J* = 2.0 Hz), 2.59 (dd, 1H, H_2 *J* = 1.1, 2.0 Hz,), 3.00 (pentuplet, *J* = 6.7 Hz, 1H), 3.74 (s, 2H), 7.33-7.20 (m, 5H), 9.64 (t, 1H, H_1, *J* = 2.0 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.1 (1C, C13) ,22.6, 26.6, 29.25, 29.27, 29.4, 29.51, 29.53, 31.9, 35.0, 35.3, 39.0 (1C, C_3), 48.6 (1C, C_2), 127.1 (1C, C_{18}), 128.5 (2C, aromatic), 128.8 (2C, aromatic), 138.1 (1C, C_{15}), 201.1 (1C, C_1)

HRMS (ESI) [M+Na+CH_3OH]+ ($C_{21}H_{36}O_2NaS$): Calculated m/z = 375.2334. Found m/z = 375.2323; **[M+Na]$^+$ ($C_{20}H_{32}ONaS$):** Calculated m/z = 343.2072. Found m/z = 343.2073.

4,4-difluoro-3-phenylsulfanyl-tridecanal (13a)



$C_{19}H_{28}F_2OS$
M = 342.49 g.mol^{-1}

Following the general procedure of thiols addition, after 21h analysis by ^{19}F NMR showed 92% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (86 mg, 88% yield), with 95% ee; $[\alpha]^{22}_D$: = + 4.5 (0.2, $CHCl_3$); R_f = 0.39 (pentane/diethyl ether = 9/1).

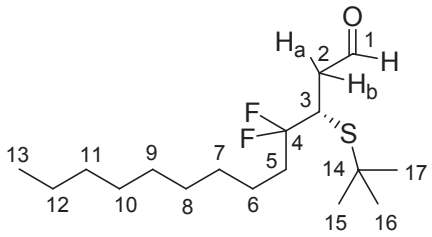
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm 0.89 (t, 3H, H_{13}, J= 6.8 Hz), 1.22-1.45 (m, 14H, $H_{6\text{-}12}$), 1.96-2.13 (m, 2H, H_5), 2.82 (ddd, 1H, $H_{a\text{ or }b}$, J= 1.6 Hz, J= 8.8 Hz, J= 18.3 Hz), 3.02 (ddd, 1H, $H_{a\text{ or }b}$, J= 0.7 Hz, J= 4.5 Hz, J= 18.3 Hz), 3.88 (dddd, 1H, Hc, J= 4.5 Hz, J_{HF}= 5.5 Hz, J= 8.8 Hz, J_{HF}= 21.4 Hz), 7.30-7.37 (m, 3H), 7.51-7.56 (m, 2H), 9.81 (dd, 1H, H_1, J= 0.7 Hz, J= 1.6 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 14.1 (1C, C_{13}), 21.9 (dd, 1C, C_6, J= 3.0 Hz, J= 5.8 Hz), 22.6, 29.17, 29.22, 29.27, 29.35, 31.8, 34.46 (t, 1C, C_5, J= 24.4 Hz), 43.0 (dd, 1C, C_2, J= 2.0 Hz, J= 3.6 Hz), 47.5 (t, 1C, C_3, J= 26.7 Hz), 125.1 (t, 1C, C_4, J= 246.4 Hz), 128.3 (1C, C_{17}), 129.26 (2C, $C_{(15\text{ and }19)\text{ or }(16\text{ and }18)}$), 133.04 (2C, $C_{(15\text{ and }19)\text{ or }(16\text{ and }18)}$), 133.19 (1C, C_{14}), 198.49 (1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: -103.87 (dddd, J_{HF}= 13.7 Hz, J_{HF}= 14.9 Hz, J_{HF}= 21.9 Hz, J= 243.9 Hz); -98.15 (dddd, J_{HF}= 5.5 Hz, J_{HF}= 19.1 Hz, J_{HF}= 21.4 Hz, J= 243.9 Hz).

HRMS (ESI) $[M+Na+CH_3OH]^+$ ($C_{20}H_{32}F_2O_2NaS$): Calculated m/z = 397.19888. Found m/z = 397.1979 (2 ppm); **$[M+Na]^+$ ($C_{19}H_{28}F_2ONaS$):** Calculated m/z = 365.17266. Found m/z = 365.1731 (1 ppm).

