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par

Pavel Ivashkin

Synthesis of original fluorinated cyclopropylcarboxylates

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Devant le jury composé de :

Pr André Charette	Université de Montréal	Rapporteur
Dr Christophe Meyer	ESPCI ParisTech	Rapporteur
Pr Günter Haufe	Université de Münster	Examinateur
Pr Bruno Linclau	University of Southampton	Examinateur
Pr Philippe Jubault	INSA de Rouen	Examinateur
Dr Samuel Couve-Bonnaire	INSA de Rouen	Examinateur
Pr Xavier Pannecoucke	INSA de Rouen	Examinateur

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Abbreviations

Ac	Acetyl
ACN	Acetonitrile
Ad_N	Nucleophilic addition
Ar	Aryl
Bn	Benzyl
CAO	Copper-containing monoamine oxidase
CNS	Central nervous system
DAST	Diethylaminosulfur trifluoride
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
de	Diastereomeric excess
dr	Diastereomer ratio
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DIEA	Diisopropylethylamine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EC_{50}	Effective concentration 50 (50% response)
EDBFA	Ethyl dibromofluoroacetate
ee	Enantiomeric excess
EtOAc	Ethyl acetate
Glu	Glutamate
GPCR	G-protein-coupled receptor
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOESY	Heteronuclear Overhauser effect spectroscopy
HRMS	High resolution mass spectra
IC_{50}	Inhibitory concentration 50 (50% response)
Im	Imidazole
J	Spin-spin coupling constant
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
LUMO	Lowest-energy unoccupied molecular orbital
MAD	Methylaluminium bis(2,6-di-tert-butyl-4-methylphenoxide)
MAO	Monoamine oxidase
mCPBA	*m*-chloro(peroxybenzoic) acid
mGluR	Metabotropic glutamate receptor
MIRC	Michael-initiated ring closure
NFSI	N-fluorobenzenesulfonimide
PBS	Phosphate-buffered saline
PE	Petroleum ether
PMP	*p*-methoxyphenyl
rt	Room temperature (*ca* 23°C)
S_N2	Synchronous nucleophilic substitution
TBAF	Tetrabutylammonium fluoride

TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBS	N-*tert*-butylsalicyladimine
THF	Tetrahydrofurane
Tf	Trifluoromethanesulfonate
TFDA	Trimethylsilyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Si(CH_3)_3$)
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TS	Transition state

Contents

Introduction

For several decades, fluorine occupies a privileged place in organic chemistry. Three main distinctive features put it into the focus of continuing research: fluorine is the smallest heteroatom accessible for an organic chemist. At the same time it is the most electronegative element, so once introduced into an organic molecule it can significantly alter the local charge distribution in its vicinity and/or the total dipole moment. This strong electronic effect together with the minimal steric perturbation resulting from the introduction of a fluorine atom, result in enormously wide application of organofluorine compounds in medicinal chemistry. Finally, due to the strong carbon-fluorine bonds, organofluorine compounds are thermally and chemically stable – the property that can be illustrated by the wide application of PTFE polymer but also by more subtle effects on the metabolic stability of the fluorinated bioactive molecules. Besides that, heavily fluorinated molecules tend to form a distinct phase, immiscible with the usual organic solvents – phenomenon lying in the basis of the fluorous chemistry.

Given the well-pronounced and specific effects of fluorine on the properties of organic compounds, it is not surprising that a great deal of effort has been directed towards the development of new and improved methods of synthesis of organofluorine compounds. However, despite the long-lasting interest to this field, the task of selective incorporation of fluorine atoms and fluorinated groups is far from completion.

Among the aliphatic organofluorine compounds, a special sub-class is constituted by the fluorinated small cycles, in particular, cyclopropanes. Cyclopropane has a well-defined, rigid structure making it one of the usual motifs found in a variety of biologically and otherwise active molecules. In addition to its unique stereochemistry, the functionalized cyclopropanes are useful intermediates in the synthesis of several classes of compounds.

From the synthetic point of view, the partially fluorinated cyclopropanes are not a trivial target. The particular structure of cyclopropane makes problematic both the nucleophilic substitution and the deprotonation-electrophilic addition – the most useful methods of fluorination of ordinary aliphatic compounds. As a consequence, the fluorine atoms are rarely introduced into the preformed cyclopropane core, but rather simultaneously (in the case of cyclopropanation with fluorinated carbenes) or before the cyclization step.

The most abundant type of fluorinated cyclopropanes are geminal difluorocyclopropanes, usually synthesized via the [2+1]-cycloaddition of a relatively stable difluorocarbene to the double C-C bonds. By contrast, the monofluorocyclopropanes are much less accessible species, and therefore new synthetic methods are needed in order to explore the potential of this class of compounds.

The present work contains two main related parts. The first one deals with the development of a new method of synthesis of the monofluorinated cyclopropanes with a quaternary fluorinated carbon starting from the electron-deficient alkenes. The second part is devoted to the synthesis of a particular fluorocyclopropane amino acid which is a promising candidate as a group III mGluR agonist.

1. Biologically active fluorinated cyclopropanes: comparison with non-fluorinated parent compounds

In this chapter, three cases will be discussed in which the fluorination of the cyclopropane moiety improved or modified the biological activity of the corresponding cyclopropane-based compounds. While in the case of monoamine oxidase inhibitors (*Section 1a*) the effect of fluorine substituent can apparently vary depending on the target enzyme (lowering of pKa, increase in the ring strain, participation in metal chelation), in bicyclic group II mGluR ligands (*Section 1b*) it can significantly improve the bioavailability without altering the in vitro activity. Finally, in the case of cyclopropane-based group III mGluR agonists (*Section 1c*) the positive effect of fluorine is thought to originate from the increased acidity of the nearby groups.

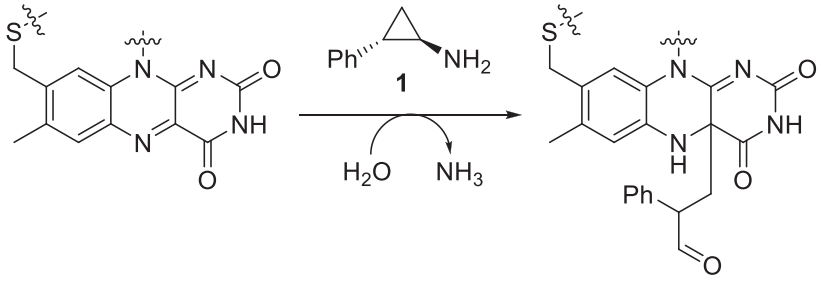
a. Fluorinated analogs of tranylcypromine

FAD-dependent monoamine oxidases (MAO) A and B are involved in the oxidative metabolism of various endogenous amines, including the neuromediators dopamine, serotonin, histamine, adrenaline and noradrenalin, but also of the monoamines ingested with food (e.g. tryptamine). Because of their major role in deactivation of neurotransmitters, CNS-localized MAOs are a very promising target for the treatment of several neurological disorders.[1] For instance, excessive activity of these enzymes can lead to abnormally low levels of dopamine (associated with depression, anxiety, aggression, etc.). MAO B is also involved in the development of Parkinson's disease via production of dopanal and hydrogen peroxide.

Tranylcypromine **1** is an irreversible nonselective inhibitor of MAO A and MAO B. It also competitively inhibits copper-containing monoamine oxidases (CAO)[2] and FAD-dependent histone demethylase LSD1.[3] Because of its low selectivity and numerous side effects it is now primarily used in the difficult cases of major depression disorder. X-ray analysis of a MAO B – tranylcypromine complex indicates the formation of a ring-opened covalent adduct[4] (Scheme 1). As the mechanism of enzymatic

[1] Youdim, M.B.H.; Edmondson, D.; Tipton, K.F.; Nature *Reviews Neurosci.* **2006**, *7*, 29 (and references therein).
[2] Saysell, C. G.; Tambyrajah, W. S.; Murray, J. M.; Wilmot, C. M.; Phillips, S. E. V.; McPherson, M. J.; Knowels, P. F. *Biochem. J.* **2002**, *365*, 809.
[3] Dawn M.; Schmidt, Z.; McCafferty, D.G. *Biochemistry* **2007**, *46*, 4408.
[4] Binda, C.; Li, M.; Hubalek, F.; Restelli, N.; Edmondson, D.E.; Mattevi, A. *Proc. Natl. Acad. Sci. USA* **2003**, 100, 9750.

catalysis by MAOs is subject to debate, the actual pathway leading to the formation of this adduct is not known.



Scheme 1.

The groups of G. Haufe and K. Kirk have published a series of reports dealing with the synthesis of fluorinated analogs of tranylcypromine and evaluation thereof as selective inhibitors of different types of monoamine oxidases. First, they tested several fluorinated cyclopropanes shown on the Fig. 1 against the commercially available tyramine oxidase (member of CAO family).[5] Compounds *cis*-**2**, *trans*-**3** and **6** were found to be more potent than tranylcypromine. The most active (competitive, reversible) inhibitor *cis*-**2** demonstrated the IC_{50} value one order of magnitude higher than the corresponding isomer of tranylcypromine (3.6±1.5 vs. 35±6 μM). Notably, *trans*-**2** is 6 times less active than any isomer of non-fluorinated tranylcypromine. Authors proposed the chelation of Cu by fluorine and amino group of *cis*-**2** in the active center of tyramine oxidase to be responsible for the enhanced activity of this compound.

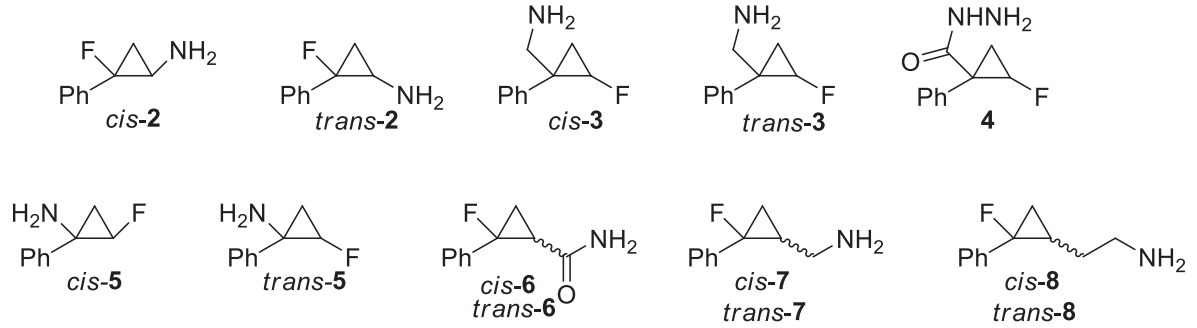


Figure 1.

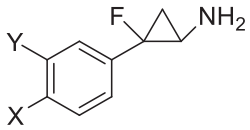
The authors then studied the activity of individual enantiomers of *cis*-**2** against bacterial tyramine oxidase as well as the effect of *para*-substitution in the phenyl group of this compound.[6] Only (*1S,2S*)-isomer of *cis*-**2** was active against tyramine oxidase (similar results were obtained in the clinical

[5] Yoshida, S.; Meyer, O.G.J.; Rosen, T.C.; Haufe, G.; Ye, S.; Sloan, M.J.; Kirk, K.L.; *J. Med. Chem.* **2004**, *47*, 1796.
[6] Rosen, T.C.; Yoshida, S.; Froehlich, R.; Kirk, K.L.; Haufe, G. *J. Med. Chem.* **2004**, *47*, 5860.

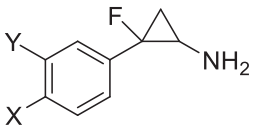
studies of tranylcypromine). *para*-Fluoro- and *para*-chloro-substituted analogs of *cis*-**2** were less active, while methyl group increased the activity 7.2-fold.

The same general effect of fluorine introduction was observed with the recombinant human liver MAO A and MAO B.[7] *Cis*-**2** is more active against both isoforms than its non-fluorinated analog (MAO A: 12 vs. 20 μM; MAO B: 6.4 vs. 19 μM), while *trans*-**2** is less or equally active than the corresponding isomer of **1** (MAO A: 65 vs. 11 μM; MAO B: 19 vs. 19 μM). The authors attributed higher activity of *cis*-**2** to the increase in ring strain in cyclopropane with introduction of fluorine.

Analogs of **2** with substituents in the aromatic ring **9a-g** (Fig. 2) were also evaluated as inhibitors of MAO[8] and tyramine oxidase.[9] Electron-withdrawing groups in the *para*-position of *cis*-**9** are associated with up to 15-fold increase in activity against MAO A compared to the parent *cis*-**2**. This systematic study allowed the authors to identify the isoform-selective inhibitors: *cis*-**9c** (MAO A/MAO B 7:1) and *trans*-**9b** (MAO A/MAO B 1:27).



cis-**9**



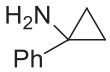
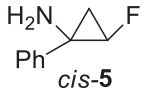
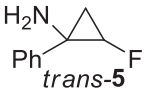
trans-**9**

9a (X = Cl, Y = H)
9b (X = F, Y = H)
9c (X = CF_3, Y = H)
9d (X = Me, Y = H)
9e (X = OMe, Y = H)
9f (X = Y = OMe)

Figure 2.

Noteworthy, compounds *cis*-**5** and *trans*-**5** demonstrated high inversed isoform selectivity compared to their non-fluorinated counterpart (Table 1). Both *cis*- and *trans*-fluorinated isomers were equally active against MAO A, while their difluorinated analog was 100-fold less active.[10] Compounds **5** as well as their *para*-substituted analogs were not active against tyramine oxidase.

Table 1. Inhibitory activity against MAO isoforms (EC_{50} values given in μM).

		 *cis*-**5**	 *trans*-**5**
MAO A	730	1.1	0.9
MAO B	190	290	72

[7] Yoshida, S.; Rosen, T.C.;. Meyer, O.G.J.; Sloan, M.J.; Ye, S.; Haufe, G.; Kirk, K.L. *Bioorg. Med. Chem.* **2004**, *12*, 2645.

[8] Hruschka, S.; Rosen, T.C.; Yoshida, S.; Kirk, K.L.; Froehlich, R.; Wibbeling, B.; Haufe, G. *Bioorg. Med. Chem.* **2008**, *16*, 7148.

[9] Hruschka, S.; Yoshida, S.; Kirk, K.L.; Haufe, G. *J. Fluorine Chem.* **2008**, *129*, 875.

[10] Ye, S.; Yoshida, S.; Froehlich, R.; Haufe, G.; Kirk, K.L. *Bioorg. Med. Chem.* **2005**, *13*, 2489.

Overall, fluorinated analogs of tranylcypromine demonstrate higher activity compared to parent compound, but also allow developing the inhibitors that are selective towards different isoforms of MAO and copper-containing tyramine oxidase.

b. Fluorinated analogs of 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

Glutamate is the major excitatory neurotransmitter in mammalian central nervous system. Metabotropic glutamate receptors (mGluR) are a family of G-protein-coupled receptors (GPCR). mGluR family consists of 8 distinct members (mGlu1 to mGlu8) falling into three groups (mGluR I, mGluR II and mGluR III).[11] mGluR family members mediate synaptic transmission and regulate transmission, neuronal excitability and plasticity via variety of molecular mechanisms.[12] mGluR dysfunction is associated with a number of pathological states, such as anxiety, panic, depression and schizophrenia.[11,13]

Numerous group-selective agonists have been developed, including both competitive and non-competitive (allosteric) variants. While competitive ligands usually demonstrate obvious structural similarity to the parent glutamate, the non-competitive ligands have much more diverse structures.

Typical feature of the best group I-selective competitive ligands is the incorporation of an aromatic ring into the Glu side chain as shown in Figure 3 (DHPG, LY367385). At the same time, in the case of group II mGluR the strategy of conformational restriction was very successful, as exemplified by highly potent and group-selective ligands LY354740 and LY341495 (Fig. 3).

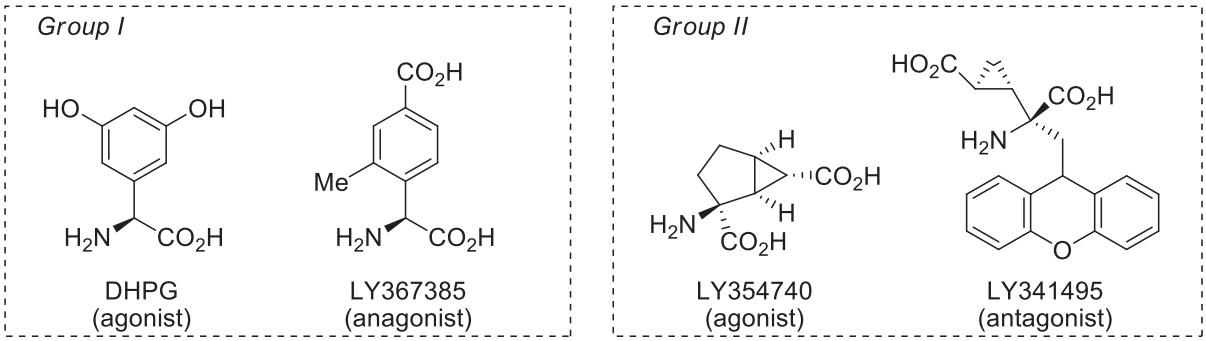


Figure 3.

[11] Swanson, C.J.; Bures, M.; Johnson, M.P.; Linden, A.M.; Monn, J.A.; Schoepp, D.D. *Nat. Rev. Drug Discov.* **2005**, *4*, 131.
[12] Kew, J.N.C.; Kemp, J.A. *Psychopharmacology* **2005**, *179*, 4.
[13] Meldrum, B.S. *J. Nutrition* **2000**, *130*, 1007S.

2-Amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid **10** mimics the fully extended conformation of Glu, and is one of the most successful scaffolds selective for mGluR II group. Both agonists[14] (**10**, **11**) and antagonists[15] (**12**, **13**) with excellent activity and group selectivity were developed on the basis of this common structure (Fig. 4).

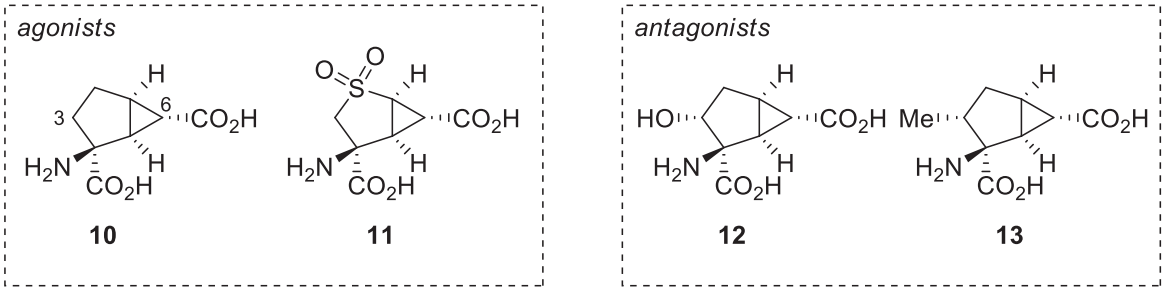


Figure 4.

Introduction of fluorine substituents in the vicinity of ionizable groups in **10** (positions 3 and 6) was considered as an optimal strategy to test the influence of altered pKa on the receptor affinity and therefore assess more active and/or selective ligands.[16] Therefore, fluorinated analogs **14**-**17** were synthesized (Fig. 5).[17]

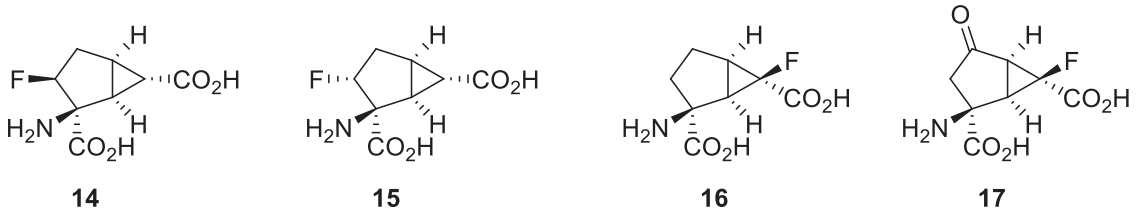


Figure 5.

Compounds **10**, **14** and **16** exhibited almost the same in-vitro agonist activity against mGluR2/3 (IC_{50} for mGluR2: 18.3, 29.4, 16.6 nM, respectively). Further modification of the fluorocyclopropane resulted in the ketone **17** which was *ca* 30 times more active than the parent **10** (IC_{50} for mGluR2: 0.57 nM). At the same time, antipsychotic effect in a rat model following oral administration of **10**, **14** and **17**

[14] a) Monn, J.A.; Valli, M.J.; Massey, S.M., Wright, R.A.; Salhoff, C.R.; Johnson, B.G.; Howe, T.; Alt, C.A.; Rhodes, G.A.; Robey, R.L.; Griffey, K.R.; Tizzano, J.P.; Kallman, M.J.; Helton, D.R.; Schoepp, D.D. *J. Med. Chem* **1997**, *40*, 528; b) Rorick-Kehn, L.M.; Johnson, B.G.; Burkey, J.L.; Wright, R.A.; Calligaro, D.O.; Marek, G.J.; Nisenbaum, E.S.; Catlow, J.T.; Kingston, A.E.; Giera, D.D.; Herin, M.F.; Monn, J.A.; McKinzie, D.L.; Schoepp, D.D. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 308.

[15] (a) Knoflach, F.; Woltering, T.; Adam, G.; Mutel, V.; Kemp, J.A. *Neuropharmacology* **2001**, *40*, 163; (b) Dominguez, C.; Prieto, L.; Valli, M.J.; Massey, S.M.; Bures, M.; Wright, R.A.; Johnson, B.G.; Andis, S.L.; Kingston, A.; Schoepp, D.D.; Monn, J.A. *J. Med. Chem.* **2005**, *48*, 3605.

[16] Nakazato, A. in "Fluorine in medicinal chemistry and chemical biology"; Ojima, I., Ed.; Wiley-Blackwell, 2009.

[17] Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *J. Med. Chem.* **2000,** *43,* 4893.

demonstrated the dramatic change of bioavailability upon introduction of fluorine atom: effective dose (ED_{50}) was 5-20 times lower for **14** and ca. 17-300 times lower for **17**, depending on the behavioral criterion used.[17,18]

The same authors have studied the effect of fluorine substitution of the antagonist activity of 3-hydroxy analog **12**. Some of the tested compounds are shown on the Fig. 6.[19] Again, similar level of binding affinity was observed for **18** and its nonfluorinated parent compound **12**. Further improvement in activity was achieved by converting the 3-hydroxyl into the corresponding ether, the best one being 3,4-dichlorobenzyl ether **22a**. Comparison of **22a** and its non-fluorinated analog 2**0** revealed the same level of binding affinity (2.51 vs. 2.38nM) and slightly lower antagonist activity (IC_{50} 34.2 vs. 20.0 nM). Most importantly, the bioavailability was 3 times higher for the fluorinated antagonist **22a** (10.9 vs. 3.6%).[19c]

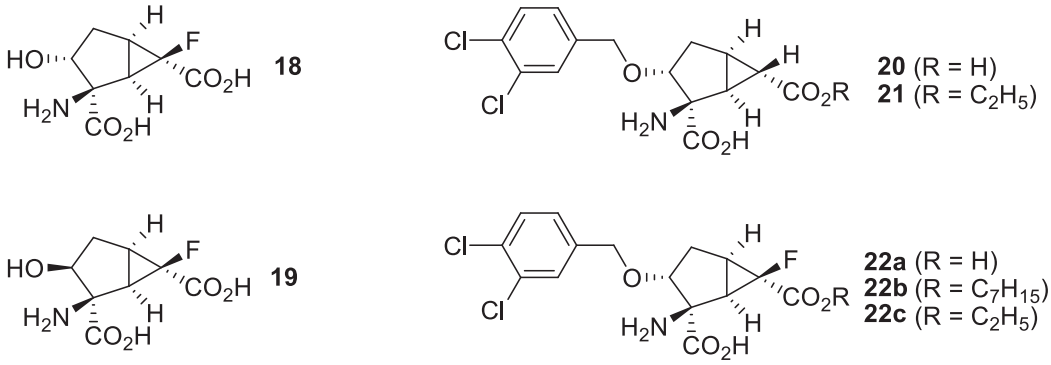


Figure 6.

In order to further improve the bioavailability of the newly developed antagonists, the authors have prepared a number of derivatives via functionalization of the carboxylic groups in **18**, **20** and **22a**.[20] Among numerous 6-esterified derivatives the heptyl ester **22b** was identified as most efficient prodrug on the basis of in-vitro hydrolysis by rat, monkey and human liver fractions and bioavailability experiments in rats and monkeys. Noteworthy, the fluorine atom dramatically enhances the rate of enzymatic hydrolysis as shown for the ethyl esters **21** and **22c** (17.8% vs. 95.9%). As a consequence,

[18] Takamori, K.; Hirota, S.; Chaki, S.; Tanaka, M. *Life Sciences* **2003**, *73*, 1721.

[19] (a) Nakazato, A.; Sakagami, K.; Yasuhara, A.; Ohta, H.; Yoshikawa, R.; Itoh, M.; Nakamura, M.; Chaki, S. *J. Med. Chem.* **2004**, *47*, 4570; (b) Chaki, S.; Yoshikawa, R.; Hirota, S.; Shimazaki, T.; Maeda, M.; Kawashima, N.; Yoshimizu, T.; Yasuhara, A.; Sakagami, K.; Okuyama, S.; Nakanishi, S.; Nakazato, A. *Neuropharmacology* **2004**, *46*, 457; (c) Yasuhara, A.; Sakagami, K.; Yoshikawa, R.; Chaki, S.; Nakamura, M.; Nakazato, A. *Bioorg. Med. Chem.* **2006**, *14*, 3405.

[20] Yasuhara, A.; Nakamura, M.; Sakagami, K.; Shimazaki, T.; Yoshikawa, R.; Chaki, S.; Ohta, H.; Nakazato, A. *Bioorg. Med. Chem.* **2006**, *14*, 4193. b) Nakamura, M.; Kawakita, Y.; Yasuhara, A.; Fukasawa, Y.; Yoshida, K.; Sakagami, K.; Nakazato, A. *Drug Metab. Dispos.* **2006**, *34*, 369.

much higher bioavailability in rats was observed for fluorinated (**22c**) compared to non-fluorinated ethyl ester (**21**) was observed (66.6% vs. 20.2%).

Sakagami et al. have also synthesized the fluorinated analog of LY341495 (Fig. 3). Again, the fluorinated analog demonstrated similar affinity for mGluR2 compared to LY341495 (IC_{50} 3.49 vs. 2.90), while the oral availability increased significantly (fivefold increase in maximum plasma concentration following oral administration to rats).[21]

c. Fluorinated α-aminocyclopropanecarboxylic acids (mGluR III agonists)

Selective agonists of group III mGluR can potentially be used for the treatment of a number of neurological disorders, including anxiety,[13a] neuropathic pain,[22] brain trauma[23] and Parkinson's decease.[24]

Potent group III-selective competitive ligands are often characterized by an additional acidic group[25] in the Glu side chain such as carboxylate or doubly ionizable phosphonate (Fig. 7). The prototypic ligand *L*-AP4 is a selective group III agonist, but does not discriminate between group III types: mGluR4 (EC_{50} in rats 0.5-1 μM), mGluR6 (EC_{50} in rats 0.6-0.9 μM) and mGluR8 (EC_{50} in rats 0.6-0.7 μM). Several type-selective competitive agonists have been reported: *homo*-AMPA (mGluR6, 58 μM), DCPG[26] (mGluR8, 31 nM), but not mGluR4,7-selective ones. By contrast, positive allosteric modulators[27] are known that are selective towards mGluR4 (VU0003423,[28] VU0359516[29]) and mGluR7 (AMN082[30]) (Fig.8).

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[21] Sakagami, K.; Yasuhara, A.; Chaki, S.; Yoshikawa, R.; Kawakita, Y.; Saito, A.; Taguchi, T.; Nakazato, A. *Bioorg. Med. Chem.* **2008**, *16*, 4359.

[22] Chen, S.-R.; Pan, H.-L. *J. Pharmacol. Exp. Ther.* **2005**,*312*, 120.

[23] Bruno, V.; Battaglia, G.; Copani, A.; D'Onofrio, M.; Di Iorio, P.; De Blasi, A.; Melchiorri, D.; Flor, P.J.; Nicoletti, F.; *J. Cereb. Blood Flow Metab.* **2001**, *21*, 1013.

[24] Conn, P.J.; Battaglia, G.; Marino, M.J.; Nicoletti, F. *Nat. Rev. Neurosci.* **2005**, *6*, 787.

[25] Importance of additional acidic group is discussed in: Selvam, C.; Goudet, C.; Oueslati, N.; Pin, J.P.; Acher, F.C. *J. Med. Chem.* **2007**, *50*, 4656.

[26] Thomas, N.K.; Wright, R.A.; Howson, P.A.; Kingston, A.E.; Schoepp, D.D.; Jane, D.E. *Neurophamacology* **2001**, *40*, 311.

[27] These ligands bind to mGluR outside of the glutamate site and enhance the response to endogeneous glutamate.

[28] Niswender, C.M.; Johnson, K.A.; Weaver, C.D.; Jones, C.K.; Xiang, Z.; Luo, Q.; Rodriguez, A.L.; Marlo, J.E.; de Paulis, T.; Thompson, A.D.; Days, E.L.; Nalywajko, T.; Austin, C.A.; Williams, M.B.; Ayala, J.E.; Williams, R.; Lindsley, C.W.; Conn, P.J. *Mol. Pharmacol.* **2008**, *74*, 1345.

[29] Zhou, Y.; Niswender, C.M.; Luo, Q.; Conn, P.J.; Lindsley, C.W.; Hopkins, C.R. *ACS Chem. Neurosci.* **2010**, *1*, 411.

[30] Mitsukawa, K.; Yamamoto, R.; Ofner, S.; Nozulak, J.; Pescott, O.; Lukic, S.; Stoehr, N.; Mombereau, C.; Kuhn, R.; McAllister, K.H.; van der Putten, H.; Cryan, J.F.; Flor, P.J. *Proc. Natl. Acad. Sci USA* **2005**, *102*, 18712.

