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Ethyl dibromofluoroacetate: a versatile reagent for the synthesis of fluorinated molecules

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1. Introduction

Ethyl dibromofluoroacetate (EDBFA) represents a commercially available source of fluorine, which is highly valuable for the synthesis of a variety of fluorinated compounds. Since the

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isolation of elemental fluorine by Henri Moissan, numerous applications with fluorinated molecules have emerged in various fields, such as nuclear industry, material science, agrochemicals, and medicinal chemistry.[1] Nowadays, fluorine is an essential element in pharmaceuticals and agrochemicals with, respectively, about 25% and 40% of the new biologically active molecules that contain at least one fluorine atom.[2] This strong interest for fluorinated molecules is due to the particular physical and chemical characteristics of fluorine, especially its small size and strong electronegativity, which impact the properties of fluorinated molecules themselves.[3] Fluorinated natural products are rare.[4] Hence organic synthesis is a major tool to access fluorinated molecules. Synthesis of those molecules is a challenging task as most of the reactions developed for the synthesis of non-fluorinated ones can't be transposed directly to fluorinated building blocks.

Since 2006, part of our research program has been devoted to the development of new zinc-promoted methodologies for the synthesis of fluorinated molecules starting from EDBFA. This account will gather and comment all the publications dealing with the use of EDBFA in organic synthesis from our research group as well as others, especially those implying the use of organometallic reagents. The diverse functionalities (two highly electrophilic carbon centers and exchangeable bromine atoms) of EDBFA have opened the door to a panel of reactions, giving easy access to relevant fluorinated compounds, such as fluoroolefins, fluorocyclopropanes, fluoro-β-lactams. On the other hand, the multiple functionalities of EDBFA require a control of the regioselectivity of those reactions.

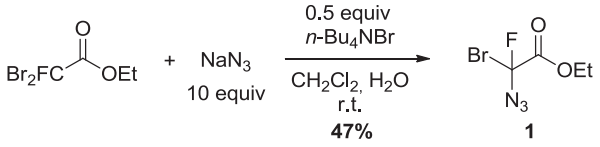
First we will display the different way to modify EDBFA either by nucleophilic attack and formation of a stereogenic center or by modification of the ester moiety. Then the different methodologies developed using EDBFA or modified EDBFA will be discussed according to the type of reactions: addition reactions, olefination reactions, zinc-mediated synthesis of fluorinated three and four-membered rings, and miscellaneous reactions.

2. Transformation of ethyl dibromofluoroacetate

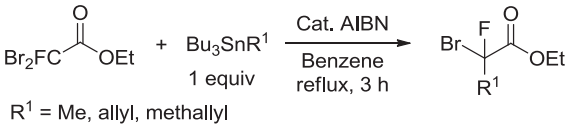
2.1. Nucleophilic attack and formation of a stereocenter

Replacement of one bromine atom in EDBFA leads to the creation of a stereocenter. In the eighties, Takeuchi studied the synthesis of compounds bearing four different labile groups, including a carbonyl group, halogen, and other heteroatom-containing groups (nitrogen, oxygen, and sulfur) from α-halo-α-fluoroesters, among which EDBFA.[5] This task turned out to be difficult due to the influence of each functional group on the reactivity of another. The first approach consisted in the electrophilic functionalization of α-fluoroenolates (Li, Na) or enol silyl ethers. However attempts to react them with nitrogen or sulfur electrophiles failed to produce the desired tri- or tetrafunctional compounds, probably because of the presence of multiple labile groups on the same carbon or because of the poor reactivity of the α-fluoroenolate towards heteroaromatic electrophiles. Nucleophilic displacement of one bromine atom using NaSPh, NaSEt, NaOEt, and $NaOCH_2Ph$ afforded the corresponding reduced products whereas the use of NaN_3 as a nucleophile under phase-transfer conditions led to the corresponding azido derivative **1** in 47% yield (Scheme 1). On the other hand, treatment of EDBFA with $HNEt_2$ to introduce an amino group failed and unexpectedly yielded $Et_2NC(O)CO_2Et$.

Monoalkylation of EDBFA was also described by Takeuchi using tin reagents in the presence of a catalytic amount of AIBN (Scheme 2).[6] There was no yield reported for these reactions.



Scheme 1. Synthesis of ethyl 2-azido-2-bromo-2-fluoroacetate **1** from EDBFA.

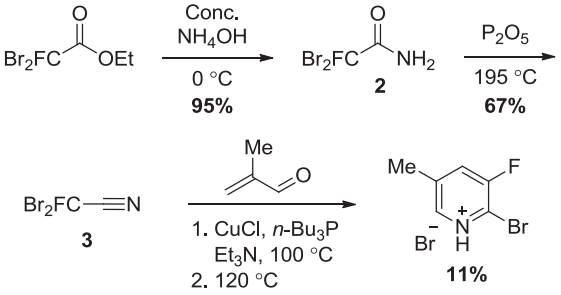


Scheme 2. Monoalkylation of EDBFA with tin reagents.

2.2. Modification of the ester moiety

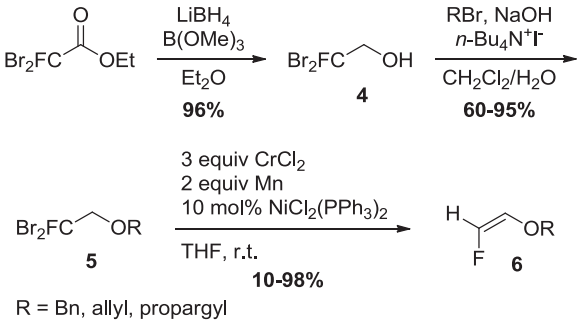
Modification of the ester moiety of EDBFA has also been the subject of few publications and has led to the synthesis of fluorinated building blocks that have next been used for various applications.

First, EDBFA can be converted in two steps into the corresponding nitrile.[7] Treatment of EDBFA with concentrated aqueous ammonium hydroxide affords dibromofluoroacetamide **2** in high yield (Scheme 3). The latter is dehydrated in the presence of phosphorus pentoxide at high temperature to get dibromofluoroacetonitrile **3** in good yield. This reaction sequence was applied to a series of haloesters and the resulting halonitriles were converted into halopyridines of interest for pharmaceutical and agrochemical applications.



Scheme 3. Synthesis of dibromofluoroacetonitrile **3** from EDBFA.

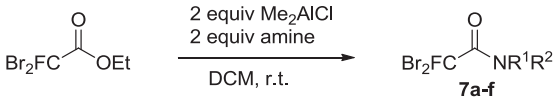
The ester moiety of EDBFA can be efficiently reduced using lithium borohydride as a reducing agent in the presence of trimethylborate to afford 2,2-dibromo-2-fluoroethanol **4** in 96% yield (Scheme 4). From this alcohol **4**, the group of Taguchi developed the synthesis of (*Z*)-1-fluoro-2-alkenyl alkyl ethers **6** in two steps: (1)



Scheme 4. Synthesis of (*Z*)-1-fluoro-2-alkenyl alkyl ethers **6** from EDBFA.

conversion of **4** into benzylic, allylic, and propargylic ethers **5** and (2) chromium-mediated stereoselective formation of (*Z*)-1-fluoro-2-alkenyl alkyl ethers **6**.[8]

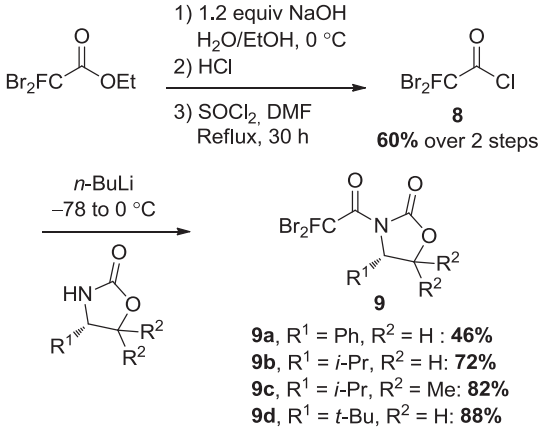
The ester moiety of EDBFA can also be easily converted into secondary and tertiary amides. The reaction of EDBFA with benzylamine and a variety of secondary amines in the presence of dimethylaluminium chloride led to the corresponding dibromofluoroacetamides **7a**–**f** in high yields (Scheme 5). They were then engaged in the zinc-mediated olefination reaction to access α-bromo-α-fluoro-β-hydroxyamides and (*Z*)-α-fluoroacrylamides (see Addition and Olefination reactions in Sections 3 and 4, respectively).[9]



7a, R^1 = H, R^2 = Bn: **85%**
7b, R^1 = Me, R^2 = Bn: **87%**
7c, R^1 = R^2 = Et: **93%**
7d, R^1 = Me, R^2 = OMe: **81%**
7e, R^1-R^2 = morpholino: **78%**
7f, R^1-R^2 = piperidyl: **79%**

Scheme 5. Synthesis of dibromofluoroacetamides **7a**–**f**.

Finally, several chiral dibromofluoroacetyloxazolidin-2-ones **9a**–**d** were synthesized with the aim to test them in an asymmetric cyclopropanation process (see Fluorinated cyclopropanes in Section 5.4.).[10] EDBFA was efficiently converted in two steps into its corresponding acyl chloride **8** by hydrolysis of the ester function and chloration of the carboxylic acid derivative with thionyl chloride (Scheme 6). Then acylation of **8** with several chiral oxazolidinones produced the desired dibromofluoroacetyloxazolidin-2-ones **9a**–**d** in moderate to good yields.



9a, R^1 = Ph, R^2 = H : **46%**
9b, R^1 = *i*-Pr, R^2 = H: **72%**
9c, R^1 = *i*-Pr, R^2 = Me: **82%**
9d, R^1 = *t*-Bu, R^2 = H: **88%**

Scheme 6. Synthesis of chiral dibromofluoroacetyloxazolidin-2-ones **9a**–**d**.

The next sections will deal with the use of EDBFA or modified EDBFA in the development of new methodologies to access a variety of fluorinated molecules and highlight some interesting applications.

3. Addition reactions

In 1994, the group of Ishihara described the one-step Zn/Et_2AlCl-mediated Reformatsky reaction starting from EDBFA to afford the corresponding α-bromo-α-fluoro-β-hydroxyesters **10** (Scheme 7, Eq. 1) or the corresponding α-fluoro-β,β′-dihydroxyesters **11** (Scheme 7, Eq. 2) depending on the ratio of reagents.[11] When a slight excess of zinc/Et_2AlCl/aldehyde (1.2/1.1/1.1 equiv) was reacted with EDBFA at −20 °C, α-bromo-α-fluoro-β-hydroxyesters **10** were isolated in moderate to good yields and with no or low diastereoselectivity, along with small amounts of the corresponding α-fluoro-β,β′-dihydroxyesters **11** (Scheme 7, Eq. 1). Diethylaluminium chloride was shown to be essential for the reaction to proceed cleanly. The reaction was suitable with aliphatic and aromatic aldehydes and one example was also described with a ketone. On the other hand, when the amount of Zn, Et_2AlCl, and aldehyde was increased to 2.1 equiv each, α-fluoro-β,β′-dihydroxyesters **11a**,**b** were the major products of the reaction from aliphatic and aromatic aldehydes (Scheme 7, Eq. 2). Compound **11** are obtained in good yields but without diastereoselectivity together with the corresponding (*Z*)-α-fluoroacrylates as by-product (less than 20% yield in all cases).