3-tert-Butylsulfanyl-4,4-difluoro-tridecanal (14a)



$C_{17}H_{32}F_2OS$
M = 342.49 g.mol^{-1}

Following the general procedure of thiols addition, after 40h analysis by ^{19}F NMR showed 76% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (66 mg, 71% yield), with 94% ee. $[\alpha]^{22}_D$: = +3.1 (0.26, $CHCl_3$); R_f = 0.42 (pentane/diethyl ether = 9/1).

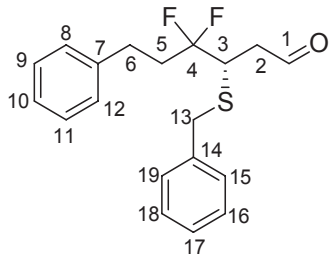
^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 0.87 (t, 3H, H_{13}, J = 6.9 Hz), 1.26-1.33 (m, 12H), 1.34 (s, 9H, $H_{15,\ 16\ and\ 17}$), 1.45-1.54 (m, 2H), 1.89-2.10 (m, 2H), 2.73 (tdd, 1H, H_2, J = 1.2 Hz, J = 5.9 Hz, J = 17.6 Hz), 3.04 (ddd, 1H, H_2, J = 1.2 Hz, J = 6.7 Hz, J = 17.6 Hz), 3.47-3.56 (m, 1H, H_3), 9.76 (t,1H, H_1, J = 1.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz,): δ ppm 14.1 (1C, C_{13}), 21.4 (t, 1C, C_6, J = 4.2 Hz), 22.6, 29.22, 29.29, 29.37, 29.39, 31.2 (3C, $C_{15,\ 16\ and\ 17}$), 3.1.8, 33.9 (t, 1C, C_5, J = 24.7 Hz), 41.4 (t, 1C, C_3, J = 27.0 Hz), 44.5, 46.7 (dd, 1C, C_2, J = 1.6 Hz, J = 4.2 Hz), 125.0 (dd, 1C, C_4, J = 245.1 Hz, J = 246.0 Hz), 199.1 (bs, 1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz,): δ (ppm) -102.57 (dddd, J_{HF} = 9.1 Hz, J_{HF} = 19.0 Hz, J_{HF} = 27.4 Hz, J_{FF} = 243.9 Hz); -99.03 (dddd, J_{HF} = 8.0 Hz, J_{HF} = 11.1 Hz, J_{HF} = 19.0 Hz, J_{FF} = 243.2 Hz).

HRMS (ESI) $[M]^+$ ($C_{17}H_{33}F_2OS$): Calculated m/z = 323.2220. Found m/z = 323.2222.

3-benzylsulfanyl-4,4-difluoro-6-phenyl-hexanal (12b)



$C_{19}H_{20}F_2OS$
M = 334.42 g.mol^{-1}

Following the general procedure of thiols addition, after 16h analysis by ^{19}F NMR showed complete conversion. The reaction mixture was subjected directly to silica gel flash chromatography to afford the desired product **12b** as a colorless oil (90 mg, 94% yield), with 96% ee; $[\alpha]^{22}_D$= +56.2 (0.5, $CHCl_3$); R_f = 0.23 (Et_2O/pentane, 1/9).