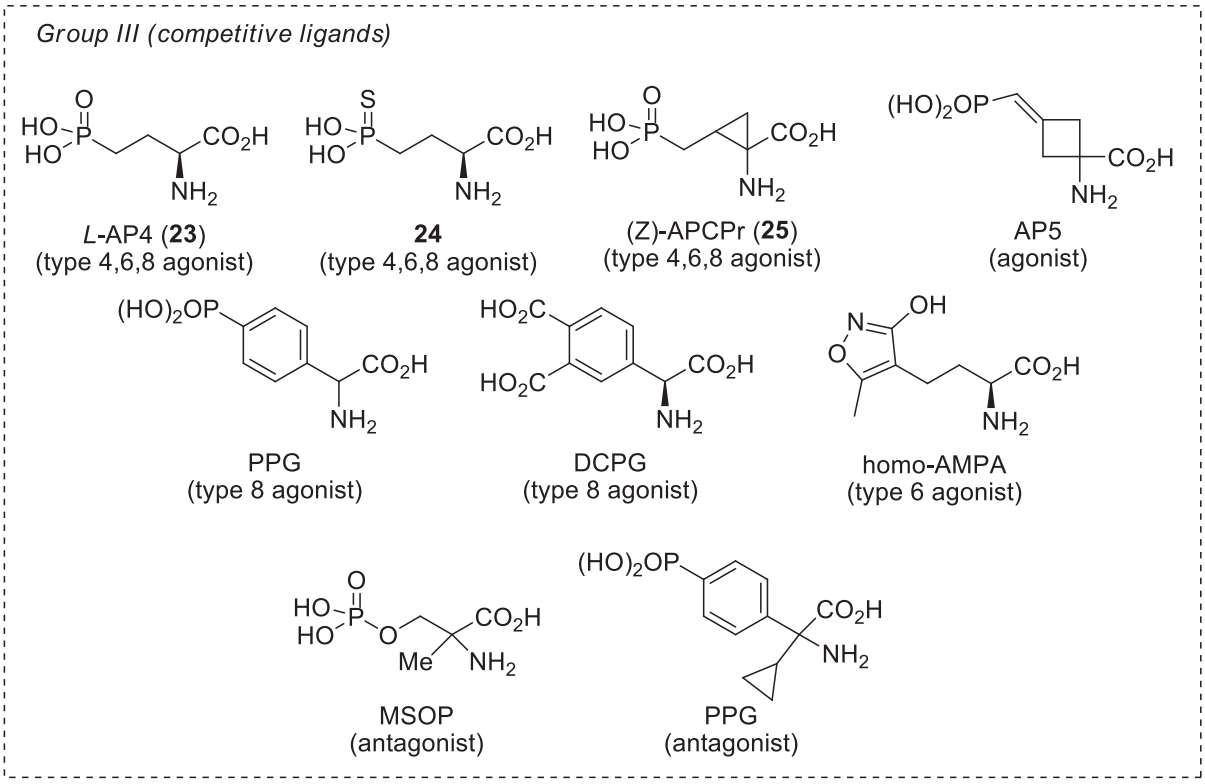


Figure 7.

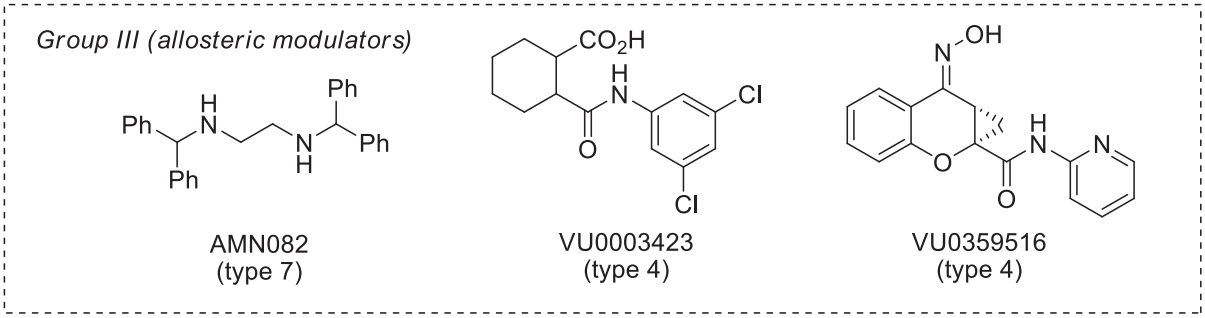


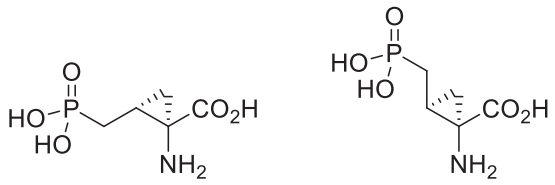
Figure 8.

Several conformationally restricted analogs of *L*-AP4 have been prepared on the basis of cyclopropane, cyclobutane and cyclopentane rings, however, most of these molecules were less active than *L*-AP4. The only exception was (1S,2R)-APCPr (**25**) [31,32] which demonstrates almost the same activity and type selectivity as *L*-AP4.

[31] Synthesis of racemic *cis*- and *trans*-APCPr and electrophysiological studies thereof: Kroona, H.B.; Peterson, N.L.; Koerner, J.F.; Johnson, R.L. *J. Med. Chem.* **1991**, *34*, 1692.

[32] Synthesis of individual stereoisomers of APCPr and studies on agonist activity against recombinant group III mGluRs: Sibille, P.; Lopez, S.; Brabet, I.; Valenti, O.; Oueslati, N.; Gaven, F.; Goudet, C.; Bertrand, H.-O.; Neyton, J.; Marino, M.J.; Amalric, M.; Pin, J.-P.; Acher, F.C. *J. Med. Chem*. **2007**, *50*, 3585.

Cyclopropane (1*S,*2*R*)-**25** demonstrates the agonist activity profile[32] similar to that of a prototype linear compound **24** ($mGluR_4$: 0.72 vs. 0.69 μM; $mGluR_7$: 602 vs. 800 μM; $mGluR_8$: 0.34 vs. 0.56 μM), therefore indicating at partial matching of cyclopropane-restricted conformation and the binding pocket of mGluR. Epimeric (1*S,*2*S*)-**25** (Fig. 9) is a slightly less active, partial agonist with the similar selectivity against mGluR types 4, 6, 7 and 8. Other stereoisomers of **25** are much less active, as anticipated from the inversed configuration at α-position with respect to glutamate and **23**.



(1*S*,2*R*)-**25** (1*S*,2*S*)-**25**

Figure 9.

The same group reported a two-fold increase in the agonist activity for thiophosphonate **24** compared to phosphonate **23**.[25] This change was attributed to the increased acidity of thiophosphonic group resulting in complete ionization at physiological pH.

The compatibility of cyclopropane scaffold with the agonist activity in APCPr **25** and the positive effect of the increased acidity illustrated by thiophosphonate **23** motivated our group to prepare the fluorinated analogs of APCPr in an attempt to develop more potent agonists and study the effect of fluorination on receptor type selectivity.

Nine racemic fluorinated analogs of APCPr **26**-**31** depicted in the Fig. 10 were tested against the $mGlu_4$ receptor expressed in HEK293 cells.[33] Closest analog of APCPr, phosphonate *cis*-**26** demonstrated the best agonist activity in the series, being 5 times more potent than the corresponding stereoisomer of APCPr *rel*-(1*S*,2*S*)-**25** and 10 times more potent than glutamate. Increase in activity is assumed to be the result of decreased second pK_a of the fluorinated phosphonate (calculated values; *cis*-**26:** 6.0; *rel*-(1*S*,2*S*)-**25**: 6.7).

[33] Lemonnier, G.; Lion, C.; Quirion, J.-C.; Pin, J.-P.; Goudet, C.; Jubault, P. *Bioorg. Med. Chem.* **2012**, *20*, 4716.

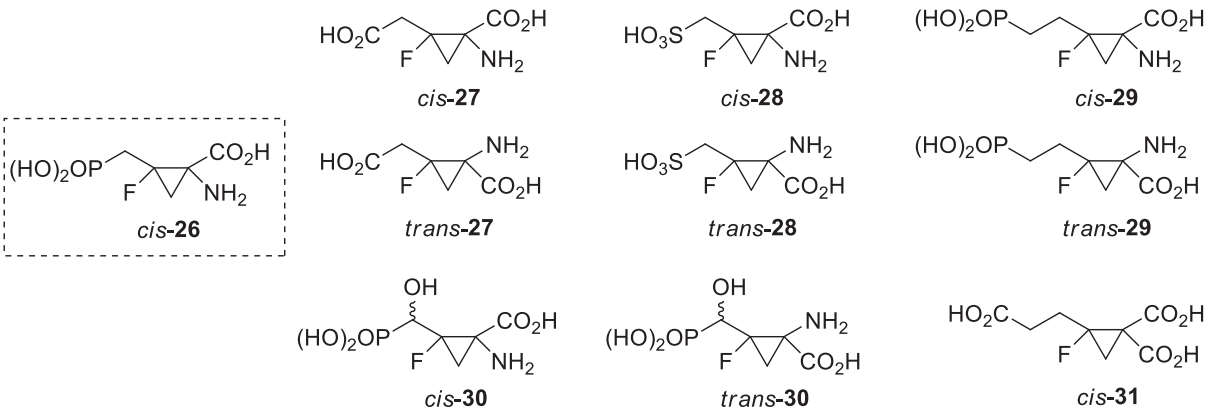
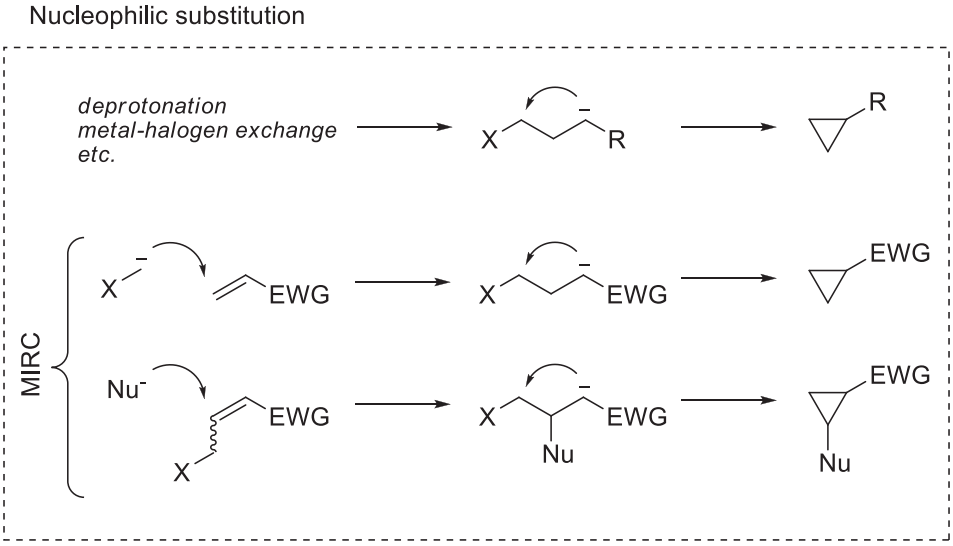

(HO)2OP
CO2H
F
NH2
cis-26
HO2C
CO2H
F
NH2
cis-27
HO3S
CO2H
F
NH2
cis-28
(HO)2OP
CO2H
F
NH2
cis-29
HO2C
NH2
F
CO2H
trans-27
HO3S
NH2
F
CO2H
trans-28
(HO)2OP
NH2
F
CO2H
trans-29
OH
(HO)2OP
CO2H
F
NH2
cis-30
OH
(HO)2OP
NH2
F
CO2H
trans-30
HO2C
CO2H
F
CO2H
cis-31

Figure 10.

2. Methods of synthesis of fluorinated cyclopropanes

a. Overview of the synthetic approaches towards cyclopropanes

Numerous methods of synthesis of cyclopropanes are known (Scheme 2). All kinds of intramolecular nucleophilic substitution (including the tandem reactions such as Michael-induced ring closure (MIRC)), [2+1]-addition of carbenes and metal carbenoids are used extensively in the construction of a three-member ring.[34] Among the other powerful methods are cycloisomerization of enynes,[35] Kulinkovich reaction,[36] electrophilic γ-substitution.[37]



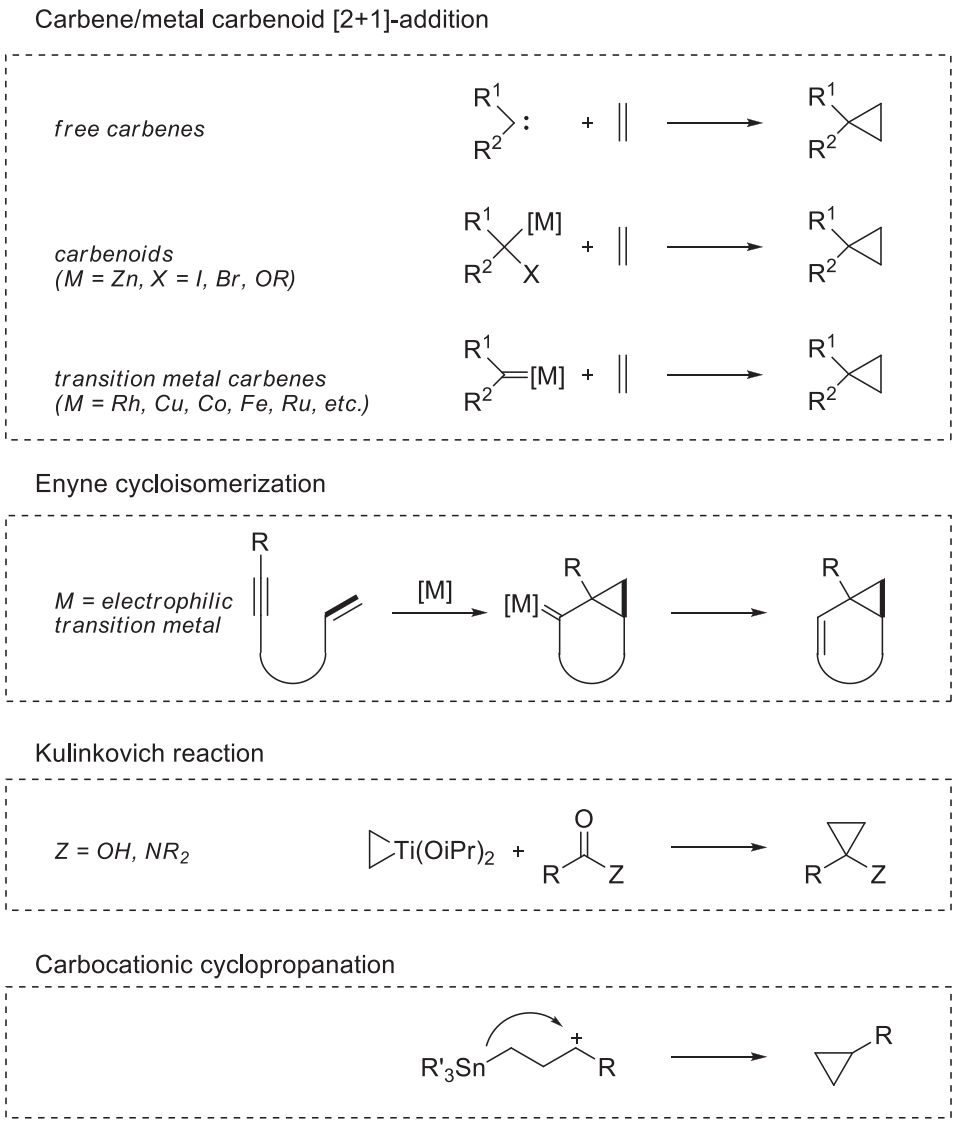
Scheme 2.

[34] (a) Lebel, H.; Marcoux, J.F.; Molinaro, C.; Charette, A.B. *Chem. Rev*. **2003**, *103*, 977; (b) Donaldson, W.A. *Tetrahedron* **2001**, *57*, 8589.

[35] (a) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; (b) Shu, X.Z.; Shu, D.; Schienebecka, C.M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698.

[36] (a) Kulinkovich, O.G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; (b) Cha, J.K.; Kulinkovich, O.G., *Org. React.* **2011**, *77*, 1; (c) Haym, I.; Brimble, M.A. *Org. Biomol. Chem*. **2012**, *10*, 7649.

[37] Yoshida, J.-I. *Synlett* **2006**, 515.



Scheme 2 (continued).

Various methods of asymmetric synthesis of cyclopropanes mainly based on the Simmons-Smith, MIRC, transition metal-catalyzed decomposition of diazo compounds and organocatalytic cyclizations have been reported. [38,34a,39]

In the following sections we will concentrate on the syntheses of fluorinated cyclopropanes.[40] Perfluoroalkylated cyclopropanes fall beyond the scope of this thesis and will not be covered here.[41]

[38] Pellisier, H. *Tetrahedron* **2008**, *64*, 7041.
[39] Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.
[40] Reviews: (a) Taguchi, T.; Okada, M. *J. Fluorine Chem.* **2000**, *105*, 279; (b) Dolbier, W.R., Battiste, M.A. *Chem. Rev.* **2003**, *103*, 1071; (c) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. Eur. J.* **2012**, *18*, 14904.

b. Addition of fluorinated carbenes and main-group metal carbenoids to double bonds

Since it is not always clear whether a particular cyclopropanation reaction involves the free carbene or the metal carbene, we will discuss all the reactions falling between free carbene addition and Simmons-Smith concerted carbenoid transfer in this section. Early examples of generation and cycloaddition reactions of fluorinated carbenes and carbenoids have been rigorously reviewed by Brahms and Dailey.[42]

Probably the most frequently used method of preparation of fluorinated cyclopropanes is the generation of difluorocarbene in the presence of alkenes (Scheme 3).[40b,43] Difluorocarbene is the most stable of all monohalo- and dihalocarbenes and can be generated by a variety of methods, including fragmentation of trihalomethyl anions CF_2X^- (X = Cl, Br), decarboxylation of $CF_2ClCO_2^-$; nucleophilic cleavage of Ph_3PCF_2Br,[44] CF_2ClCO_2Me and $FSO_2CF_2CO_2TMS$[45] (TFDA); Br-centered substitution in CF_2Br_2;[46] photodissociation of difluorodiazirine, reduction of CF_2Br_2 with Zn(0), thermal decomposition of (trifluoromethyl)mercury, cadmium and tin compounds. Some of the recent developments in this field include the use of CF_2BrCO_2Na as a more reactive and non-hygroscopic analog of CF_2ClCO_2Na;[47] $FSO_2CF_2CO_2Me$/KI/TMSCl as a cheaper and more stable alternative to very popular TFDA;[48] use of the Ruppert-Prakash reagent $TMSCF_3$ with TBAT (tetrabutylammonium difluorortriphenylsilicate) under low-temperature conditions or NaI as initiators.[49]

---

[41] Trifluoromethylated cyclopropanes are subject of a recent review: Grygorenko, O.O.; Artamonov, O.S.; Komarov, I.V.; Mykhailiuk, P.K. *Tetrahedron* **2011**, *67*, 803.

[42] Brahms, D.L.S.; Dailey, W.P. *Chem. Rev.* **1996**, *96*, 1585.

[43] Fedorynski, M. *Chem Rev.* **2003**, *103*, 1099.

[44] Burton, D.J.; Naae, D.G. *J. Am. Chem. Soc.* **1973**, *95*, 8467.

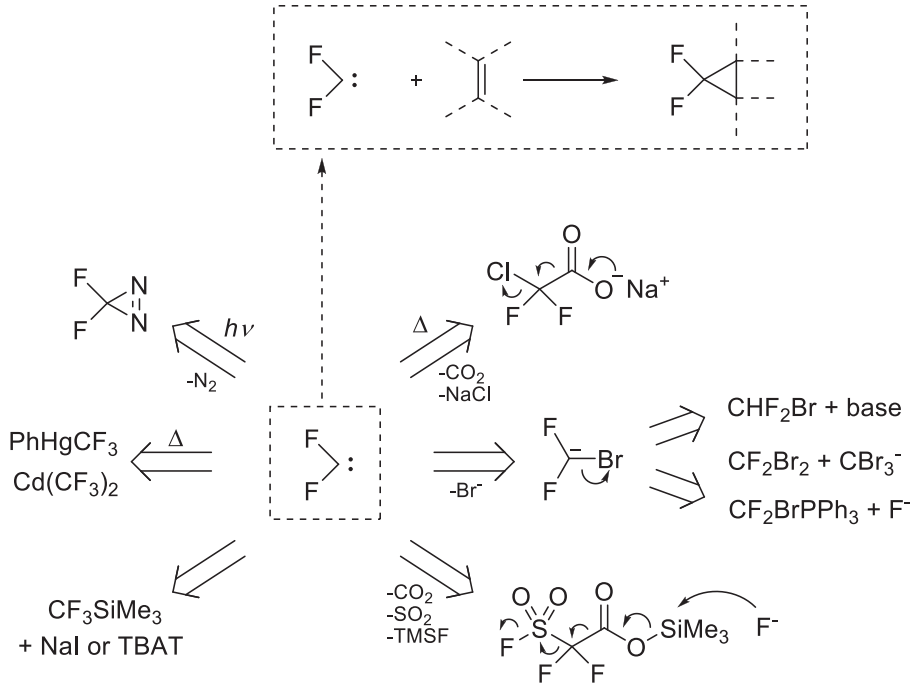
[45] Suitable for cyclopropanation of electron-deficient alkenes such as alkyl acrylates: Tian, F.; Kruger, V.V.; Bautista, O.; Duan, J.-X.; Li, A.R.; Dolbier, W.R.; Chen, Q.Y. *Org. Lett.* **2000**, *2*, 563.

[46] CBr_3^--anion as a nucleophile: Balcerzak, P.; Fedorynski, M.; Jonczyk, A. *J. Chem. Soc., Chem. Commun.* **1991**, 826.

[47] Oshiro, K.; Morimoto, Y.; Amii, H. *Synthesis* **2010**, 2080.

[48] Eusterwiemann, S.; Martinez, H.; Dolbier, W.R. *J. Org. Chem*. **2012**, *77*, 5461.

[49] Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H.S.; Jog, P.V.; Ganesh, S.K.; Prakash, G.K.; Olah, G.A. *Angew. Chem. Int. Ed.* **2011**, *50*, 7153.



Scheme 3.

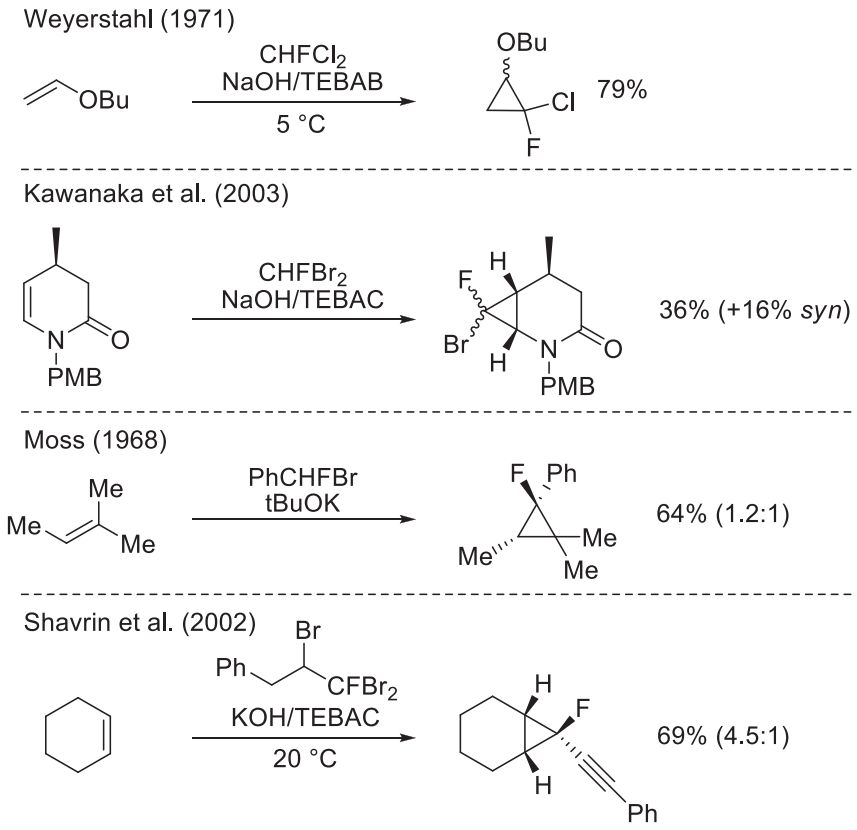
The most frequently used method of *mono*fluorocyclopropanation deals with the base-promoted carbene generation using $CHFCl_2$ and $CHFBr_2$ (Scheme 4).[50] Similarly to difluorocarbene, phase transfer conditions provide highest yields of cyclopropanes.[51] $(CCl_2F)_2CO$, $CFX_3/P(NMe_2)_3/CsF$, $CFX_3/BuLi$ (X = Cl, Br) and $CCl_3F/Mg/LiCl$ were used as alternative sources of halofluorocarbenes.[42] In a similar way, PhCHFCl and PhCHFBr were used as fluoro(phenyl)carbene precursors for cyclopropanation.[52] Finally, fluoro(alkynyl)carbenes were prepared from 1,1,2-tribromo-1-fluoroalkanes under standard basic or phase-transfer conditions and used for the cyclopropanation of several olefins in moderate to good yields and moderate *exo* selectivity.[53]

[50] (a) Zhoua, S.; Zemlicka, J.; Kern, E.R.; Drach, J.C. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 231; (b) Kawanaka, Y.; Kobayashi, K.; Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.; Fujii, A.; Hirai, K.; Naka, M.; Komeno, M.; Odagaki, Y.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2003**, *11*, 1723; (c) Kilbas, B.; Azizoglu, A.; Balci, M. *J. Org. Chem.* **2009**, *74*, 7075; (d) Allmendinger, T.; Felder, E.; Hungalbuehler, E. *Tetrahedron Lett.* **1990**, *31*, 7301; (e) Averina, E.B.; Sedenkova, K.N.; Borisov, I.S.; Grishin, Y.K.; Kuznetsova, T.S.; Zefirov, N.S. *Tetrahedron* **2009**, *65*, 5693; (f) Sedenkova, K.N.; Averina, E.B.; Grishin, Y.K.; Rybakov, V.B.; Kuznetzova, T.S.; Zefirov, N.S. *Eur. J. Org. Chem.* **2010**, 4145.

[51] Weyerstahl, P.; Blume, G.; Mueller, C.*Tetrahedron Lett.* **1971**, *42*, 3869.

[52] (a) Moss, R.A. *Tetrahedron Lett* **1968**, *9*, 1961; (b) Ando, T.; Kotoku, Y.; Yamanaka, H.; Funasaka, W. *Tetrahedron Lett.* **1968**, *9*, 2479.

[53] Shavrin, K.N.; Gvozdev, V.D.; Nefedov, O.M. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 1237.



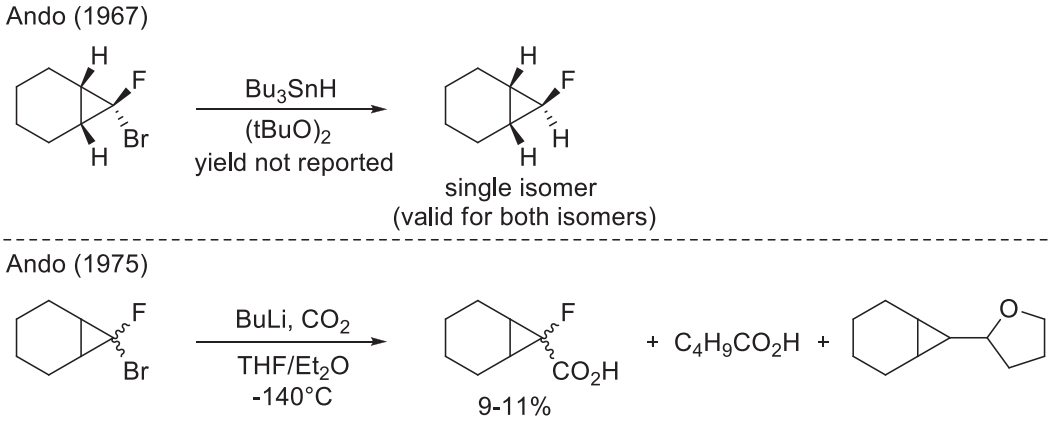
Scheme 4.[54]

Noteworthy, the resulting *gem*-halofluorocyclopropanes can be radically reduced into the corresponding monofluorocyclopropanes generally with retention of configuration (Scheme 5).[55] 1-Bromo-1-fluorocyclopropane has also been converted into the corresponding fluorocyclopropylcarboxylic acid via lithiation-carboxylation, albeit in very low yield.[56]

[54] Here and below the ratio in parentheses is between the isomer shown on the scheme and the alternative one.

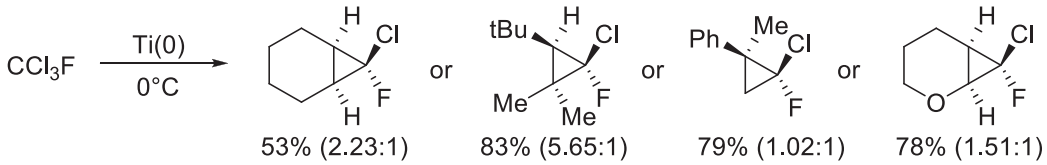
[55] (a) Ando, T.; Namigata, F.; Yamanaka, H.; Funasaka, W. *J. Am. Chem. Soc*. **1967**, *89*, 5712; (b) Oliver, J.P.; Rao, U.V.; Emerson, M.T. *Tetrahedron Lett.* **1964**, *5*, 3419; (c) Ando, T.; Yamanaka, H.; Namigata, F.; Funasaka, W. *J. Org. Chem.* **1970**, *35*, 33; (d) Johnson, W.M.P.; Holan, G.; Jarvis, K.E. *Aust. J. Chem.,* **1986**, *39***,** 271; (e) Kawanaka, Y.; Kobayashi, K.; Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.; Fujii, A.; Hirai, K.; Naka, M.; Komeno, M.; Odagaki, Y.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2003**, *11*, 1723.

[56] Ishihara, T.; Hayashi, K.; Ando, T.; Yamanaka, H. *J. Org. Chem.* **1975**, *40*, 3264.



Scheme 5.

Other reactions that presumably involve the free monofluorinated carbenes were reported. W.R. Dolbier reported an efficient method of generation of CClF in very mild conditions based on the use of Ti(0) prepared in situ from $TiCl_4$ and $LiAlH_4$ (Scheme 6).[57] Electron-rich alkenes provided high yields of *gem*-chlorofluorocyclopropanes, while primary olefins were not reactive enough. Participation of free carbene was postulated based on the comparison of $CCl_3F/TiCl_4/LiAlH_4$, $CBr_2ClF/TiCl_4/LiAlH_4$ and $(CCl_2F)_2CO$/tBuOK carbene precursors.

