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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
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. 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. 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. Fluorinated natural products are rare. 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, fluoro-cyclopropanes, 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 dibromofluoracetate

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. 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 tetra-functional 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 NaSH, NaSBr, NaOEt, and NaOCH2Ph afforded the corresponding reduced products whereas the use of NaN3 as a nucleophile apparently reduced using lithium borohydride as a reducing agent in the presence of trimesoylborate to afford 2,2-dibromo-2-fluorooctanol 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)

The ester moiety of EDBFA can be efficiently reduced using lithium borohydride as a reducing agent in the presence of triphenylphosphine to afford 2,2-dibromo-2-fluorooctanol 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)

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. Treatment of EDBFA with concentrated aqueous ammonium hydroxide affords dibromofluorooacetamide in high yield (Scheme 3). The latter is dehydrated in the presence of phosphorus pentoxide at high temperature to get dibromofluoroacetimidine 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.

Monoalkylation of EDBFA was also described by Takeuchi using tin reagents in the presence of a catalytic amount of AIBN (Scheme 2). There was no yield reported for these reactions.
conversion of 4 into benzylc, allylic, and propargylic ethers 5 and (2) chromium-mediated stereoselective formation of (Z)-1-fluoro-2-alkenyl alkyl ethers 6,9.

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 dimethylaluminum chloride led to the corresponding dibromo-fluoroacetamides 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).10

Finally, several chiral dibromofluorooctylazolidin-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 chlorolation of the carboxylic acid derivative with thionyl chloride (Scheme 6). Then acylation of 8 with several chiral oxazolidinones produced the desired dibromooctylazolidin-2-ones 9a–d in moderate to good yields.

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/ Et2AlCl-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/Et2AlCl/styrene (1.2/1.1/1.1 equiv) was treated 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′-dihydroxyster 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, Et2AlCl, 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 altogether 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-hydroxyesters 12a,b11a,12b and the radical allylation reaction to access the corresponding α-allylated-α-fluoro-β-hydroxyesters 12b,c (Scheme 7, Eq. 1).11b

Few years later, the group of Iséki described the enantioselective synthesis of α-bromo-α-fluoro-β-hydroxyesters in two steps from EDBFA using a chiral Lewis acid as a catalyst.13 In the first step, bromofluoro-α,b-dihaloalkane 13 is synthesized from chiral silyl acetal by addition of EDBFA to a mixture of TMSCl and activated Zn powder in THF at −20 °C (Scheme 7). 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 19F NMR).

The second step consists in the catalytic enantioselective Mukaiyama-aldol reaction of aldehydes with 13 in the presence of Masumune’s chiral catalyst (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 excess 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, 19F NMR analyses of a 1:1 mixture of acetals 13 and catalyst 14 in C2D5NO2 at −78 °C and −30 °C showed two different spectra, giving a clue for the mechanism: at −78 °C, the 19F NMR spectrum showed two singlets corresponding to the acetals 13 in its two isomeric forms; at −20 °C, the apparition of four new peaks lets suggest transmetallation from the silyl acetal to the boron one 13 sometimes improved the enantiomeric excess (e.g.: from 83 to 95% ee with (E)-cinnamaldehyde).

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.
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.

Application of this protocol to N-benzyl-2,2-dibromo-2-fluoroacetamide 7a led to the corresponding a-bromo-a-fluoro-b-hydroxyamides 15 (Scheme 10). It was necessary to use an excess of 7a as well as 4 or 6 equiv of Et2Zn in order to get good yields of 15 and minimize the formation of the corresponding fluoroacylamides (see Olefination reactions in Section 4.1 for conditions towards acrylamides). Both aldehydes and ketones are 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.