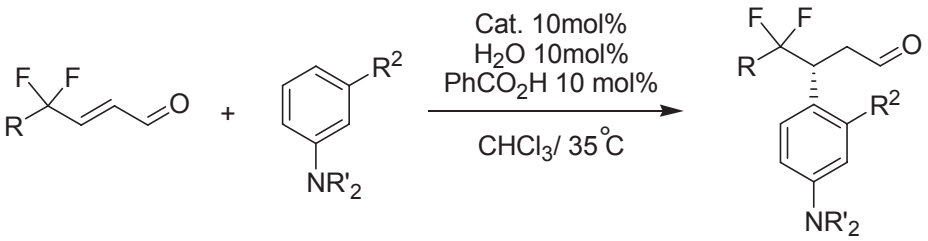
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 1.99-2.28 (m, 2H, H_5); 2.61-2.69 (m, 2H, H_6); 2.60 (ddd, 1H, H2, J_1= 2.1 Hz, J_2= 9.4 Hz, *J3*= 17.8 Hz); 2.82 (ddd, 1H, H2, J_1= 0.6 Hz, J_2= 4.4 Hz, J_3= 17.8 Hz); 3.29 (dddd, 1H, H3, J_1= 4.4 Hz, J_{2HF}= 7.1 Hz, J_3= 9.3 Hz, J_{4HF}= 19.4 Hz); 7.05-7.24 (m, 5H, aromatic); 9.45 (dd, 1H, H1, J_1= 0.6 Hz, J_2= 2.1 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) : 27.6 (t, 1C, C_6, *J*= 4.8 Hz); 35.5 (t, 1C, C_5, *J*= 24.5 Hz); 36.8 (1C, C_{13}) ; 42.8 (t, 1C, C_3, *J*= 26.9 Hz); 43.3 (dd, 1C, C_2, J_1= 1.6 Hz, J_2= 4.2 Hz); 125.1 (t, 1C, C_4, *J*= 246.4 Hz); 126.2 (1C, $C_{10\ or\ 17}$) ; 127.5 (1C, $C_{10\ or\ 17}$) ;128.3; 128.5; 128.7; 129.2; 137.1 (1C, $C_{7\ or\ 14}$); 140.3 (1C, $C_{7\ or\ 14}$); 198.5 (1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz): δ ppm -102.68 (dddd, J_{HF} = 8.9 Hz, J_{HF} = 19.4 Hz, J_{HF} = 23.6 Hz, J_{FF} = 244.9 Hz); -99.04 (dddd, J_{HF} = 7.1 Hz, J_{HF} = 12.2 Hz, J_{HF} = 25.1 Hz, J_{FF} = 244.9 Hz).

HRMS (ESI) $[M+Na]^+$ ($C_{19}H_{20}F_2ONaS$): Calculated m/z = 357.1101. Found m/z = 357.1102.

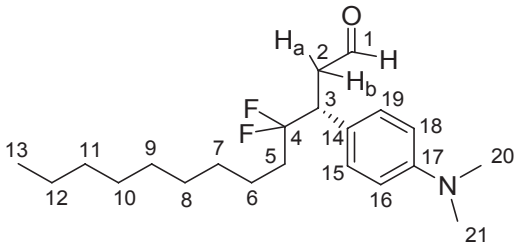
General procedure for the enantioselective organocatalyzed aniline conjugated addition



Enal (0. 43 mmol, 1equiv.), catalyst (25.6 mg, 10 mol%), benzoic acid (5.3 mg, 10 mol%), water (86 µl, 0.5M in dioxane, 10 mol%) and aniline derivative (0.65 mmol, 1.5 equiv.) were stirred in $CHCl_3$ (1ml) at 35 °C for 24-52 h. The course of reaction was monitored by $^{19}F/^{1}H$ NMR. The reaction mixture was directly subjected to silica gel column chromatography to give corresponding products in high purity.

All anilines 1,4 additions have been performed starting from the same quantity (0.43 mmol.) of enals.

3-(4-dimethylaminophenyl)-4,4-difluorotridecanal (15a)



$C_{21}H_{33}F_2NO$
Mol. Wt.: 353.49

Following the general procedure of aniline addition, after 48 h analysis by ^{19}F NMR showed 82% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (117 mg, 77% yield), with 98% ee; $[\alpha]^{22}_D$: = +15.4 (0.24, $CHCl_3$); R_f = 0.34 (pentane/diethyl ether = 9/1).

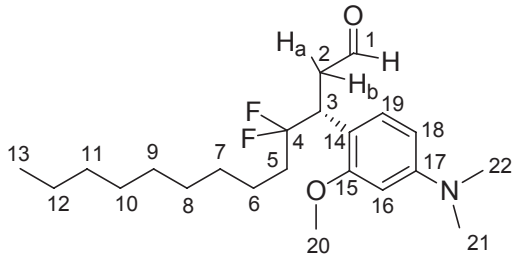
^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 0.89 (t, 3H, H_{13}, *J*= 6.91 Hz); 1.21-1.71 (m, 16H, $H_{5\text{-}12}$); 2.89 (ddd, 1H, $H_{a\text{ or }b}$, *J*=1.89 Hz, *J* = 9.15 Hz, *J* = 17.41 Hz); 2.94 (s, 6H, $H_{20\text{ and }21}$); 3.12 (ddd, 1H, Ha or Hb, *J* = 1.39 Hz, *J* = 4.87 Hz, *J* = 17.41Hz); 3.51-3.66 (m, 1H, H_3); 6.65-6.70 (m, 2H, H16 and H18); 7.13-7.16 (m, 2H, H15 and H19); 9.67 (s, 1H, H1).