Later on, the same group demonstrated the utility of α-bromo-α-fluoro-β-hydroxyesters **10** as versatile building blocks by developing the stereoselective radical reduction to access the corresponding α-fluoro-β-hydroxyester **12a**[12,14a] and the radical allylation reaction to access the corresponding α-allylated-α-fluoro-β-hydroxyesters **12b**,**c** (Scheme 7, Eq. 1).[13]

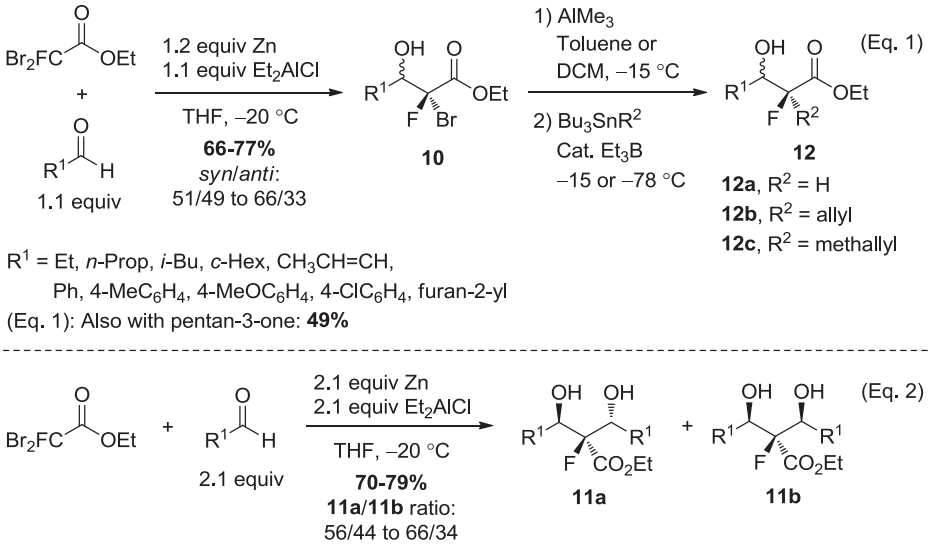
Few years later, the group of Iseki described the enantioselective synthesis of α-bromo-α-fluoro-β-hydroxyesters in two steps from EDBFA using a chiral Lewis acid as a catalyst.[14] In the first step, bromofluoroketene ethyl trimethylsilyl acetal **13** is synthesized by addition of EDBFA to a mixture of TMSCl and activated Zn powder in THF at −20 °C (Scheme 8). After dilution in *n*-pentane, filtration to remove the zinc salts and concentration in vacuo (sequence repeated twice), **13** was isolated by distillation in 64% yield as a mixture of *E*/*Z*: 62/38 isomers (ratio determined by ^{19}F NMR).

The second step consists in the catalytic enantioselective Mukaiyama-aldol reaction of aldehydes with **13** in the presence of Masamune's chiral catalyst **14** (Table 1) to afford optically active α-bromo-α-fluoro-β-hydroxyesters **10**. When the reaction was carried out at −78 °C, both *syn*- and *anti*-aldols **10** were obtained from a variety of aldehydes with excellent enantiomeric excesses. The reaction proceeded in good to high yield but with poor diastereoselectivity (*syn*/*anti*: 69/31–39/61). Use of bromofluoroketene isopropyl trimethylsilyl acetal in place of the ethyl one **13** sometimes improved the enantiomeric excess (e.g.,: from 83 to 95% ee with (*E*)-cinnamaldehyde).

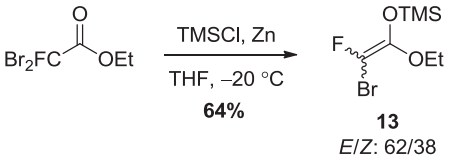
Next, the authors observed an effect of the reaction temperature on the enantiofacial selection of aldehydes. Indeed, elevating the reaction temperature to −20 °C significantly improved the diastereoselectivity of the process and the *anti*-aldol **10** was selectively obtained with good enantiomeric excesses in most cases. On the other hand, enantiomeric excesses of the *syn*-aldol **10** were modest. It is noteworthy that at this temperature, both *anti* and *syn*-aldols **10** showed opposite signs of optical rotation to that at −78 °C.

In terms of mechanism, the reason for which the enantiofacial selection depends on the reaction temperature is not clear. However, ^{19}F NMR analyses of a 1:1 mixture of acetal **13** and catalyst **14** in $C_2D_5NO_2$ at −78 °C and −20 °C showed two different spectra, giving a clue for the mechanism: at −78 °C, the ^{19}F NMR spectrum showed two singlets corresponding to the acetal **13** in its two isomeric forms; at −20 °C, the apparition of four new peaks lets suggest transmetallation from the silyl acetal **13** to the boron one. Based on this observation and on a previous related work with a fluorine-free dimethylketene acetal showing the same enantiofacial selection,[15] the authors proposed chair-like transition states to explain the selectivity of the aldol reaction.

In 2011, our group described the diethylzinc-mediated synthesis of α-bromo-α-fluoro-β-hydroxyesters **10** from EDBFA (Scheme 9).[16] This one-step reaction proceeds in good to high yields with both aliphatic and aromatic aldehydes using 2 equiv of Et_2Zn at room temperature. However, as in the case of the Zn/Et_2AlCl-mediated approach described by Ishihara,[11] the corresponding *anti*- and *syn*-α-bromo-α-fluoro-β-hydroxyesters **10** are formed without



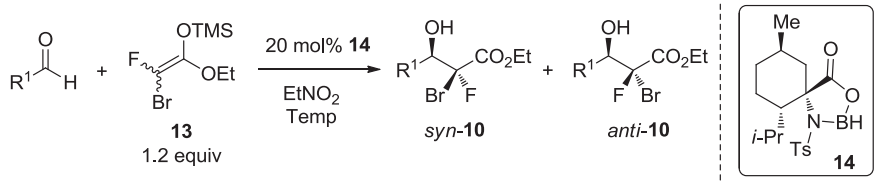
Scheme 7. Zn/Et_2AlCl-mediated Reformatsky reaction with EDBFA.



Scheme 8. Synthesis of **13** from EDBFA.

Application of this protocol to *N*-benzyl-2,2-dibromo-2-fluoroacetamide **7a** led to the corresponding α-bromo-α-fluoro-β-hydroxyamides **15** (Scheme 10).[9] It was necessary to use an excess of **7a** as well as 4 or 6 equiv of Et_2Zn in order to get good yields of **15** and minimize the formation of the corresponding fluoroacrylamides (see Olefination reactions in Section 4.1. for conditions towards acrylamides). Both aldehydes and ketones are

Table 1
Enantioselective Mukaiyama-aldol reaction of aldehydes with **13**



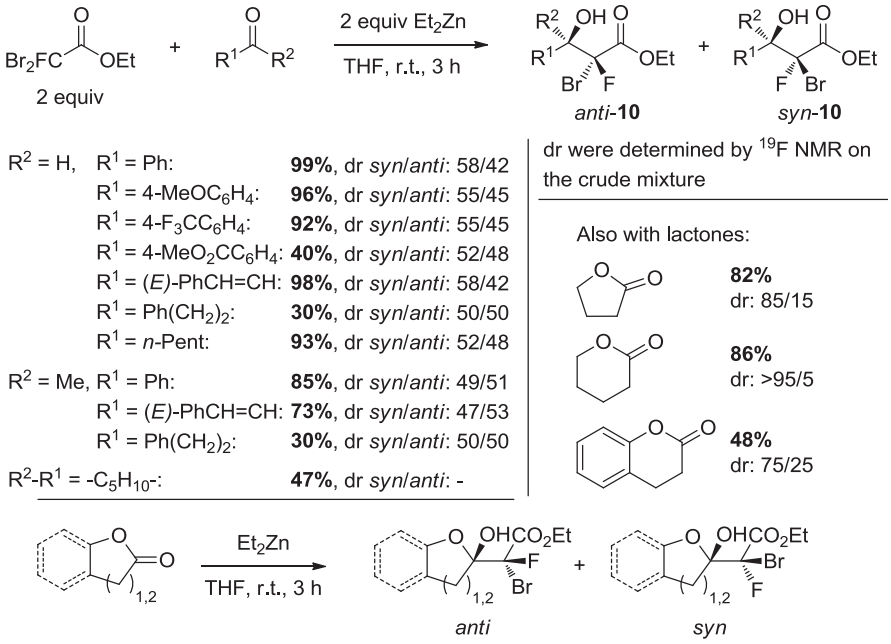
R^1CHO	Isolated yield of **10**		dr *syn*/*anti*-**10**[a]		ee (*syn*-**10**)[b]		ee (*anti*-**10**)[b]	
	−78 °C	−20 °C	−78 °C	−20 °C	−78 °C	−20 °C	−78 °C	−20 °C
PhCHO	90%	89%	69/31	49/51	98% (2*S*,3*R*)[c]	13% (2*S*,3*R*)[c]	90% (2*R*,3*R*)	13% (2*S*,3*S*)
$Ph(CH_2)_2CHO$	89%	85%	46/54	13/87	98% (+)	48% (−)	98% (+)	92% (−)
$PhCH_2OCH_2CHO$	81%	80%	57/43[d]	26/74[d]	97% (−)[d]	29% (+)[d]	97% (−)[d]	72% (−)[d]
c-HexCHO	74%	90%	52/48	20/80	94% (+)	18% (−)	89% (+)	81% (−)
n-PropCHO	90%	87%	46/54	11/89	97% (+)[e]	49% (−)[e]	98% (+)	93% (−)
Et_2CHCHO	70%	85%	54/46	23/77	99% (+)	21% (−)	98% (+)	74% (−)
i-PrCHO	96%	—	48/52	—	98% (+)	—	98% (+)	—
(*E*)-PhCH=CHCHO	96%	—	57/43	—	83% (+)	—	83% (+)	—
i-BuCHO	96%	87%	48/52	11/89	98% (+)	31% (−)	98% (+)	91% (+)

[a] Based on isolated yields of *syn*- and *anti*-aldols **10**.
[b] Measured by HPLC using a Daicel Chiralcel OD-H, OB-H or AD column.
[c] Stereochemistry was determined by X-ray analysis of the camphanate obtained from *syn*-aldol and (−)-camphanic chloride.
[d] Determined using the corresponding acetate.
[e] Enantiomeric excess was determined using the corresponding 3,5-dinitrobenzoate.

