Synthesis of fluorinated Biomolecules

Chimie Organique et Bioorganique; Réactivité et Analyse, UMR CNRS 6014, FR3038
Université de Rouen-INSA de Rouen, IRCOF, 1 rue Tesnière, 76130 Mont Saint-Aignan.

Keywords **: Asymmetry, Fluoroalkenes, Carbohydrates, Cyclopropane, Heterocycles**

Staff members:

X. Pannecoucke
PR INSA Rouen

T. Besset
CR CNRS

J-P. Bouillon
PR Univ Rouen

D. Cahard
DR CNRS

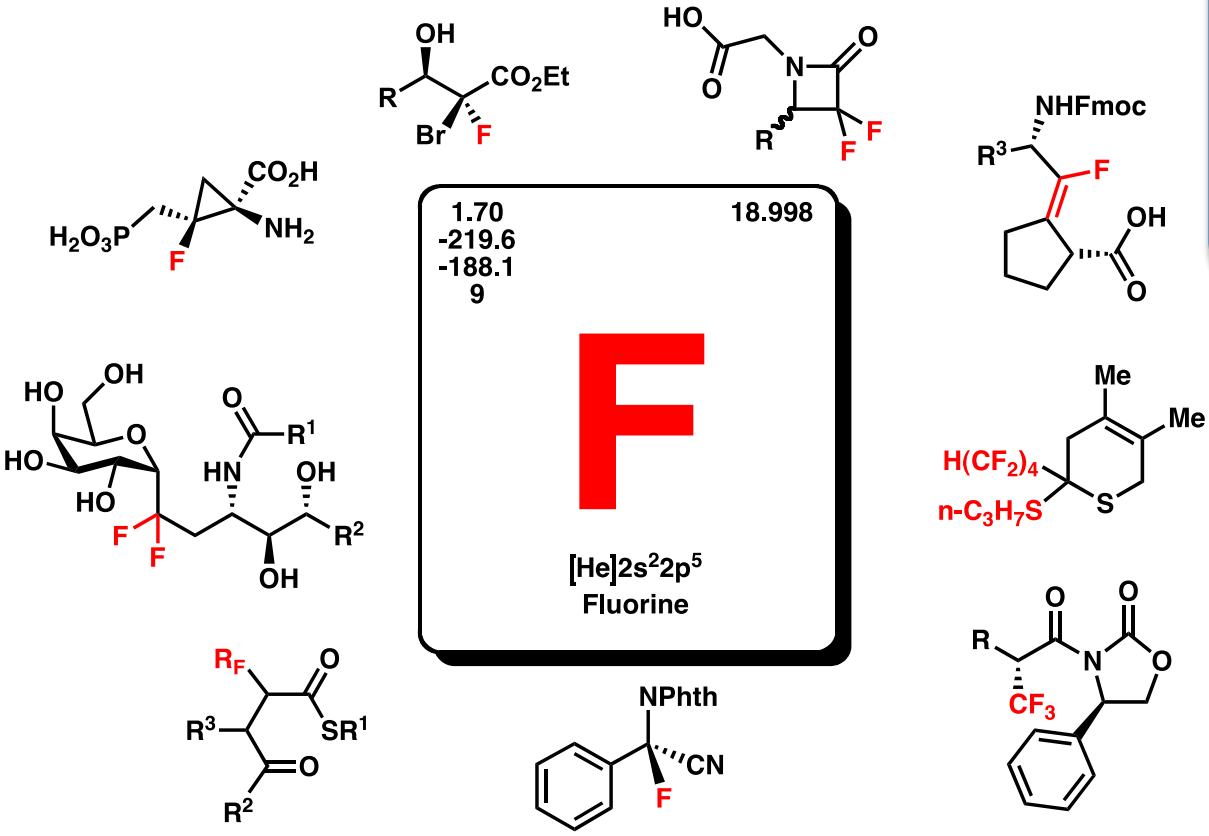
S. Couve-Bonnaire
MCF INSA Rouen

P. Jubault
PR INSA Rouen

T. Poisson
MCF INSA Rouen

Synthesis and Biological Evaluation of Fluorinated Biomolecules

Due to its unique physicochemical properties, Fluorine atom induces specific properties to biomolecules such as higher biodisponibility, stronger metabolic resistance…



Methodologies

Fluor and Asymmetry :
direct fluorination, direct trifluoro-methylation, chiral fluorinated product