^{13}C NMR (CDCl3, 75 MHz) δ, ppm: 14.03 (1C, C13) 21.67 (dd, 1C, C_6, *J*= 3.21 Hz, J2= 5.73 Hz), 22.32, 29.21, 29.23, 29.32, 29.34, 31.8; 35.0 (t, C_5, *J* = 25.0 Hz), 40.39 (2C, C20 and C21), 43.63 (t, C_2, *J* = 3.25 Hz), 45.02 (dd, C_3, *J* = 23.2 Hz, *J* = 24.9 Hz), 112.50 (2C, $C_{16\text{ and }18}$), 124.60 (d, C_{14}, *J* = 7.85 Hz), 125.44 (dd, C_4, *J* = 245.45 Hz, J2= 246.73 Hz), 129.54, 129.56 (2C, $C_{15\text{ and }19}$), 149.91 (1C, C_{17}), 200.40 (1C, C1).

^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm): -106.48 (dddd, J_{HF} = 13.5, J_{HF} = 16.4, J_{HF} = 25.4 Hz, J_{FF} = 240.6 Hz), -100.16 (dtd, J_{HF} = 5.5, J_{HF} = 19.9 Hz, J_{FF} = 240.6 Hz).

HRMS (ESI) $[M+ Na]^+$ ($C_{21}H_{33}NF_2ONa$): Calculated m/z = 376.2428. Found m/z = 376.2430; **HRMS (ESI) $[M+ H]^+$ ($C_{21}H_{34}NF_2O$):** Calculated m/z = 354.2608. Found m/z = 354.2616; **HRMS (ESI) $[M+Na+ CH_3OH]^+$ ($C_{22}H_{37}NF_2O_2Na$):** Calculated m/z = 408.2690. Found m/z = 408.2685.

3-(4-dimethylamino-2-methoxyphenyl)-4,4-difluorotridecanal (16a)



$C_{22}H_{35}F_2NO_2$
Mol. Wt.: 353.49

Following the general procedure of aniline addition, after 24h analysis by ^{19}F NMR showed 95% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (143 mg, 87% yield), with 98% ee; $[\alpha]^{22}_D$: = -5.9 (0.61, $CHCl_3$); R_f = 0.36 (pentane/diethyl ether = 85/15).

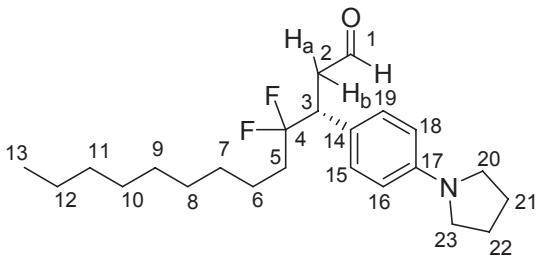
^{1}H NMR ($CDCl_3$, 300 MHz): δ, ppm: 0.88 (t, 3H, H_{13}, J= 6.8Hz); 1.22- 1.75 (m, 16H, $H_{5\text{-}12}$); 2.76 (ddd, 1H, $H_{a\text{ or }b}$, J= 2.5 Hz, J= 9.1 Hz, J= 16.7 Hz), 2.96 (s, 6H, $H_{21\text{ and }22}$), 3.06 (ddd, 1H, $H_{a\text{ or }b}$, J= 1.9 Hz, J= 5.54 Hz, J= 16.7 Hz), 3.85 (s, 3H, H20), 4.23 (dddd, 1H, H_3, J= 5.5 Hz, J_{HF}= 5.5 Hz, J= 9.1 Hz, J_{HF}= 26.8 Hz), 6.21 (d, 1H, H_{16}, J= 2.4 Hz), 6.31 (dd, 1H, H_{18}, J= 2.4 Hz, J= 8.6 Hz), 7.11 (dd, 1H, H_{19}, J= 2.2 Hz, J= 8.5Hz), 9.6 (bs, 1H, H_1).