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

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**Table 1**

| R¹CHO                  | Isolated yield of 10 | dr syn/anti-10 | ee (syn-10) | ee (anti-10) |
|------------------------|----------------------|----------------|-------------|--------------|
|                        | −78 °C | −20 °C | −78 °C | −20 °C | −78 °C | −20 °C | −78 °C | −20 °C |
| PhCHO                  | 90%    | 89%    | 69/31 | 49/51 | 98% (25,3R) | 13% (25,3R) | 90% (26,3R) | 13% (25,35) |
| Ph(CH₃)₂CHO            | 89%    | 85%    | 46/54 | 13/87 | 98% (+) | 48% (−) | 98% (+) | 92% (−) |
| PhCH₂OCH₂CHO           | 81%    | 80%    | 57/43 | 26/74 | 97% (−) | 29% (+) | 97% (−) | 72% (−) |
| c-HexCHO               | 74%    | 90%    | 52/48 | 20/80 | 94% (+) | 18% (−) | 89% (+) | 81% (−) |
| n-PropCHO              | 90%    | 87%    | 46/54 | 11/89 | 97% (−) | 49% (+) | 98% (+) | 93% (−) |
| BrCH₂CO₂Et            | 87%    | 85%    | 54/46 | 23/77 | 99% (+) | 21% (−) | 98% (+) | 74% (−) |
| i-PrCHO                | 96%    | —      | 48/52 | —     | 98% (+) | —     | 98% (+) | —     |
| (E)-PhCH=CH₂CHO       | 96%    | —      | 57/43 | —     | 83% (+) | —     | 83% (+) | —     |
| i-BuCHO                | 96%    | 87%    | 48/52 | 11/89 | 98% (+) | 31% (−) | 98% (+) | 91% (+) |

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*a Based on isolated yields of syn- and anti-aldols 10.

b Measured by HPLC using a Daicel Chiralpak 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.
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 mono-fluorinated and -brominated C-glycosides was synthesized by reaction of EDBFA with lactones of type in the presence of 2 equiv of Et₂Zn. Compound 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 (Scheme 12) is used as an intermediate for the synthesis of monofluorinated cyclopropanes having high potency in the treatment of neurological disorders. Its synthesis was patented by Taisho Pharmaceutical Co., LTD and by Eli Lilly and Company. 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 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-fluorooacylates are useful building blocks for the preparation of biologically active
fluorinated molecules. A number of synthetic routes have been developed to access α-fluoroacrylates. The main strategies are the Wittig24 and thia-Wittig25 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-1,4-dioate sodium salt,29f the deoxygenation–elimination sequence with of β,β'-dihydroxy carboxylic esters in the presence of vanadium(V) trichloride oxide,29g the Zn/CuCl-mediated reaction of methyl dichlorofluoroacetate with aldehydes29h or the alkenylation reaction from 3-aryl-2-fluoro-3-hydroxy-2-organoselenylacetates under acidic conditions.29i 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 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 = 1.22 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 ketones30 (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 carboxyl derivatives.32

![Scheme 13. Synthesis of gem-bromofluoroolefins via diethylzinc-promoted Wittig reaction.](image)

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-bromo-fluoroolefins 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 mixture of products.28 There are also miscellaneous routes,29 such as 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-bromo-fluoroolefins 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.

![Scheme 14. Synthesis of α-fluoroacrylates 19 via diethylzinc-promoted Wittig reaction.](image)
(ratio (Z)-19/10: 51:49). Switching the solvent from THF to DCM gave a better 84% global yield of pure (Z)-α-fluorooacrylate 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-fluorooacrylates 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-Fluorooacrylates 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-fluorooacrylate 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-fluorooacrylates. The corresponding α-bromo-α-fluoro-β-hydroxyesters were not formed under those reaction conditions. α-Fluorooacrylates 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).

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 aldol 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-fluorooacrylate (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-fluorooacrylate 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 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.

\[
\begin{align*}
\text{R}^1 = \text{Alk, Ar} & & \text{2 equiv} \\
\text{R}^2 = \text{H, Alk, Ar} & & \text{2 equiv} \\
\text{Br}_2\text{C}(\text{OEt}) & & \text{2 equiv} \\
\text{Et}_2\text{Zn} & & \text{DCM, r.t.} \\
\text{10 min} & & \text{10 equiv} \\
\text{DCM, r.t.} & & \text{3 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 = & \text{4-MeOC}_6\text{H}_{14} & 84\% & 63/37 & >99/1 & >1/99 \\
\text{R}^1 = & \text{Ph} & 80\% & 35/75 & >99/1 & >1/99 \\
\text{R}^1 = & \text{4-FC}_6\text{H}_{14} & 90\% & 59/41 & >99/1 & >1/99 \\
\text{R}^1 = & \text{4-BrC}_6\text{H}_{14} & 74\% & 47/53 & >99/1 & >1/99 \\
\text{R}^1 = & \text{4-MeO}_2\text{C}_6\text{H}_{14} & 64\% & 56/44 & >99/1 & >1/99 \\
\text{R}^1 = & \text{4-NC}_6\text{H}_{14} & 62\% & 56/44 & >99/1 & >1/99 \\
\text{R}^1 = & \text{3,4,5-Fluoroc}_6\text{H}_{14} & 96\% & 62/38 & >99/1 & >20/80 \\
\text{R}^1 = & \text{PhCH} & 66\% & 68/32 & >99/1 & >1/99 \\
\text{R}^1 = & \text{PhNCH}_{2} & 67\% & 58/42 & >99/1 & >1/99 \\
\text{R}^1 = & \text{4-Methylpent} & 85\% & 63/37 & >99/1 & >45/55 \\
\text{R}^1 = & \text{i-But} & 43\% & 59/41 & >99/1 & >25/75 \\
\text{R}^1 = & \text{TBDPSO(CH}_{2})_{2} & 61\% & 85/15 & >99/1 & >1/99 \\
\end{align*}
\]