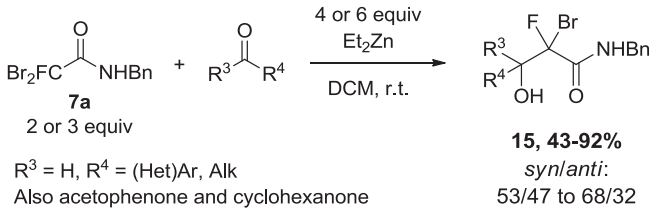
diastereoselectivity. The novelty of this process is the suitability of aliphatic and aromatic ketones as well as lactones. As in the case of aldehydes, addition products derived from ketones are generally obtained in good yields but no diastereoselectivity was observed. On the other hand, products derived from lactones were produced in moderate to good yields with good to high diastereoselectivity but it was not possible to determine, which isomer was the major one.

suitable but no diastereoselection was observed under those conditions. One example of the formation of compound **15** from **7a** and benzaldehyde has also been reported using a combination of diethylzinc and Wilkinson's catalyst.[17]

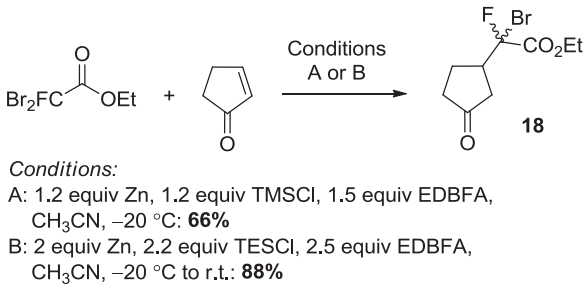
The Reformatsky addition with EDBFA was also applied to the synthesis of monofluorinated *C*-glycosides.[18] Sugars constitute a large class of biomolecules, which are involved in cellular recognition processes and therefore present an ideal profile for the



Scheme 9. Scope of the Et_2Zn-mediated synthesis of α-bromo-α-fluoro-β-hydroxyesters **10**.



Scheme 10. Synthesis of α-bromo-α-fluoro-β-hydroxyamides **15** from **7a**.



Scheme 12. Michael addition of EDBFA.

development of new drug candidates. However, their chemical instability under acido-basic or enzymatic hydrolysis conditions makes them difficult to synthesize and purify and decreases their bioavailability, which limit their use. In this context and knowing that introduction of a fluorine atom into a molecule can improve its pharmacological profile (in particular, strength of the C–F bond can improve the resistance, hence the stability, of a molecule to chemical and biological degradation processes), a series of monofluorinated and -brominated *C*-glycosides **17** (Scheme 11) was synthesized by reaction of EDBFA with lactones of type **16** in the presence of 2 equiv of Et_2Zn. Compound **17** are produced in moderate yields and with moderate to high diastereoselectivities.

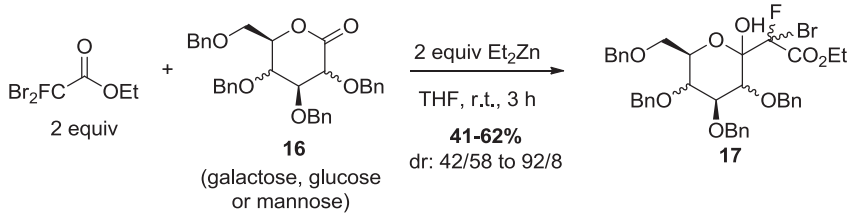
Such monofluorinated *C*-glycosides could find applications in various fields, such as cosmetics, immunology, medical imaging or medicinal chemistry.

Finally, building block **18** (Scheme 12) is used as an intermediate for the synthesis of monofluorinated cyclopropanes having high potency in the treatment of neurological disorders.[19] Its synthesis was patented by Taisho Pharmaceutical Co., LTD[20] and by Eli Lilly and Company.[21] Both approaches consisted in the Michael addition of EDBFA with cyclopenten-2-one as the electrophile, in the presence of Zn and a silyl chloride derivative. Ethyl 2-bromo-2-fluoro-2-(3-oxocyclopentyl)acetate **18** was obtained as a mixture of diastereoisomers in 66% yield (Conditions A from Taisho Pharmaceutical Co., LTD) or 88% yield (Conditions B from Eli Lilly and Company).

4. Olefination reactions

4.1. Zinc-mediated olefination

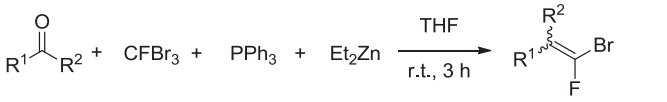
α-Fluoro-α,β-unsaturated esters, also called α-fluoroacrylates are useful building blocks for the preparation of biologically active



Scheme 11. Reformatsky addition for the synthesis of monofluorinated *C*-glycosides **17**.

fluorinated molecules.[22] A number of synthetic routes have been developed to access α-fluoroacrylates.[23] The main strategies are the Wittig[24] and thia-Wittig[25] reactions, the Horner–Wadsworth–Emmons reaction,[26] the Peterson,[27] and the Julia olefinations.[28] There are also miscellaneous routes,[29] such as the reaction between aldehydes and diethyl-2-oxo-3-fluorobutan-I,4-dioate sodium salt,[29e] the deoxygenation–elimination sequence with of β,β′-dihydroxy carboxylic esters in the presence of vanadium(V) trichloride oxide,[29f] the Zn/CuCl-mediated reaction of methyl dichlorofluoroacetate with aldehydes[29g] or the alkenylation reaction from 3-aryl-2-fluoro-3-hydroxy-2-organoselanylacetates under acidic conditions.[29h] Some of the above methodologies are stereoselective but they don't often offer the advantage of using commercially available starting materials. The only existing Wittig approach to α-fluoroacrylates is a one-pot synthesis from alkoxycarbonylmethyltriphenylphosphonium bromides and aldehydes that was developed by generating in situ the fluorinated phosphoranes with Selectfluor® as a fluorinating agent. However, α-fluoroacrylates were obtained in moderate yields (26–57%) and with moderate (*Z*)-selectivity (*E*/*Z* ratio=1/2.2 to 1/11).

Based on the diethylzinc-promoted Wittig reaction developed by our group for the synthesis of *gem*-bromofluoroolefins from tribromofluoromethane and both aldehydes and ketones[30] (Scheme 13) inspired by Hiyama's initial work,[31] we investigated the use of diethylzinc as a promoter for the synthesis of α-fluoroacrylates from EDBFA and carbonyl derivatives.[32]



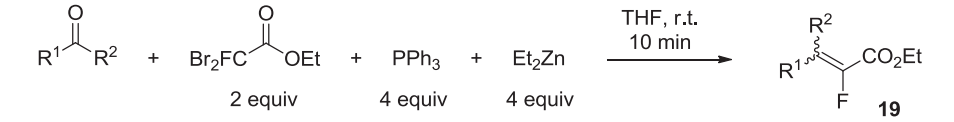
Scheme 13. Synthesis of *gem*-bromofluoroolefins via diethylzinc-promoted Wittig reaction.

After optimization of the conditions, it was found that α-fluoroacrylates **19** can be synthesized using 4 equiv of both triphenylphosphine and diethylzinc and 2 equiv of EDBFA in THF at room temperature in a very short reaction time (Scheme 14). Both aliphatic and aromatic aldehydes bearing a variety of functional groups (halogen, ester, protected alcohol) can be converted in very good yields (75–95%) and moderate (*Z*)-selectivity (*E*/*Z*: 1/1.8 to 1/5.6). The reaction was also applied to ketones to provide the corresponding α-fluoroacrylates **19** in good yields (77–98%) albeit with low selectivity (*E*/*Z* ratio=1/0.5 to 1/1.5).

Regarding the mechanism, the zinc carbenoid resulting from the reaction between diethylzinc and EDBFA can react with triphenylphosphine to form the corresponding ylide. This latter can then react with the aldehyde or ketone to afford the α-fluoroacrylate. It is worth noting that the order of addition of the reactants is crucial for the success of the reaction. Contrary to the case of *gem*-bromofluoroolefins synthesis (Scheme 13), all reactants have to be added prior to the aldehyde or ketone in order to get a full conversion and to avoid the formation of the corresponding α-bromo-α-fluoro-β-hydroxyesters as side-products (see Addition reactions in Section 3, product **10**). This means that in this case, the nucleophilic zinc carbenoid reacts more rapidly with the aldehyde (or ketone) than with the phosphine.

One drawback of these methods is the difficulty to separate the remaining triphenylphosphine and the triphenylphosphine oxide from the desired α-fluoroacrylates. In order to overcome this difficulty, a phosphonium-supported triphenylphosphine methodology was developed using SCG-PPh_3 **20** in place of triphenylphosphine (Scheme 15).[33] This low-molecular-weight support has a similar reactivity as triphenylphosphine and presents the following advantages: (1) it is soluble in solvents of medium polarities (CH_3CN, CH_2Cl_2, DMSO, etc.) for the attachment of reagents; (2) it is insoluble in solvents of low polarities, which makes easier the removal of the support after reaction by precipitation.[34] As SCG-PPh_3 **20** is not much soluble in THF (solvent used in the initial process), the olefination reaction was performed in CH_2Cl_2 to afford α-fluoroacrylates **19** with similar good yields and moderate selectivity from both aldehydes and ketones. Purification process was simplified as SCG-PPh_3 **20** can be completely removed by precipitation in diethylether to recover very clean crude products (by NMR analysis).

Further studies on this Wittig reaction led to the development of a highly stereoselective synthesis of (*Z*)-α-fluoroacrylates **19** from aldehydes.[35] In this approach, triphenylphosphine was not necessary anymore and only diethylzinc was used as a mediator. Treatment of a solution of EDBFA and *p*-anisaldehyde in THF with 4 equiv of diethylzinc led to the corresponding (*Z*)-α-fluoroacrylate **19** as a single diastereoisomer together with the α-bromo-α-fluoro-β-hydroxyester **10** (*syn*/*anti*: 75/25) in moderate 51% global yield



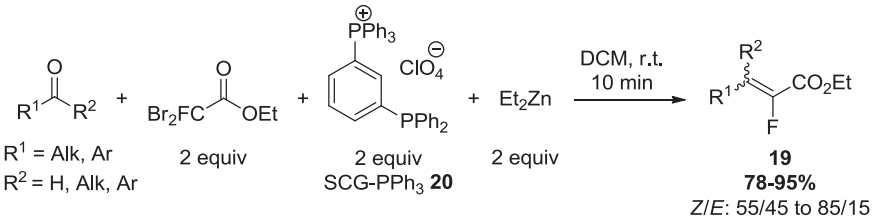
Aldehydes

R^2 = H, R^1 = 4-$MeOC_6H_4$:	**91%**, *Z*/*E* = 85/15
R^1 = Ph:	**98%**, *Z*/*E* = 80/20
R^1 = 4-$F_3CC_6H_4$:	**98%**, *Z*/*E* = 75/25
R^1 = 4-BrC_6H_4:	**77%**, *Z*/*E* = 80/20
R^1 = 4-$MeO_2CC_6H_4$:	**88%**, *Z*/*E* = 70/30
R^1 = 4-pyridyl:	**30%**, *Z*/*E* = 85/15
R^1 = $Ph(CH_2)_2$:	**94%**, *Z*/*E* = 68/32
R^1 = $Me(CH_2)_4$:	**98%**, *Z*/*E* = 70/30
R^1 = Me_2CHCH_2:	**88%**, *Z*/*E* = 70/30
R^1 = $TBDPSO(CH_2)_2$:	**83%**, *Z*/*E* = 65/35

Ketones

R^2 = CF_3, R^1 = Ph:	**92%**, *Z*/*E* = 35/65
R^2 = Me, R^1 = Ph:	**77%**, *Z*/*E* = 60/40
R^2 = Me, R^1 = $Ph(CH_2)_2$:	**98%**, *Z*/*E* = 60/40
-R^2–R^1- = -$(CH_2)_5$-:	**80%**, *Z*/*E* = -

Scheme 14. Synthesis of α-fluoroacrylates **19** via diethylzinc-promoted Wittig reaction.