Use of ethyl dibromofluoroacetate
New fluorinated scaffolds

Biomolecules

Fluorinated Heterocycles
Toward trifluoromethyl heterocycles

Difluorinated Carbohydrates
Non hydrolysable glycosidic bond
➔ Pharmaceutical applications

Difluorinated β-aminoacides or Fluorinated peptidomimetics
Increased bioavailability

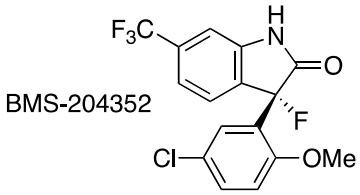
Development of New Synthetic Methodologies

Aims:

➤ **1 - Fluor and Asymmetry** : Synthesis of chiral fluorinated molecules by direct fluorination, direct trifluoromethylation, redox isomerization, transfer hydrogenation …

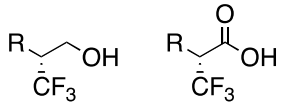
Target molecules resulting of :

an enantioselective electrophilic fluorination

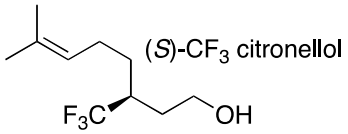


BMS-204352

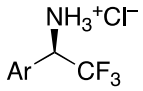
a diastereoselective electrophilic trifluoromethylation



an enantiospecific redox isomerization



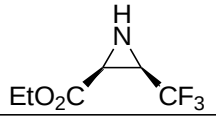
an enantioselective transfer hydrogenation



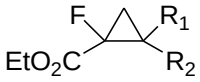
➤ **2 - Building Blocks Approach** : Search for new applications of small fluorinated building blocks such as ethyl dibromofluoracetate, trifluoromethyl diazomethane …

Target molecules using small building blocks :

from CF_3CHN_2



from $CFBr_2CO_2Et$



Recent publications (Aim 1) : Synthesis of α-CF_3-substituted carbonyl compounds with relative and absolute stereocontrol using electrophilic CF_3-transfer reagents."
V. Matoušek, A. Togni, V. Bizet, D. Cahard. **Org. Lett.**, *13*, 5762-5765, **2011**
Ruthenium Catalyzed Redox Isomerization of Trifluoromethylated Allylic Alcohols: Mechanistic Evidence for an Enantiospecific Pathway."
V. Bizet, X. Pannecoucke, J. L. Renaud, D. Cahard. **Angew. Chem. Int. Ed.**, *51*, 6467-6470, **2012**
(Aim 2) :
Chiral Brønsted Acid-Catalyzed Diastereo- and Enantioselective Synthesis of CF_3-Substituted Aziridines."
Z. Chai, J.P. Bouillon, D. Cahard. **Chem. Commun.**, *48*, 9471-9473, **2012**
Asymmetric synthesis of cyclopropanes with a monofluorinated quaternary stereocenter. P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke **Org. Lett.**, *14*, 5130-5133, **2012**.
One-step synthesis of highly functionalized monofluorinated cyclopropanes from electron-defficient alkenes. P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke **Org. Lett.**, *14*, 2270-2273, **2012**.

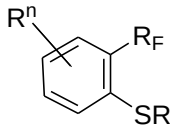
Collaborations: *Pr Jean Luc Renaud (Caen), Johnson-Matthey (UK)*

Development of New Synthetic Methodologies

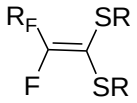
Aims:

➤ **3 –Fluor and carbocycles**: synthesis of polyfluorinated aromatic sulfides via Diels Alder reaction of perfluoro-ketenedithioacetals…

Target molecules using small building blocks :



from



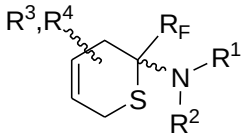
R = Alk, Ar

R_F = F, CF_3, C_2F_5

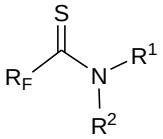
➤ **4 – Fluor and Heterocycles**:

a) Synthesis of dihydrothiopyrans from hetero Diels Alder reactions of electron-rich dienes and perfluorothioamides :

Target molecules using small building blocks :



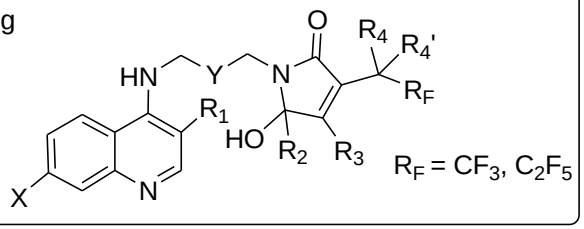
from



R_F = CF_3, $(CF_2)_nCF_3$

b) Synthesis of mixed 4-aminoquinolin -γ-lactam structures as new anti-malarial agents :

Target molecules using small building blocks :



R_F = CF_3, C_2F_5

Recent publications

(Aim 3) : J.-P. Bouillon, S. Mykaylychenko, S. Melissen, A. Martinez, D. Harakat, Y.G. Shermolovich **Tetrahedron,** *68*, 8663, **2012**.