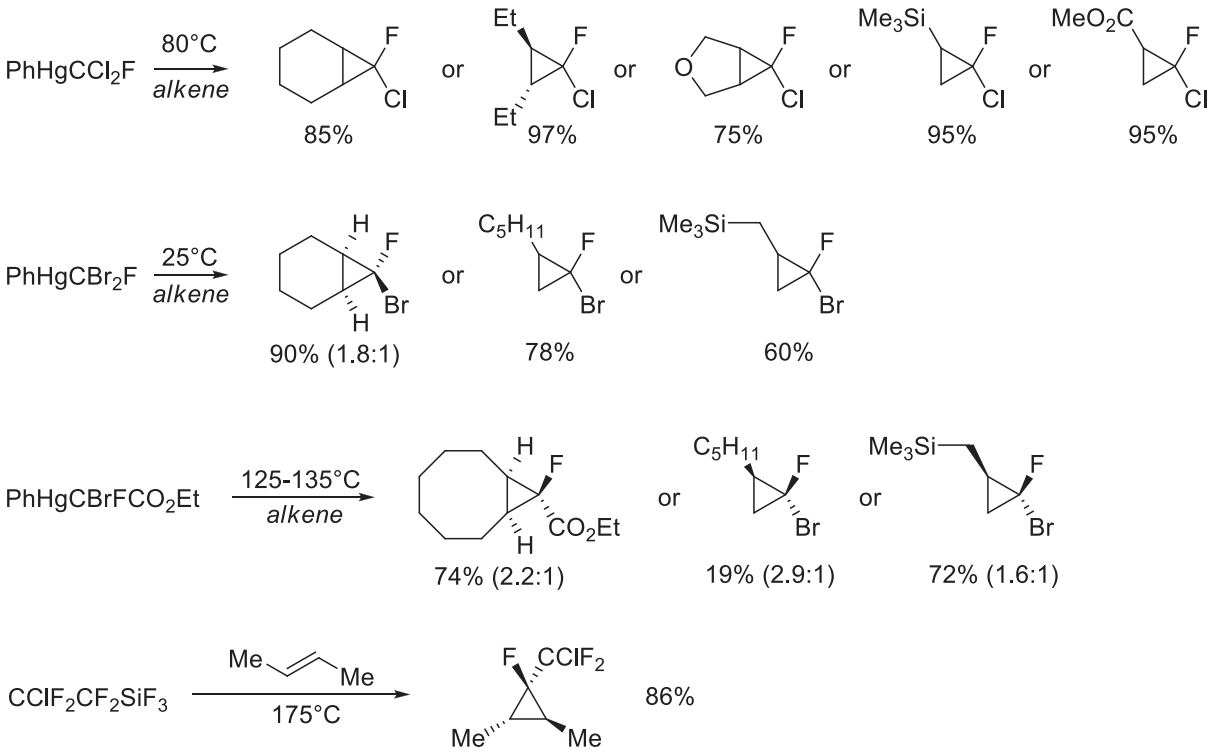


Scheme 6.

One of the most powerful methods of fluorocyclopropanation is based on the thermolysis of organomercury compounds reported by D. Seyferth with co-workers (Scheme 7). High yields of structurally diverse cyclopropanes can be obtained under neutral conditions. Both electron-rich and electron-deficient (such as methyl acrylate, acrylonitrile, trimethyl(vinyl)silane) alkenes react successfully with Seyferth's reagents featuring Cl,[58] Br,[59] CF_3[60] and CO_2Et[61] as substituents. As in the other cases of carbene-mediated cyclopropanation, the reactions are stereospecific with respect to the double bond configuration, but not diastereoselective. Similar thermolytic approach towards

[57] Dolbier, W.R.; Burkholder, C.R. *J. Org. Chem.* **1990**, *55*, 589.
[58] Seyferth, D.; Darragh, K.V. *J. Org. Chem*. **1970**, *35*, 1297.
[59] Seyferth, D.; Haas, C.K.; Hopper, S.P. *J. Organomet. Chem.* **1971**, *33*, C1.
[60] Seyferth, D.; Murphy, G.; Woodruff, R. *J. Organomet. Chem.* **1975**, *92*, 7.
[61] Seyferth, D.; Woodruff, R.A. *J. Org. Chem.* **1973**, *38*, 4031.

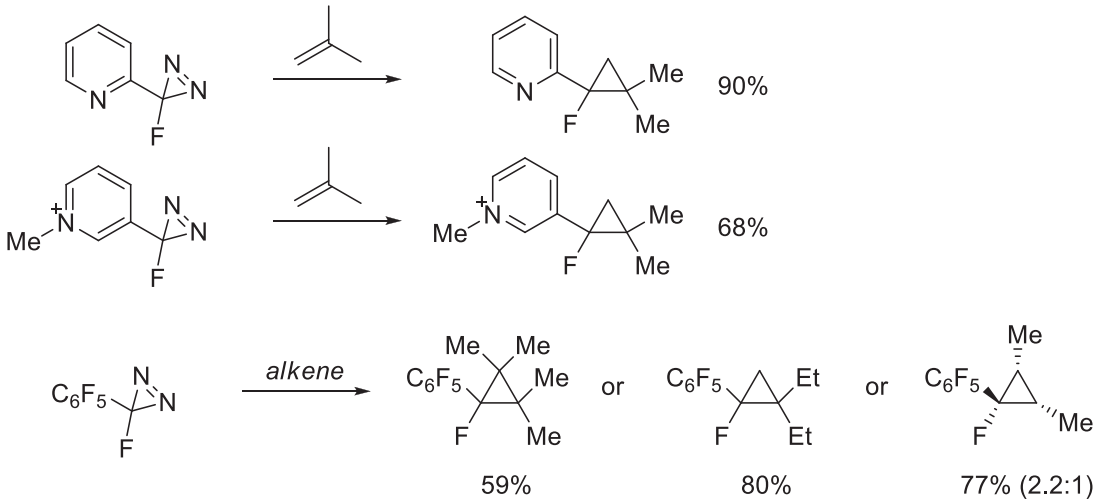
fluorocarbenes was reported by R.N. Haszeldine who used trifluoro(perfluroalkyl)silanes in cyclopropanation of few simple olefins.[62]



Scheme 7.

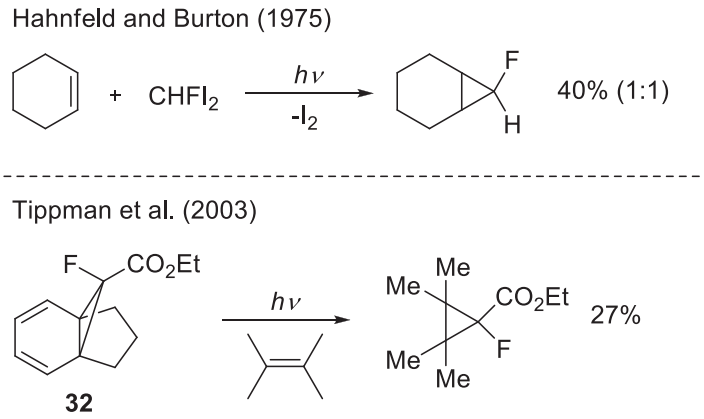
Fluorinated diazirines were extensively used by R.A. Moss and co-workers as precursors of several types of fluorocarbenes. Some of these carbenes were efficient in cyclopropanation reactions, among them fluoro(pentafluorophenyl)carbene,[63] *ortho*- and *meta*-(pyridyl)fluorocarbenes,[64] (phenoxy)fluorocarbene[65] (Scheme 8).

[62] (a) Haszeldine, R.N.; Pool, C.R.; Tipping, A.E.; Watts, R.O. *J. Chem. Soc., Perkin Trans. 1* **1976**, 513; (b) Haszeldine, R.N.; Rowland, R.; Speight, J.G.; Tipping, A.E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 314.
[63] Moss, R.A.; Shen, Y.; Wang, L.; Krogh-Jespersen, K. *Org. Lett.* **2011**, *13*, 4752.
[64] Moss, R.A.; Jang, E.G.; Kim, H.-R.; Ho, G.-J. Baird, M.S. *Tetrahedron Lett.* **1992**, *33*, 1427.
[65] Moss, R.A.; Kmiecik-Lawrynowicz, G.; Krogh-Jespersen, K. *J. Org. Chem.* **1986**, *51*, 2168.



Scheme 8.

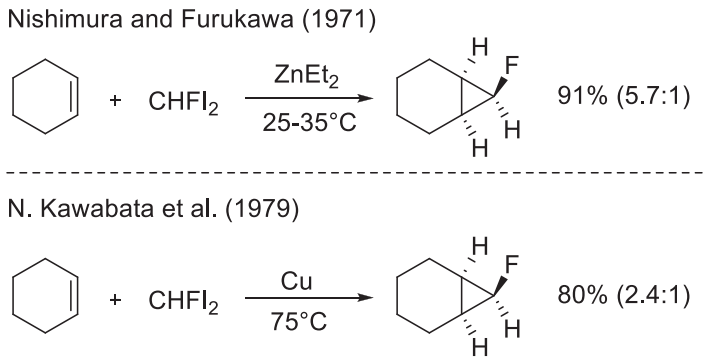
Two other fluorocarbenes capable of [2+1]-addition to alkenes were reported (Scheme 9). Free CHF was generated by Hahnfeld and Burton via photochemical elimination of I_2 from $CHFI_2$.[66] Free (ethoxycarbonyl)fluorocarbene was generated photochemically from the compound **32**.[67]



Scheme 9.

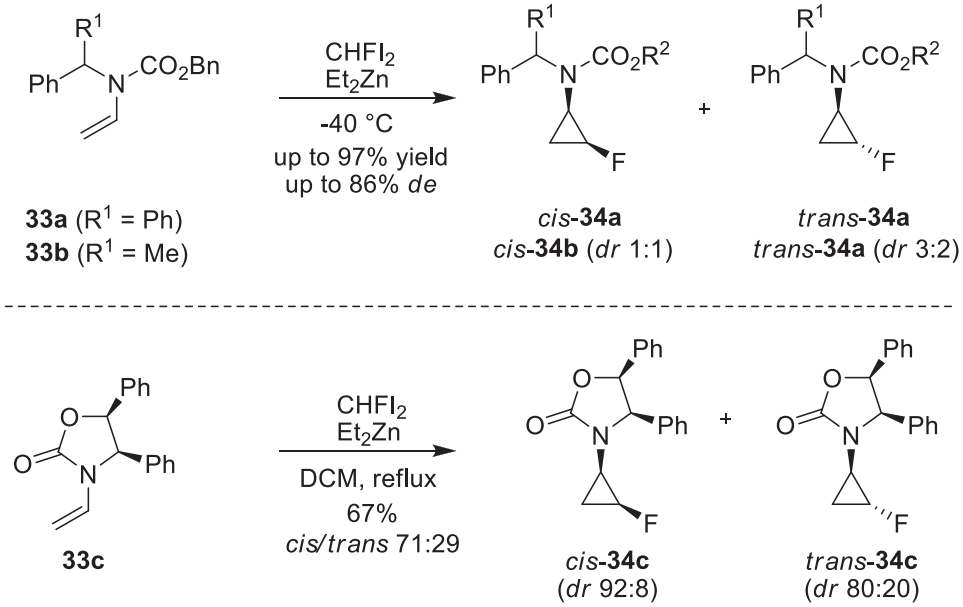
Simmons-Smith reaction is widely used for stereocontrolled cyclopropanation. First example of the Simmons-Smith reaction with a fluorinated zinc carbenoid derived from $CHFI_2$ was reported by Nishimura and Furukawa in 1971 (Scheme 10).[68] Copper-mediated version of this cyclopropanation was reported by N. Kawabata et al.[69]

[66] Hahnfeld, J.L.; Burton, D.J. *Tetrahedron Lett.* **1975**, *22*, 1819.
[67] Tippmann, E.M.; Holinga, G.; Platz, M.S. *Org. Lett.* **2003**, *5*, 4919.
[68] Nishimura, J.; Furukawa, J. *J. Chem. Soc., Chem. Commun.* **1971**, 1375.
[69] Kawabata, N.; Tanimoto, M.; Fujiwara, S. *Tetrahedron* **1979**, *35*, 1919.



Scheme 10.

In three consecutive articles Tamura et al. reported their studies on stereoselective Simmons-Smith cyclopropanation of N-vinylcarbamates (Scheme 11). For N-diphenylmethyl-N-vinylcarbamate **33a** cis/trans ratio up to 93:7 was obtained (yield 90%).[70] In the case of unsymmetrical substrates **33b**, both *cis*- and *trans*-**34b** were obtained as almost equimolar mixtures of diastereoisomers. Using 4,5-diphenyloxazolidin-2-one as a chiral auxiliary, they obtained 67% of cyclopropane **34c** as a mixture of four stereoisomers.[71]

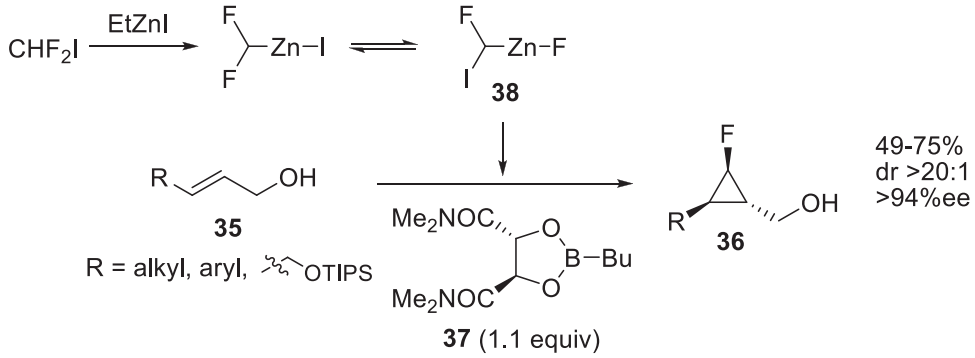


Scheme 11.

[70] (a) Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron Lett.* **1992**, *33*, 3483; (b) Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 3889.

[71] Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron Lett.* **1992**, *33*, 3487.

Very recently the group of A. Charette has reported an improved method of Simmons-Smith monofluorocyclopropanation of allylic alcohols **35** (Scheme 12).[72] Using equimolar amount of chiral dioxaborolane ligand **37** excellent diastereo- and enantioselectivity was observed (dr>20:1; ≥94%ee for monosubstituted *trans*-allylic alcohols). Lower enantioselectivity was observed with a trisubstituted alkene (2-methyl-5-phenylpent-2-en-1-ol), while the *cis*-cinnamic alcohol afforded a 4:1 mixture of diastereomers. The key feature of this method is the use of readily available trihalomethane (CHF_2I instead of $CHFI_2$) which gives rise to the desired zinc carbenoid **38** in situ via the "halogen scrambling" process.



Scheme 12.

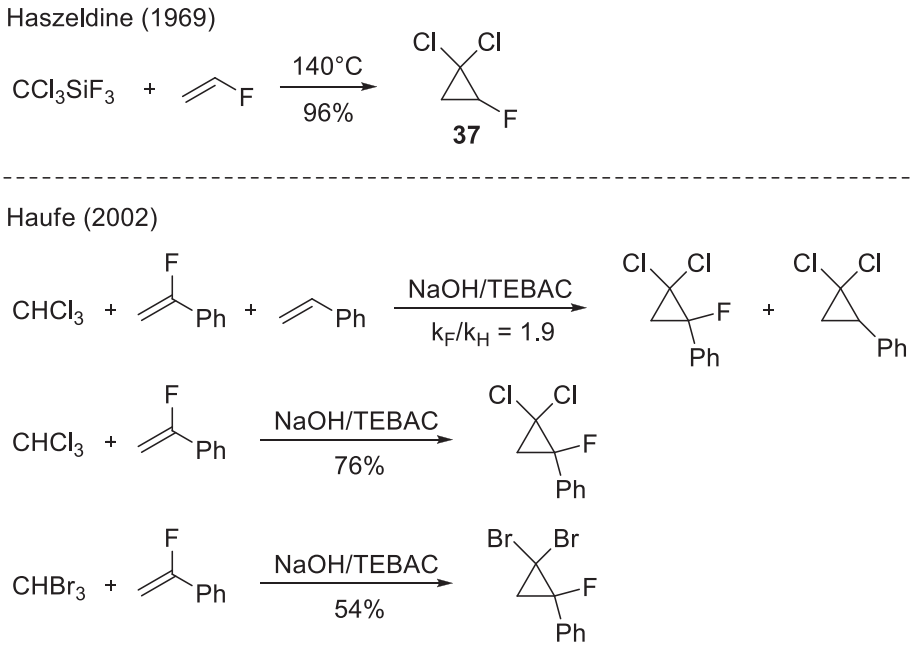
c. Cyclopropanation of fluoroalkenes

Several well-known methods of cyclopropanation, namely [2+1]-addition of carbenes, dipolar addition of diazomethanes, Simmons-Smith reaction and transition metal-catalyzed decomposition of diazo compounds have been applied to fluoroalkenes.

The first example of carbene addition to fluorinated double bonds was reported by R.N. Haszeldine and co-workers. Vapor-phase pyrolysis of CCl_3SiF_3 in excess of fluoroethylene afforded 1,1-dichloro-2-fluorocyclopropane **37** in 96% yield.[73] In 2002 G. Haufe et al. directly compared the reactivity of styrene and α-fluorostyrene towards dichlorocarbene generated from $CHCl_3$ under basic conditions.[74] Remarkably, α-fluorostyrene was found to be slightly more reactive than styrene (k_F/k_H = 1.9). Semi-empirical calculations of the reaction transition state performed by the authors were not able to account for the observed effect of fluorine substitution. Cyclopropanations of 1,1-difluoroalkenes with

[72] Beaulieu, L.B.; Schneider, J.F.; Charette, A.B. *J. Am. Chem. Soc.* **2013**, *135*, 7819.
[73] Fields, R.; Haszeldine, R.N.; Peter, D. *J. Chem. Soc. C* **1969**, 165.
[74] Haufe, G.; Meyer, O.G.J.; Muck-Lichtenfeld, C. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1493.

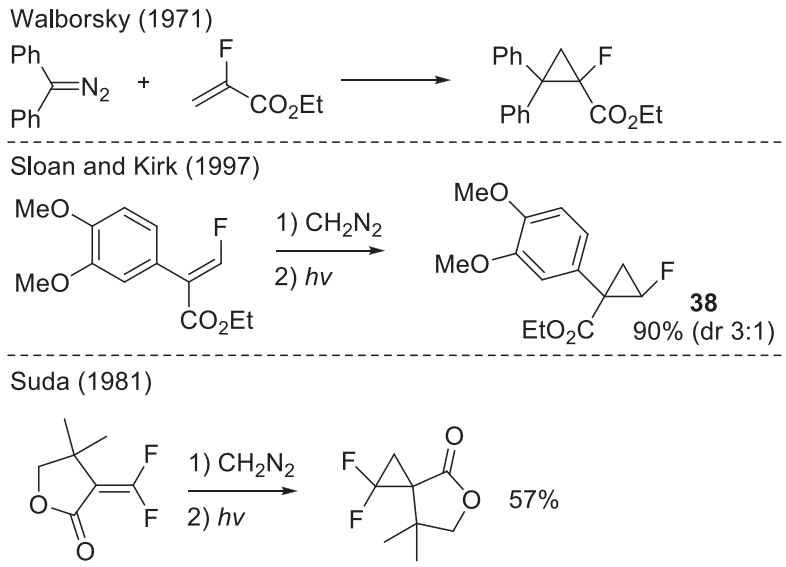
dichlorocarbene,[75,76] dibromocarbene[77] and difluorocarbene[42] have also been reported. More heavily fluorinated cyclopropanes have been prepared from trifluoroalkenes[78] and in the reactions of fluorocarbenes with fluorinated alkenes.[42]



Scheme 13.

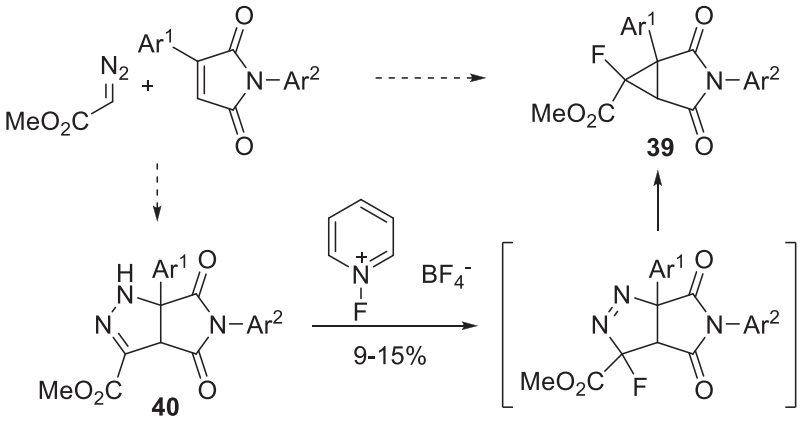
Diazo compounds were used in both catalyzed and non-catalyzed cycloadditions with fluoroalkenes. Diphenyldiazomethane was shown to give a product of cyclopropanation with ethyl α-fluoroacrylate upon heating in pentane/benzene mixture (Scheme 14).[79] Synthesis of 2-fluoro-1-arylcyclopropanecarboxylate **38** was achieved in high yield via dipolar addition of diazomethane with the subsequent photochemical extrusion of N_2.[80,5] 1,1-Difluoroalkenes also successfully react with diazomethane to provide the corresponding *gem*-difluorocyclopropanes.[10,81]

[75] Seyferth, D.; Wursthorn, K.R.; Lim, T.F.O.; Sepelak, D.J. *J. Organomet. Chem.* **1981**, *205*, 301.
[76] Lee, C.C.; Lin, S.-T. *Synthesis* **2000**, 496.
[77] Deem, M.L. *J. Chem. Soc. D Chem. Commun.* **1969**, 993.
[78] (a) Williamson, K.L.; Braman, B.A. *J. Am. Chem. Soc.* **1967**, *89*, 6183; (b) Birchall, J.M.; Fields, R.; Haszeldine, R.N.; Kendall, N.T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1773.
[79] Walborsky, H.M.; Allen, L.E.; Traenckner, H.-J.; Powers, E.J. *J. Org. Chem.* **1971**, *36*, 2937.
[80] Sloan, M.J.; Kirk, K. L. *Tetrahedron Lett.* **1997**, *38*, 1677.
[81] Suda, M. *Tetrahedron Lett.* **1981**, *22*, 1421.



Scheme 14.

Kostikov's group reported an original method of synthesis of α-fluorinated cyclopropylcarboxylates **39** via electrophilic fluorination of pyrazolines **40** that can be readily prepared via dipolar addition of methyl diazoacetate to maleimides. Fluorination leads to extrusion of nitrogen and formation of a mixture of *endo*- and *exo*-isomers of **39** in low yield. [82]

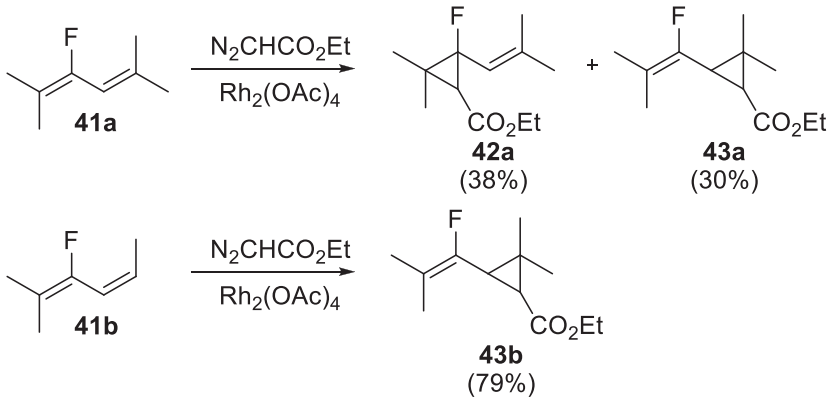


Scheme 15.

Transition metal-catalysed decomposition of diazo compounds in the presence of fluorinated alkenes is one of the most efficient methods of synthesis of fluorocyclopropanes. In their early report Cottens and Schlosser described the first application of rhodium catalysis to the cyclopropanation of

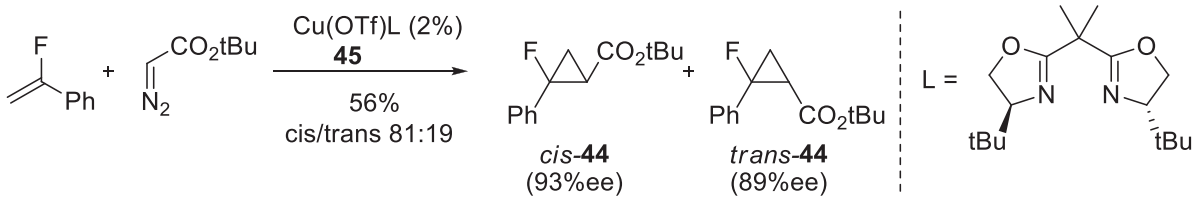
[82] Molchanov, A.P.; Stepakov, A.V.; Boitsov, V.M.; Kostikov, R.R. *J. Fluorine Chem.* **2002**, *114*, 35.

fluorodienes **41a,b**.[83] Almost equimolar mixture of fluorinated and nonfluorinated cyclopropanes **42a/43a** was obtained, while the diene **41b** failed to provide the corresponding fluorocyclopropane.[84]



Scheme 16.

In 2000 the group of G. Haufe reported the first enantioselective synthesis of α-fluorostyrene-derived cyclopropanes **44** using alkyl diazoacetates and a copper-bisoxazoline complex.[85] The best results were obtained with *tert*-butyl diazoacetate and complex **45** as a catalyst (Scheme 17). The reaction demonstrated similar efficiency with 1-fluoro-1-(p-chlorophenyl)ethylene (64%, *ee*(*cis*): 93%, *ee*(*trans*): 91%), but not with (*E*)-1-fluoro-1-phenylpropene or 2-fluorohex-1-ene. In the article, the authors compared the efficiency of several achiral catalysts in the same standard conditions (DCM, 40°C, 6-7h): $PdCl_2$, $Pd(OAc)_2$, $RhCl_3$, $Rh_2(OAc)_4$ all provided the yields ≤25%, while copper catalysts were much more efficient ($[CuOTf]_2C_6H_6$ 39%; $Cu(OAc)_2$ 62%; $Cu(acac)_2$ 93%). Remarkably, complex **45** used in the asymmetric version of this reaction also increased the *cis/trans* selectivity of cyclopropanation (cf. *cis/trans* 50:50 with $Cu(acac)_2$).



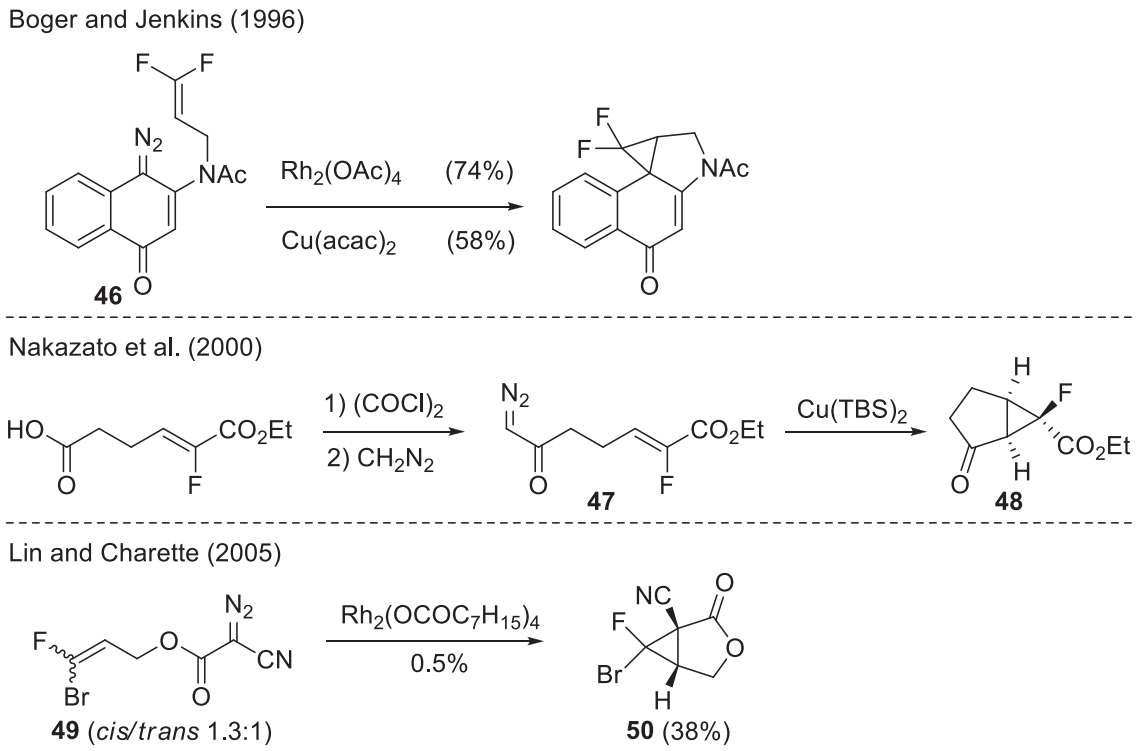
Scheme 17.

[83] Cottens, S.; Schlosser, M. *Tetrahedron* **1988**, *44*, 7127.

[84] The authors explain the difference in terms of electron-donating effect of methyl groups in the cyclopropanation transition state with high zwitterionic character (positive charge localized on the allyl system).

[85] Meyer, O.G.J.; Froehlich, R.; Haufe, G. *Synthesis* **2000**, 1479.

Intramolecular Rh- and Cu-catalyzed cyclopropanation of the difluoroalkene **46** was reported by Boger and Jenkins.[86] $Cu(TBS)_2$[87]-catalyzed cyclopropanation of the *mono*fluoroalkene **47** bearing a diazoketone moiety was described by Nakazato et al.[17] Bicyclic compound **48** was obtained in 27.3% yield (from acid) as a single isomer and was used in the synthesis of group II mGluR ligands (see section 1b). Intramolecular Rh-catalysed cyclopropanation of a *gem*-bromofluoroalkene was reported by Charette, in the course of his studies towards enantioselective cyclopropanation with cyanodiazoacetates.[88] In the presence of rhodium octanoate substrate **49** (used as a 1.3:1 mixture of *cis*- and *trans*-isomers) was converted into **50** in moderate yield.

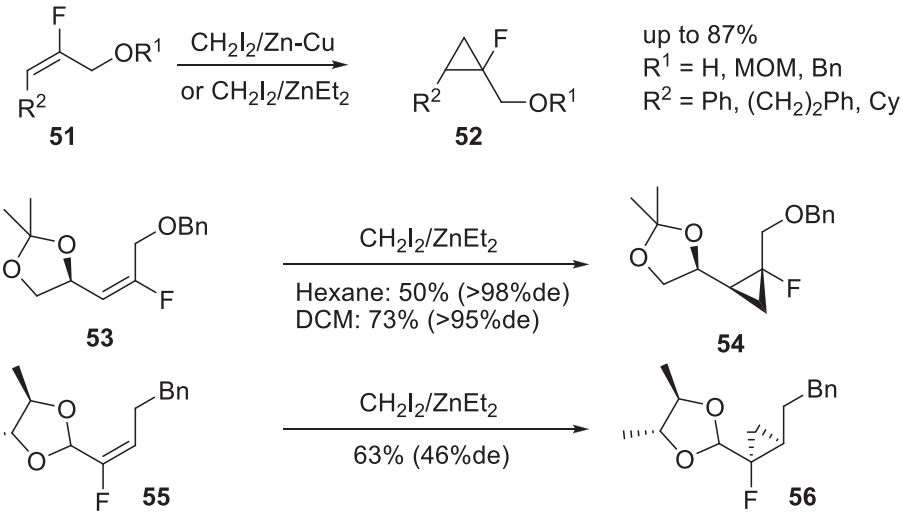


Scheme 18.