Scheme 15. SCG-PPh_3-supported improved synthesis of α-fluoroacrylates **19**.

(ratio (*Z*)-**19**/**10**: 51/49). Switching the solvent from THF to DCM gave a better 84% global yield of pure (*Z*)-α-fluoroacrylate **19** and pure *syn*-α-bromo-α-fluoro-β-hydroxyesters **10** (ratio (*Z*)-**19**/**10**: 63/37). Those optimal conditions were applied to a series of aldehydes to stereoselectively synthesize (*Z*)-α-fluoroacrylates **19** and *syn*-α-bromo-α-fluoro-β-hydroxyesters **10** (Scheme 16). Both aromatic and aliphatic aldehydes bearing a variety of functional groups give good yields of products. α-Fluoroacrylates are always obtained in their pure (*Z*) form and the *syn*-α-bromo-α-fluoro-β-hydroxyester is selectively obtained in most cases. However the ratio (*Z*)-α-fluoroacrylate **19**/*syn*-α-bromo-α-fluoro-β-hydroxyester **10** is generally moderate. These compounds **10** and **19** can be easily separated and purified by chromatography on silica gel.

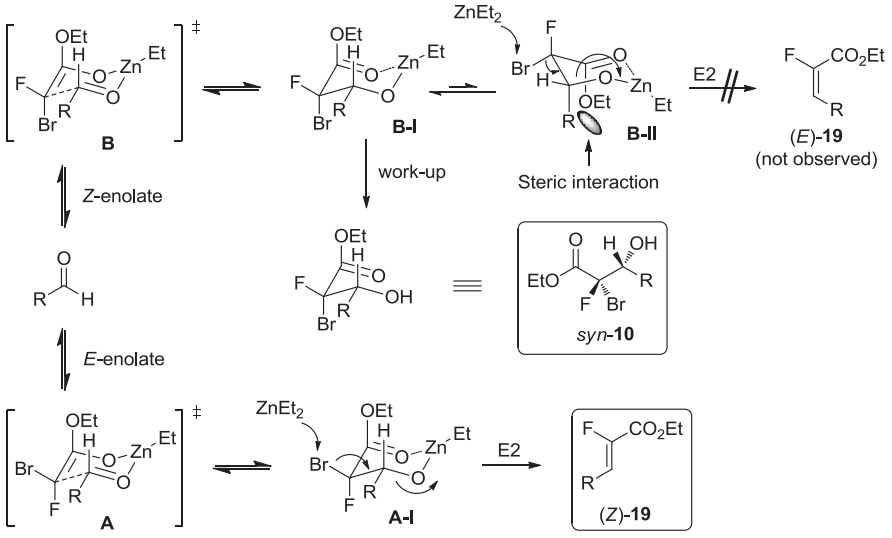
In the case of ketones, it is necessary to carry out the reaction in refluxing dichloromethane (instead of room temperature for aldehydes) to get α-fluoroacrylates. The corresponding α-bromo-α-fluoro-β-hydroxyesters were not formed under those reaction conditions. α-Fluoroacrylates **19** were isolated from a variety of ketones with moderate to complete selectivity for the (*E*)-isomer and in moderate to very good yields (Table 2). Reverse stereoselectivity was obtained with pinacolone (entry 6) and 4,4-dimethyl-2-pentanone (entry 7) because of the inversion of priorities of the substituents. Results show that the stereoselectivity of the reaction depends on the hindrance of the substituents on the ketone (entries 1–4). Indeed, ketones bearing one hindered group led to complete stereoselectivity (entries 3, 4, 6).

	Global yield	Ratio (*Z*)-**19**/**10**	Ratio *Z*/*E*-**19**	Ratio *anti*/*syn*-**10**
R^1 = 4-$MeOC_6H_4$:	**84%**	63/37	>99/1	>1/99
R^1 = Ph:	**80%**	35/75	>99/1	>1/99
R^1 = 4-FC_6H_4:	**90%**	59/41	>99/1	>1/99
R^1 = 4-BrC_6H_4:	**74%**	47/53	>99/1	>1/99
R^1 = 4-$MeO_2CC_6H_4$:	**64%**	56/44	>99/1	>1/99
R^1 = 4-NCC_6H_4:	**62%**	56/44	>99/1	10/90
R^1 = 3,4,5-$(MeO)_3C_6H_2$:	**96%**	62/38	>99/1	20/80
R^1 = (*E*)-PhCH=CH:	**66%**	68/32	>99/1	>1/99
R^1 = $Ph(CH_2)_2$:	**67%**	58/42	>99/1	>1/99
R^1 = *n*-Pent:	**85%**	63/37	>99/1	45/55
R^1 = *i*-Bu:	**43%**	59/41	>99/1	25/75
R^1 = TBDPSO$(CH_2)_2$:	**61%**	85/15	>99/1	>1/99

Scheme 16. Scope of aldehydes for the stereoselective synthesis of (*Z*)-α-fluoroacrylates **19** and *syn*-α-bromo-α-fluoro-β-hydroxyesters **10**.

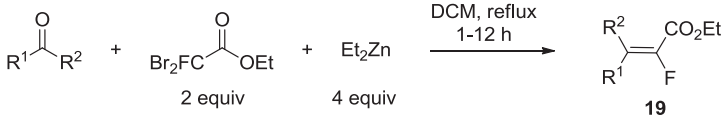
A Zimmerman–Traxler model can explain the selectivity of the reaction. Reaction of diethylzinc with EDBFA gives rise to a mixture of *E*- and *Z*-enolates (see Transition states **A** and **B**, Scheme 17). Each of them reacts with the aldehyde via a chair-like transition state to produce, respectively, the zinc aldolate **A**-**I** and **B**-**I**. Reaction of diethylzinc with aldolate **A**-**I** affords the (*Z*)-α-fluoroacrylate (*Z*)-**19** via an E2-elimination process, which is permitted because of the antiperiplanar arrangement of the bromine atom and the zinc ethoxy leaving group. In the case of aldolate **B**-**I**, the bromine atom and the leaving group are not in an antiperiplanar relationship, which prevents an E2-elimination and consequently the formation of the (*E*)-α-fluoroacrylate **19**. Equilibrium to aldolate **B**-**II** would permit the E2-elimination to occur. However, this conformation is excluded because of the destabilizing non-bonding 1,3-diaxial interactions between R^1 and the OEt group. As a consequence, aldolate **B**-**II** remains as such in the reaction mixture and provides the *syn*-α-bromo-α-fluoro-β-hydroxyester **10** upon acidic work-up.

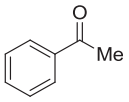
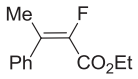
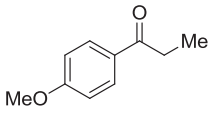
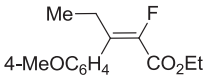
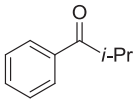
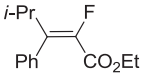
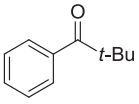
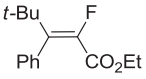
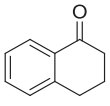
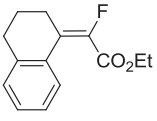
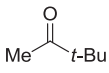
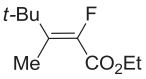
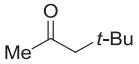
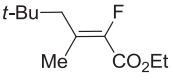
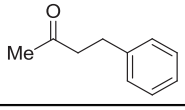
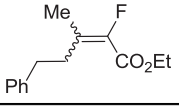
^{19}F NMR spectroscopic analyses were conducted in order to better understand the mechanism of the reaction. It was found that the intermediate *syn*-α-bromo-α-fluoro-β-hydroxyester was consumed more rapidly than the anti-isomer. Moreover, when the reaction was carried out whether from the *syn*- or the *anti*-α-bromo-α-fluoro-β-hydroxyester, the *E*/*Z* ratio of α-fluoroacrylates remained constant, which implies the formation of a common intermediate from each isomer. In case of ketones, a chelation-control model was assumed to explain the stereoselectivity of the process (Scheme 18). Metalation of the *syn*- and *anti*-zinc alkoxide **20a** and **20b** leads to enol intermediate **A**, which is stabilized by chelation of the $Zn^{(II)}$ center with the oxygen of the alcohol to form a six-membered ring. Intermediate **A** can adopt two different conformations **A**-**I** and **A**-**II** that will deliver the (*E*)- or the (*Z*)-α-fluoroacrylates **19**. Based on Cancellón mechanism studies about the stereoselective synthesis of substituted acrylates,[36] a general intermediate **B** was proposed with the larger group (R_L) in the equatorial position and the smaller group (R_S) in the axial one.



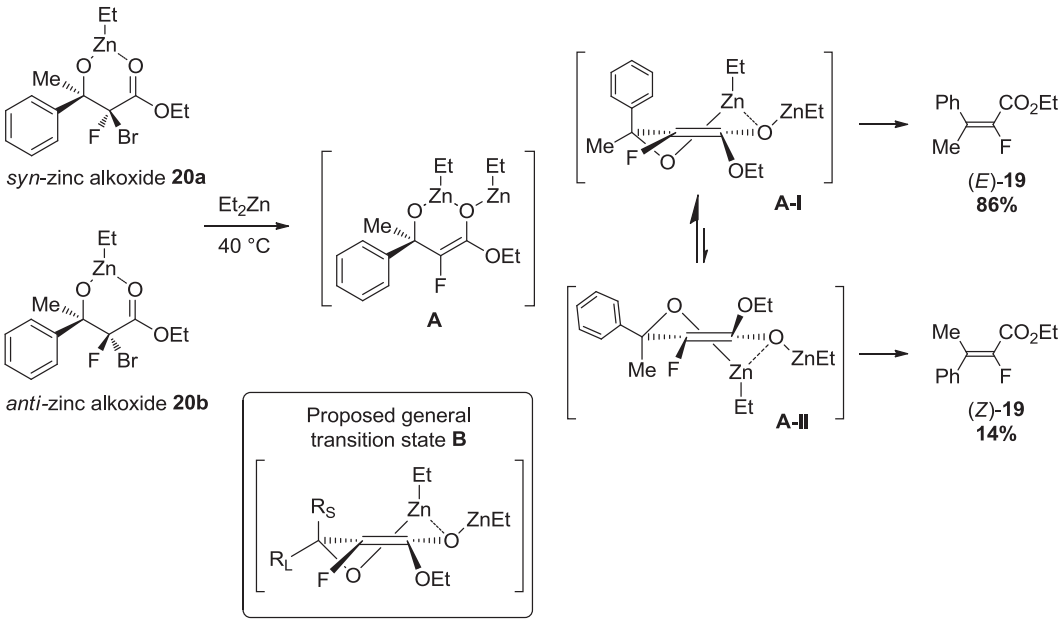
Scheme 17. Proposed mechanism of the stereoselective olefination with aldehydes.