^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm 14.1 (1C,C_{13}), 21.6 (dd, 1C, C_6, J= 3.3 Hz, J= 5.6 Hz), 22.2, 22.3, 22.6, 29.3, 29.4, 31.8, 34.9 (t, 1C, C5, J= 24.7 Hz), 36.5 (dd, 1C, C3, J= 23.0 Hz, J= 25.9 Hz), 40.4 (2C, $C_{21\text{ and }22}$), 43.3 (dd, 1C, C_2, J= 2.5 Hz, J= 3.5 Hz), 55.3 (1C, C_{20}), 95.4 (1C, C_{16}), 105.1 (1C, C_{18}), 113.1 (d, 1C, C_{14}, J= 9.2 Hz), 125.8 (dd, 1C, C_4, J= 245.0 Hz, J= 247.0 Hz), 129.2 (d, 1C, C_{19}, J= 3.2 Hz), 151.1 (1C, C_{17}), 157.8 (1C, C_{15}), 201.4 (1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz): δ ppm -106.36 (dddd, J_{HF} = 9.7 Hz, J_{HF} = 18.7 Hz, J_{HF} = 26.8 Hz, J_{FF} =238.5 Hz); -99.17 (dddd, J_{HF} = 5.5 Hz, J_{HF} = 16.6 Hz , J_{HF} = 21.9 Hz, J_{FF} = 238.5 Hz).

HRMS (ESI) M+. ($C_{22}H_{35}F_2NO_2$): Calculated m/z = 383.26359; Found m/z = 383.2633 (1 ppm).

4,4-difluoro-3-(4-pyrrolidin-1-yl-phenyl)-tridecanal (17a)



$C_{23}H_{35}F_2NO$
Mol. Wt.: 353.49

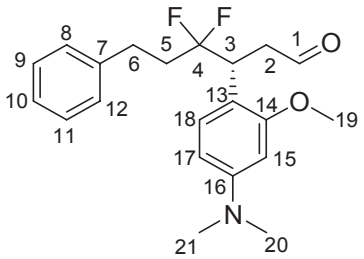
Following the general procedure of aniline addition, after 51h analysis by ^{19}F NMR showed 53% conversion. The reaction mixture was subjected directly to silica gel chromatography to afford the product as a colorless oil (65 mg, 40% yield), with 87% ee; $[\alpha]^{22}_D$: = 14.4 (0.25, $CHCl_3$); R_f = 0.37 (pentane/diethyl ether = 9/1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 0.87 (t, 3H, H_{13}, J= 6.8 Hz); 1.22-1.71 (m, 16H, $H_{5\text{-}12}$); 1.97-2.01 (m, 4H, $H_{21 \text{ and } 22}$); 2.88 (ddd, 1H, $H_{a \text{ or } b}$, J= 1.9 Hz, J= 9.2 Hz, J= 17.3 Hz); 3.10 (ddd, 1H, $H_{a \text{ or } b}$, J= 1.4 Hz, J= 4.9 Hz, J= 17.3 Hz); 3.24-3.29 (m, 4H, $H_{20 \text{ and } 23}$); 3.56 (dddd, 1H, H_3, J= 4.9 Hz, J_{HF}= 5.3 Hz, J= 9.2 Hz, J_{HF}= 25.4 Hz); 6.46-6.53 (m, 2H, $H_{16 \text{ and } 18}$); 7.10-7.13 (m, 2H, $H_{15 \text{ and } 19}$); 9.66 (bs, 1H, H_1).

^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 14.0 (1C, C_{13}); 21.6 (dd, 1C, C_6, J= 3.2 Hz, J= 5.7 Hz); 22.6; 25.4 (2C, $C_{21 \text{ and } 22}$); 29.18; 29.22; 29.31, 29.32; 31.8; 34.9 (t, 1C, C_5, J= 24.9 Hz); 43.6 (t, 1C, C_2, J= 3.3 Hz); 45.1 (dd, 1C, C_3, J= 23.3 Hz, J= 24.8 Hz); 47.5 (2C, $C_{20 \text{ and } 23}$); 111.6 (bs, 2C, $C_{16 \text{ and } 18}$); 123.3 (d, 1C, C_{14}, J= 8.7 Hz); 125.5 (dd, 1C, C_4, J= 245.5 Hz, J= 246.8 Hz); 129.61 (1C, $C_{15 \text{ or } 19}$); 129.62 (1C, ($C_{15 \text{ or } C19}$); 147.9 (1C, C_{17}); 200.6 (1C, C_1).
^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm): -106.40 (dm, J_{FF}= 240.3Hz); -100.11 (ddt, J_{HF}= 5.4 Hz, J_{HF}= 20.0 Hz, J_{FF}= 240.3 Hz).