Simmons-Smith reaction with monofluorinated allylic ethers **51** was reported by T. Taguchi with co-workers. Using 3-to-15-fold excess of CH_2I_2/Zn-Cu or CH_2I_2/$ZnEt_2$-derived carbenoid reagents the fluorinated cyclopropanes **52** were prepared in moderate to good yield.[89] Glyceraldehyde-derived alkene **53** was converted into the corresponding cyclopropanes **54** with excellent diastereoselectivity. Further studies on non-fluorinated analogs of **53** allowed the authors to conclude that selective

[86] Boger, D.L; Jenkins, T.J. *J. Am. Chem. Soc.* **1996**, *118*, 8860.
[87] Bis(N-*tert*-butylsalicyladimine)-copper(II)
[88] Lin, W.; Charette, A.B. *Adv. Synth. Cat.* **2005**, *347*, 1547.
[89] Marikawa, T.; Sasaki, H.; Mori, K.; Shiro, M.; Taguchi, T. *Chem. Pharm. Bull.* **1992**, *40*, 3189.

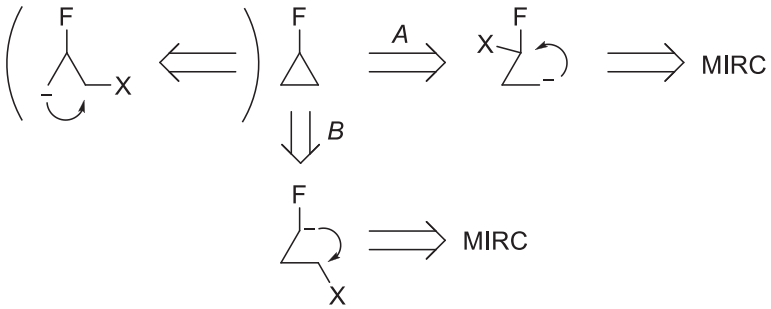
coordination of dioxolane oxygen to zinc carbenoid is the key to high stereoselectivity.[90] Chiral acetal **55** afforded the cyclopropane **56** with much lower diastereoselectivity.[89]



Scheme 19.

d. Intramolecular nucleophilic substitution and Michael-initiated ring closure (MIRC)

Nucleophilic substitution leading to cyclopropanes can be implemented in three possible ways shown on the Scheme 20. So far, fluorinated cyclopropanes were synthesized from substrates bearing fluorine at one of the reacting centers (fluorinated electrophile – pathway *A*, fluorinated nucleophile – pathway *B*). Both these cyclizations have been realized in the course of MIRC cyclopropanation.

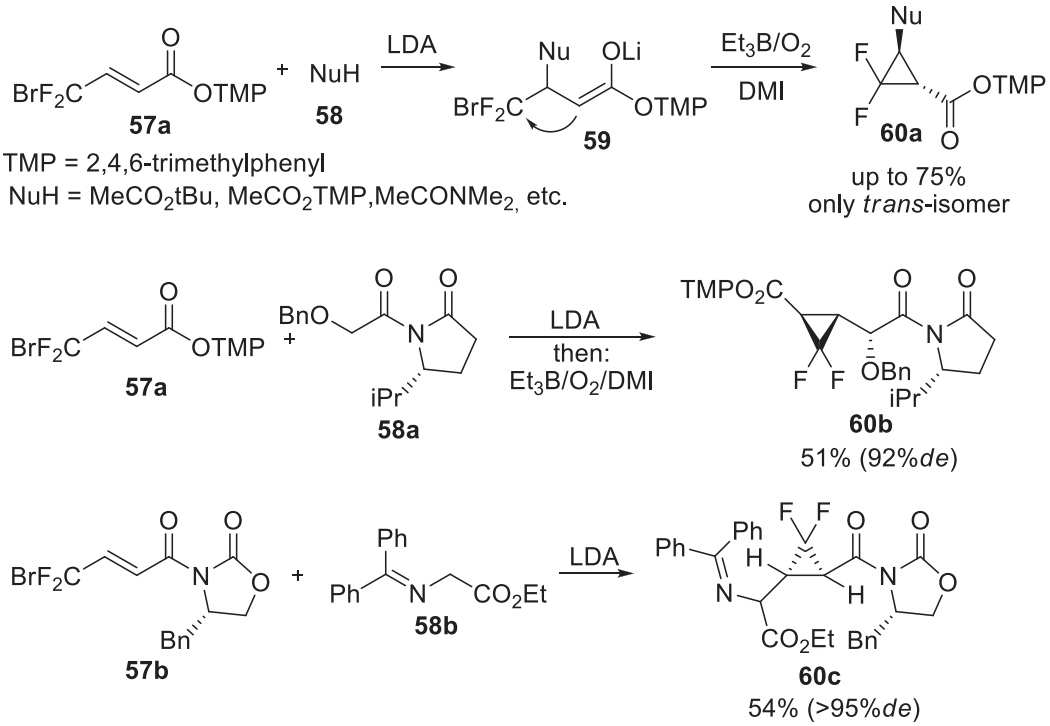


Scheme 20.

Taguchi's group reported two different cyclopropanations that follow pathway A on the scheme 20. The first one is a MIRC of bromodifluorocrotonate derivatives **57** triggered by addition of several nucleophiles (Scheme 21). Remarkably, in the case of **57a** and lithium enolates of carbonyl compounds

[90] Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97.

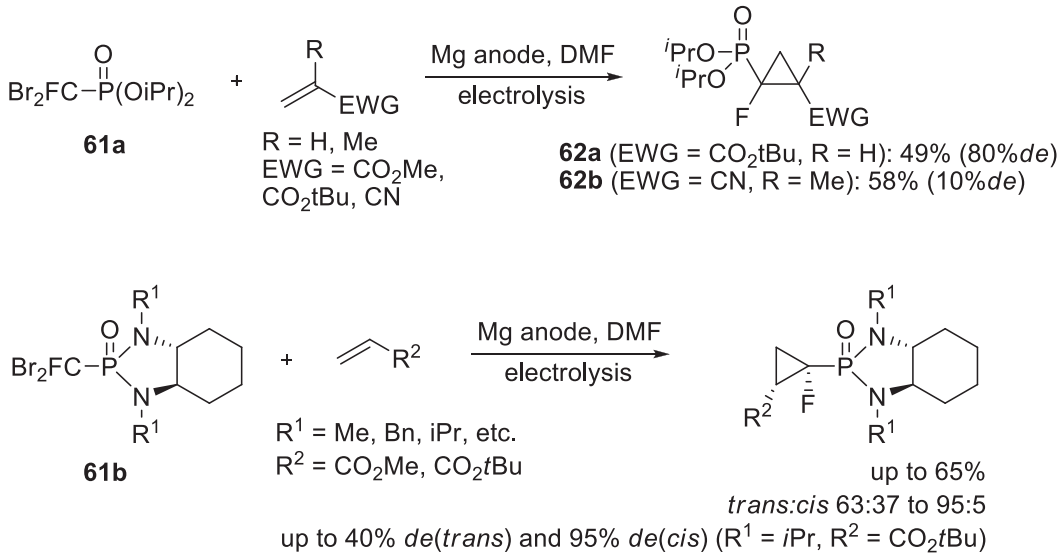
58, the intermediate **59** was resistant to cyclization unless Et_3B/O_2 and DMI were added.[91] The authors hypothesized that the radical cleavage of C-Br bond is responsible for the effect of these additives. Chiral auxiliaries were introduced in either nucleophile[92] (**58a**) or Michael acceptor[93] (**57b**) resulting in excellent diastereoselectivity. Notably, reactions with **57b** did not require the addition of Et_3B/O_2.



Scheme 21.

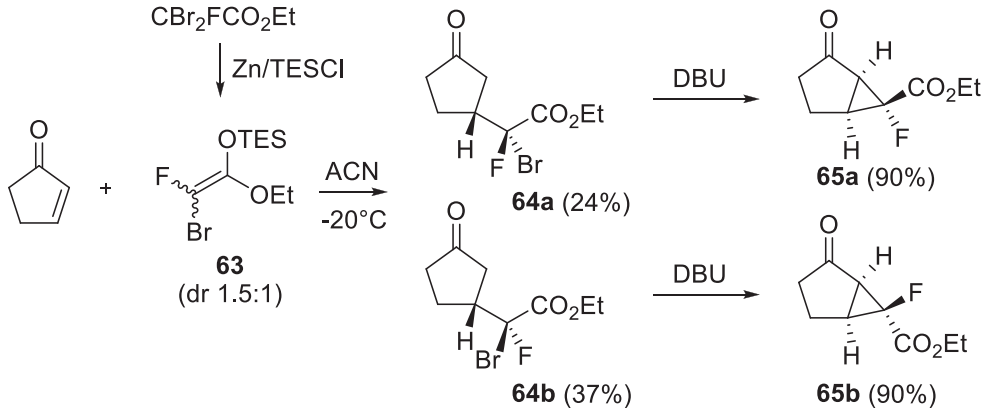
C. Feasson and co-workers described the first synthesis of α-fluorinated cyclopropylphosphonates **62** via electrolysis of diisopropyl dibromofluoromethylphosphonate **61a** in the presence of Michael acceptors using sacrificial magnesium anode (Scheme 22).[94] Although the mechanism of the reaction was not studied, we can hypothesize that, analogously to our results (Section 3), MIRC operates in this case. Notably, substoichiometric amounts of electricity were needed for complete conversion of **61a**. The same authors later reported the asymmetric version of this reaction using the chiral phosphonamides **61b**.[95] Moderate diastereoselectivity was observed (up to 40%de for the major isomer).

[91] Taguchi, T.; Sasaki, H.; Shibuya, A.; Morikawa, T. *Tetrahedron Lett.* **1994**, *35*, 913.
[92] Taguchi, T.; Shibuya, A.; Sasaki, H.; Endo, J.; Morikawa, T.; shiro, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1423.
[93] Shibuya, A.; Kurishita, M.; Ago, C. ; Taguchi, T. *Tetrahedron* **1996**, *52*, 271.
[94] Goumain, S.; Jubault, P.; Feasson, C.; Quirion, J.-C. *Tetrahedron Lett*. **1999**, *40*, 8099.
[95] Goumain, S.; Oulyadi, H.; Jubault, P.; Feasson, C.; Ouirion, J.-C. *J. Chem. Soc. Perkin Trans. 1* **2001**, 701.



Scheme 22.

Taguchi's group later reported the Mukaiyama-Michael addition of the bromofluoroketene silylacetal **63** to ketones (Scheme 23).[96] Addition of **63** to pentenone results in two diastereomers of a monofluorinated precursor **64** capable of stereospecific base-catalysed cyclization (pathway A) leading to monofluorinated cyclopropanes **65**. Unfortunately, compound **63** is prepared from ethyl dibromofluoroacetate as a 1.5:1 mixture of inseparable isomers,[97] thus precluding the development of a more stereoselective approach to monofluorocyclopropanes.

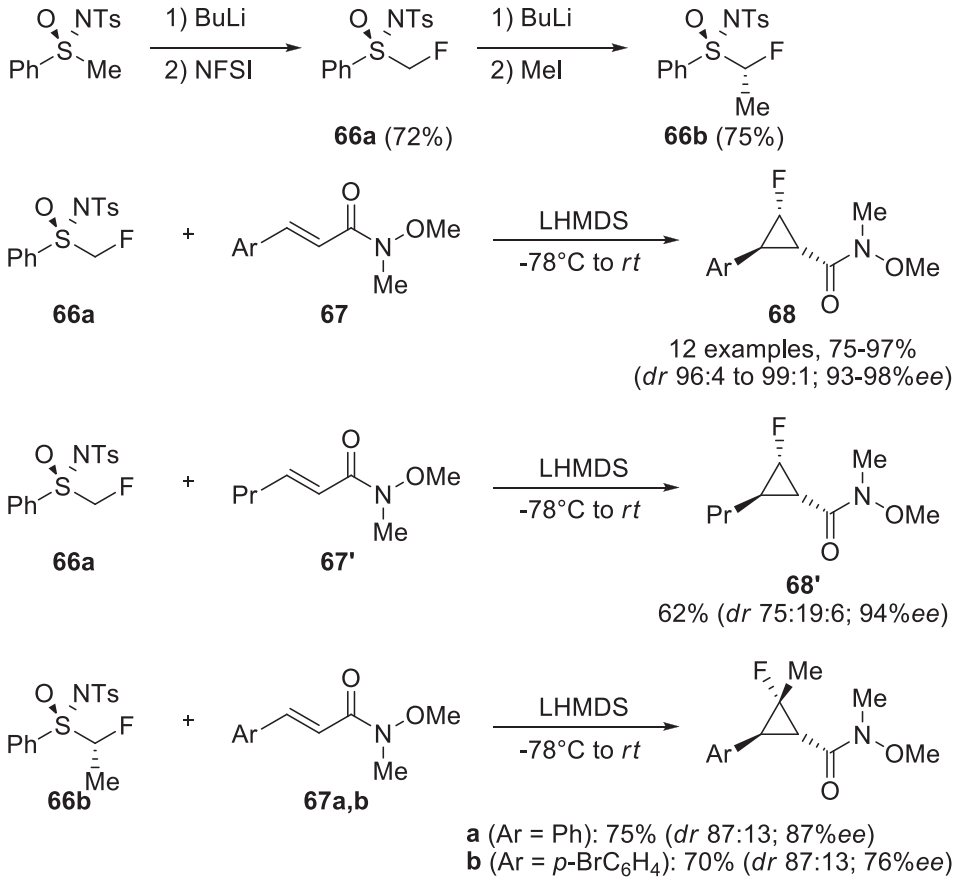


Scheme 23.

During the development of our own asymmetric approach (*Section 4*) a new method of MIRC cyclopropanation according to pathway A was published by the group of J. Hu.[98] They used the chiral

[96] Saito, A.; Ito, H.; Taguchi, T. *Tetrahedron* **2001**, *57*, 7487.
[97] Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 2225.
[98] Shen, X.; Zhang, W.; Luo, T.; Wan, X.; Gu, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6966.

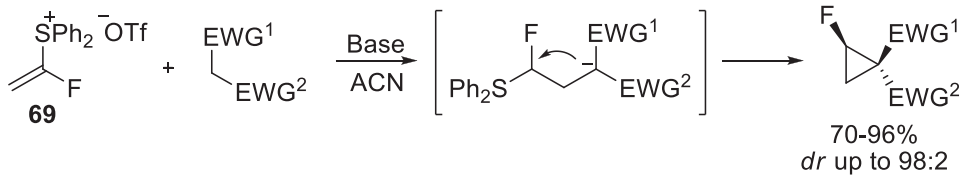
fluorinated sulfoximines **66a** and **66b** as a cyclopropanating agent for α,β-unsaturated Weinreb amides **67** (Scheme 24). Excellent diastereo- and enantioselectivity was observed while using fluoromethylsulfoximine **66a**. Reactions with α-fluoroethylsulfoximine **66b** as well as with an aliphatic Weinreb amide **67'** were less stereoselective.



Scheme 24.

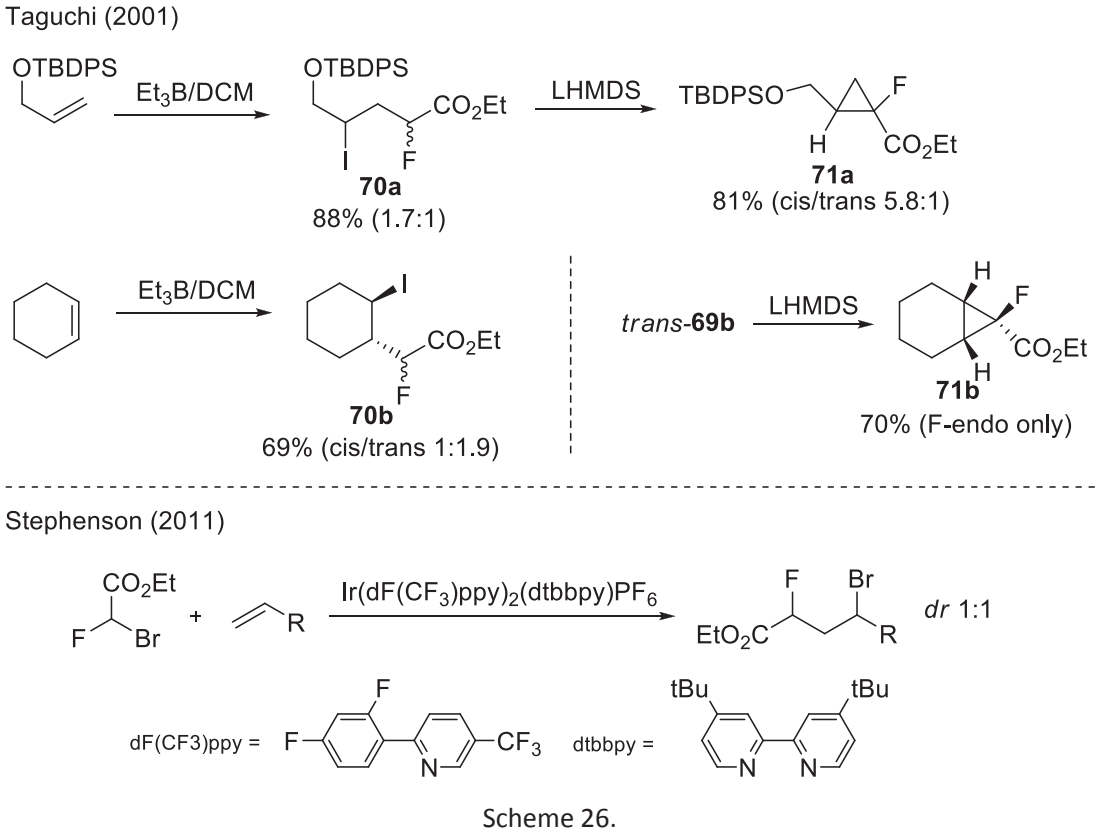
Very recently, Hanamoto and co-authors used the α-fluorovinyl diphenyl sulfonium salt **69** as an original two-carbon building block for cyclopropanation of active methylene compounds[99] (Scheme 25). Original monofluorinated cyclopropanes were produced with good yields and generally good stereoselectivity (when $EWG^1 \neq EWG^2$).

[99] Hirotaki, K.; Takehiro, Y.; Kamaishi, R.; Yamada, Y.; Hanamoto, T. *Chem. Commun.* **2013**, *49*, 7965.



Scheme 25.

Concerning the fluorinated nucleophiles (pathway B, Scheme 20), Taguchi's group developed an alternative two-step cyclopropanation[96] (Scheme 26). Radical addition of ethyl iodofluoroacetate to a series of alkenes lead to diastereomeric mixtures of α-fluoro-γ-iodoesters **70** (preferentially *trans* in the case of cyclic alkenes). Treatment of **70** (*trans*-**70** in the case of cyclic alkenes) with LHMDS afforded the corresponding cyclopropanes **71** in highly stereoselective manner (only F-*endo* isomer for cyclic alkenes).



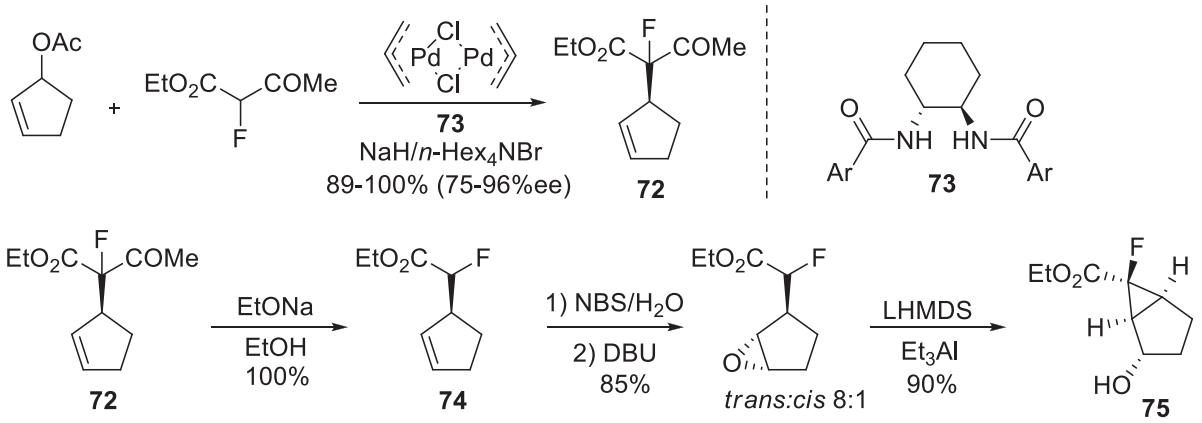
Scheme 26.

Recently, Stephenson's group reported photocatalytic atom transfer radical addition (ATRA) of ethyl bromofluoroacetate to primary alkenes catalysed by an iridium complex (Scheme 26).[100] Although

[100] Nguyen, J.D.; Tucker, J.W.; Konieczynska, M.D.; Stephenson, C.R.J. *J. Am. Chem. Soc*. **2011**, *133*, 4160.

the synthesis of fluorinated cyclopropanes was not described in their article, it is clear that their new ATRA methodology can be readily applied to this class of compounds.

Original method of asymmetric synthesis of 6-fluorobicyclo[3.1.0]hexanecarboxylate core (see *Section 1b* for discussion of biological activity) was developed by T. Zhang et al. of Merck.[101] They used Trost asymmetric allylic alkylation as a key enantioselective step that defined the stereochemistry of the allylic chiral center in **72**. Precise information on the ligand **73** was not disclosed, except its (*R,R*)-configuration. Additional advantage of this method is the use of cheap and non-toxic ethyl α-fluoroacetoacetate as a fluorinated building block. Remarkable *cis/trans* selectivity of bromohydration of **74** allowed preparation of the cyclopropane **75** in high overall yield.

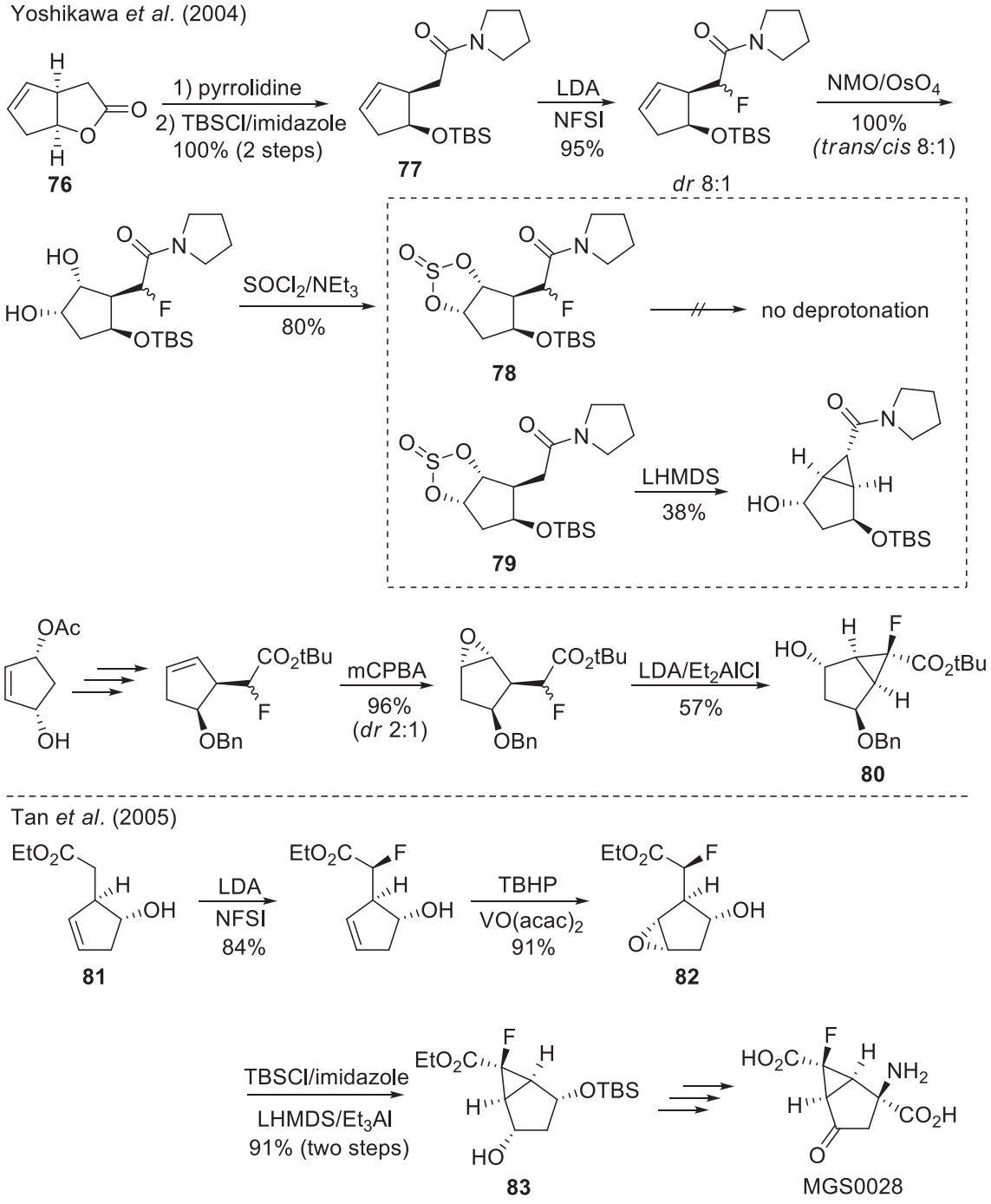


Scheme 27.

Two other asymmetric syntheses of 6-fluorobicyclo[3.1.0]hexanecarboxylate core featuring a similar final cyclization step were published by Merck researchers. Yoshikawa et al.[102] used a commercially available chiral lactone **76** to prepare alkene **77**, which, after fluorination with NFSI was transformed into cyclic sulfite **78**. Curiously, all attempts of cyclization of **78** were unsuccessful, while the non-fluorinated analog **79** was readily converted into the corresponding cyclopropane. The authors hypothesized that the conformation of **78** with orthogonal C-H bond and amide fragment needed for deprotonation is not accessible because of the steric effect of fluorine atom. They finally achieved the synthesis of a desired 6-fluorobicyclo[3.1.0]hexanecarboxylate **80** by changing their strategy and using the Lewis acid-facilitated epoxide opening as the key step. Tan et al. [103] used a similar epoxidation – anionic cyclopropanation strategy for the preparation of an epimer of **80** starting from the compound **81**

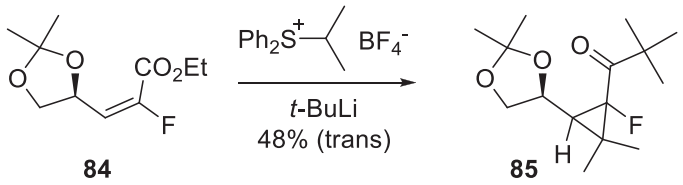
[101] Zhang, F.; Song, Z.J.; Tschaen, D.; Volante, R.P. *Org. Lett.* **2004**, *6*, 3775.
[102] Yoshikawa, N.; Tan, L.;Yasuda, N.; Volante R.P.; Tillyer, R.D. *Tetrahedron Lett*. **2004**, *45*, 7261.
[103] Tan, L.; Yasuda, N. Yoshikawa, N.; Hartner, F.W.; Eng, K.K.; Leonard, W.R.; Tsay, F.-R.; Volante, R.P.; Tillyer, R.D. *J. Org. Chem.* **2005**, *70*, 8027.

easily accessible on multigram scale. In this case, fluorination was followed by hydroxyl-directed epoxydation to give the key non-cyclized precursor **82**. Hydroxyl protection and epoxide-opening cyclopropanation lead to the fluorinated bicyclo[3.1.0]hexanecarboxylate **83** that was used in the highly robust synthesis of MGS0028 (10 steps, 43%; see *Section 1b* for discussion of biological activity).



Scheme 28.

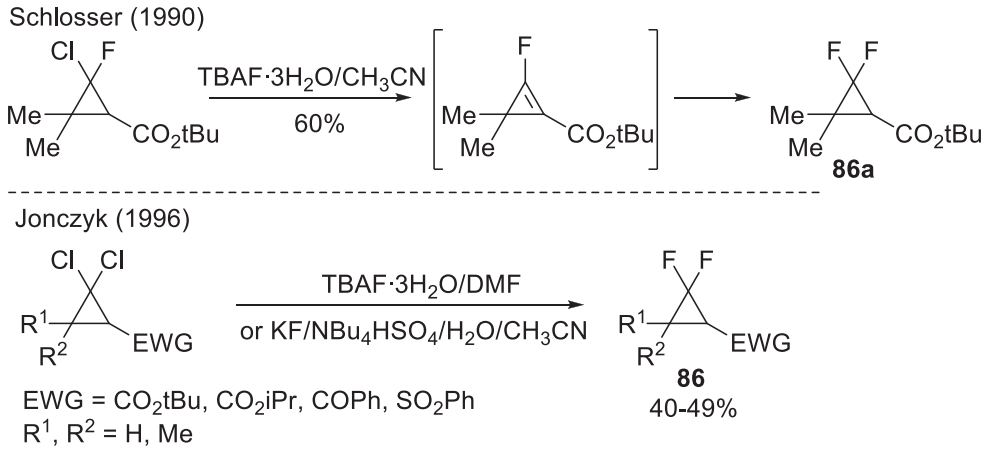
Michael-induced ring closure according to the pathway B (Scheme 20) was reported by Patrick and Neal who used a classical sulfonium ylide reagent for the cyclopropanation of a chiral fluoroacrylate **84**. [104] The product **85** was obtained as a pure *trans*-isomer, however, diastereomeric ratio and absolute configuration of cyclopropane ring were not reported. The authors were obliged to use excess of *t*-BuLi, so the resulting *tert*-butyl ketone was then converted back to an ester via Bayer-Villiger oxidation.



Scheme 29.

e. Direct fluorination of cyclopropanes and related methods.