Table 2
Scope of ketones for the stereoselective synthesis of α-fluoroacrylates **19**



Entry	Ketone	Major or sole α-fluoroacrylate **19**	Isolated yield (%)	*Z*/*E* ratio of **19**[a]
1			91	16/84
2			80	5/95
3			97	<1/99
4			82	<1/99
5			62	14/86
6			52	>99/1
7			97	70/30
8			91	52/48

[a] Determined by ^{19}F NMR and GC/MS spectroscopies of the crude mixture.



Scheme 18. Proposed mechanism for the diastereoselective olefination with ketones.

Hindered groups on the ketones (Table 2, entries 3, 4, 6) will then adopt the equatorial position leading to the (*E*)-α-fluoroacrylates **19**.

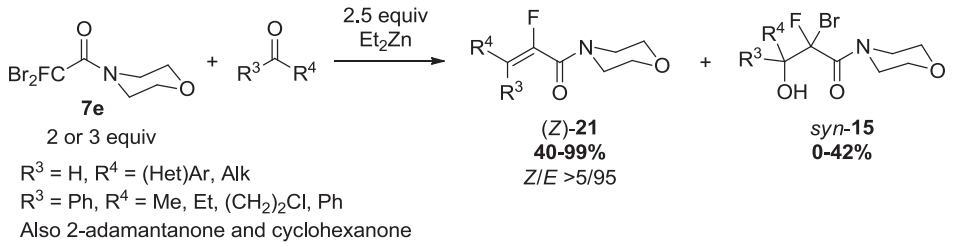
The difference of kinetic in the consumption of the *syn*- and *anti*-α-bromo-α-fluoro-β-hydroxyester was explained by a proximity effect of the second equivalent of Et_2Zn and the bromine atom during the metalation step in the case of the syn-isomer.

Overall, this diethylzinc-mediated approach represents a one-step and highly diastereoselective access to fluoroacrylates from commercially available starting materials. Aldehydes give rise to (*Z*)-α-fluoroacrylates whereas ketones gives rise to (*E*)-α-fluoroacrylates.

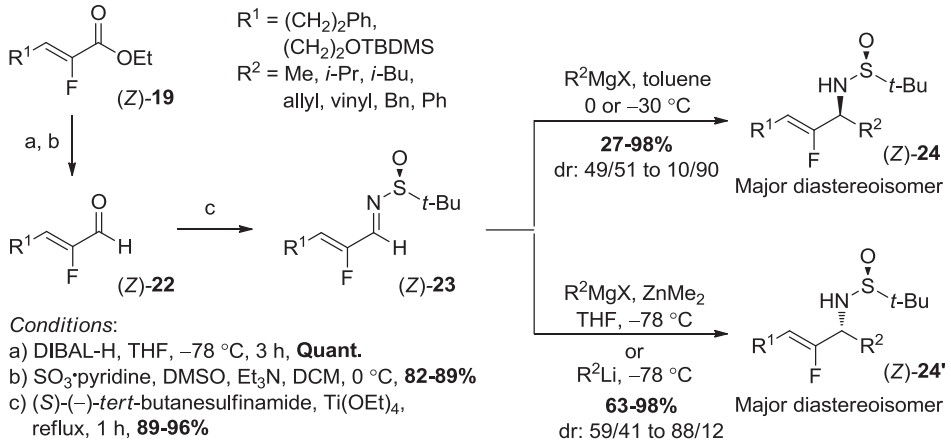
Based on this zinc-mediated olefination reaction,[32,35] the synthesis (*Z*)-α-fluoroacrylamides **21** (Scheme 19) was developed in two steps from EDBFA and dibromofluoroacetamide **7e** derived, respectively, from morpholine.[9] Whereas attempts to find conditions toward the formation of fluoroacrylamides failed from the secondary *N*-benzyl-2,2-dibromo-2-fluoroacetamide **7a** (see Scheme 10 in Section 3.), changing the starting material from secondary to tertiary amides allowed the development of conditions towards the stereoselective synthesis of (*Z*)-α-fluoroacrylamides **21**. Best results were obtained from tertiary acetamide **7e** (Scheme 19). Both aliphatic and diversely substituted aromatic aldehydes were converted into (*Z*)-α-fluoroacrylamides **21** with moderate yields and high diastereoselectivity (*Z*/*E* >95/5). In this process, the corresponding *syn*-α-bromo-α-fluoro-β-hydroxyamides **15** were also formed stereoselectively. Interestingly, when the reaction is carried out from ketones, (*Z*)-α-fluoroacrylamides **21** are the sole products of the reaction and are obtained with excellent yields and high diastereoselectivity.

4.2. Applications of the zinc-mediated olefination

(*Z*)-α-Fluoroacrylates derived from aldehydes were further used as starting building blocks for the diastereoselective synthesis of β-fluoroallylamines.[37] The latter are key synthons for the synthesis of fluorinated pseudopeptides. Indeed, the fluoroolefin moiety possesses steric and electronic similarities with the amide bond, allowing the use of the fluoroolefin as an effective peptide bond mimic.[38] The ester functionality of (*Z*)-α-fluoroacrylates **19** was subjected to a reduction–oxidation sequence to afford the corresponding (*Z*)-α-fluoro-α,β-unsaturated aldehydes **22** in good yields (Scheme 20). The latter were efficiently converted to α-fluoroenimines **23** using the (*S*)-(−)-*tert*-butanesulfinamide developed by Ellman.[39] Next, the addition of organometallic reagents was studied to access α-substituted-β-fluorinated allylamines **24** and **24′**. It was found that the configuration of the newly created stereogenic center depends on the nature of the organometallic reagent used (Grignard or zincates). The desired β-fluoroallylamines were synthesized with good yields, moderate to good diastereoselectivities and one to them (**24** with $R^1=(CH_2)_2TBDMS$, $R^2=Me$) was efficiently converted to the Fmoc-Ala-ψ[(*Z*)CF=CH]-Gly dipeptide analogue.



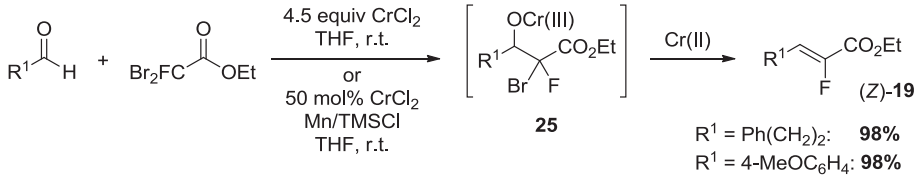
Scheme 19. Synthesis of (*Z*)-α-fluoroacrylamides **21**.



Scheme 20. Diastereoselective synthesis of β-fluoroallylamines from (*Z*)-α-fluoroacrylates.

4.3. Other metal-mediated methodologies

Other metals than zinc have been used to mediate the synthesis of α-fluoroacrylates from EDBFA. In 2003, the group of Mioskowski and Falck developed a straightforward diastereoselective Cr(II)-mediated olefination starting from commercially available trihaloacetates and aliphatic or aromatic aldehydes.[40] A series of α-haloacrylates have been synthesized in very high yields and with full stereocontrol (>99%) for the (*Z*)-isomer using $CrCl_2$ as a mediator. The chromium salt can be used alone in excess (4.5 equiv) or in substoichiometric quantity (50 mol %) in combination with Mn/TMSCl regeneration system. Ketones are also suitable for this transformation giving high level of diastereoselectivity but moderate yields. Using this methodology, EDBFA was reacted with aliphatic and aromatic aldehydes to afford exclusively the corresponding (*Z*)-α-fluoroacrylates **19** in very high yields (Scheme 21).

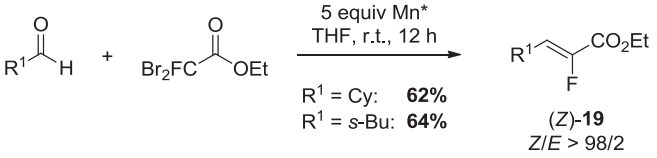


Scheme 21. Cr(II)-mediated olefination to (*Z*)-α-fluoroacrylates **19**.

The authors suggested that a Reformatsky-type adduct **25** is formed by oxidative addition of Cr(II) into the C–X bond (X=Br, Cl) via two consecutive single electron transfers followed by addition to the carbonyl of the aldehyde. Subsequent metalation results in an E2-elimination from the most favored antiperiplanar conformation (Fig. 1, minimum interactions between R^1 and the ester group) leading exclusively to the (*Z*)-α-haloacrylate. In order to support this mechanism, a series of dihalohydrins derived from the Reformatsky-type adduct **25** were isolated by carrying out the reaction with lower quantity of chromium and at low temperature. Those dihalohydrins were then subjected to the Cr(II)-mediated olefination conditions and gave rise to (*Z*)-α-haloacrylates exclusively with comparable yields, which is consistent with the proposed mechanism.

Overall, this Cr(II)-mediated olefination is a powerful one-pot and highly stereoselective approach to (*Z*)-α-fluoroacrylates **19** from EDBFA. However, the main drawback is the relative toxicity and high cost of the chromium salt.

A few years later, the group of Cancellón developed a similar reaction using manganese as a mediator.[41] Manganese is less-toxic and cheaper than chromium salts but is coated by an outer shell of oxide, which requires a preliminary activation (Mn*). The stereoselective synthesis of (*Z*)-α-haloacrylates (ratio *Z*/*E* >98:2) was possible by reacting 5 equiv of Mn* with aldehydes and trihaloesters in refluxing THF. The reaction was applied to EDBFA with two aliphatic aldehydes (cyclohexanal and *s*-butanal) to get the corresponding (*Z*)-α-fluoroacrylates **19** in moderate yields and very high diastereoselectivity (Scheme 22). In this case, it was necessary to carry the reaction at room temperature to avoid the formation of the non-halogenated acrylate as a side-product.



Scheme 22. Mn-mediated stereoselective synthesis of (*Z*)-α-fluoroacrylates **19**.