19F 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-fluorooacrylates 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[19] 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-fluorooacrylates 19. Based on Cancell mechanism studies about the stereoselective synthesis of substituted acrylates, 30 a general intermediate B was proposed with the larger group (R₃) in the equatorial position and the smaller group (R₂) 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-fluoroacylates 19

| Entry | Ketone | Major or sole α-fluoroacrylate 19 | Isolated yield (%) | Z/E ratio of 19† |
|-------|--------|---------------------------------|-------------------|-----------------|
| 1     | ![Image](image1) | ![Image](image2) | 91 | 16/84 |
| 2     | ![Image](image3) | ![Image](image4) | 80 | 5/95 |
| 3     | ![Image](image5) | ![Image](image6) | 97 | <1/99 |
| 4     | ![Image](image7) | ![Image](image8) | 82 | <1/99 |
| 5     | ![Image](image9) | ![Image](image10) | 62 | 14/86 |
| 6     | ![Image](image11) | ![Image](image12) | 52 | >99/1 |
| 7     | ![Image](image13) | ![Image](image14) | 97 | 70/30 |
| 8     | ![Image](image15) | ![Image](image16) | 91 | 52/48 |

* Determined by 19F NMR and GC/MS spectroscopies of the crude mixture.
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 Et2Zn 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 dibromo fluoroacetamide 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.57 The latter are key synths 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-butanesulfinimide developed by Ellman.39 Next, the addition of organometallic reagents was studied to access α-substituted-β-fluorinated allylamines 24 and 240. 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 R1=(CH2)2TBDMS, R2=Me) was efficiently converted to the Fmoc-Ala-ψ((Z)CF=CH]-Gly dipeptide analogue.
4.3. Other metal-mediated methodologies

Other metals than zinc have been used to mediate the synthesis of α-fluorocarboxylates 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. A series of α-haloacrylates have been synthesized in very high yields and with full stereocontrol (>99%) for the (Z)-isomer using CrCl2 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 in very high yields (Scheme 21).

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 metatation results in an E2-elimination from the most favored antiperiplanar conformation (Fig. 1, minimum interactions between R1 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-fluorocarboxylates 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. 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-fluorocarboxylates 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.
elastase.\textsuperscript{42} Based on their previous work regarding the Rh
catalyzed synthesis of difluoro-\(\beta\)-lactams from imines using Et\(_2\)Zn,\textsuperscript{43} the group of Ando looked at the same reaction using EDBFA in place of ethyl bromodifluoroacetate.\textsuperscript{17,44} Using the same conditions with the \(N\)-benzylimine derived from benzaldehyde, (1 mol \% RhCl(PPh\(_3\))\(_3\), Et\(_2\)Zn (3 equiv) in THF at \(-10^\circ\text{C}\), the desired \(\alpha\)-bromo-\(\alpha\)-fluoro-\(\beta\)-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 diethyl ether 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-\(\beta\)-lactams 26 in good yields and complete diastereoselectivity. However, aliphatic imines were not suitable for this reaction. The syn configuration of one fluorinated \(\beta\)-lactam was confirmed by single X-ray analysis.

The synthesis of fluorinated \(\beta\)-lactams was realized in a non-coordinating solvent, diethyl ether. 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 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-\(\beta\)-lactam.