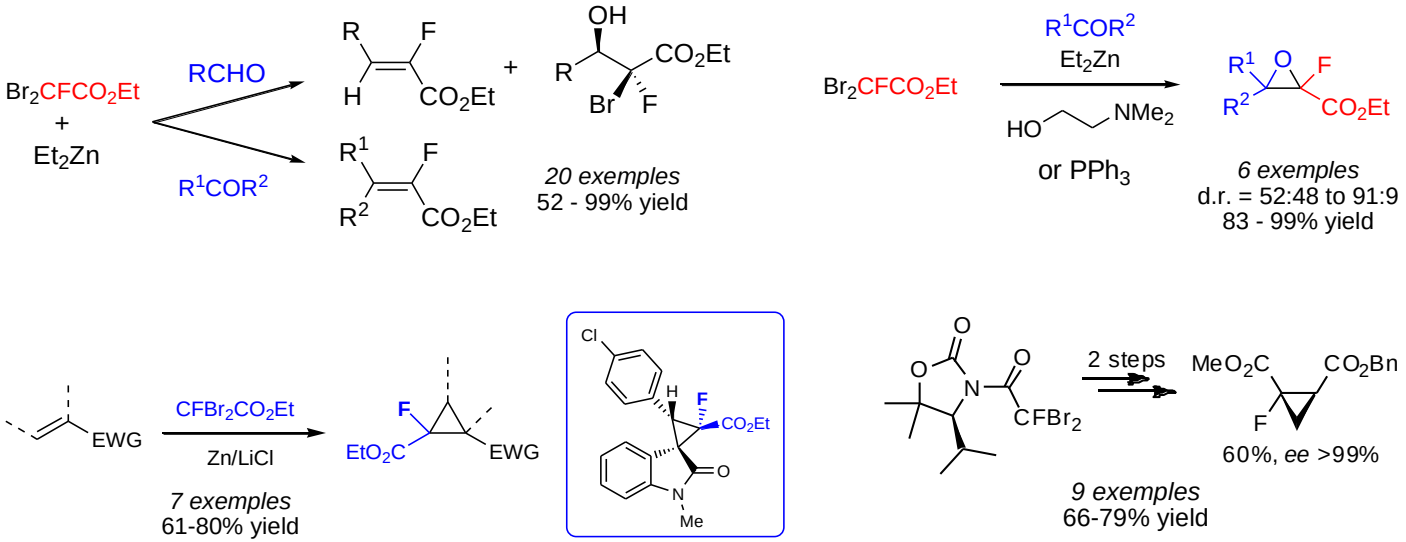
(Aim 4) : M. Médebielle, J.-P. Bouillon, S. Picot, patent PCT application: January 31, **2012**, WO 2012104538, CAN: 157: 356567,

Collaborations and financial support: ANR Quinolac (Dr. M. Medebielle, Pr. S. Picot)

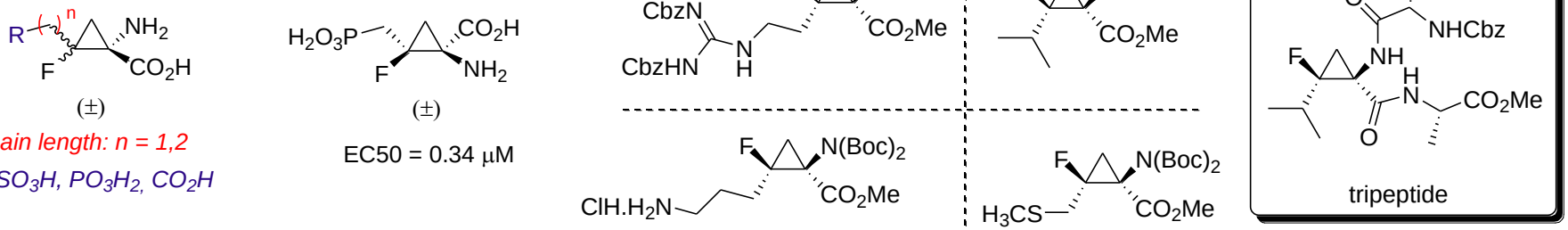
Design, Synthesis and applications of new fluorinated scaffolds from ethyl dibromofluoroacetate