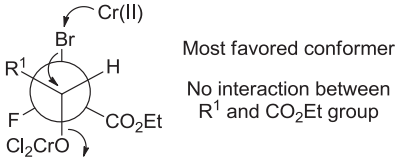


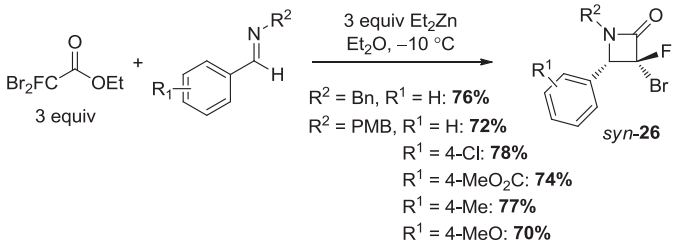
Fig. 1. Most favored conformation of the Reformatsky-type adduct **25**.

5. Zinc-mediated synthesis of fluorinated three and four-membered rings

5.1. Fluorinated β-lactams

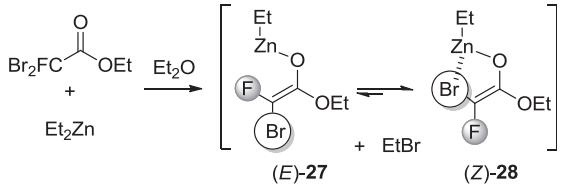
Fluorinated β-lactams represent interesting molecules for biological applications, such as the inhibition of human leukocyte

elastase.[42] Based on their previous work regarding the Rh-catalyzed synthesis of difluoro-β-lactams from imines using Et_2Zn,[43] the group of Ando looked at the same reaction using EDBFA in place of ethyl bromodifluoroacetate.[17,44] Using the same conditions with the *N*-benzylimine derived from benzaldehyde, (1 mol % $RhClPPh_3)_3$, Et_2Zn (3 equiv) in THF at −10 °C, the desired α-bromo-α-fluoro-β-lactam was obtained as the syn isomer exclusively in 63% yield along with 15% of the corresponding fluorinated aziridine. Further investigations of the reaction conditions showed that the transformation was more efficient in diethylether and without Rh-catalyst (Scheme 23). Hence, the reaction was applied to a variety of aromatic imines bearing both electron-withdrawing and -donating groups to afford the corresponding *syn*-β-lactams **26** in good yields and complete diastereoselectivity. However, aliphatic imines were not suitable for this reaction. The syn configuration of one fluorinated β-lactam was confirmed by single X-ray analysis.



Scheme 23. Zinc-mediated synthesis of *syn*-α-bromo-α-fluorolactams **26**.

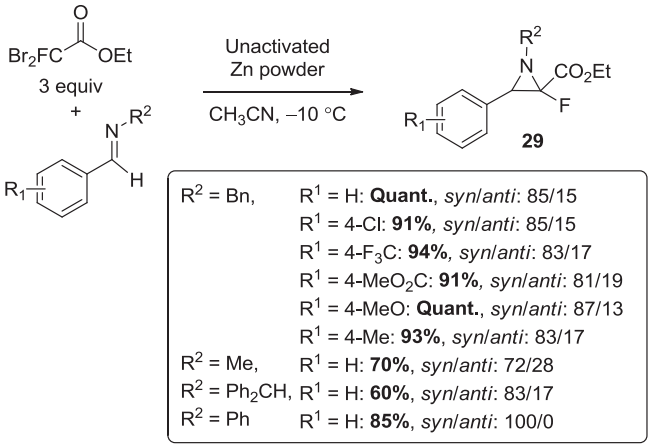
The synthesis of fluorinated β-lactams was realized in a non-coordinative solvent, diethylether. Hence, the mechanism of the reaction might be explained by the predominant formation of the (*Z*)-zinc enolate **28** due to coordination between the bromine atom and zinc to form a five-membered ring (Scheme 24). This hypothesis was supported by DFT calculations. This (*Z*)-zinc enolate **28** adds to the imine leading to chair-like transitions states. 1,3-Diaxial repulsion between the bromine atom and the *N*-substituent as well as between the aryl and the ethoxy groups explains the selectivity towards the fluorinated *syn*-β-lactam.



Scheme 24. Enolization of EDBFA in presence of Et_2Zn in Et_2O.

5.2. Fluorinated aziridines

Aziridine-2-carboxylates are useful building blocks to access α- and β-amino acids by ring-opening reactions. They also present interesting biological properties, such as antimicrobial activity[45] or SARS-CoV protease inhibitor.[46] More particularly, the synthesis of 2-fluoroaziridine-2-carboxylates is very scarcely reported.[47] During its investigations on the reaction between EDBFA and imines in the presence of Et_2Zn to synthesis α-bromo-α-fluoro-β-lactams **26** (Scheme 23),[43,44] Ando's group noticed the simultaneous formation of 2-fluoroaziridine-2-carboxylates as minor products. Hence they investigated the possibility to chemo- and diastereoselectively synthesize 2-fluoroaziridine-2-carboxylates via the Reformatsky-type aza-Darzens reaction with imines and EDBFA.[44,48] Optimization of the reaction was realized from the *N*-benzylimine derived from benzaldehyde. Using the conditions depicted in Scheme 25,



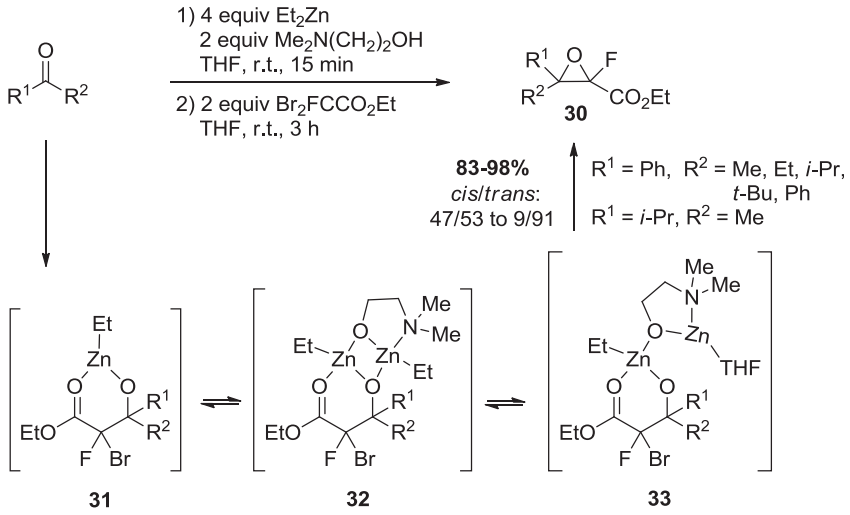
Scheme 25. Zinc-mediated synthesis of 2-fluoroaziridine-2-carboxylates.

switching the solvent from diethylether to acetonitrile drastically improved the yield of 2-fluoroaziridine-2-carboxylate **29** from 8 to 91% and reversed the diastereoselectivity of the process (*syn*/*anti*: 0/100–82/18). Replacing Et_2Zn by unactivated zinc powder finally gave the desired 2-fluoroaziridine-2-carboxylate in quantitative yield and good diastereoselectivity (*syn*/*anti*: 85/15). The scope of the reaction was then examined. A variety of aromatic imines gave the desired 2-fluoroaziridine-2-carboxylates **29** in high yields and good diastereoselectivities. However, ketimines and aliphatic imines were not suitable for this transformation. Changing the substituent on the nitrogen didn't affect the diastereoselectivity of the process but required longer reaction time to get good yields.

Regarding the mechanism, the strong coordinating acetonitrile might coordinate to zinc and leads to a reversible equilibrium of *E*/*Z* zinc enolate derived from the reaction of Et_2Zn and EDBFA. After addition of the zinc enolate into the imine to form the Reformatsky adduct, an aza-Darzens-type intramolecular cyclization leads to the corresponding fluorinated aziridines. Acetonitrile would remain coordinated to zinc avoiding the activation of the ester carbonyl and the formation of the fluorinated β-lactams. The selective generation of the *syn*-aziridine was proposed to occur via dynamic kinetic resolution.

5.3. Fluorinated epoxides

The synthesis of fluorinated epoxides, also called fluorinated glycidic esters, is scarcely reported in the literature probably due to the instability of such compounds.[49–52] When we studied the zinc-mediated reactivity of EDBFA with ketones using PPh_3, we found out that depending on the order of addition of the reagents, can be formed either the corresponding α-fluoroacrylates or the fluorinated epoxides via a Darzens reaction.[53] On one hand, it is crucial to add the ketone as the last reagent to a solution of EDBFA (2 equiv), Et_2Zn (4 equiv), and PPh_3 (4 equiv) to get α-fluoroacrylates. One the other hand, when 4 equiv of Et_2Zn were added to a solution of ketone, EDBFA (2 equiv), and PPh_3 (4 equiv) in THF, complete conversion to the corresponding fluorinated epoxides was observed by ^{19}F NMR spectroscopy. However, the large residual amount of triphenylphosphine and the instability of the desired products during the purification by silica gel column chromatography permitted the isolation of only two fluorinated epoxides. Further studies on this reaction led to the identification of *N*,*N*-dimethylethanolamine in combination with diethylzinc (to form ethylzinc *N*,*N*-dimethylaminoethoxide) for the efficient preparation of a variety of fluorinated epoxides (Scheme 26). The conversion of ketones was complete after 3 h of reaction and the



Scheme 26. Et_2Zn- and *N*,*N*-dimethylaminoethanol-mediated synthesis of fluorinated epoxides **30**.

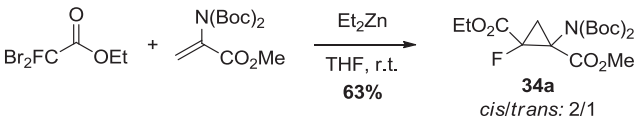
fluorinated epoxides **30** were isolated in high yields and with good purity by simple liquid-liquid extraction. A good cis/trans diastereoselectivity was obtained in few cases. Due their instability as pure compounds, fluorinated epoxides are better kept in solution in most cases. Concerning the mechanism, it was observed that EDBFA doesn't react with ethylzinc *N*,*N*-dimethylaminoethoxide. However, addition of Et_2Zn to a solution of EDBFA and a ketone led to the zinc alkoxide **31** (Scheme 26) (the corresponding bromofluorohydrin was isolated after aqueous work up), which upon addition of ethylzinc *N*,*N*-dimethylaminoethoxide, gave the desired fluorinated epoxide **30**. Based on these observations, we proposed a two-step pathway involving the formation of the zinc alkoxide **31**, which is activated by coordination to ethylzinc *N*,*N*-dimethylaminoethoxide[54] leading to dimer **32** in equilibrium with intermediate **33**.

One limitation of this process is the impossibility to isolate the fluorinated epoxides derived from aldehydes, although those products were detected by ^{19}F NMR spectroscopy.