HRMS (ESI) M+. ($C_{23}H_{35}F_2NO$): Calculated m/z = 379.26867; Found m/z = 379.2688 (0 ppm).

3-(4-dimethylamino-2-methoxy-phenyl)-4,4-difluoro-6-phenyl-hexanal (16b)



$C_{21}H_{25}F_2NO_2$
M = 334.42 g.mol^{-1}

Following the general procedure of aniline addition, after 24h analysis by ^{19}F NMR showed 88% conversion. The reaction mixture was subjected directly to silica gel flash chromatography to afford the product as a colorless oil (130 mg, 84% yield), with 98% ee; $[\alpha]^{22}_D$ = -10.9 (1.53, $CHCl_3$); R_f = 0.33 (pentane/diethyl ether = 85/15).

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 1.79-2.02 (m, 2H, H_5), 2.59-2.81 (m, 2H, H_6), 2.71 (ddd, 1H, H2, J = 2.4 Hz, J = 9.1 Hz, J = 16.7 Hz); 2.86 (s, 6H, $H_{20 \text{ and } 21}$); 3.01(ddd, 1H, H_2, J = 1.9 Hz, J = 5.6 Hz, J = 16.7 Hz); 3.74 (s, 3H, H_{19}), 4.22 (dddd, J = 5.4 Hz, J_{HF} = 5.4 Hz, J = 9.1 Hz, J_{HF} = 27.0 Hz), 6.12 (d, 1H, H_{15}, J = 2.4 Hz), 6.23 (dd, 1H, H_{17}), 7.00-7.09 (m, 4H, aromatic), 7.13- 7.17 (m, 2H, aromatic), 9.54 (bs, 1H, H_1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 28.1 (dd, 1C, C6, , J = 4.3 Hz, J = 5.9 Hz), 36.7 (dd, 1C, C_3, J = 22.8 Hz, J = 25.7 Hz); 36.8 (t, 1C, C_5, J = 24.8 Hz), 40.5 (2C, $C_{20 \text{ and } 21}$), 43.4 (dd, 1C, C_2, J = 2.3 Hz, J = 3.6 Hz), 55.5 (1C, C_{19}), 95.7(1C, C_{15}), 105.4 (1C, C_{17}), 112.9 (d, 1C, C_{13}, J = 9.3 Hz), 125.4 (dd, 1C, C_4, J = 245.7 Hz, J = 247.8 Hz), 126.0 (1C, C_{10}), 128.3 (2C, C $_{(9 \text{ and } 11)}$ or $_{(8 \text{ and } 12)}$), 128.4 (2C, C $_{(9 \text{ and } 11) \text{ or } (8 \text{ and } 12)}$), 129.4 (d, 1C, C_{18}, J = 3.1 Hz), 141.0 (1C, C_7), 151.3 (1C, C16 or $_{C14}$), 158.0 (1C, $C_{14 \text{ or } 16}$), 201.1 (1C, C_1).

^{19}F NMR ($CDCl_3$, 282 MHz): δ ppm -107.05 (dddd, J_{HF}= 10.2 Hz, J_{HF} = 19.5 Hz, J_{HF} = 27.0 Hz, J_{FF} = 239.14 Hz); -99.14 (dddd, J_{HF} = 5.4 Hz, J_{HF} = 15.5 Hz, J_{HF} = 21.5 Hz, J_{FF}= 239.1 Hz).

HRMS (ESI) $[M+Na]^+$. ($C_{21}H_{25}F_2NO_2Na$): Calculated m/z = 384.1751; Found m/z = 384.1750.