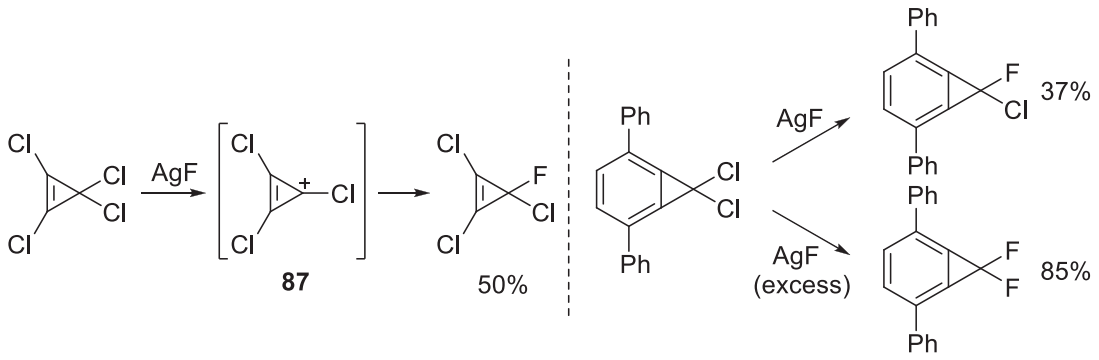
Nucleophilic fluorination of *gem*-dichloro- and *gem*-chlorofluorocyclopropanes bearing an electron-withdrawing group was reported by Schlosser with co-workers[105] and later exemplified under slightly different conditions by Jonczyk and Kaczmarczyk[106] (Scheme 30). Substitution necessitates the presence of an acidic β-hydrogen and apparently proceeds through elimination-addition mechanism to give the gem-difluorocyclopropanes **86** in moderate yield.



Scheme 30.

[104] Patrick, T.B.; Neal, B.E. *Synlett.* **1996**, 1227.
[105] Bessard, Y.; Kuhlmann, L.; Schlosser, M. *Tetrahedron* **1990**, *46*, 5230.
[106] Jonczyk, A.; Kaczmarczyk, G. *Tetrahedron Lett.* **1996**, *37*, 4085.

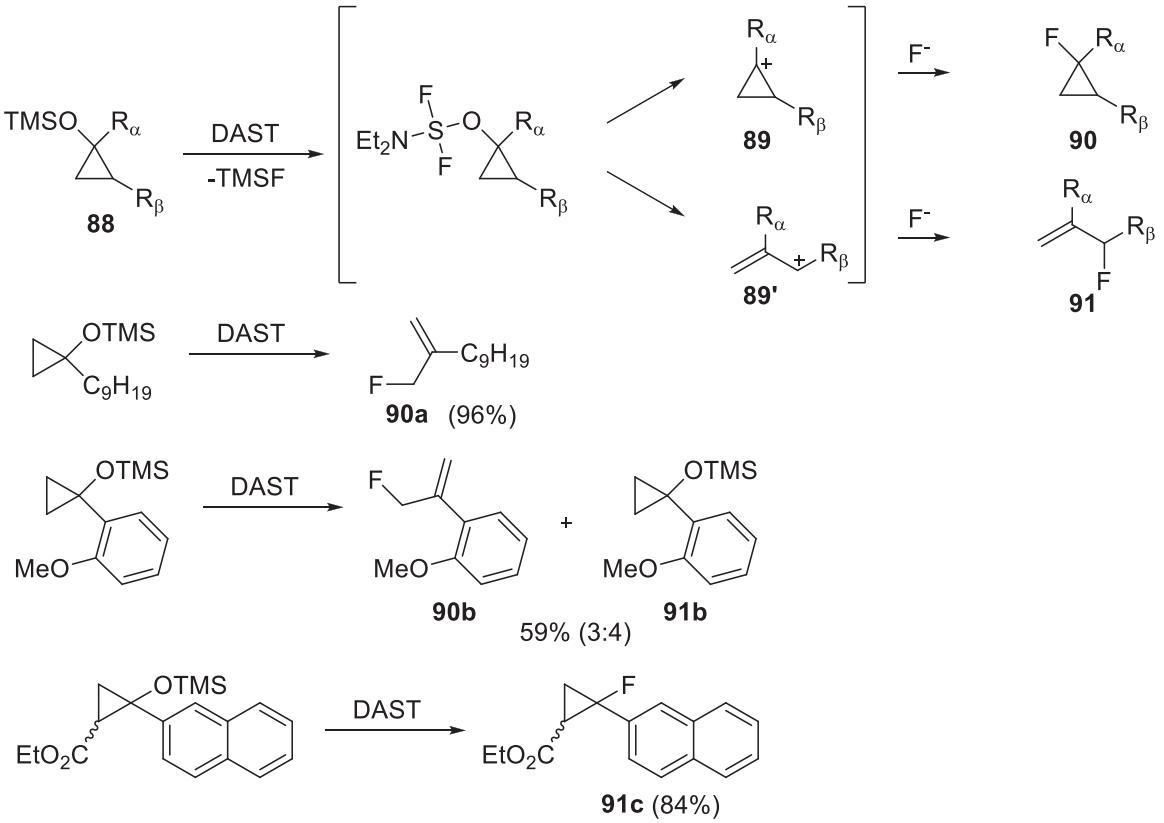
Another type of three-membered cycles susceptible to nucleophilic fluorination is represented by halogenated cyclopropenes (or benzocyclopropanes) due to aromatic character of S_N1 cationic intermediates **87** (Scheme 31).[107]



Scheme 31.

Kirihara *et al.* used DAST to transform the cyclopropyl silyl ethers **88** into the corresponding fluorocyclopropanes **90** (Scheme 32).[108] The result of this reaction, i.e. formation of **90** or the ring-opening product **91** strongly depended on the nature of substituents in α and β positions. Electron-donating α-substituents and electron-withdrawing β-substituents shifted the selectivity towards cyclopropane **90**. These results were rationalized in terms of concurrence between carbocationic intermediates **89** and **89'**. While the cyclic form (**89**) is stabilized by electron-donating α-substituents, the linear form (**89'**) is stabilized by electron-donating and destabilized by electron-withdrawing β-substituents.

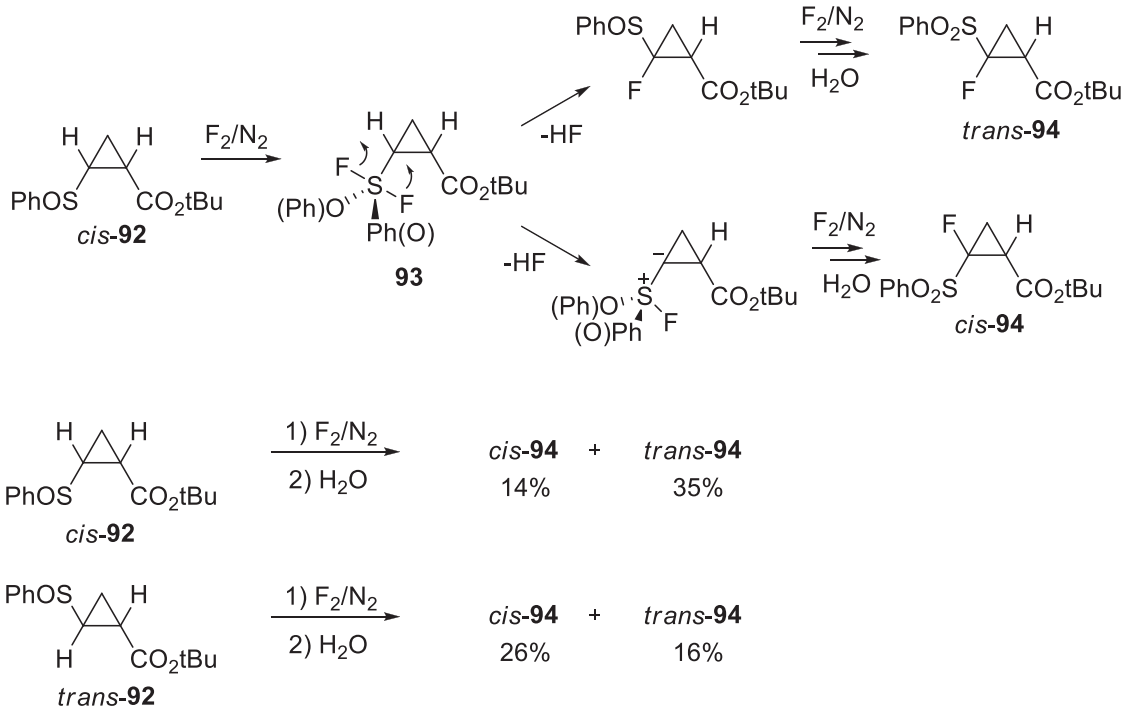
[107] Miiller, P.; Etienne, R.; Pfyffer, J.; Pineda, N.; Schipoff, M. Helv. Chim. Acta 1978, 61, 2482.
[108] Kirihara, M.; Kakuda, H.; Tsunooka, M.; Shimajiri, A.; Takuwa, T.; Hatano, A. *Tetrahedron Lett*. **2003**, *44*, 8513.



Scheme 32.

Fluorination of cyclopropylsulfoxides *cis*-**92** and *trans*-**92** with F_2 was realized by Toyota et al. (Scheme 33).[109] Remarkably, this reaction is accompanied by partial inversion of configuration. The authors supposed that sulfur(IV) is first oxidized by F_2 leading to a hexacoordinate intermediate **93** that can undergo *syn*-elimination of HF accompanied by S-to-C migration of the second fluorine atom. Such a rearrangement should restore sulfur(IV) moiety that is further oxidized by excess F_2. If the loss of HF is not accompanied by fluorine migration, a product with retention of configuration can be produced.

[109] Toyota, A.; Ono, Y.; Kaneko, C.; Hayakawa, I. *Tetrahedron Lett.* **1996**, *37*, 8507.



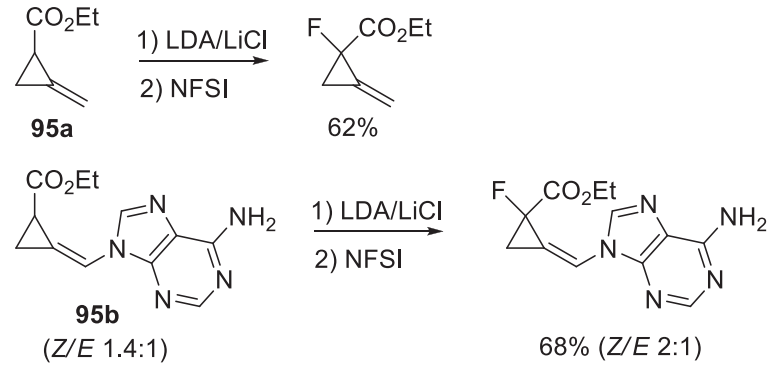
Scheme 33.

Two methods of electrophilic fluorination have been applied to methylenecyclopropanes (Scheme 34). First one, reported by Zemlicka's group,[110] is based on the deprotonation of the allylic position in methylenecyclopropane **95** followed by fluorination with NFSI that restores the original methylenecyclopropane core. The second method, described by X. Huang with co-workers,[111] deals with the halohydration of (diarylmethylene)cyclopropanes **96** with N-fluorosuccinimide in aqueous acetone.

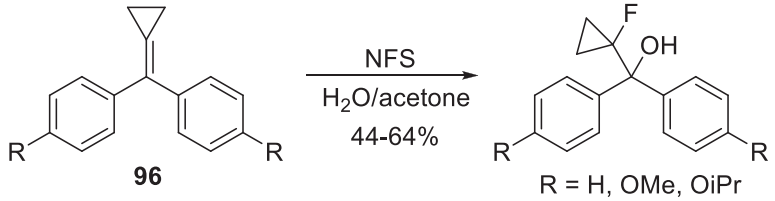
[110] (a) Zhou, S.M.; Kern, E.R.; Gullen, E.; Cheng, Y.C.; Drach, J.C.; Matsumi, S.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 6964; (b) Zhou, S.; Zemlicka, J. *Tetrahedron* **2005**, *61*, 7112.

[111] Yang, Y.; Su, C.; Huang, X.; Liu, Q.Y. *Tetrahedron Lett.* **2009**, *50*, 5754.

Zemlicka (2004, 2005)



Huang (2009)



Scheme 34.

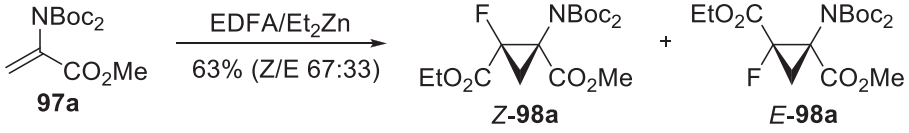
3. Cyclopropanation of Michael acceptors with ethyl dibromofluoroacetate

a. Arguments for the selected approach

In the present project we tried to develop a general method for the synthesis of highly functionalized monofluorinated cyclopropanes using a readily available fluorinated building block. As such, we selected the commercially available ethyl dibromofluoroacetate ($CFBr_2CO_2Et$, EDBFA) possessing an ester group suitable for further functionalization. Metalation of EDBFA would lead to an α-carbonyl organometallic intermediate with sufficient nucleophilicity to undergo 1,4-addition with the Michael acceptors. Subsequent intramolecular nucleophilic substitution would lead to the monofluorinated cyclopropane carboxylate.

b. Previous work

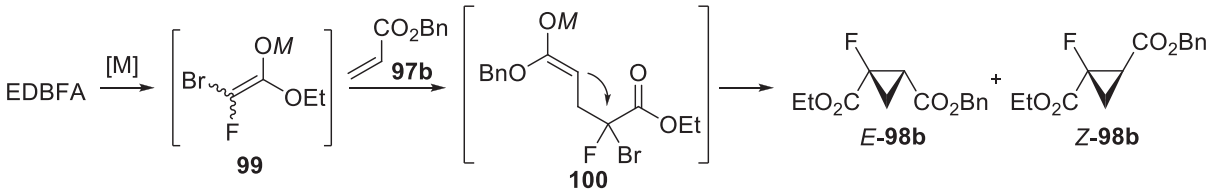
Earlier in our laboratory the MIRC reaction of EDBFA was successfully applied to the synthesis of a protected fluorocyclopropane amino acid **98** (Scheme 35). The product of cyclopropanation was used in the synthesis of a variety of mGluR4 agonists **26**-**31** (See Section 1c for details). However, the attempts to apply this reaction to the other Michael acceptors were unsuccessful. Polymerization of the starting electron-deficient alkenes under the reaction conditions was identified as the probable cause of this failure.



Scheme 35.

c. Screening of the reaction conditions

We started this project with an attempt to find a suitable metalating agent that would be compatible with a wide range of substrates. Benzyl acrylate **97b** was chosen as a model compound because of its high reactivity and susceptibility to polymerization (Scheme 36). The main results of this study are given in the Table 2.



Scheme 36.

Table 2.Cyclopropanation of benzyl acrylate.

entry	[M]	yield **98b**, %	*dr* (*E:Z*)
1	$ZnEt_2$, $ZnEt_2/RhCl(PPh_3)_3$	traces	-
2	$ZnEt_2/NiCl_2(PPh_3)_2$ EtZnBr, ZnMe2 $ZnMe_2/RhCl(PPh_3)_3$ $ZnMe_2/NiCl_2(PPh_3)_2$	0	-
3	iPrMgCl (-94° to 0°C)	17	3.8:1
4	iPrMgCl, $ZnBr_2$ (-94° to 0°C)	30	2.4:1
5	Zn, Mg, Mn, In, Cu, Sm, SmI_2, $CrCl_2$/LiI (0-60°C)	traces	-
6	$Zn/CoBr_2$ Zn/Cp_2TiCl_2 Mn/Cp_2TiCl_2	0	-
7	Zn-Cu/THF, Zn/CH_3CN Zn/HMPA/THF	0	-
8	Zn/DMSO (rt)	20	1:1.5
9	$Mg/ZnCl_2$/LiCl (0°C)	30	2.8:1
10	Rieke-Zn (-20°C)	35	2.1:1
11	Zn/LiCl (-20°C)	88	2.6:1

Under variety of conditions (temperature, solvent, ratio of reagents, mode of addition), the diethylzinc-mediated reaction resulted in only trace amounts of cyclopropanes as detected by ^{19}F NMR monitoring of the reaction mixture. Total consumption of benzyl acrylate was observed, and no particular low-molecular-weight by-product could be identified. Attempts to catalyse the metal-halogen exchange with diethylzinc by Wilkinson's catalyst or $NiCl_2(PPh_3)_2$ were unsuccessful as well[112,113] (entries 1, 2).

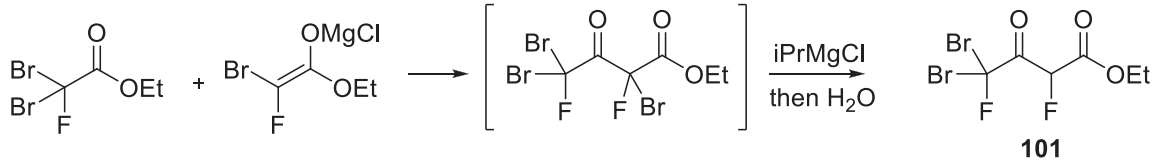
In most cases reasonably stable Reformatsky reagents can be prepared by the reaction of an α-halogenated carbonyl compound with zinc metal or dialkylzinc. Subsequent addition of an electrophile

[112] Transition metal-catalysed halogen-zinc exchange was used with various types of halogenated substrates, including the α-halogenated carbonyl compounds: Adrian, J.C.; Snapper, M.L. *J. Org. Chem*. **2003**, *68*, 2143.

[113] Difluorinated Reformatsky reagents can also be generated in this way: Tarui, A.; Kondo, K.; Taira, H.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Heterocycles* **2007**, *73*, 203.

(sometimes preceded by the filtration/decantation of the organozinc solution) can therefore lead to the clean reaction with minimal interference from the reactive Zn metal or dialkylzinc. However, in the case of EDBFA we were not able to generate the corresponding organozinc intermediate Zn-**99** before the addition of the Michael acceptor using either Zn(0) or diethylzinc. NMR monitoring of the mixture of diethylzinc (zinc metal) and EDBFA in THF clearly shows the formation of dozens of fluorine-containing by-products. Formation of (ethoxycarbonyl)fluorocarbene and its subsequent reactions with the solvent can be a possible explanation for this result. Relatively high temperatures required for the generation of Zn-EDBFA apparently result in its immediate degradation in the absence of a suitable electrophile.

To overcome this stability problem we next tried to generate the magnesium enolate Mg-**99** at low temperature using the highly reactive iPrMgCl for metal-halogen exchange. Indeed, this approach afforded the desired cyclopropane product, but only in low yield (entry 3, Table 1). Under these conditions the degradation of benzyl acrylate was suppressed, but, at the same time, formation of a substantial amount of benzyl alcohol was observed (apparently resulting from the 1,2-addition to benzyl acrylate or to the cyclopropanation product). A product of self-condensation of EDBFA **101** was the main fluorine-containing compound detected in the crude reaction mixture by ^{19}F NMR (scheme 37). The amount of this by-product can be minimized by reversing the order of addition, i.e. adding EDBFA to the excess of iPrMgCl.

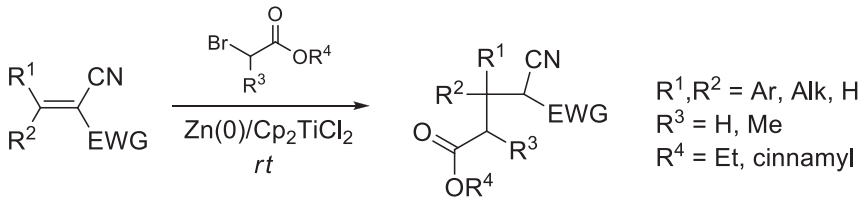


Scheme 37.

In order to inhibit the 1,2-addition of the metal enolate we performed the Mg-to-Zn transmetallation before adding the Michael acceptor. This modification slightly increased the yield of the desired product (entry 4). However, under various conditions tested, the yield never exceeded 30%, which can be possibly attributed to the same carbene-mediated degradation of the metalated species as observed in the above-mentioned experiments on direct zincation of EDBFA. In a parallel set of experiments, SmI_2 was found to give no cyclopropane product at all.

As an alternative to low-temperature generation of **99** we tested several metals in the Barbier conditions (i.e. generation of a reactive intermediate in the presence of Michael acceptor). An ultimate goal of these trials was to identify the metalating reagent that would be selective towards the C-Br bond insertion versus the single-electron transfer to the conjugated system of a Michael acceptor. Few

examples of successful generation of a Reformatsky-type reagent in the presence of a Michael acceptor has been reported before our work using Cp_2TiCl_2 as a catalyst (Scheme 38).[114,115]



13 examples, 43.2-92.7%

Scheme 38.

Magnesium,[116] zinc, indium,[117] manganese,[118] samarium, copper[119] metals were tested under various conditions giving at best the traces of cyclopropane. With all these metals complete degradation of benzyl acrylate occurred before a substantial conversion of EDBFA could be detected (entry 5). SmI_2 and $CrCl_2$/LiI[120] were inefficient as well.

Various methods of activation of Mg, Zn and Mn metals were tested (including washing with HCl, in situ activation with dibromoethane/TMSCl, DIBAL-H), but, although we were able to lower the temperature of reaction (from above 50 to 20°C in the case of Zn), the selectivity towards the reduction of benzyl acrylate was unchanged. The notable exception was the Riecke Zn[121] (entry 9), highly dispersed form of metal prepared in situ via reduction of $ZnCl_2$ with lithium naphthalenide (used in this work) or potassium.

Then we focused our attention on the special additives that are known to facilitate the zinc insertion into the carbon-halogen bonds. The only catalysts of metalation that have been applied to the preparation of Reformatsky-type reagents are $RhCl(PPh_3)_3$ and several Ni salts such as $NiCl_2(PPh_3)_3$ used in combination with diethylzinc, and the above-mentioned Cp_2TiCl_2. As discussed earlier, diethylzinc-based approach did not work, possibly because the $ZnEt_2$-induced polymerization of benzyl acrylate is

[114] Ding, Y.; Zhao, Z.; Zhou, C. *Tetrahedron* **1997**, *53*, 2899.
[115] One unsuccessful attempt is described in: Bailey, J.H.; Cherry, D.T.; Dyer, J.; Moloney,M.G.;. Bamford, M.J.; Keeling, S.; Lamont, R.B. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2783.
[116] Oudeyer, S.; Leonel, E.; Paugam, J.P.; Sulpice-Gaillet, C.; Nedelec, J.Y. *Tetrahedron*, **2006**, *62*, 1583.
[117] Shen, Z.L.; Wang, S.Y.; Chok, Y.K.; Xu, Y.H.; Loh, T.P. *Chem Rev.* **2013**, *113*, 271.
[118] (a) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373; (b) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett*. **1996**, *37*, 7049.
[119] Kawabata, N.; Tanimoto, M. *Tetrahedron* **1980**, *36*, 3517.
[120] Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772.
[121] Rieke R.D.; Hanson, M.V. *Tetrahedron* **1997**, *53*, 1925.

still faster than the Rh- or Ni-mediated Zn-Br exchange in EDBFA. $CoBr_2/Zn$,[122] Cp_2TiCl_2/Zn[114] and Cp_2TiCl_2/Mn[123] were inefficient as well (entry 6).

Finally we found out that in the presence of LiCl the metalation occurs under very mild conditions (temperatures below 0°C). Good yields of the desired cyclopropanes were obtained. Notably, the Riecke Zn prepared with lithium metal is known to contain considerable amounts of LiCl (the by-product of the redox reaction) unless rigorously washed with THF or another suitable solvent. We suppose that the presence of LiCl, and not its highly activated character, is responsible for the efficiency of Riecke Zn in our reaction (in comparison to other methods of activation of zinc). Activated Mg was also used in the presence of $ZnCl_2$ and LiCl and afforded the cyclopropane in low yield along with substantial amount of EDBFA dimerization product (entry 9).

Given the outstanding effect of LiCl we tested other salts as possible metalation activators. LiBr catalysed the metalation at low temperature so that traces of cyclopropane could be detected even at 0°C. However, increasing the temperature led to the same degradation of benzyl acrylate as in the absence of any salt additive. LiF, LiI, CsF, CsCl, $MgCl_2$, $ZnCl_2$, $ZnBr_2$, NBu_4Cl produced no effect on the reactivity of activated zinc metal.

LiCl was introduced by the group of P. Knochel as a powerful additive capable of greatly facilitating the insertion of various metals into the carbon-halogen bonds.[124] Even earlier Mg/LiCl was used by Tu and Hu for metalation of $CFCl_3$ (addition of LiCl was essential for high-yielding addition of CFCl2- to aldehydes and tetramethylethylene).[125] However, before our work, this approach has never been applied to the α-halogenated carbonyl compounds, which are usually considered reactive enough without additional activation. In the reports by Knochel and co-workers the superior activating ability of LiCl compared to any other salt was demonstrated as well. LiCl is known to facilitate both metal insertion step and the subsequent reactions of the resulting organometallic compounds.[126]

C.-Y. Liu et al.[127] have performed DFT calculations of the reaction between bromobenzene and an isolated zinc atom with and without LiCl (one molecule of dimethyl ether included in the model system as a solvent mimic). In the absence of LiCl the transition state **102** with triangular arrangement of

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[122] Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc*. **2003**, *125*, 3867.

[123] Parrish, J.D.; Shelton, D.R.; Little, R.D. *Org. Lett.* **2003**, *5*, 3615.

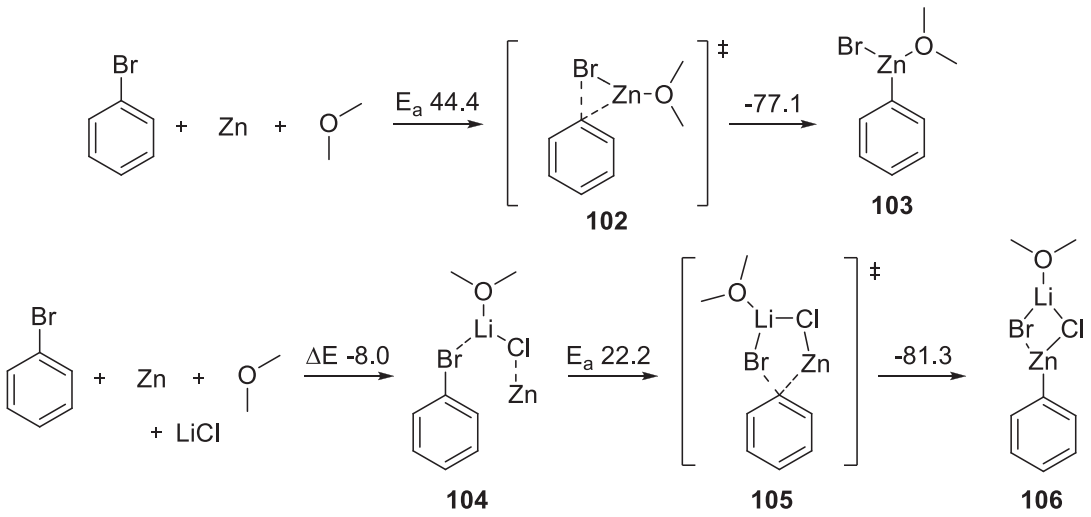
[124] Zn: Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040. Mg: Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. In: Chen, Y.-H.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 7648. Mn: Peng, Z.; Knochel, P. *Org. Lett.* **2011**, *13*, 3198.

[125] Hu, C.-M.; Tu, M.-H. *J. Fluorine Chem.* **1994**, *67*, 9.

[126] Fleckenstein, J.E.; Koszinowski, K. *Organometallics* **2011**, *30*, 5018 (and references therein).

[127] Liu, C.Y.; Wang, X.; Furuyama, T.; Yasuike, S.; Muranaka, A.; Morokuma, K.; Uchiyama, M. *Chem. Eur. J*. **2010**, *16*, 1780.

reacting carbon, zinc and bromine atoms was found with the activation energy E_a = 44.4 kcal/mol (Scheme 39). Organozinc derivative **103** is the product of metalation. In the presence of one equivalent of LiCl the local minimum corresponding to an intermediate complex **104** was found (ΔE = -8.0 kcal/mol). Transition state **105** corresponding to the zinc insertion in the presence of LiCl is characterised by much lower activation energy (E_a = 22.2 kcal/mol) and C, Br, Li, Cl and Zn atoms arranged in a five-member cycle. Similar difference in activation energy (ca. 20 kcal/mol) was predicted from the analogous calculations of several substituted bromobenzenes. Natural population analysis confirmed that the charges of Li and Cl atoms do not change throughout the reaction, i.e. these atoms do not participate in the redox process which is therefore confined to the triad C-Zn-Br. In the presence of LiCl the authors identified the anionic zincate complex **106** as the final product of zinc insertion. Such anionic zincates were earlier detected by mass and NMR spectrometry and were suggested as the actual reacting species in the reactions of organozinc compounds with electrophiles in the presence of LiCl.[126]



Scheme 39. Energy values are given in kcal/mole.

Although the results of Liu *et al.* argue for the strongly stabilizing interaction between a molecule of LiCl and the Zn-C-Br reacting center, it is not clear whether the authors' minimalistic model with an isolated Zn(0) atom is a valid approximation of the reaction at the surface of the bulk metal in a concentrated solution of LiCl (also, it is not clear from the article whether bulk solvent was considered in calculation). Moreover, although the authors explicitly postulate a 5-membered cyclic transition state **105** in the presence of LiCl, they also say that **105** is a much earlier TS than **102**. Indeed, closer inspection of their calculation results reveals that the Zn-Br distance difference between **102** and **105** (2.89 Å vs. 3.27 Å) is roughly proportional to the corresponding Zn-C distance difference (2.23 Å vs. 2.45

Å).[128] Therefore, although LiCl apparently stabilizes an earlier TS, the dramatic change in the mechanism underlined by different topology of the structural formulae used in this work is not likely to really take place.

One of the key factors responsible for the successful cyclopropanation with Zn/LiCl is the chemical activation of Zn. As mentioned above, the main role of LiCl is to increase the selectivity of metalation (in favour of C-Br insertion). This increase in selectivity is accompanied by overall increase in reactivity, i.e. the metalation occurs at much lower temperature. However, reactions with zinc metal as well as other metals capable of forming oxide film on the surface[129] are usually highly sensitive to the initial quality of metal and the treatment before reaction. In the case of cyclopropanation of highly reactive Michael acceptors efficient zinc activation is very important: e.g. for dibenzyl maleate increasing the temperature from -20 to ca. 0°C decreases the yield from 61% to less than 10%. In the course of this study we tried several activating reagents. First of all, washing with HCl or another acid in the air (the standard procedure for the activation of commercial zinc powder of mediocre quality) was completely inefficient and apparently even worsened the reactivity of zinc powder in our hands (Acros, 99.8%). By contrast, several methods of in situ activation allowed us to perform the metalation at temperatures around 0°C: dibromoethane, TMSCl, dibromoethane/TMSCl,[124] DIBAL-H.[130] At the same time, while decreasing the temperature to -20°C we faced the problem of low reproducibility of the reaction with all of these activators. While screening the solvents for cyclopropanation we found out that zinc metal reacts vigorously with the DMSO solution of EDBFA at room temperature even without zinc activation. The reaction mixture emitted the characteristic odour of dimethyl sulfide indicating the reduction of DMSO with zinc. Then we used DMSO as an activating agent for Zn in THF. Stirring the suspension of Zn in THF/LiCl with 2%mol DMSO and 2-4%mol TMSCl at 50°C for 10 min provides the highly activated zinc powder that reacts reproducibly with EDBFA at -20°C. All the subsequent work was done using this method of zinc activation.