5.4. Fluorinated cyclopropanes

5.4.1. Methodological aspects. Monofluorocyclopropanes represent prime synthetic targets as they combine the advantages of organofluorine compounds with the structural rigidity and metabolic stability of cyclopropanes. Indeed, cyclopropane is the smallest and most constrained cycloalkane and constitutes the core of many natural products and synthetic biomolecules.[55] Incorporation of a cyclopropane to rigidify a structure can have positive effect on the bioavailability, the selectivity and the affinity of a bioactive molecule for biological receptors.[56]

Recently, we succeeded in the first synthesis of a fluorinated cyclopropane containing an amino acid moiety thanks to the efficient combination of EDBFA and diethylzinc. The methodology is based on the 1,4-addition of a zinc enolate generated from EDBFA to a Boc protected aminoacrylate, followed by an in situ nucleophilic cyclization (Scheme 27). The fluorinated cyclopropane **34a**



Scheme 27. Et_2Zn-promoted synthesis of fluorinated cyclopropane **34a**.

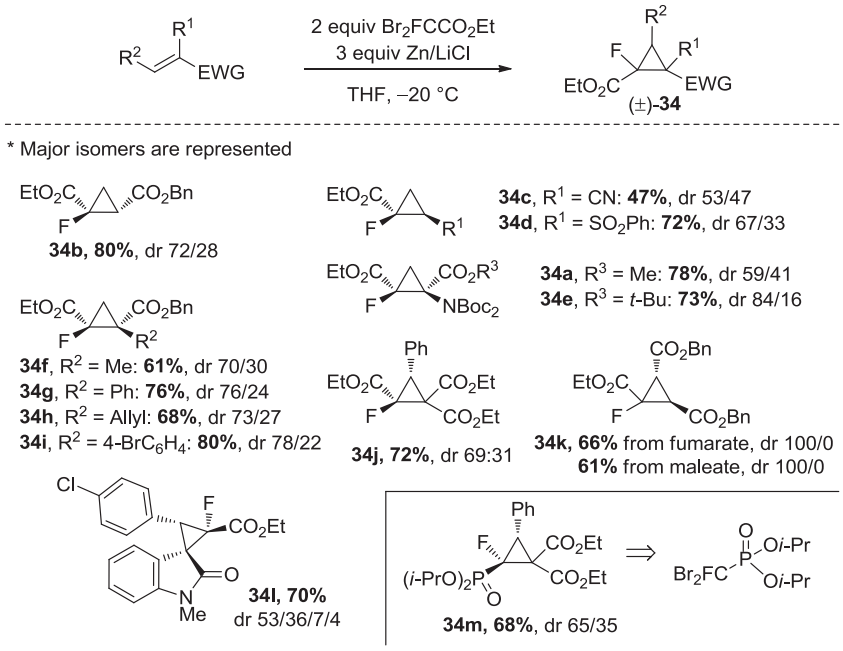
obtained as a mixture of *cis*/*trans*: 2/1 isomers is a very useful precursor for the synthesis of fluorinated constrained amino acids. However, the major drawback of this method lies in the ability of diethylzinc to promote polymerization of acrylates, which prevents to extend the scope of this strategy.

To extend the cyclopropanation reaction to a wider range of Michael acceptors, further methodological investigations led to the identification of Zn/LiCl as an efficient combination for the preparation of highly functionalized monofluorinated cyclopropanes.[57] LiCl was proposed to promote the selective metal–halogen exchange in presence of electron-deficient alkenes. Experiments showed that Zn activation is crucial for the success of the cyclopropanation and the best results were obtained after heating the solution of Zn/LiCl in THF with 2 mol % each of DMSO and TMSCl. Compared to diethylzinc, the non-nucleophilic Zn metal afforded the corresponding cyclopropanes (±)-**34** in moderate to very good yields and moderate to complete diastereoselectivities in presence of various Michael acceptors (Scheme 28).

2-Substituted acrylates required to increase the temperature at 30 °C to get optimal conversions (see products **34f**–**i**). Functional groups, such as the allyl group or aryl halides are tolerated in this process. Steric hindrance on the ester moiety of aminoacrylate improved the diastereoselectivity of the process (see product **34e**). However, using *tert*-butyl dibromofluoroacetate instead of EDBFA had no effect on the diastereoselectivity. One example of cyclopropanation using diisopropyl (dibromofluoromethyl)phosphonate ($Br_2FCP(O(Oi\text{-}Pr)_2)$) was also reported to give the corresponding fluorinated cyclopropylphosphonate **34m** in good yield and moderate diastereoselectivity. A single crystal X-ray analysis of the spiro-oxindole **34l** confirmed the stereochemistry of the fluorinated cyclopropanes (±)-**34**.

Finally, both dibenzyl fumarate and maleate led exclusively to the same isomer **34k** for which the two ester groups are in a trans configuration. A control experiment also showed that dibenzyl maleate doesn't isomerize into the corresponding fumarate under the reaction conditions. Moreover, it was possible to isolate the 1,4-adduct derived from the reaction of EDBFA and dibenzylidene malonate by protonation upon aqueous work-up. This set of experiments excluded the possibility that ethoxycarbonylfluorocarbene could be involved in the reaction and supports a 1,4-addition/nucleophilic cyclization mechanism.

An asymmetric version of the cyclopropanation was then developed, giving access to chiral cyclopropanes **35** bearing a fluorinated quaternary stereocenter (Table 3).[10] The strategy was based



Scheme 28. Scope of Michael acceptor for the cyclopropanation from EDBFA.

on the use of chiral dibromofluoroacetyl derivatives bearing a chiral oxazolidinone as auxiliary. Among the different ones tested, the dibromofluoroacetyl oxazolidinone **9c** gave the best results in terms of diastereoselectivities and stability and was chosen to extend the scope of the cyclopropanation. After investigations on the metalating agents, the combination of Zn/LiCl provided the best results in terms of yield and diastereoselectivity as in the case of the achiral version.[57] Conditions depicted in Table 3 proved to be applicable to a large scope of Michael acceptors and afforded the corresponding cyclopropanes **35** in moderate to very good overall yields. The cis/trans ratios are moderate to good and the level of diastereoselectivity on each isomer is generally good. In most cases, the diastereomerically pure fluorinated cyclopropanes can be separated by flash column chromatography.

Cleavage of the chiral auxiliary under both acidic ($Yb(OTf)_3$, MeOH) and basic (LiOH, H_2O_2, THF/H_2O) conditions lead, respectively, to the corresponding methyl ester and carboxylic acid derivatives in good yields, without epimerization and with good recovery of the chiral auxiliary.

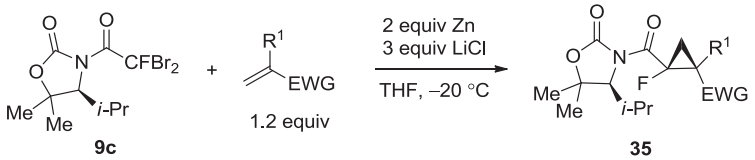
The absolute configurations of the major isomers (*cis* and *trans*) of **35a** were determined by single crystal X-ray chromatography in order to better understand the good diastereoselectivity for each cis and trans isomer but the high variability of the *cis*/*trans* ratios depending on the substrates. Analyses showed the same absolute (*S*) configuration of the fluorinated center for each isomer and opposite absolute configuration of the center bearing the benzyl ester group. Hence, formation of a pair of epimeric products during the Michael Initiated Ring Closure type (MIRC-type) reaction is consistent with a highly stereoselective 1,4-addition and a less selective cyclization step, which finally lead to a mixture of cis and trans isomers.

5.4.2. Applications. Cyclopropane (±)-**34a** (from Scheme 27) was further used to synthesize a family of fluorinated constrained analogues of glutamic acid.[58] The family of compounds was tested for the agonist activity towards metabotropic glutamate receptor subtype 4 (mGluR4). The nature of the distal acidic function in glutamate analogues being essential to increase both selectivity and affinity for mGlu receptors,[59] the fluorine atom was expected to increase the acidity of the distal function, hence improving the agonist activity. Among all compounds tested, cyclopropane (±)-(*Z*)-FAP4 **39** (Scheme 29) displayed the best agonist activity and is much more potent (7-times) than its racemic non-fluorinated analogue (*E*)-APCPr.[60] Calculations of the dissociation constants (using I-lab 2.0 program) showed that, at physiological pH, the phosphonic acid function of (±)-(*Z*)-FAP4 **39** exists exclusively in dianionic form (pK_{a3}=6.0) whereas (±)-(*E*)-APCPr exists as a mix of mono- and dianionic phosphonic acid (pK_{a3}=6.7). This difference in ionization states might explain the difference of binding of these two compounds with the mGlu4 receptor.

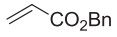
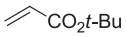
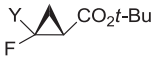
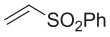
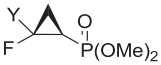
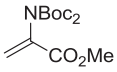
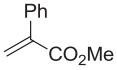
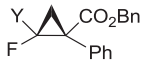
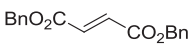
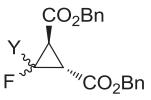
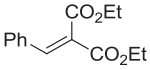
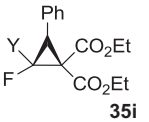
(±)-(*Z*)-FAP4 **39** was stereoselectively synthesized from cyclopropane (±)-**34a** isolated as a mixture of *Z*/*E* isomers. Diastereoselective and regioselective saponification of the ethyl ester led to the corresponding carboxylic acid (±)-(*Z*)-**36**, which can be separated from the remaining (±)-(*E*)-**36** ethyl ester derivative (Scheme 29) by a simple acido–basic extraction. Reduction of the carboxylic acid of (±)-(*Z*)-**36** to the corresponding alcohol followed by mesylation and iodination led to the iodinated product (±)-(*Z*)-**37**. This latter undergoes a Michaelis–Arbuzov reaction using triethylphosphite to afford the corresponding phosphonate (±)-(*Z*)-**38** in modest yield. Further deprotection under acidic conditions leads to the desired cyclopropane (±)-(*Z*)-FAP4 **39** in 12% overall yield from the starting cyclopropane (±)-**34a**. Unfortunately, this synthetic route currently remains unsuccessful for the *E* isomer, the Michaelis–Arbuzov reaction leading to complete decomposition of the material.