GENERAL CONCLUSION

General Conclusion

This work is part of a collaborating program between *Lebanese University, Doctoral School for Sciences and Technology, "Laboratory for Medicinal Chemistry and Natural Products"* and University of Rennes 1, Institut des Sciences Chimiques de Rennes, CNRS UMR 6226, Team *"Produits Naturels, Synthèses et Chimie Médicinale" (PNSCM).*

In the first part (chapter I), starting from 12-HETE, 13-HODE and their analogues, already reported in literature as platelet aggregation inhibitors, we have designed and prepared two series of new very simple compounds. These molecules have been tested as platelet aggregation inhibitors. Five of them demonstrated a significant inhibition of platelet aggregation and human recombinant COX-1 activity.

In the second part (chapters III and IV), *novel* methodologies for preparation of CF_2-containing molecules were designed:

In chapter III, a new flexible strategy has been developed for the preparation of *gem*-difluoro-bisarylic derivatives and their mixed aryl/heteroaryl analogues. This strategy is based on the easy synthesis and the reactivity of *gem*-difluoropropargylic intermediates. By a Diels-Alder-aromatization sequence we could obtain in good yields bisarylic derivatives with CF_2 as a linker. In the same way, by using 1,3-dipolar cycloadditions, the desired mixed arylic/heteroarylic compounds have been prepared. Further, since the prepared bisarylic scaffold had two sites of molecular diversity (ester and bromine), we could use them to prepare focused chemical libraries as representative examples.

In Chapter IV, after preparation of *gem*-difluoroenals from their difluoropropargylic precursors, asymmetric organocatalytic were performed for the first time on such molecules. In the case of Diels-Alder cycloaddition, the product was obtained unfortunately with a moderate enantioselectivity (76% ee): competition between Diels-Alder cycloaddition and side reactions, such as nucleophilic addition of water, was noticed. However, these *gem*-difluoroenals proved to be excellent substrates for asymmetric organocatalytic 1,4-additions of thiols and anilines. Using diarylsilylprolinol ether as catalyst, the products were successfully obtained in high yields with excellent ee's (up to 98%). Moreover, the CF_2R group strongly activates enals towards organocatalytic 1,4-conjugated additions.

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RESUME

Dans la première partie nous décrivons la synthèse et l'évaluation biologique de nouveaux inhibiteurs de l'agrégation plaquettaire, composés dont la structure a été établie en partant du 12-HETE et du 13-HODE. Dans la seconde partie nous développons de nouvelles méthodologies pour la préparation de molécules contenant des motifs CF_2R. Tout d'abord une stratégie très flexible a été mise au point pour la préparation de composés *gem*-difluorobisaryliques et de leurs analogues hétéroaromatiques. Elle est basée sur l'emploi d'intermédiaires *gem*-difluoropropargyliques faciles d'accès. Par une séquence de Diels-alder-aromatisation on obtient les molécules cibles de la première série. Pour la seconde, des réactions de cycloaddition dipolaire 1,3 ont été utilisées. A partir de ces intermédiaires, des chimiothèques ciblées de molécules fluorées ont été préparées. Nous nous sommes intéressés ensuite à la synthèse de composés fluorés fonctionnalisés et chiraux à travers des réactions d'organocatalyse asymétrique. A partir d'énals *gem*-difluorés des réactions de Diels-Alder et des additions 1,4 asymétriques ont été réalisées avec succès.

ABSTRACT

The first part of the thesis deals with the synthesis and biological evaluation of new platelets aggregation inhibitors, based on 12-HETE, 13-HODE and their analogues. In the second part we are interested in novel methodologies for the preparation of CF_2-containing molecules: First, a flexible strategy for the synthesis of *gem*-difluoro-bisarylic derivatives and heteroaromatic analogues was designed based on the easy synthesis and the reactivity of *gem*-difluoro propargylic intermediates, which by Diels-Alder cycloaddition and 1,3-dipolar cycloadditions afforded respectively the bisarylic and mixed arylic heteroarylic scaffolds. In addition, two small libraries were constructed around a bisarylic scaffold as representative examples. Second, we were interested in the synthesis of optically active functionalized molecules containing a *gem*-difluoro group, using asymmetric organocatalysis protocols. After preparation of the *gem*-difluoro enals, from their difluoropropargylic precursors, asymmetric organocalytic Diels-Alder cycloaddition and 1,4-conjugated additions were successfully performed.

Key words:

- cyclooxygenase-1
- anti-thrombotic
- inhibitors
- medicinal chemistry
- fluorine chemistry
- *gem*-difluoro compounds
- chemical library
- asymmetric organocatalysis
- Michael addition