Overall, our work demonstrates the potential utility of Zn/LiCl system for the selective in situ generation of highly unstable Reformatsky-type reagents **99** that are inaccessible by the conventional two-step Reformatsky procedure.

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[128] ∠C-Br-Zn = 49° in both **102** and **105**; ∠C-Zn-Br = 53° (**102**) and 43° (**105**); ∠Zn-C-Br = 78° (**102**) and 88° (**105**); C-Br bond length: 2.36 Å (**102**), 2.24 Å (**105**).

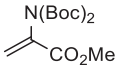
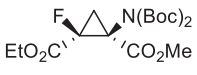
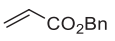
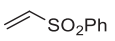
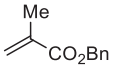
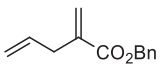
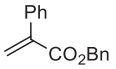
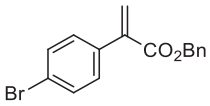
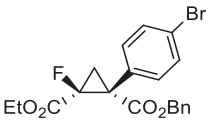
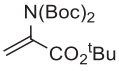
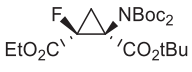
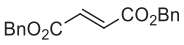
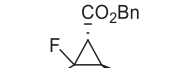
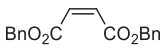
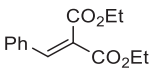
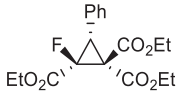
[129] In addition to zinc oxide, traces of Pb are known to greatly decrease the reactivity of zinc metal. Opposite effect is reported for Mn: see ref. 118b.

[130] Girgis, M.J.; Liang, J.K.; Du, Z. Slade, J.; Prasad, K. *Org. Process Res. Dev.* **2009**, *13*, 1094.

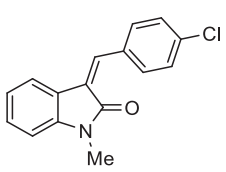
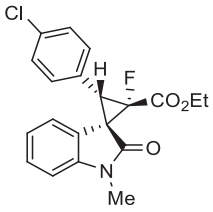
d. Scope of cyclopropanation

The scope of the Michael acceptors **97** in our cyclopropanation reaction is illustrated by the Table 2. Various α,β-unsaturated esters, as well as a nitrile (entry 3), sulfone (entry 4) and amide (entry 13) can be converted to the corresponding fluorinated cyclopropanes.[131] Mono-, di- and trisubstituted alkenes are suitable substrates. Mixtures of diastereomers were obtained in most cases.

Table 2. Scope of cyclopropanation with Zn/LiCl

entry	substrate (**97**)		**98** (major isomer)	T, °C	equiv. of EDBFA	yield	*dr*[a]
1		**a**		0 -5	2 1.6	78 93[b]	59:41
2		**b**		-20	2	80	72:28
3		**c**		-20	2	47	53:47
4		**d**		-20	1.1	72	67:33
5		**e**		30	3	61	70:30
6		**f**		30	3	68	73:27
7		**g**		30	3	76	76:24
8		**h**		30	3	80	78:22
9		**i**		-20	2	73	84:16
10		**(*E*)-97j**		-20	1.1	66	100:0
11		**(*Z*)-97j**		-20	1.1	61	100:0
12		**k**		-20 to rt	2	72	69:31

[131] Vinylphosphonates can also be converted into cyclopropanes as illustrated in the *Section 4*.

13		**l**		0	1.1	70	53:36:7:4

[a] by ^{19}F NMR of the crude product; [b] 0.10 mole of **97a** was used.

Order of addition of reagents is an important factor contributing to the success of cyclopropanation. As described above, the organozinc intermediate **99** is very short-lived at typical temperatures of metalation. Therefore, the Michael acceptor should be introduced prior to, or simultaneously with EDBFA. In the case of relatively unreactive acceptors (entries 5-8), slow addition of EDBFA was shown to slightly improve the yields (by 10-15%). By contrast, with highly reactive Michael acceptors (entries 10, 11) rapid introduction of EDBFA (or rapid simultaneous introduction of both EDBFA and acceptor) allows minimizing the acceptor loss and therefore increasing the yield (complete degradation of a reactive alkene is possible when applying the procedure optimized for the unreactive one). As expected from the extremely low stability of the organozinc intermediate, the simultaneous slow addition of EDBFA and Michael acceptor (benzyl acrylate) results in only trace amounts of the cyclopropane.

2-Alkyl- and 2-aryl-acrylates (entries 5-8) were not reactive enough under the standard conditions (-20°C) leading to yields well below 20%. Using benzyl methacrylate as a model substrate we studied the influence of temperature on the reaction with 3 equiv of EDBFA (Fig. 11). The yield of the reaction reaches its maximum at *ca* 30°C and then gradually decreases. This complex behaviour apparently results from the concurrence of two pairs of parallel processes: a) metalation of EDBFA (*1*) and degradation (reduction) of electron-deficient alkene (*2*), b) degradation (probably via carbene species) of the highly unstable organozinc intermediate (*3*) and addition thereof to the alkene (*4*). For less electron-deficient alkenes (alkyl- or aryl-substituted) the ratio (*1*):(*2*) is high (observed yields are close to conversion values), while both rates (*3*) and (*4*) are comparable. Differences in the reaction order can possibly account for the observed temperature dependence. By contrast, in the case of the most reactive alkenes (entries 3, 10-13) alkene degradation (*2*) becomes much more important, while the ratio (*4*):(*3*) is high (almost equimolar amount of EDBFA can be used to provide the maximum yield). Fig. 11 also shows that the stereoselectivity of cyclopropanation slightly increases with temperature.

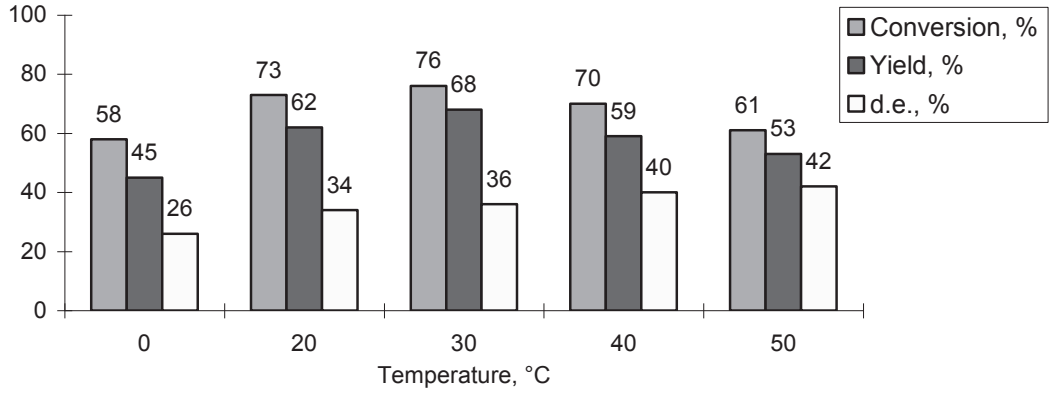
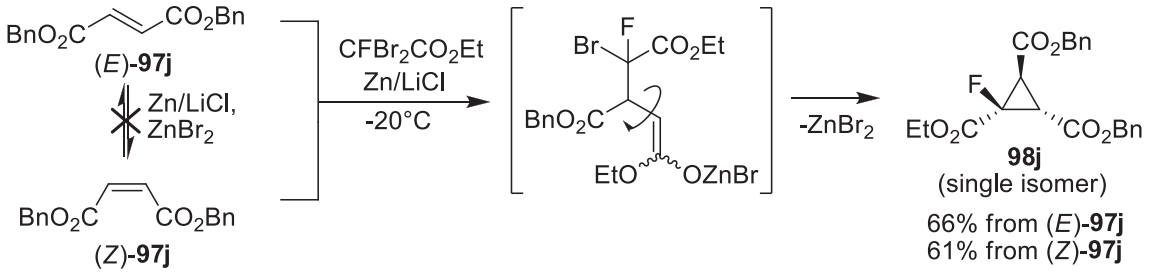


Figure 11.

Our procedure allows the selective cyclopropanation of an electron-deficient alkene bearing an additional unactivated double bond (entry 6). Notably, aromatic bromine (entry 8) and chlorine (entry 13) atoms are preserved throughout the reaction (aryl bromides are the substrates of original work on Zn/LiCl by the group of P. Knochel).

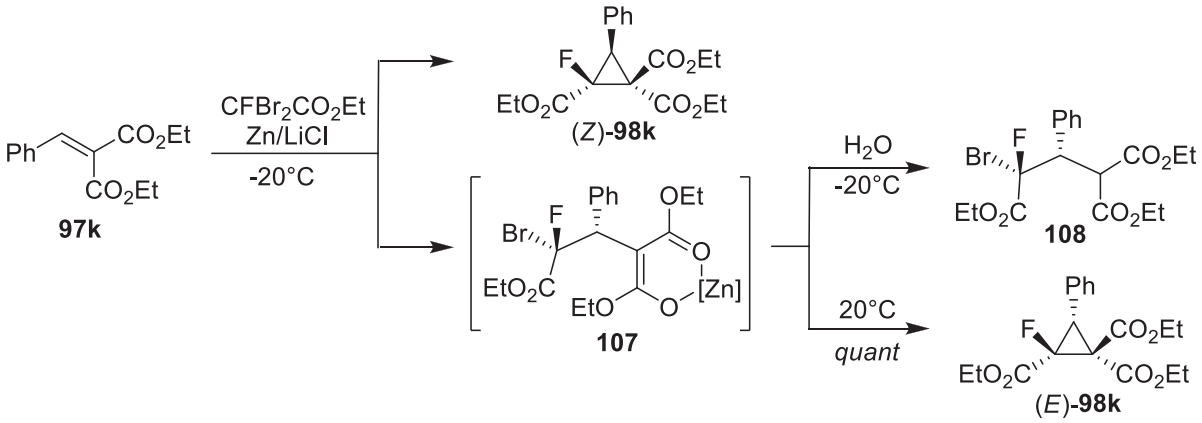
Our method was successfully applied to the synthesis of the fluorinated amino acid **98a** (entry 1) that has already been evaluated as a key precursor in the synthesis of fluorinated group III mGluR agonists.[33] The synthesis of **98a** can be easily performed on a 0.1 mol scale (30.1 g of Michael acceptor) with 93% isolated yield. More than 400 g of **98a** has been manufactured according to this procedure in our laboratory. A similar amino acid **98i** (entry 9) with a *tert*-butyl ester group was synthesized with a better *dr* value (84:16 vs. 59:41).

Reactions with both dibenzyl fumarate (*E*)-**97j** (entry 10) and dibenzyl maleate (*Z*)-**97j** (entry 11) led to the exclusive formation of the same *(E)*-isomer of cyclopropane **98j** with comparable yield. This result clearly indicates the formation of a relatively long-lived intermediate that undergoes rotation before the final cyclization to the cyclopropane. To exclude the possible isomerization of the starting alkene we performed a control experiment (Scheme 40): dibenzyl maleate (*Z*)-**97j** was added to the mixture of activated Zn/LiCl and $ZnBr_2$ in THF under standard cyclopropanation conditions. Gradual decomposition of maleate was observed (probably reduction and/or polymerization), but no trace of dibenzyl fumarate (*E*)-**97j** was detected by NMR.



Scheme 40.

The same long-lived intermediate can be directly observed in the cyclopropanation of diethyl benzylidenemalonate **97k**. Quenching the reaction at -20 °C leads to the exclusive formation of a minor isomer of cyclopropane (*Z*)-**98k** along with the non-cyclized intermediate **107** which can be trapped by protonation upon aqueous work-up (Scheme 41). When the reaction mixture is warmed to *rt*, this intermediate is converted quantitatively into the major isomer of cyclopropane (*E*)-**98k**.[132] This result also indicates that the nucleophilic substitution at sp^3 carbon by a Reformatsky reagent is stereospecific (probably, S_N2), since the ratio (*Z*)-**98k** : **107** is equal to the final ratio of diastereomeres of cyclopropane.



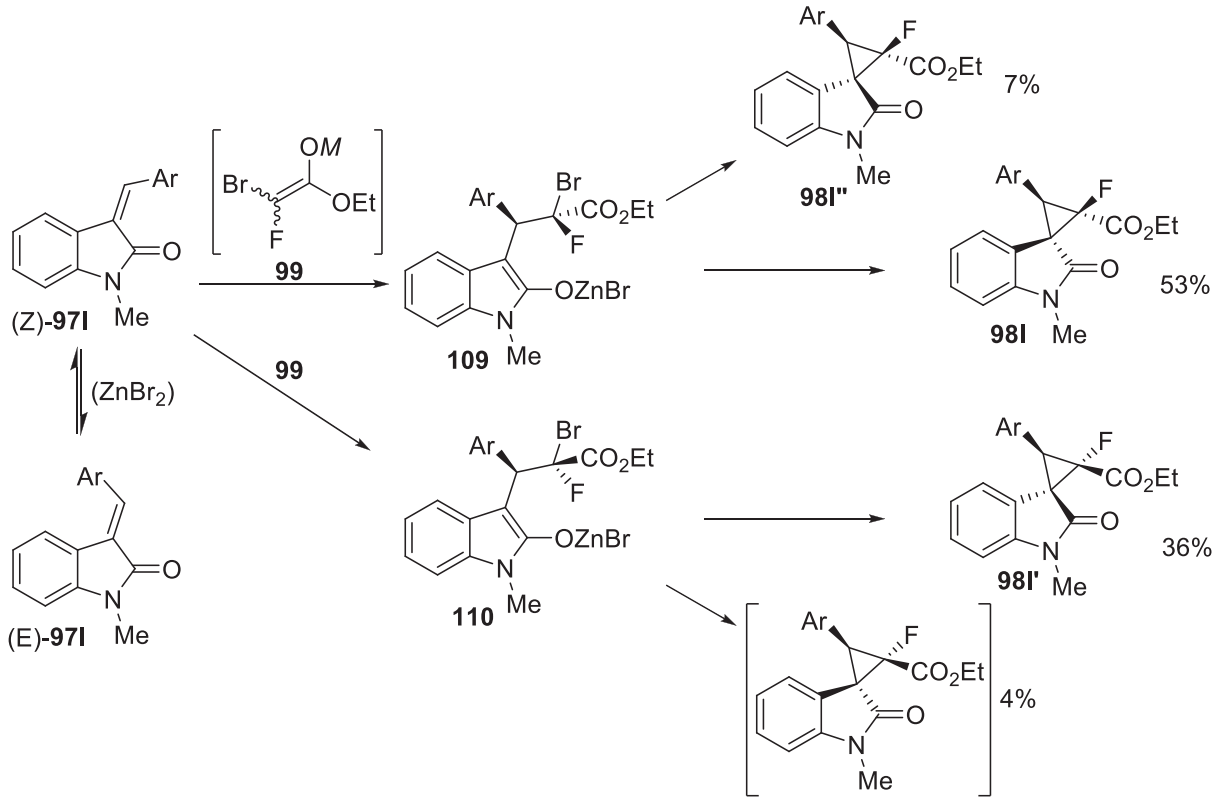
Scheme 41.

Based on the above experiments, we can conclude that the cyclopropanation with EDBFA – Zn/LiCl proceeds via the 1,4-addition – nucleophilic substitution and does not involve the formation of the corresponding (ethoxycarbonyl)fluorocarbene. This hypothesis is further supported by the fact that no cyclopropanation was observed with electron-rich alkenes, namely styrene and ethyl vinyl ether.

Unlike maleate/fumarate pair (*Z*)/(*E*)-**97j**, (*Z*)- and (*E*)-isomers of oxyindole **97l** undergo rapid equilibration under reaction conditions (same control experiment with $ZnBr_2$ instead of EDBFA as for

[132] Our attempts to trap the non-cyclized intermediate with benzaldehyde and (N-tosyl)benzaldimine were unsuccessful: quantitative formation of cyclopropane (*Z*)-**98k** was observed upon warming the reaction mixture to rt.

dibenzyl maleate). This fact apparently accounts for the same distribution of stereoisomers of cyclopropane **98l** for both (*Z*)- and (*E*)-oxyindoles (Scheme 42). Based on the difference in the overall yield (71% vs. 61%) we can hypothesize that the (*Z*)-isomer of oxyindole is actually the reactive one and gives rise to the whole set of four diastereomers, while the (*E*)-isomer is rather inert towards 1,4-addition, but can isomerize under reaction conditions.



Scheme 42.

Despite considerable effort we were not able to perform the cyclopropanation of some highly reactive or non-reactive alkenes (Fig. 12). β-Nitrostyrene, N-acryloyloxazolidin-2-one and N,N-dimethylacrylamide completely inhibited the metalation of EDBFA.[133] N-phenyl- and N-benzyl-maleimides underwent complete degradation under the most mild reaction conditions (-40°C, 1 equiv of EDBFA). Complex mixtures of products with minor quantities of desired cyclopropanes were obtained with more inert alkenes (ethyl cinnamate, ethyl *p*-cyanocinnamate, $Ph_2C{=}C(CO_2Et)_2$), chalcone and 2-cyclopentenone.

[133] Inhibition of zinc insertion by nitro compounds has been observed earlier (see reference 114). Standard two-step Reformatsky procedure is usually an adequate solution to this problem (not possible in the case of unstable **99**)

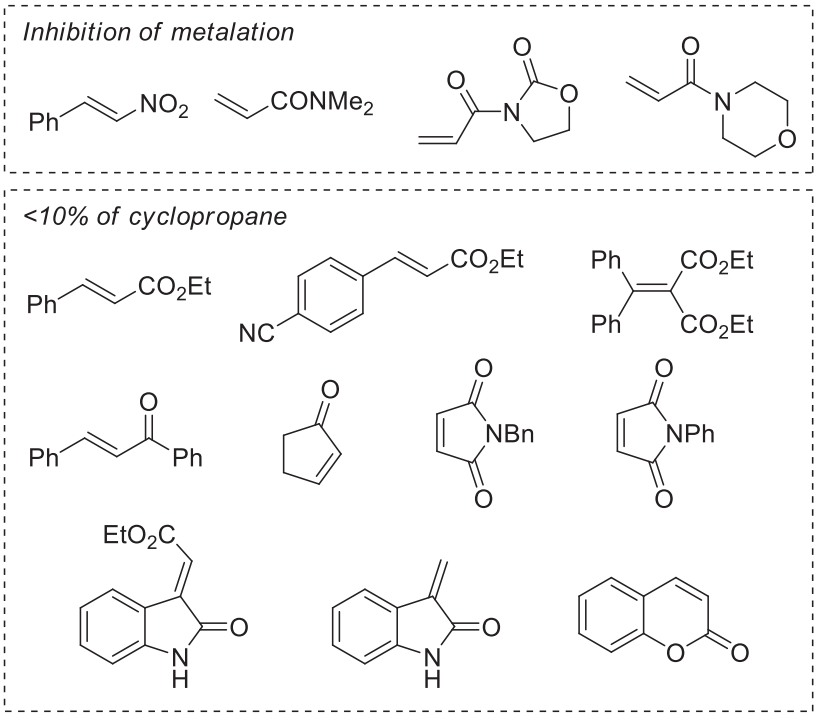
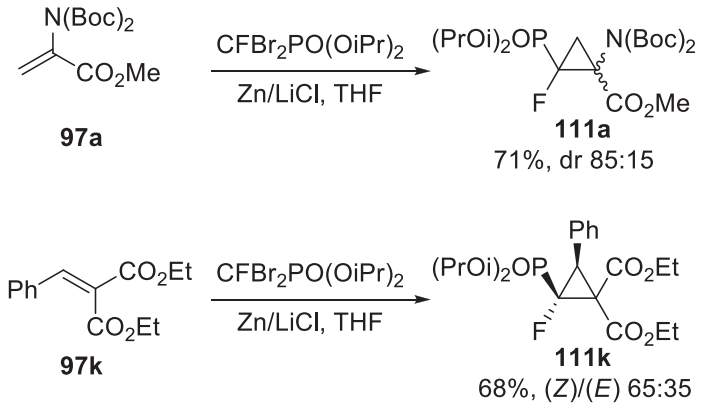


Figure 12.

The scope of the Zn/LiCl-mediated cyclopropanation can be further extended to the fluorinated cyclopropylphosphonates as exemplified by the synthesis of the α-fluoro-phosphonates **111a** and **111k** (Scheme 43).



Scheme 43.

e. Stereochemistry

For the majority of cyclopropanes the relative configurations of isomers were established on the basis of $^3J_{HF}$ and $^3J_{CF}$ spin-spin coupling values in NMR spectra. As a general rule,[134] larger value of $|^3J|$ is associated with *cis*-relationship of the corresponding atoms at the vicinal positions of the cyclopropane ring. Application of this rule usually allows internally consistent attribution of *cis*- and *trans*-isomers as shown on the Fig. 13.

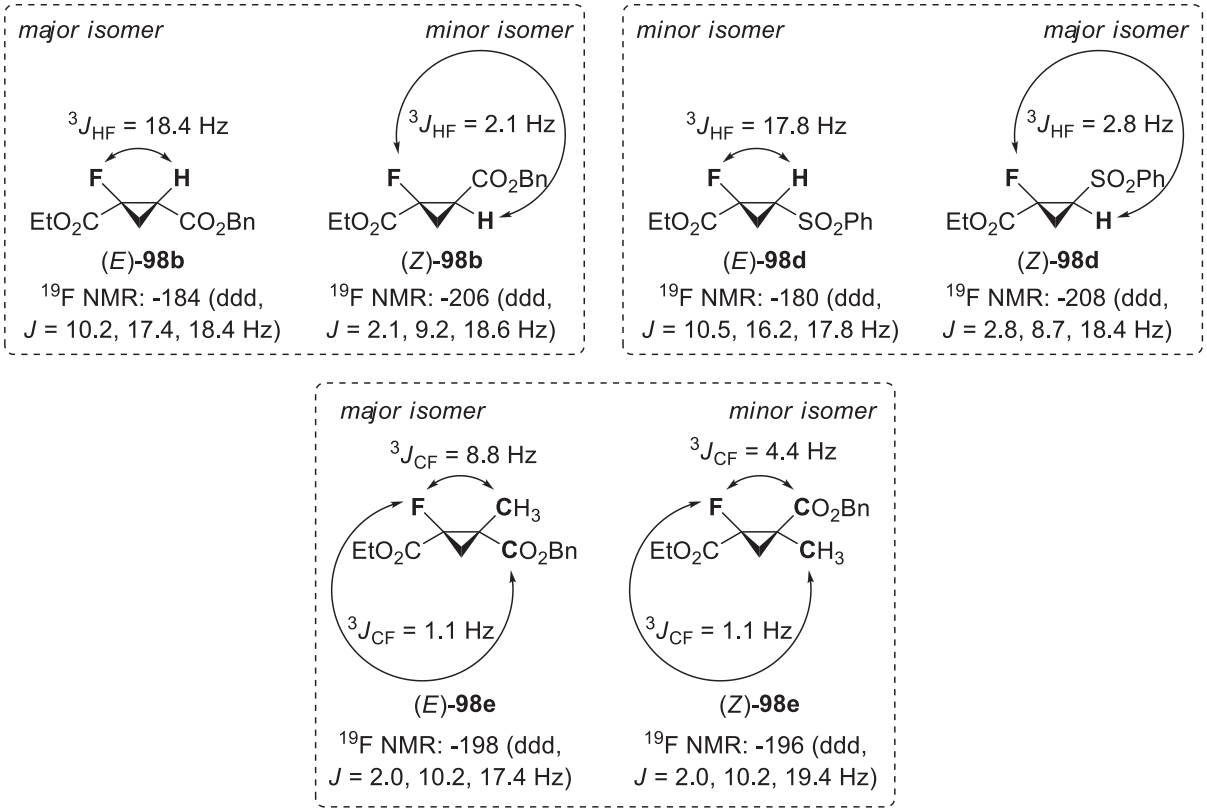


Figure 13.

The assignment of configuration based on $|^3J_{CF}|$ becomes more ambiguous when both vicinal carbon atoms are sp^2-hybridized because of smaller coupling values. Further support for the $|^3J_{CF}|$-based assignment comes from NOESY experiments (Fig. 14).

[134] Based on the application of the Karplus equation to the rigid cyclopropane system: W.R. Dolbier, "Guide to fluorine NMR for organic chemists", Wiley 2009.

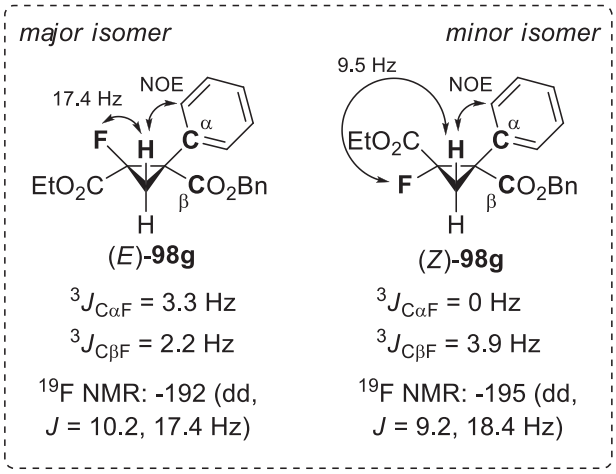


Figure 14.

One notable exception to the general trend of $|^3J_{CF}|$ values comes from the fluorinated amino acid **98a**. Its configuration was earlier determined by means of the ^{19}F-^{1}H HOESY experiment.[33] At the same time the $|^3J_{CF}|$ values lead to the opposite conclusion (Fig. 15). Unambiguous assignment of configuration by means of X-Ray crystallography was done by G. Milanole et al.[135] and coincides with the predictions of the HOESY experiment.

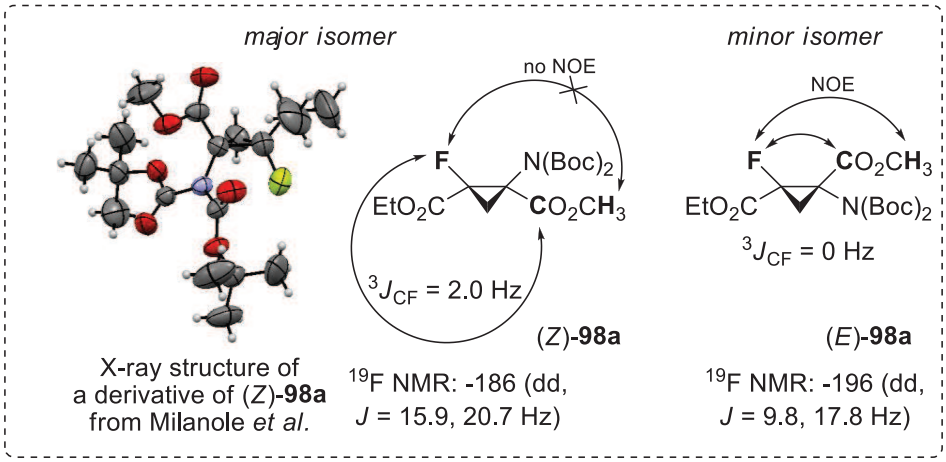


Figure 15.

Finally, the configurations of the oxyindole-derived cyclopropanes **98l**, **98l'** and **98l''** were determined by X-Ray analysis of the major isomer and comparison of $|^3J|$ values of individual isomers[136] (Fig. 16). This analysis together with the information about the reactivity of *Z*- and *E*-isomers of the

[135] Milanole, G.; Couve-Bonnaire, S.; Bonfanti, J.F.; Jubault, P.; Pannecoucke, X. *J Org Chem.* **2013**, *78*, 212.

[136] Full assignment of ^{1}H and ^{13}C signals was done using HSQC and HMBC spectra. Remarkably, large "through-space" spin-spin coupling constant between Cγ and F in **98l** is observed, apparently resulting from the forced proximity of these atoms. Cf. ref. 134.

starting alkene (see *Section 2d*) clearly show that the two most abundant isomers result from the low facial selectivity of 1,4-addition. The minor isomers come from the not completely stereoselective cyclization step. The whole stereochemical description of the reaction is given on the Scheme 42.

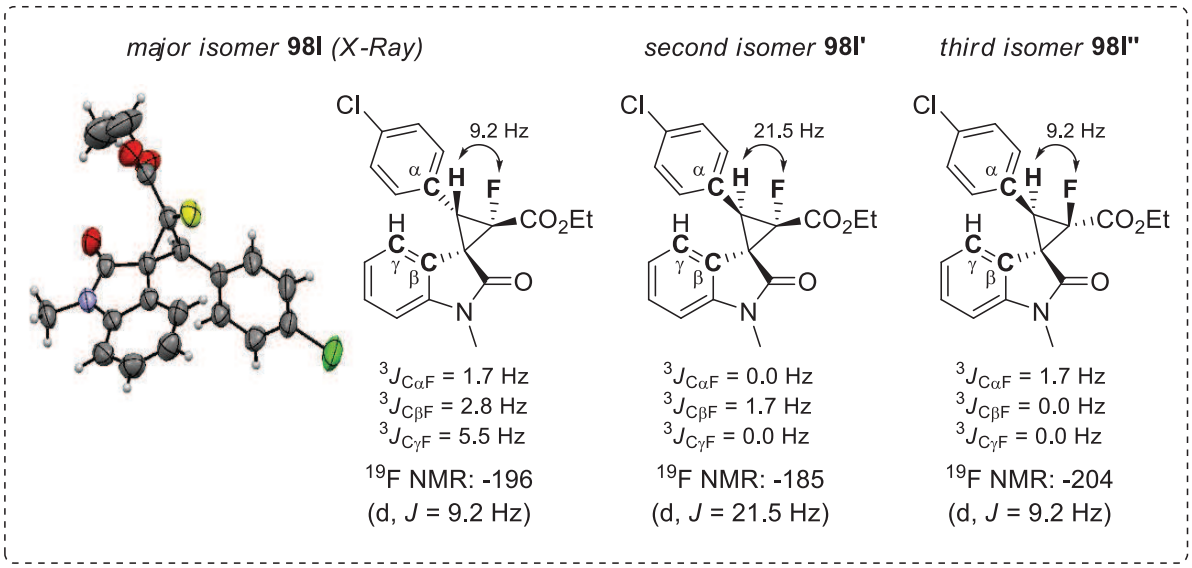


Figure 16.