Another application was directed towards the synthesis of constrained amino acids, such as cyclopropyl ones that have been reported as attracting targets showing interesting biological activities and specific conformations.[61] Fluorinated amino acids also represent useful targets to design hyperstable proteins folds and to direct highly specific protein–protein interactions. Hence, fluorinated cyclopropyl amino acids represent valuable building blocks that could be incorporated in peptide analogues and implied new localized features that may be used in structural and biological studies of bioactive molecules. We recently described the first

Table 3
Scope of the asymmetric synthesis of monofluorinated cyclopropanes **35**



9c **35**

Entry	Michael acceptor	Major isomer	Overall yield[a]	*cis*/*trans*[b]	de[b] *cis* (yield[a])	de[b] *trans* (yield[a])
1		 **35a**	79	21/79	84 (14)	93 (65[c])
2		 **35b**	69	16/84	76 (8)	94 (61)
3		 **35c**	79	78/22	88 (62[c])	92 (17[c])
4		 **35d**	62	85/15	>94 (55[c])	80 (7)
5		 **35e**	70[d]	50/50	94 (36[c])	>94 (34[c])
6		 **35f**	78	73/27	80 (56[c])	84
7		 **35g**	74	45/55	>90 (33[c])	>92 (41)
8		 **35h**	79	5/95[e]	—	64
9		 **35i**	66	36/64	>94 (24[c])	>94 (42[c])

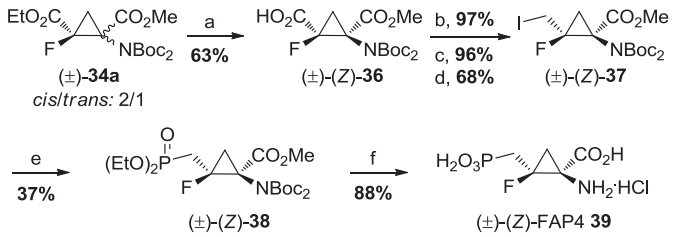
[a] Isolated yield of both isomers.
[b] Determined by ^{19}F NMR of the crude product.
[c] Single isomer by ^{19}F NMR of the isolated product.
[d] Acrylonitrile (1.5 equiv) was used.
[e] *cis*/*trans* ratio refers to the stereochemistry of the ester groups.

synthesis of peptidomimetics containing a fluorinated cyclopropyl amino acid moiety using our zinc-mediated cyclopropanation strategy to build the well-functionalized fluorinated cyclopropane scaffold (±)-**34a** (Scheme 27).[62] This latter was further derivatized to synthesize the (±)-(*E*)- and (±)-(*Z*)-methionine **41**, (±)-(*E*)- and (±)-(*Z*)-leucine **42**, (±)-(*Z*)-arginine **43** and, (±)-(*E*)- and (±)-(*Z*)-lysine **44** analogues, and a fluorinated cyclopropyl-containing tripeptide **45** (Scheme 30).

(±)-(*Z*)-**36** and (±)-(*E*)-**36**, synthesized and separated as mentioned in the previous paragraph (See Scheme 29), can be converted to their corresponding (±)-(*Z*)-**40** and (±)-(*E*)-**40** methyl alcohols that are starting materials for the synthesis of each fluorinated amino acid analogues. Those analogues could be further used for the synthesis of peptides that might present singular conformations, physical and chemical properties as well as biological activities.

In order to demonstrate the high values of those constrained fluorinated amino acids analogues, the selective deprotection (of the ester or of the Boc-amino group) of the leucine analogue (±)-(*Z*)-**42** as well as its full deprotection was carried out. The *N*-Fmoc protection of the fully deprotected (±)-(*Z*)-**42** was then successfully performed, showing the potency of these type of analogues in peptidomimetics and in peptide solid-phase synthesis.

Starting from the (±)-(*Z*)-**42** leucine analogue, tripeptide **45** was synthesized in four steps and 30% overall yield. This synthesis represents the first example of a tripeptide containing a fluorinated cyclopropyl amino acid scaffold.



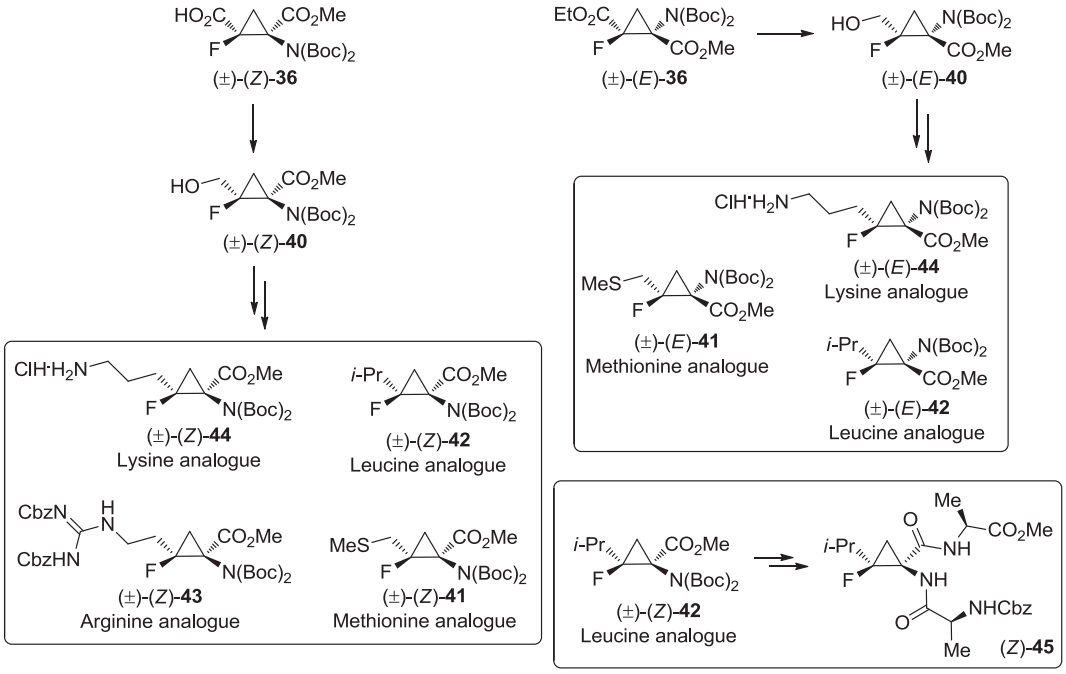
Conditions: a) LiOH, THF/H_2O, 0 °C; b) BH_3 [1M] in THF, 0 °C to r.t.; c) MsCl, Et_3N, Et_2O, 0 °C to r.t.; d) NaI, TBAI, acetone, reflux; e) $P(OEt)_3$, 120 °C, sealed tube; f) HCl 12N, AcOH, 80 °C

Scheme 29. Synthesis of (±)-(*Z*)-FAP4 **39** from fluorinated cyclopropane (±)-**34a**.

departure to give a stable allylic cation **48** precursor of the silylated fluoropentadiene **49**.

7. Conclusion

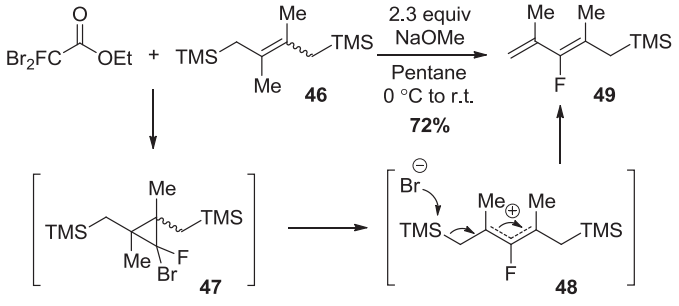
In this account, we showed the utility of EDBFA as a multifunctional source of fluorine, which is commercially available, by highlighting the different strategies that have been developed using this reagent. EDBFA can be used as such, or after modification of one of its functionality, to further build new fluorinated systems, such as α-bromo-α-fluorohydroxyesters, fluoroolefins, fluoro-β-lactams, fluoroaziridines, fluoroepoxides, fluorocyclopropanes, fluorodienes… Those fluorinated building blocks find applications in various fields, such as pharmaceuticals or agrochemicals.



Scheme 30. Synthesis of fluorinated cyclopropyl amino acids analogues.

6. Miscellaneous reactions

Addition of EDBFA to 2,3-dimethyl-1,4-bis(trimethylsilyl)but-2-ene **46** in the presence of sodium methoxide afforded the silylated fluoropentadiene **49** in 72% yield (Scheme 31).[63] Reaction of the EDBFA with MeONa generates bromofluorocarbene that adds into **46** to form the corresponding bromofluorocyclopropane **47**. Disrotatory electrocyclic ring opening of the unstable cyclopropane **47** spontaneously occurs at room temperature with bromine



Scheme 31. Addition of EDBFA to allylsilane **46**.

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Biographical sketch

Emilie David received her Ph.D. from the Université Claude Bernard Lyon 1 in France in 2006. She carried doctoral studies in heterocyclic chemistry under the supervision of Pr. Marc Lemaire. After a postdoctoral position tackling the synthesis of triterpenoids under the guidance of Dr. Tadashi Honda (Dartmouth College, NH, USA), she worked 2 years for Archimica (based in Frankfurt, Germany) in the laboratory of Pr. Victor Snieckus (Queen's University, Canada). Since October 2011, she is working as a postdoctoral fellow in the laboratory of Pr. Xavier Pannecoucke (INSA/Université de Rouen). She is developing new methodologies to access organofluorinated compounds including cyclopropanes.

Philippe Jubault received his Engineer Diploma in 'Chemistry and Process' from the National Institute of Applied Sciences of Rouen. In 1992, he joined the research group of Pr. Collignon and Pr. C. Feasson at the INSA of Rouen where he obtained his Ph.D. in January 1996. After one year as a post-doctoral student at Hydro-Québec (Shawinigan, Québec, Canada), he was a Marie Curie research fellow in the laboratory of Pr. V. K. Aggarwal at the University of Sheffield. In 1998, he returned to the INSA of Rouen and assumed in 2000 an assistant professor position. His research interests include the development of new methodologies for the synthesis of original fluorinated building blocks, the development of new ligands for asymmetric synthesis and the developments of new heterocyclic scaffolds for medicinal chemistry.

Samuel Couve-Bonnaire was born in 1976 in Lille (France). He received his Ph.D. dealing with homogeneous catalysis in 2001 from the University of Lille 1 in the laboratory of Pr. André Mortreux. Then he carried out his postdoctoral studies in Canada in the laboratory of Pr. Prabhat Arya at the Steacie Institute for Molecular Sciences, Ottawa, working in the area of natural product-like synthesis. Back to France, he was postdoctoral researcher with Sanofi-Aventis as industrial partner. Since February 2005, he is working in the group of 'fluorinated biomomecules synthesis' as a Maître de Conférences at the COBRA laboratory, INSA & Université de Rouen. His current interests deal with organometallic chemistry, peptide chemistry and new methodology dedicated to the synthesis of organofluorinated compounds.

Pannecoucke Xavier was born in Lille (France) in 1967. He got his Ph.D. in BioOrganic Chemistry in 1993 from the University Louis Pasteur of Strasbourg (France), under the supervision of Professors Guy Ourisson and Bang Luu. He then moved to Japan for one year to carry out his first postdoctoral studies in the laboratory of Pr. Koichi Narasaka at the University of Tokyo. He moved again to Great Britain for fourteen months to carry out his second postdoctoral studies in the laboratory of Pr. Steven V. Ley at the University of Cambridge. He then went back to France as a Maître de Conférences at the University of Rouen in the group of Pr. J. -C. Quirion. In 2003, he took a position of Professor at the INSA of Rouen, leading the group of fluorinated biomolecules synthesis and heading from 2011 COBRA laboratory (UMR 6014). His main research interests are dealing with development of new methodologies to access fluorinated biomolecules (peptidomimetics, carbohydrates, nucleosides, heterocycles…).