5.2. Fluorinated aziridines

Aziridine-2-carboxylates are useful building blocks to access \(\alpha\)- and \(\beta\)-amino acids by ring-opening reactions. They also present interesting biological properties, such as antimicrobial activity\textsuperscript{45} or SARS-CoV protease inhibitor.\textsuperscript{46} More particularly, the synthesis of 2-fluorooaziridine-2-carboxylates is very scarcely reported.\textsuperscript{47} During its investigations on the reaction between EDBFA and imines in the presence of Et\(_2\)Zn to synthesis \(\alpha\)-bromo-\(\alpha\)-fluoro-\(\beta\)-lactams 26 (Scheme 23),\textsuperscript{41,44} Ando’s group noticed the simultaneous formation of 2-fluorooaziridine-2-carboxylates as minor products. Hence they investigated the possibility to chemo- and diastereoselectively synthesize 2-fluorooaziridine-2-carboxylates via the Reformatsky-type aza-Darzens reaction with imines and EDBFA.\textsuperscript{44,48} Optimization of the reaction was realized from the \(N\)-benzylimine derived from benzaldehyde. Using the conditions depicted in Scheme 25, switching the solvent from diethyl ether to acetonitrile drastically improved the yield of 2-fluorooaziridine-2-carboxylate 29 from 8 to 91 \% and reversed the diastereoselectivity of the process (syn/anti: 0/100–82/18). Replacing Et\(_2\)Zn by unactivated zinc powder finally gave the desired 2-fluorooaziridine-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-fluorooaziridine-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\(_2\)Zn 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 \(\beta\)-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.\textsuperscript{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 \(\alpha\)-fluoroacrylates or the fluorinated epoxides via a Darzens reaction.\textsuperscript{53} On one hand, it is crucial to add the ketone as the last reagent to a solution of EDBFA (2 equiv), Et\(_2\)Zn (4 equiv), and PPh\(_3\) (4 equiv) to get \(\alpha\)-fluoroacrylates. One the other hand, when 4 equiv of Et\(_2\)Zn 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 \(\text{\(^{19}F\)}\)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 \(N,N\)-dimethylthanolamine 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
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 to 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 Et2Zn 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-dimethylaminoethoxide54 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 19F 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 rigify 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 intramolecular nucleophilic cyclization (Scheme 27). The 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 disopropyl (dibromofluoromethyl)phosphonate (Br2FPC(O(Or-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 34i 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 ethoxycarbonyl-fluorocarbene 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...
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, H2O2, THF/H2O) conditions lead, respectively, to the corresponding methyl ester and carboxylic acid of (3S)-34a in 53% and 60% overall yields. Further deprotection under acidic conditions (using 1-lab 2.0 program) showed that, at physiological pH, the phosphonic acid function of (3S)-34a exists exclusively in dianionic form (pKa¼6.0) whereas (3I)-34a exists as a mix of mono- and dianionic phosphonic acid (pKa¼6.7). This difference in ionization states might explain the difference of binding of these two compounds with the mGlu4 receptor.

(3I)-34a was stereoselectively synthesized from cyclopropane (3S)-34a isolated as a mixture of Z/E isomers. Diastereoselective and regioselective saponification of the ethyl ester led to the corresponding carboxylic acid (3S)-36, which can be separated from the remaining (3E)-36 ethyl ester derivative (Scheme 29) by a simple acid–basic extraction. Reduction of the carboxylic acid of (3S)-36 to the corresponding alcohol followed by mesylation and iodination led to the iodinated product (3I)-37. This latter undergoes a Michaelis−Arbuzov reaction using triethylphosphite to afford the corresponding phosphonate (3S)-38 in modest yield. Further deprotection under acidic conditions leads to the desired cyclopropane (3S)-38 in 12% overall yield from the starting cyclopropane (3I)-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.58 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