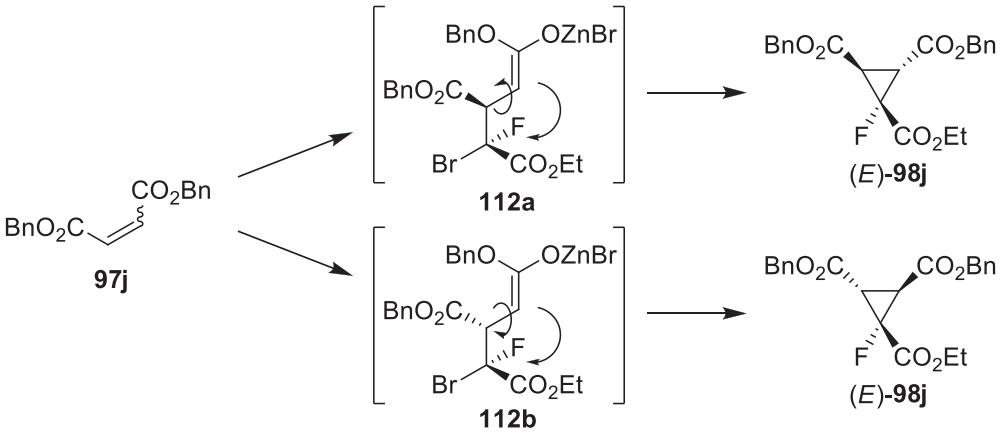
f. Studies on stereoselectivity

Taking into account the available mechanistic information (free rotation in the non-cyclized intermediate, stereospecificity of the intramolecular substitution – see Section 2d), the stereoselectivity for the cyclopropanation of mono- and 1,1-disubstituted alkenes is determined on the cyclization stage. Interestingly, conjugated esters (**97a,b,e-i**) with very different substituents at position 2 (H, methyl, allyl, phenyl, bis(tert-butoxycarbonyl)amino) all provide the cyclopropanes with *syn* ester groups as the major products (Table 2). One of the possible explanations can be a coordination of zinc enolate by the ethyl ester group during the cyclization. Remarkably, more sterically demanding *tert*-butyl ester provides even better diastereoselectivity. This is in contrast with acrylonitrile, phenyl vinyl sulfone and dimethyl vinylphosphonate.[137] The latter fact may originate from a different structure of non-cyclized intermediate, such as C-metalated species instead of zinc enolate.[138,139]

[137] Dimethyl vinylphosphonate was used in the asymmetric cyclopropanation (see *Section 4*).

[138] Few studies have dealt with the structures of Reformatsky reagents and their analogs. Ester- and amide-derived Reformatsky reagents crystallize as 8-member cyclic dimers and exist as tetramers (C_6D_6), dimers (C_6D_6-THF-d_8 9:1), or monomers (DMSO-d_6) depending on the basicity of the solvent (according to DOSY experiments). At the same time, ketone-derived Reformatsky reagents are true enolates in solid state (4-membered Zn-O-Zn-O cycle) and are dimeric in non-polar solvents, but monomeric in DMSO-d_6. (a) Dekker, J.;

On the other hand, for the alkenes bearing substituents at both olefinic atoms the stereochemical outcome depends on the selectivity of both stages of the reaction. In the simplest case of diethyl benzylidenemalonate the modest *de* value reflects the lack of stereoselectivity during 1,4-addition. The same lack of selectivity is revealed in the cyclopropanation of oxyindole derivative. In this case the non-selective 1,4-addition is followed by a more selective cyclization: ratios of cyclopropanes resulting from the cyclization of major **109** and minor **110** organozinc intermediate are 88:12 and 90:10, respectively (Scheme 42). The selectivity of cyclization is apparently based on the repulsion between chlorophenyl group and the substituents at the adjacent prochiral center. The cyclopropanation of dibenzyl fumarate/maleate is completely *trans*-selective due to the repulsion of benzyl ester groups (both possible isomers of the organozinc intermediate **112** converge into opposite enantiomers of the *trans*-cyclopropane **98j**, as shown on the Scheme 44.



Scheme 44.

In order to check the possible stereochemical effect of an ester group in EDBFA on the 1,4-addition and cyclization stages we prepared the *tert*-butyl dibromofluoroacetate and tested them it the reactions with diethyl benzylidenemalonate and benzyl acrylate, respectively. In both cases only minor

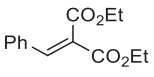
---

Budzelaar, P.H.M.; Boersma, J.; van der Kerk, G.J.M. *Organometallics* **1984**, *3*, 1403; (b) Hlavinka, M.L.; Hagadorn, J.R. *Organometallics* **2005**, *24*, 4116; (c) Greco, J.F.; McNevin, M.J.; Shoemaker, R.K.; Hagadorn, J.R. Organometallics 2008, 27, 1948.

[139] Conventional mechanism of the classical Reformatsky reaction (e.g. between $BrZnCH_2CO_2Et$ and PhCHO) is largely based on one semi-empirical computational study: Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P. *Tetrahedron Lett.* **1993**, *34*, 6111. The authors claimed that the equilibrium between C-metalated dimeric structure and O-metalated zinc enolate exists, and that the zinc enolate is the actual reacting intermediate that interacts with the aldehyde molecule. To the best of our knowledge, no experimental proof of this model has been reported, and no other reaction of Reformatsky and related reagents has been studied computationaly. Concerning the present work, it is not clear whether 1,4-addition and nucleophilic substitution by Reformatsky reagents proceeds via C- or O-metalated species, and what is the nature of α-sulfonyl, α-cyano and α-phosphonyl organozinc intermediates.

changes in *dr* were observed, indicating that the size of the ester group has almost no effect on the stereoselectivity of either 1,4-addition or cyclization.[140] N,N-Diethyl dibromofluoroacetamide demonstrated similar diastereoselectivity with **97b** as well.

Table 3.

	 **97b**	 **97k**
$CFBr_2CO_2Et$	72:28	69:31
$CFBr_2CO_2t$-Bu	75:25	64:36
$CFBr_2CONEt_2$	81:19	-

Some increase in the diastereoselectivity was observed while substituting *tert*-butyl ester for methyl ester in the Michael acceptor **97a** (*dr* 84:16 for **97i** vs. 59:41 for **97a**; see Table 2, entries 1 and 9), but almost no difference was observed between *tert*-butyl acrylate and benzyl acrylate (*dr* 84:16 vs. 79:21; asymmetric cyclopropanation, see *Section 4*).

While studying the diethylzinc-promoted cyclopropanation of dehydroamino acid **97a** we noticed a pronounced effect of the solvent and strongly coordinating TMEDA on the stereoselectivity (Table 4). Unfortunately, deviation from the optimized conditions (THF, 50°C) resulted in very low yields even in the case of a relatively robust Michael acceptor **97a**. Attempts to apply these diethylzinc-based conditions to benzyl acrylate were completely unsuccessful.

[140] Similarly, formation of trimethylsilyl bromofluoroketene acetals $CFBr{=}C(OSiMe_3)OR$ from $CFBr_2CO_2R$ (Zn, TMSCl) proceeds with the same stereoselectivity irrespective of the size of R (E/Z = 61:39 for Me; 62:38 for Et; 62:38 for *i*-Pr). However, it is not clear whether this E/Z ratio is kinetically control. See ref. 97.

Table 4.

Conditions		Yield by NMR, %	*cis:trans*
Toluene	50°C	<10	6:1
DME	50°C	25	5:1
THF	50°C	56	2:1
	50°C	33	1:3
THF + TMEDA	20°C	<10	1:6
	0°C	<10	1:9

Inspired by these results we studied the influence of various solvents and additives on the stereoselectivity of Zn(0)-promoted cyclopropanation. The choice of solvents for our reaction is limited to relatively polar and highly coordinating ones by the initial zinc insertion step. For example, substituting diethyl ether for THF completely inhibits the metalation of EDBFA. As mentioned earlier, DMSO was found to greatly facilitate the metalation in the absence of LiCl leading to the desired cyclopropane in low yield and with inversed stereoselectivity (Table 1, entry 8). DMSO is the only solvent that supported the metalation of EDBFA by activated Zn(0) in the absence of LiCl at temperatures below 20°C.

TMEDA was found to slightly influence the stereoselectivity of Zn/LiCl-promoted cyclopropanation, as illustrated in Table 5. However, increasing the ratio TMEDA:LiCl from 1:2 to 1:1 and beyond completely inhibited the metalation of EDBFA. Increasing the temperature of the reaction leads to complete decomposition of benzyl acrylate. Apparently, coordination of TMEDA to Li cation[141] disrupts the catalytic function of LiCl in C-Br bond metalation which is the basis of successful cyclopropanation with Zn/LiCl. Given this inhibiting effect, Lewis bases seem to be incompatible with our reaction (with a possible exception of a hypothetic ligand with high Zn vs. Li selectivity).

Table 5.

Conditions	Yield by NMR, %	*cis: trans*
Zn/LiCl (standard conditions)	80	1:2
Zn/TMEDA, THF, rt to 40°C	0	-
Zn/TMEDA/LiCl (1:2), THF, rt	70-80	1:3
Zn/Me_2AlCl, THF	0	-
$Zn/Me_2AlCl/LiCl$ (1:2), THF	50	1:1
$Zn/Ti(OiPr)_4$, THF, rt	traces	1:1
Zn/MAD, THF-Toluene	40	3.2:1
Zn/MAD/LiCl, THF-Toluene	25	1:1

[141] Quenching of LiCl was used to suppress the background reaction in asymmetric arylzinc addition to aldehydes: (a) Salvi , L.; Kim, J.G.; Walsh, P.J. *J. Am. Chem. Soc*. **2009**, *131*, 12483. (b) Hevia, E.; Mulvey, R.E. *Angew. Chem. Int. Ed.* **2011**, *50*, 2.

As discussed above, the propensity for *syn*-orientation of the vicinal ester groups in cyclopropanes can be explained by the coordination of the intermediate zinc enolate to the ethyl ester group. To probe this possible interaction, we used three oxophilic Lewis acids that could coordinate to the ethyl ester of the non-cyclized intermediate and thus increase the yield of the (*Z)*-isomer of **98b** (cis-relationship of fluorine and ester). Indeed, in the presence of Me_2AlCl or $Ti(OiPr)_4$ the reaction became non-selective, while the sterically hindered aluminium Lewis acid MAD[142] inversed the usual ratio of diastereomers. Notably, MAD supports the zinc insertion even in the absence of LiCl, thus making this Lewis acid a promising additive for obtaining the complementary stereoisomers of mono- and 1,1-disubstituted cyclopropanes.

[142] MAD = methylaluminium bis(2,6-di-tert-butyl-4-methylphenoxide), prepared in situ as a toluene solution according to: Denmark, S.E.; Schnute M.E. *J. Org. Chem.* **1991**, *56*, 6738.

4. Development of a chiral fluorinated cyclopropanating reagent bearing the dibromofluoroacetyl group

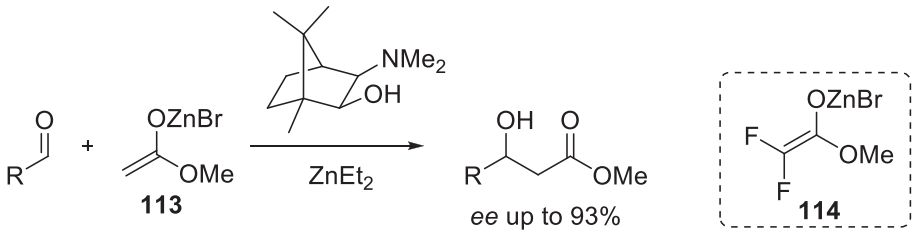
Having established the new method of synthesis of monofluorinated cyclopropanes, we focused on the development of an asymmetric version thereof. Here we will briefly discuss the reported approaches to asymmetric reactions of Reformatsky-type reagents.

a. Overview of the asymmetric approaches to Reformatsky and related reactions.

Since the original report by Oguni and Omi[143] the enantioselective ligand-accelerated addition of dialkylzincs to aldehydes has become one on the most powerful asymmetric methods of synthesis of enantioenriched alcohols.[144] At the same time, analogous reaction of Reformatsky reagents is greatly complicated by their high intrinsic reactivity towards carbonyl compounds resulting in high levels of background reaction and the need to use stoichiometric amounts of chiral ligands. First examples of such a reaction were reported by M. Guetté *et al.* in 1971 using (-)-sparteine as a chiral ligand.[145] Moderate yields and variable *ee* values (up to 98% *ee*) were obtained. Numerous examples of ligand-promoted Reformatsky reaction followed.[146]

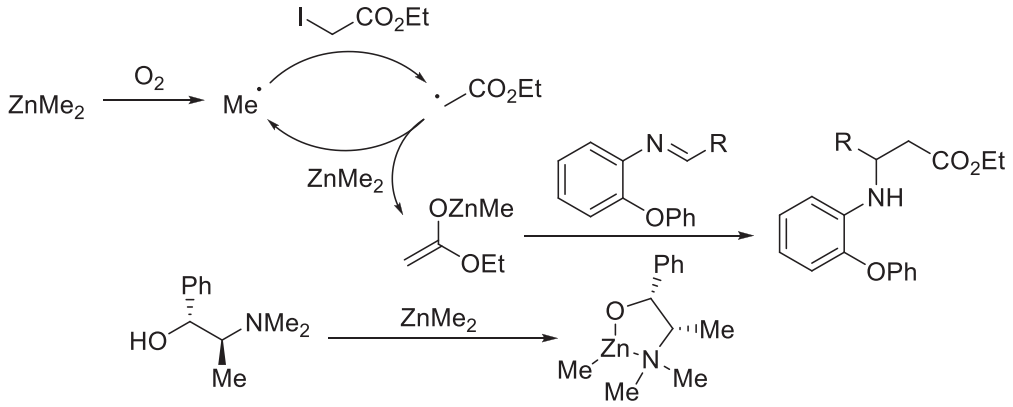
One of the most efficient and general implementations of this approach was reported by the group of P. Knochel (Scheme 45). In the presence of 1.2 equiv of amino alcohol (-)-DAIB and 0.6 equiv of $ZnEt_2$ the preformed Reformatsky reagent **113** added to a variety of aldehydes with consistently high *ee* values up to 93%.[147] Notably, this method was successfully applied to the difluorinated Reformatsky reagent **114**. Unfortunately, it was not possible to reduce the amount of a chiral ligand without the loss of enantioselectivity (19% *ee* with 10%mol of (-)-DAIB).

[143] Oguni, N.; Omi, T. *Tetrahedron Lett*. **1984**, *25*, 2823.
[144] Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
[145] Guetté, M.; .Guetté, J.-P.; Capillon, J. *Tetrahedron Lett*. **1971**, *12*, 2863.
[146] Lombardo, M.; Trombini, C. in "The chemistry of organozinc compounds", Rappoport, Z.; Marek, I. Eds. Wiley, 2006.
[147] Kloetzing, R.J.; Thaler, T.; Knochel, P. *Organic Letters* **2006**, *8*, 1125.



Scheme 45.

The first enantioselective Reformatsky reaction that was efficient with substoichiometric amounts of a chiral ligand was reported by P.G. Cozzi in 2006.[148] His approach was based on the use of ClMn(salen) complex as a catalyst for $ZnMe_2$-mediated reaction between an iodoacetate and a ketone. Mechanism of this reaction was not studied in detail. In the same year P.G. Cozzi reported the N-methylephedrine-catalysed enantioselective imino-Reformatsky reaction (Scheme 46).[149] Dimethylzinc was used as the metalating agent in the presence of air. Slow generation of $MeZnCH_2CO_2Et$ via a radical chain reaction under homogeneous conditions is crucial for the efficient asymmetric induction by catalytic amounts of a chiral ligand. Later on, similar catalytic reactions with aldehydes were reported by groups of P.G. Cozzi[150] and B. Feringa.[151]



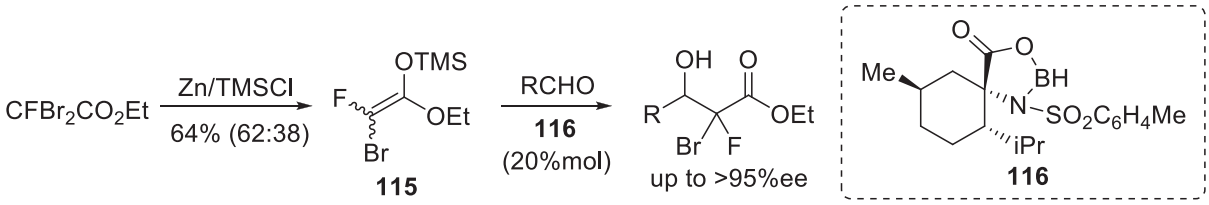
Scheme 46.

Catalytic enantioselective reactions are generally considered as a preferred, efficient, atom-economical approach to the enantioenriched molecules. However, the examples from the literature outlined above demonstrate that the constraints of the existing enantioselective Reformatsky methodology are hardly compatible with the particular case of cyclopropanation using EDBFA. First, organozinc derivatives **99** are highly unstable and can not be prepared in advance. Second, dialkylzincs

[148] Cozzi, P.G. *Angew. Chem. Int. Ed*. **2006**, *45*, 2951.
[149] Cozzi, P.G. *Adv. Synth. Catal.* **2006**, *348*, 2075.
[150] Cozzi, P.G.; Benfatti, F.; Capdevila, M.G.; Mignogna, A. *Chem. Commun.* **2008**, 3317.
[151] Fernandez-Ibanez, M.A.; Macia, B.; Minnaard, A.J.; Feringa, B.L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1317.

are not reactive enough towards EDBFA and tend to cause the polymerization of electron-deficient alkenes even in the absence of activating ligands. Finally, the most powerful methodology based on the controlled generation of reactive radicals can be difficult to implement in the case of Michael acceptors prone to radical polymerization.

Among the other catalytic reactions the one of the special relevance to the present project is the enantioselective Mukaiyama reaction with the silyl bromofluoroketene acetal **115** derived from EDBFA (Scheme 47).[97,152] **115** was prepared by the reaction of EDBFA with Zn metal and TMSCl in THF and purified by distillation to give a 62:38 mixture of inseparable (*E*)- and (*Z*)-isomers. Notably, substituting isopropyl for ethyl in EDBFA does not change the *E*/*Z* ratio. **115** reacts with aldehydes without any catalysis at temperatures as low as -78°C. In the presence of 20%mol of oxazaborolidine **116** it provides high levels of ee (up to >95% ee in most cases) and high yields of the corresponding aldols. At the same time, almost equimolar mixtures of *syn*- and *anti*-isomers are obtained (*syn*/*anti* 39:61 to 69:31 depending on the aldehyde).



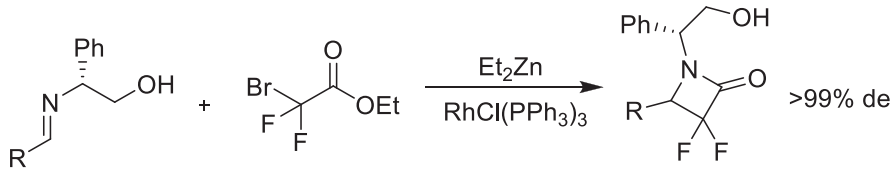
Scheme 47.

Enantioselective Mukaiyama-Michael reaction has become a powerful catalytic method for the synthesis of a wide range of chiral 1,5-dicarbonyl compounds.[153] Application of this approach to fluorinated silylated compounds such as **115** could be an efficient solution to the problem of the synthesis of corresponding cyclopropanes (via a two-step Mukaiyama-Michael reaction/nucleophilic substitution sequence). One inherent drawback of using **115** in such a way would be the inseparability of Z- and E-isomers that can result in low stereoselectivity of 1,4-addition, as already reported in the non-catalysed reaction with 2-pentenone (see *Section 2d* and ref. 96).

[152] (a) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett*. **1997**, *38*, 7209; (b) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Synlett* **1998**, 437.

[153] (a) Evans, D.A.; Scheidt, K.A.; Johnston, J.N.; Willis, M.C. *J. Am. Chem. Soc.* **2001**, *123*, 4480; (b) Brown, S.P.; Goodwin, N.C.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2003**, *125*, 1193; (c) Borths, C.J.; Carrera, D.E.; MacMillan, D.W.C. *Tetrahedron* **2009**, *65*, 6746 (and references therein).

A less straightforward but more easily implemented approach to asymmetric Reformatsky-type reaction is by using the enantiopure reagents.[154,155] Probably the most well-developed reaction of this class is the 1,2-addition to chiral imines. Zn(0) was used as a metalating agent in the reactions with sulfoximines,[156] imines derived from chiral amino alcohols[157] and amino acids,[158] as well as hemiacetals.[159] As a general rule, organozinc reagent is prepared in advance. Diethylzinc was also used in the Rh(I)-catalysed addition to imines with excellent diastereoselectivity (Scheme 48).[160]



Scheme 48.

Analogous additions to chiral carbonyl compounds can sometimes be highly diastereoselective.[161] Few reactions of Reformatsky reagents with chiral Michael acceptors are known.[162] In one particular case reported by Yang and Wang[163] the chiral amino group is eliminated after the 1,4-addition and therefore acts as a true chiral auxiliary (scheme 49). High level of asymmetric induction in the latter case apparently stems from the fact that the chiral auxiliary is directly attached to the β-carbon and is therefore in the vicinity to the reacting center.

[154] Review of diastereoselective Reformatsky reactions: Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert, F. *Chem. Soc. Rev*. **2013**, *42*, 937.

[155] Comprehensive review covering various aspects of Reformatsky reaction, including comparison of different modes of asymmetric induction: Ocampo, R.; Dolbier, W.R. *Tetrahedron* **2004**, *60*, 9325.

[156] Soloshonok, V.A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett*. **2002**, *43*, 5445.

[157] Clark, J.D.; Weisenburger, G.A.; Anderson, D.K.; Colson, P.-J.; Edney, A.D.; Gallagher, D.J.; Kleine, H.P.; Knable, C.M.; Lantz, M.K.; Moore, C.M.V.; Murphy, J.B.; Rogers, T.E.; Ruminski, P.G.; Shah, A.S.; Storer, N.; Wise, B.E. *Org. Proc. Res. Develop*. **2004**, *8*, 51.

[158] (a) van Maanen, H.L.; Kleijn, H.; Jastrzebski, J.T.B.H.; Verweij, J.; Kieboom, A.P.G.; van Koten, G. *J. Org. Chem.* **1995**, *60*, 4331; (b) March, T.L.; Johnston, M.R.; Duggan, P.J.; *Org. Lett*. **2012**, *14*, 182.

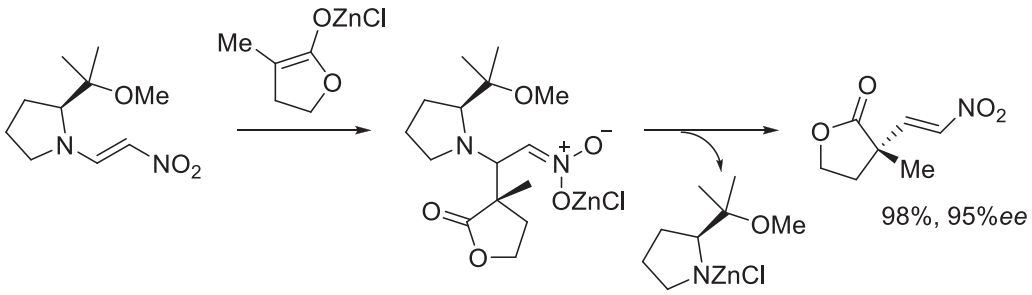
[159] Gouge, V.; Jubault, P.; Quirion, J.-C. *Tetrahedron Lett*. **2004**, *45*, 773.

[160] Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307.

[161] (a) Rauter, A.P.; Oliveira, O.; Canda, T.; Leroi, E.; Ferreira, H.; Ferreira, M.J.; Ascenso, J.A. *J. Carbohydrate Chem.* **2002**, *21*, 257; (b) Kotra, L.P.; Xiang, Y.; Newton, M.G.; Schinazi, R.F.; Cheng, Y.-C.; Chu, C.K. *J. Med. Chem.* **1997**, *40*, 3635.

[162] (a) Dyer, J.; Keeling, S.; Moloney, M.G.; *Tetrahedron Lett*. **1996**, *37*, 4573; (b) Brewster, A.G.; Broady, S.; Hughes, M.; Moloney, M.G.; Woods, G. *Org. Biomol. Chem.* **2004**, *2*, 1800; (c) Bailey, J.H.; Cherry, D.; Dyer, J.; Moloney, M.G.; Bamford, M.J.; Keeling, S.; Lamont, R.B. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2783.

[163] Yang, X.; Wang, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3275.

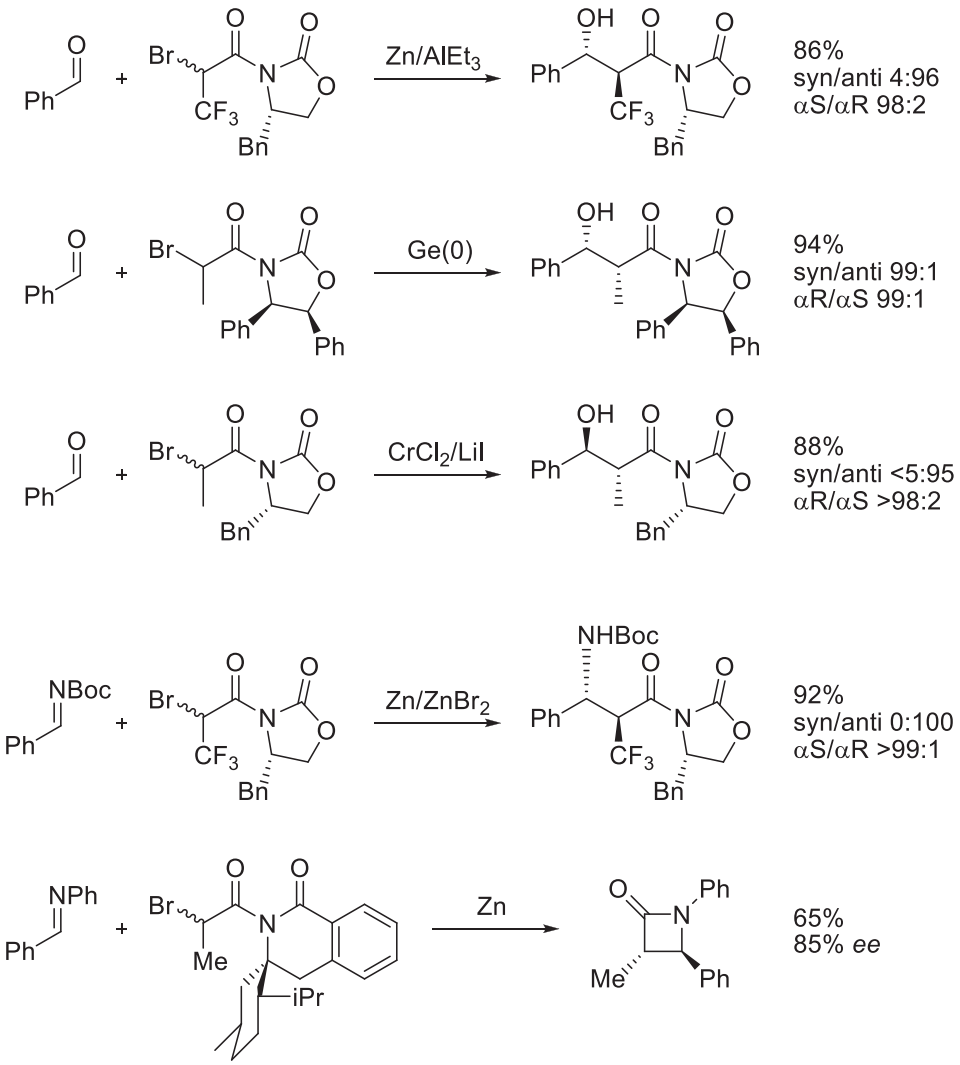


Scheme 49.

Examples of enantiomerically pure Reformatsky reagents are rare and often provide mixtures of diastereoisomers in reactions with prochiral electrophiles.[155] Chiral alcohols[164] and oxazolidinones[165] are the most frequently used chiral auxiliaries in these reactions. Carbohydrate-derived Reformatsky reagent (without a removable chiral auxiliary) was also used in combination with benzaldehyde with a moderate enantiomeric excess.[166]

Aldehydes[167] and imines[164,168] were used as electrophiles for chiral auxiliary-directed Reformatsky additions. Other metalating agents such as SmI_2,[169] $CrCl_2$,[170] Ge(0)[171] in combination with oxazolidinone or sulfoxide[172] chiral auxiliaries demonstrated the improved and/or altered stereoselectivity in these reactions (Scheme 50).

[164] Shankar, B.B.; Kirkup, M.P.; McCombie, S.W.; Clader, J.W.; Ganguly, A.K. *Tetrahedron Lett*. **1996**, *37*, 4095.
[165] Zn(0): Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Org. Lett.*, **2006**, *8*, 1131. Diethylzinc: Yu, L.-T.; Ho, M.-T.; Chang, C.-Y.; Yang, T.-K. *Tetrahedron: Asymmetry* **2007**, *18*, 949.
[166] Lichtenthaler, F.W.; Lergenmuller, M.; Schwidetzky, S. *Eur. J. Org. Chem*. **2003**, 3094.
[167] Ito, Y.; Terashima, S. *Tetrahedron* **1991**, *47*, 2821.
[168] (a) Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Chem. Commun.* **2006**, 3628; (b) Yuan, Q.; Jian, S.-Z.; Wang, Y.-G. *Synlett* **2006**, 1113.
[169] (a) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *Org. Chem.* **2000**, *65*, 1702; (b) Obringer, M.; Colobert, F.; Neugnot, B.; Solladie, G. *Org. Lett.* **2003**, *5*, 631.
[170] Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 4387.
[171] Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691.
[172] Obringer, M.; Colobert, F.; Neugnot, B.; Solladie, G. *Org. Lett.* **2003**, *5*, 629.



Scheme 50. Selected examples of 1,2-addition of chiral Reformatsky reagents

Overall, the diastereoselective Reformatsky reaction with aldehydes and imines is known to provide high level of stereoselectivity, especially when oxazolidinones are used as chiral auxiliaries.

Despite numerous examples of successful 1,2-addition of Reformatsky-type reagents to aldehydes and imines using various methods of asymmetric induction (stoichiometric/catalytic amounts of chiral ligands, chiral auxiliaries incorporated into Reformatsky reagents or substrates), asymmetric 1,4-addition is limited to reactions with chiral alkenes.[162,163] To the best of our knowledge, no example of 1,4-addition of chiral Reformatsky reagents has been reported.

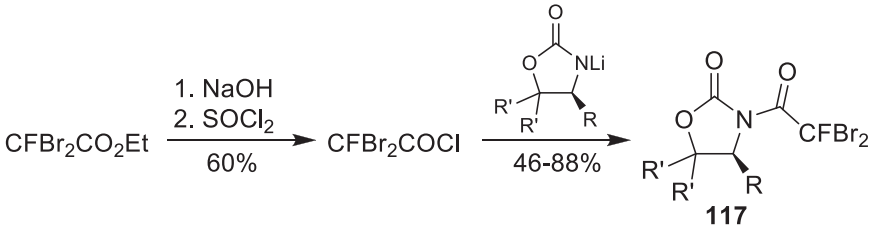
Given the already established Zn/LiCl-promoted MIRC cyclopropanation with a substantial substrate scope, we decided to develop an asymmetric version of cyclopropanation based on the previously unexplored 1,4-addition of a chiral Reformatsky reagent.