Aims:

➤ **1 – Original synthesis of fluoroacrylates, fluorinated glycidic esters and fluorinated cyclopropanes:**



➤ **2 – Applications to peptidomimetics and biologically active compounds:**



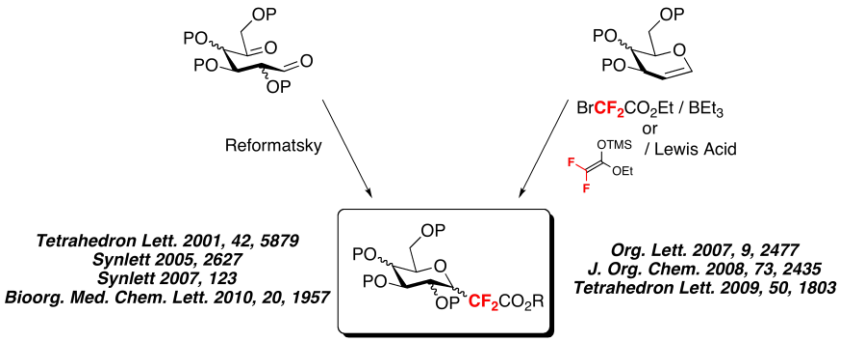
Recent publications: Synthesis **2006**, 3409; THL **2006**, *47*, 7931, JOC **2009**, *74*, 4124, OL **2010**, *12*, 844, OL **2012**, *14*, 2270, OL **2012**, *14*, 5130, Bioorg. Med. Chem. **2012**, *20*,4716, Chem. Eur. J. **2012** in press.

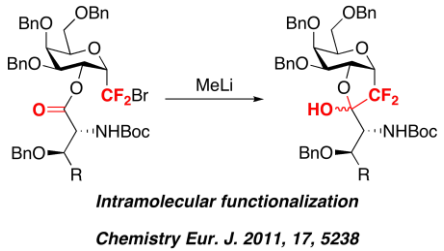
Collaborations: J-P Pin (IGF Montpellier), Janssen

Difluorinated Glycomimetics: Stable Mimics of Biologically Actives Carbohydrates

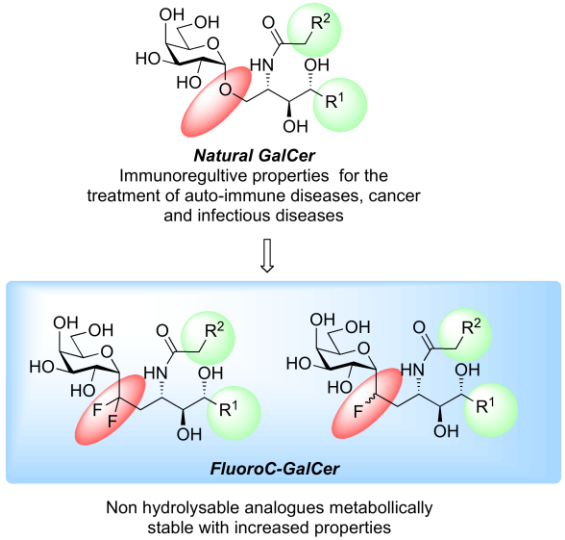
Aims:

➤ **1 - New Methods to introduce the CF_2 moiety**





➤ **2 - Synthesis of fluorinated analogs of bioactive glycosides**



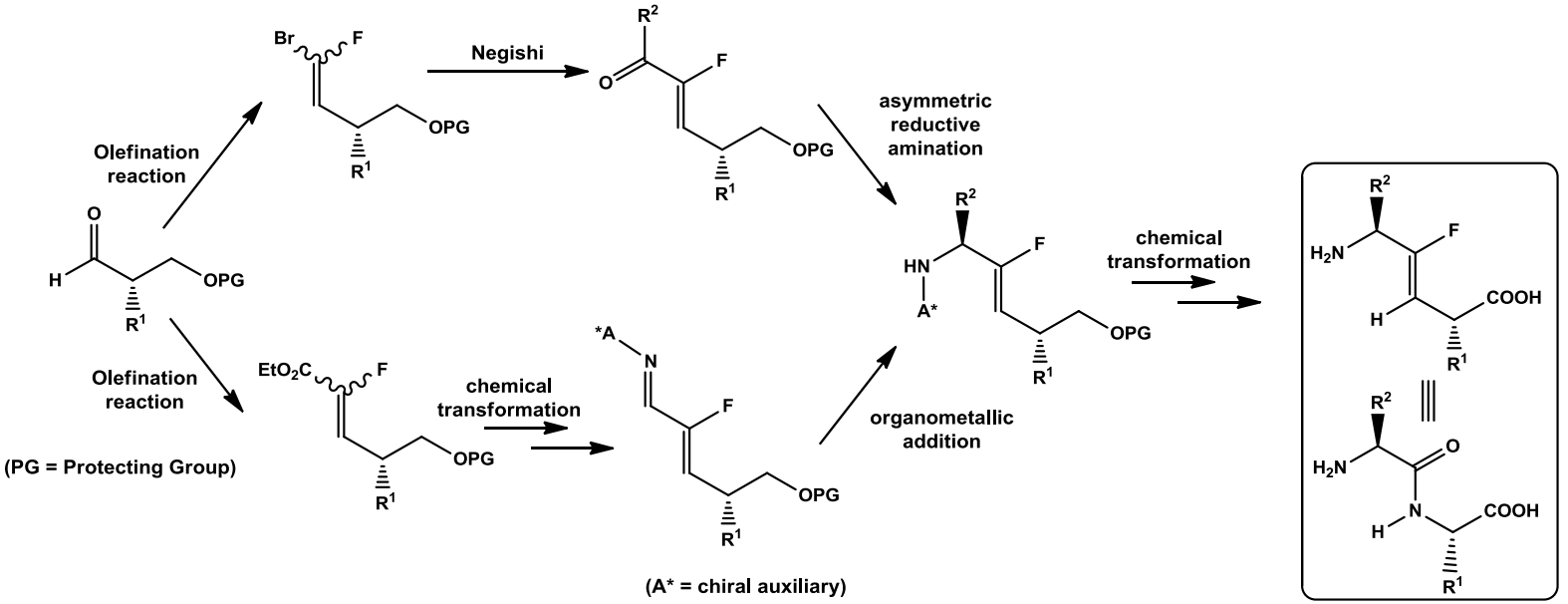
Recent publications: *Chem. Eur. J.* **2011**, *17*, 5238, *Org. Lett.* **2007**, *9*, 2477, *J. Org. Chem.* **2008**, *73*, 2435.

Collaborations: E. Leclerc (Montpellier), B. Linclau (Southampton), I. Gillaizeau (Orléans).

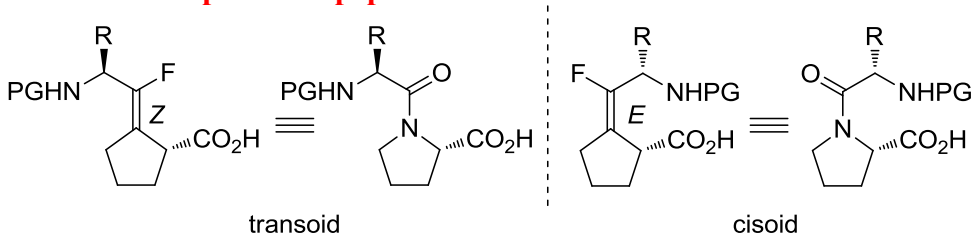
Development of asymmetric syntheses toward fluoropeptidomimetics Ψ[CF=CH]

Aims:

➤ **1 – Development of new asymmetric synthesis to fluoropeptidomimetics AA-Ψ[CF=CH]-AA** (AA = any amino acid).



➤ **2 – Stereoselective access to fluorinated proline dipeptides in both cisoid and transoid form :**



PG = Protecting group (Boc, Fmoc...)

➤ **3 - Synthesis of analogs of biologically active compounds containing an amide bond.**

Recent publications: JOC **2006**, 71, 4316-4319;, Angew. Chem. Int. Ed. **2007**, *46*, 1290-1292; Tetrahedron, **2009**, *65*, 6034-6038; Tetrahedron Lett. **2009**, *50*, 264-266; OBC, **2011**, *9*, 2378–2386,

Collaborations: J. Leprince (Rouen).