5.4.2. Applications. Cyclopropane (3S)-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 (3S)-34a (Scheme 29) displayed the best agonist activity and is much more potent (7-times) than its racemic non-fluorinated analogue (3I)-34a. Calculations of the dissociation constants (using 1-lab 2.0 program) showed that, at physiological pH, the phosphonic acid function of (3S)-34a exists exclusively in dianionic form (pKa¼6.0) whereas (3I)-34a exists as a mix of mono- and dianionic phosphonic acid (pKa¼6.7). This difference in ionization states might explain the difference of binding of these two compounds with the mGlu4 receptor. (3I)-34a was stereoselectively synthesized from cyclopropane (3S)-34a isolated as a mixture of Z/E isomers. Diastereoselective and regioselective saponification of the ethyl ester led to the corresponding carboxylic acid (3S)-36, which can be separated from the remaining (3E)-36 ethyl ester derivative (Scheme 29) by a simple acid–basic extraction. Reduction of the carboxylic acid of (3S)-36 to the corresponding alcohol followed by mesylation and iodination led to the iodinated product (3I)-37. This latter undergoes a Michaelis−Arbuzov reaction using triethylphosphite to afford the corresponding phosphonate (3S)-38 in modest yield. Further deprotection under acidic conditions leads to the desired cyclopropane (3S)-38 in 12% overall yield from the starting cyclopropane (3I)-34a. Unfortunately, this synthetic route currently remains unsuccessful for the E isomer, the Michaelis−Arbuzov reaction leading to complete decomposition of the material.

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synthesis of peptidomimetics containing a fluorinated cyclopropyl amino acid moiety using our zinc-mediated cyclopropanation strategy to build the well-functionalized fluorinated cyclopropane scaffold (\(/{C_6}\))-34a (Scheme 27).62 This latter was further derivatized to synthesize the (\(/{C_6}\))-\((/E)\))- and (\(/{C_6}\))-\((/Z)\))-methionine 41, (\(/{C_6}\))-\((/Z)\))- and (\(/{C_6}\))-\((/E)\))-leucine 42, (\(/{C_6}\))-\((/Z)\))-arginine 43 and, (\(/{C_6}\))-\((/E)\))- and (\(/{C_6}\))-\((/Z)\))-lysine 44 analogues, and a fluorinated cyclopropyl-containing tripeptide 45 (Scheme 30).

Starting from the (\(/{C_6}\))-\((/Z)\))-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.

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

| Entry | Michael acceptor | Major isomer | Overall yield | cis/trans | de cis (yield) | de trans (yield) |
|-------|------------------|--------------|---------------|-----------|---------------|-----------------|
| 1     | \(-C{\text{O}}_{2}{\text{Bn}}\) | 35a          | 79            | 21/79     | 84 (14)       | 93 (65\(^e\))  |
| 2     | \(-C{\text{O}}_{2}{\text{t-Bu}}\) | 35b          | 69            | 16/84     | 76 (8)        | 94 (61)         |
| 3     | \(-\text{SO}_2\text{Ph}\) | 35c          | 79            | 78/22     | 88 (62\(^e\)) | 92 (17\(^e\))  |
| 4     | \(-\text{PO(OMe)}_2\) | 35d          | 62            | 85/15     | >94 (55\(^e\)) | 80 (7)         |
| 5     | \(-\text{CN}\) | 35e          | 70\(^d\)     | 50/50     | 94 (36\(^e\)) | >94 (34\(^e\)) |
| 6     | \(-\text{NBoc}_2\) | 35f          | 78            | 73/27     | 80 (56\(^e\)) | 84              |
| 7     | \(-\text{Ph}\) | 35g          | 74            | 45/55     | >90 (33\(^e\)) | >92 (41)       |
| 8     | \(-\text{BnO}_2{\text{C}}{\text{=C}}{\text{O}}_{2}{\text{Bn}}\) | 35h          | 79            | 5/95\(^e\) | —             | 64              |
| 9     | \(-\text{Ph}\) | 35i          | 66            | 36/64     | >94 (24\(^e\)) | >94 (42\(^e\)) |

\(^a\) 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.

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 (\(/{C_6}\))-\((/Z)\))-42 as well as its full deprotection was carried out. The N-Fmoc protection of the fully deprotected (\(/{C_6}\))-\((/Z)\))-42 was then successfully performed, showing the potency of these type of analogues in peptidomimetics and in peptide solid-phase synthesis.
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 bromo-fluorocarbene that adds into 46 to form the corresponding bromo-fluorocyclopropane 47. Disrotatory electrocyclic ring opening of the unstable cyclopropane 47 spontaneously occurs at room temperature with bromine 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, fluoroolesins, fluoro-β-lactams, fluoroaziridines, fluoroepoxides, fluorocyclopropanes, fluorodienes... Those fluorinated building blocks find applications in various fields, such as pharmaceuticals or agrochemicals.

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Biographical sketch

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