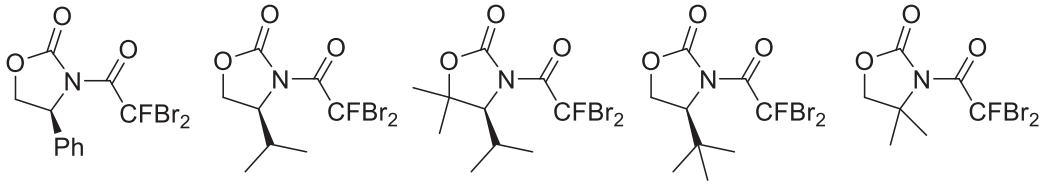
b. Choice of a source of chirality

As already mentioned above, the best results in the Reformatsky reaction with aldehydes and imines were obtained with the oxazolidinones as chiral auxiliaries. In addition to that, we and others have already shown that the size of the ester group in dibromofluoroacetate does not have any influence on the stereoselectivity of 1,4-addition (see *Section 3f*) or silylation.[152] Therefore, for the present project it seemed reasonable to replace the ester with the oxazolidinone which is capable of chelation and eventually more pronounced stereodiscrimination.

c. Synthesis of dibromofluoroacetyl-oxazolidinones

Several dibromofluoroacetyl-oxazolidinones **117** were prepared in three steps from EDBFA according to the Scheme 51. Dibromofluoroacetic acid was prepared via basic hydrolysis of EDBFA and was directly converted to the dibromofluoroacetyl chloride. Subsequent acylation of chiral oxazolidinones afforded the desired **117**. These compounds are usually crystalline and stable for several weeks at -20°C. They are nevertheless slowly hydrolysed in the air at ambient temperature. Stability towards hydrolysis apparently increases with the steric hindrance of the auxiliary.





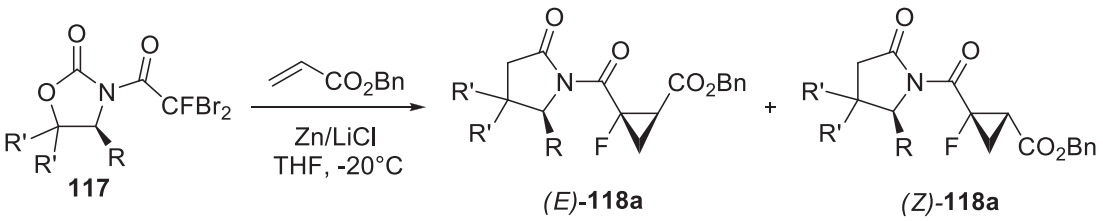
	117a	**117b**	**117c**	**117d**	**117e**
Yield from EDBFA:	28%	43%	49%	53%	46%

Scheme 51.

3. Comparison of stereodiscriminating ability of different auxiliaries

All the oxazolidinones were tested in the model cyclopropanation of benzyl acrylate using the conditions optimized for EDBFA (Scheme 52, Table 6). Two opposite trends are observed: increase in the size of the oxazolidinone side chain results in lower (*E*)/(*Z*)-selectivity, but at the same time leads to

better diastereomeric excess for both (Z)-**118a** and (E)-**118a**.[173] Given the high *de* values, the best stability demonstrated by **117c** and the lower cost of the corresponding auxiliary we decided to use this reagent for the further cyclopropanation studies.



Scheme 52.

Table 6.

117	(*Z*):(*E*)	*de*(*Z*)	*de*(*E*)
a	3:97	52	68
b	16:84	84	86
c	21:79	84	93
d	27:73	86	88
e	18:82	-	-

d. Comparison of metalating agents, conditions with Zn/LiCl

We then applied some of the alternative metalating agents that were found to be compatible with the racemic version of cyclopropanation (Table 7). Despite higher (*Z*):(*E*)-selectivity, all of them demonstrated poorer yields and, more importantly, lower *de* of the major (*E*)-isomer when **117c** was used.[174] However, these reactions can be of interest for the development of a highly *E/Z*-selective cyclopropanation using the achiral oxazolidinone **117e**. Notably, in the presence of LiCl magnesium enolate demonstrated better *de*(*E*) value. Unfortunately, similar comparison of Zn/LiCl and Zn is not possible. Higher yields obtained with the oxazolidinone **117c** in comparison to EDBFA (cf. Table 1) apparently arise from higher stability of the corresponding organometallic intermediates probably stabilized in the enolate form by chelation with oxazolidinone carbonyl. The best results in terms of the yield and asymmetric induction were obtained with Zn/LiCl.

[173] *de*(*Z*) and *de*(*E*) values refer to the ratios of diastereoisomers with the opposite configuration. E.g. for benzyl acrylate: (2S,3R) vs. (2R,3S) for *de*(*E*) and (2S,3S) vs. (2R,3R) for *de*(*Z*). These values are equivalent to enantiomeric excess of the corresponding isomers after removal of the chiral auxiliary.

[174] The results obtained with reagents other than Zn/LiCl should be regarded as preliminary, since neither of these reactions was fully optimized.

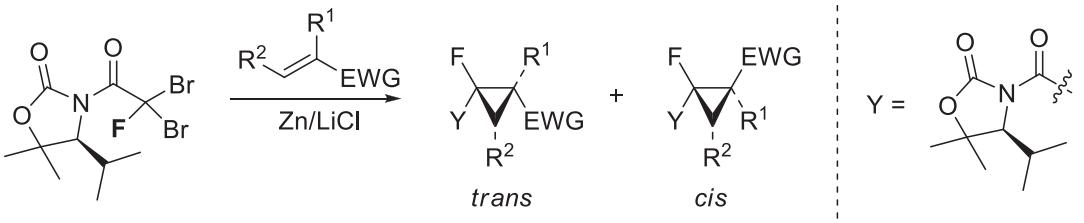
Table 7. Reaction of **117c** with benzyl acrylate

reagent	yield **118a**, %	(*Z*):(*E*)	*de*(*E*)
^{t}BuLi	23	4:96	74
iPrMgCl	64	7:93	18
iPrMgCl/LiCl	43	5:95	46
Et_2Zn	<5	-	-
Zn/LiCl	79[b]	21:79	93

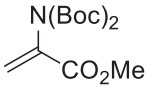
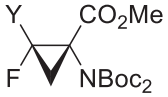
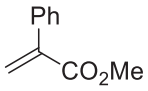
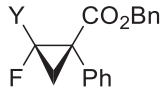
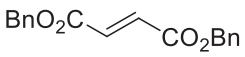
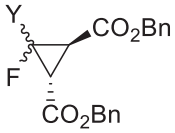
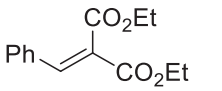
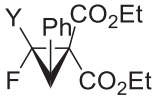
e. Scope of cyclopropanation

Similarly to EDBFA the chiral fluorinated oxazolidinone **117c** can be used in cyclopropanation of a variety of Michael acceptors (Table 8). Reaction takes place with diverse monosustituted Michael acceptors bearing ester (entries 1,2) , sulfone (entry 3), phosphonate (entry 4) or nitrile (entry 5) as electron-withdrawing group leading to the expected fluorinated cyclopropanes in good overall yields. Di- and trisubstituted alkenes also react with good overall yields and generally the same level of diastereoselectivity (entries 6-9). In most cases the diastereomerically pure fluorinated cyclopropanes can be easily separated by column chromatography.

Table 8. Scope of asymmetric cyclopropanation.



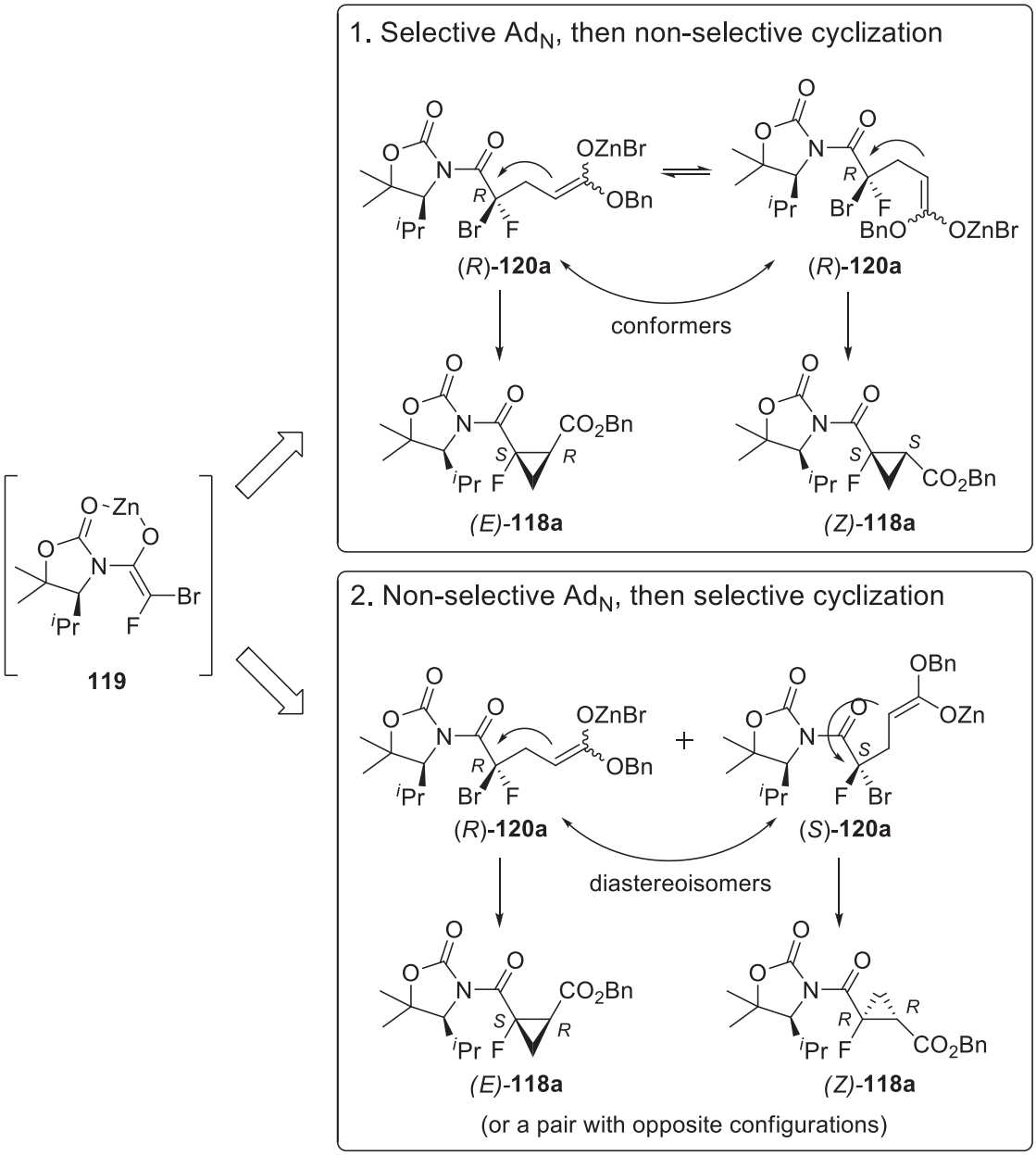
entry	alkene	major product (**118**)		overall yield of **118**, %[b]	(*Z*):(*E*)[a]	*de*[a] (yield[b]) *Z*-**118**	*de*[a] (yield[b]) *E*-**118**
1	CO_2Bn	Y, CO_2Bn, F	**a**	79	21:79	84 (14)	93 (65[c])
2	$CO_2{}^{t}Bu$	Y, $CO_2{}^{t}Bu$, F	**b**	69	16:84	76 (8)	94 (61)
3	SO_2Ph	Y, F, SO_2Ph	**c**	79	78:22	88 (62[c])	92 (17[c])
4	$PO(OMe)_2$	Y, F, $PO(OMe)_2$	**d**	62	85:15	>94 (55[c])	80 (7)

5			**e**	70	50:50	94 (36[c])	>94 (34[c])
6			**f**	78	73:27	80 (56[c])	84
7			**g**	74	45:55	>90 (33[c])	>92 (41)
8			**h**	79	5:95[d]	-	64
9			**i**	66	36:64	>94 (24[c])	>94 (42[c])

[a] by ^{19}F NMR of the crude product; [b] isolated yield; [c] single isomer by ^{19}F NMR of the isolated product; [d] *E/Z* ratio refers to the stereochemistry of the ester groups (absolute configuration cannot be deduced from our stereochemical model: see below).

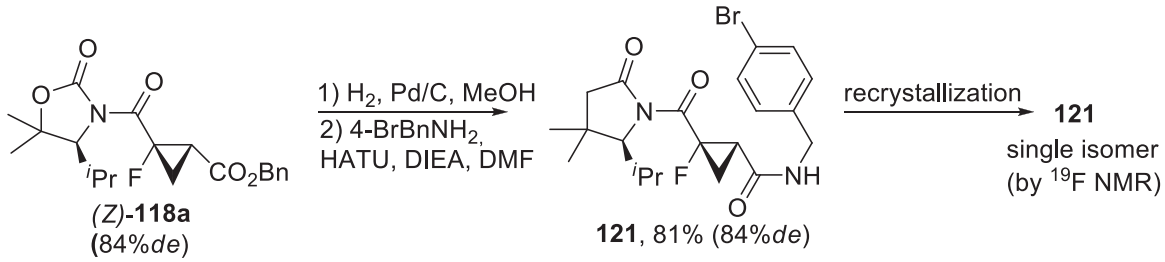
Relative configurations of cyclopropane cores in the products **118** were determined analogously to the previous work with EDBFA. The same stereochemical trends are observed for reactions with **117c** and with EDBFA (cf. table 2): *cis*-relationship of ester groups (entries 1,2, 6,7), *trans*-configuration of **118h** forced by 1,2-repulsion in the non-cyclized intermediate, low *cis-trans* selectivity in the case of 2-substituted Michael acceptors (entry 9).

As shown in Table 7, good *de*(*Z*) and *de*(*E*) values were observed for the majority of cyclopropanes. At the same time, highly variable (*Z*):(*E*) ratios were observed. These results could be in principle explained according to two mutually exclusive mechanistic hypotheses: 1) highly stereoselective (with respect to the fluorinated stereocenter) 1,4-addition followed by the non-selective cyclization, and 2) non-selective 1,4-addition followed by stereocontrolled cyclization. In line with this dichotomy the Scheme 53 illustrates the formation of two major products (one (*Z*) and one (*E*)) out of four possible ones. As evident from this scheme the alternative pathways can be discriminated by determining the absolute configuration of both (*Z*)- and (*E*)-isomers of a cyclopropane. The same configuration of the fluorinated stereocenter would argue for the pathway 1, while the opposite configuration thereof would argue for the pathway 2.



Scheme 53.

In order to determine the absolute configuration of the isomers of **118a** we prepared the monocrystals suitable for X-Ray analysis. While the major *(E)*-isomer of **118a** readily crystallized even from the crude mixture of isomers, we were not able to obtain the crystals of (*Z*)-**118a**. This was finally accomplished after a two-step modification of (*Z*)-**118a** according to the Scheme 54. The *de*(*Z*) value was preserved throughout the synthesis and the pure major (*Z*)-isomer of **121** was obtained after recrystallization. The latter was used for the preparation of monocrystals.



Scheme 54.

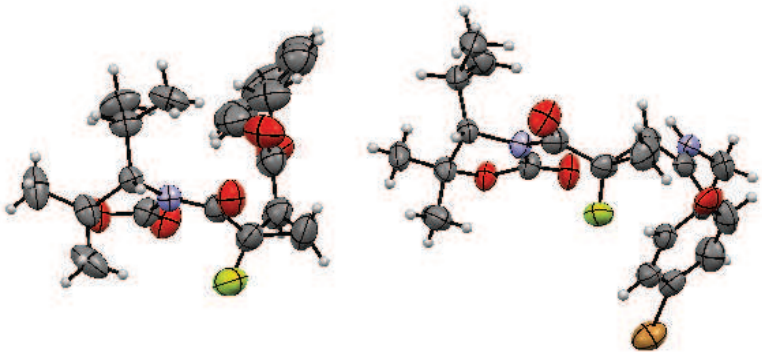
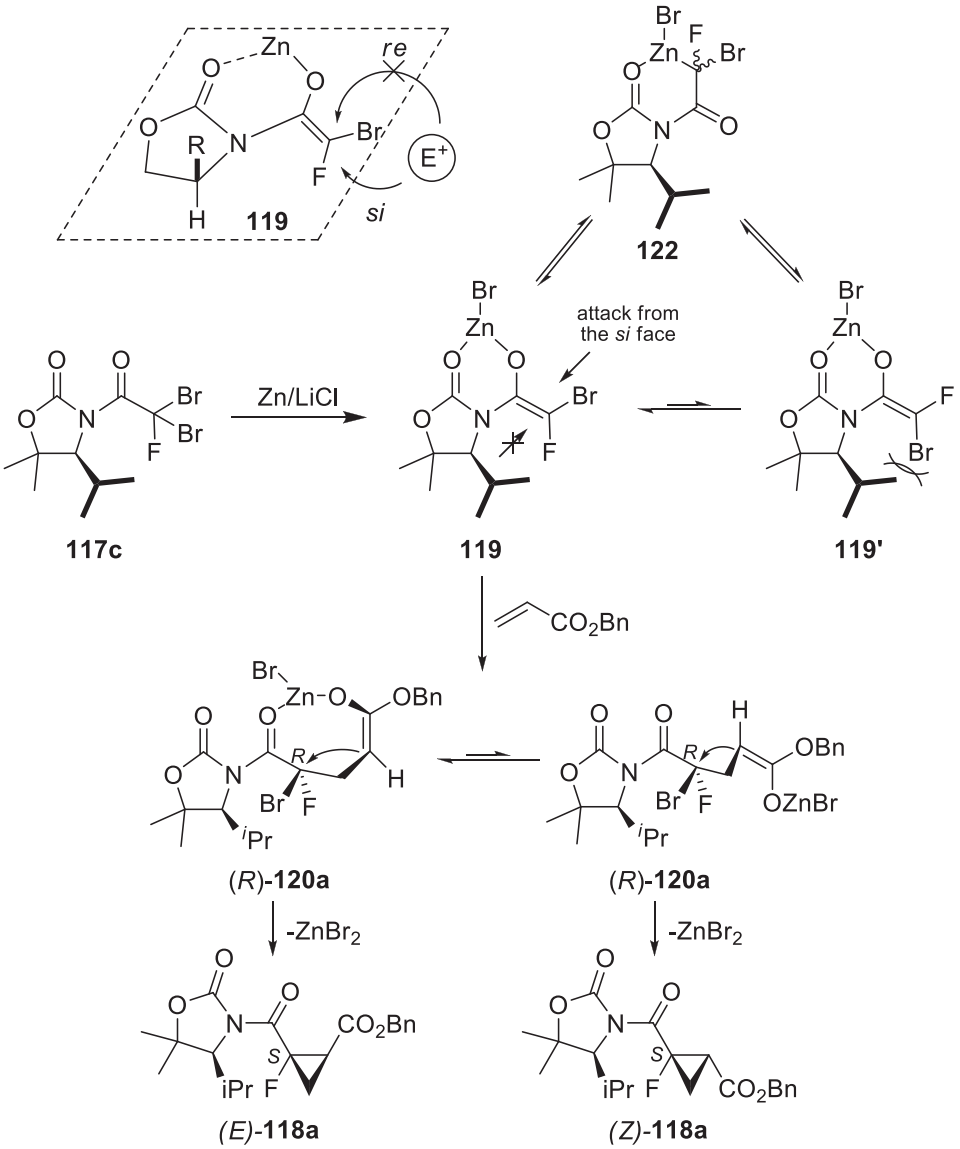


Figure 17. X-Ray structures of (*E*)-**118a** and **121**.

The results of X-Ray analysis let us to assign the *S* configuration to the fluorinated stereocenter of both *(Z)*- and *(E)*-isomers of **118a**. Therefore, the two major isomers result from the non-stereoselective cyclization of the same intermediate (*R*)-**120a** (Scheme 53). This conclusion is consistent with the similar trends in *E/Z*-selectivity of the reactions with both EDBFA and **117** and with generally high *de* values for both isomers of cyclopropane irrespective of the nature of the Michael acceptor.

Given that the 1,4-addition to acrylate is very stereoselective and leads to the single non-cyclized intermediate, one can propose a hypothetic structure of the actual reacting intermediate **119** as shown on the Schemes 53 and 55, in line with the standard Evans aldol mechanism.[175]

[175] Evans , D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

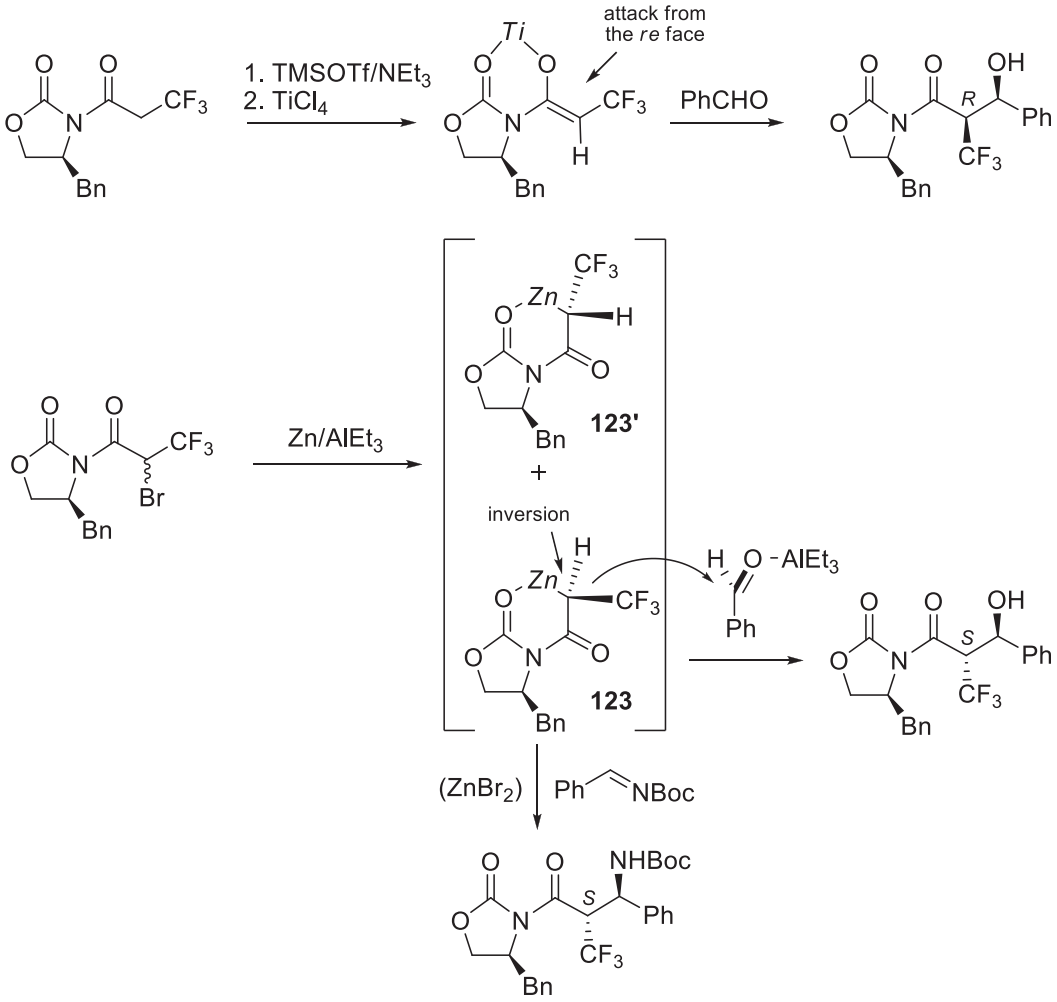


Scheme 55.

Although it is not known whether Reformatsky reagents undergo 1,4-addition as C- or O-metalated species, we suppose that the chelated enolate **119** is the actual reacting species.[176] This hypothetical enolate is predisposed to exist mainly in (*Z*)-configuration because of the repulsion of the voluminous bromine atom and the chiral auxiliary and the favorable dipole interaction between C=O and C-F bonds. In such a chelated form the *re*- and *si*- faces of the enolate are strongly discriminated by the steric effect of the isopropyl group. Overal, this model offers a reasonable explanation of high stereoselectivity of 1,4-addition.

[176] As discussed earlier, the classical Reformatsky reaction with aldehydes is supposed to proceed via the enolate form. See reference 138.

The group of T. Ishihara recently proposed an alternative model for asymmetric Reformatsky reaction with aldehydes[165a] in the presence of $AlEt_3$ and imines[168a] in the presence of $ZnBr_2$. The authors obtained the aldols with opposite configuration at the trifluoromethylated position while performing $AlEt_3$-mediated Reformatsky and traditional Evans aldol reactions (Scheme 56).



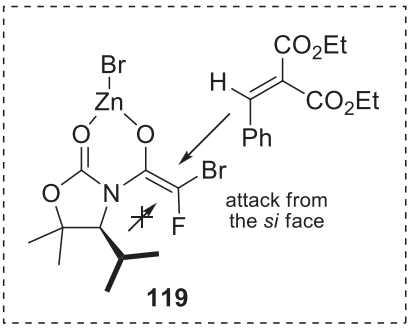
Scheme 56.

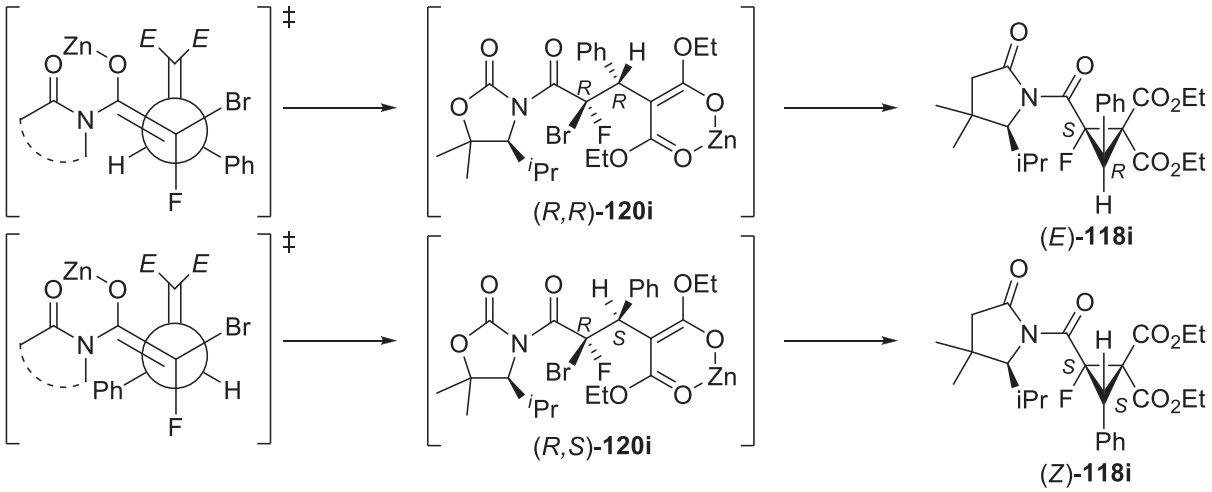
To account for this striking difference they propose that the C-metalated intermediate **123** undergoes 1,2-addition with inversion of configuration of the metalated carbon.[177] Notably, at least in the case of imines the stereochemical outcome does not depend on the presence of extra Lewis acid (same stereoselectivity using only zinc metal).[168a] Ishihara's model is consistent with the studies that claim that the Reformatsky reagents exist in C-metalated form or as the C/O-bridged dimers.[138] Clearly,

[177] Although this model can "explain" the formation of the actual aldol product, to our knowledge there is no precedent of the postulated nucleophile inversion in organozinc chemistry and it is not clear what is the basis of differential reactivity of hypothetical **123** and **123'** (cf. steric repulsion in the chelated enolate **119**).

the qualitative considerations about the stereochemistry and reactivity of oxazolidinone-based Reformatsky reagents are insufficient to resolve the controversy between Ishihara's and our own results. Further studies are needed in order to clarify the mechanism of 1,2- and 1,4-addition of Reformatsky reagents.

Low (*Z*)/(*E*)-selectivity and high *de*(*Z*) and *de*(*E*) values in the case of benzylidenemalonate allow for the following adjustment of our model: 1,4-addition is very stereoselective only with respect to the *Si*- and *Re*-faces of zinc enolate, while the corresponding faces of a Michael acceptor are not well discriminated (Scheme 57). One of the possible reasons for such a low selectivity can be the presence of highly polar species (reaction takes place in a concentrated solution of LiCl in THF) that disrupt the coordination between the Michael acceptor and the enolate in the transition state of 1,4-addition.[178] The same salt effect can account for the low stereoselectivity of cyclization for mono- and 1,1-disubstituted alkenes and probably the difference between our own and Ishihara's results.





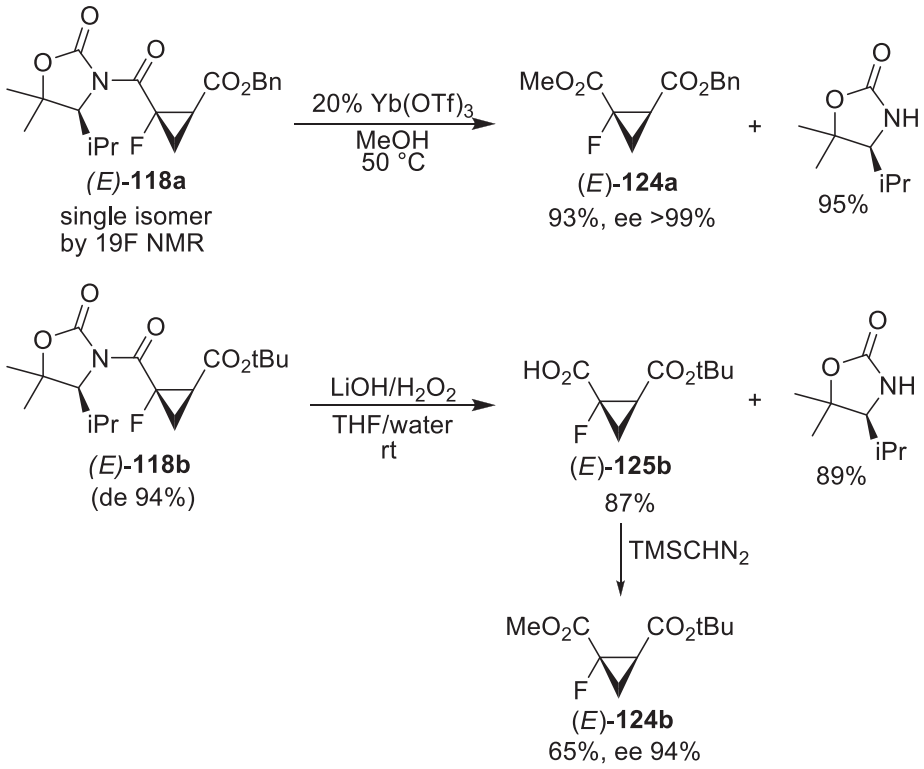
Scheme 57.

[178] LiCl is known to form anionic organozincate complexes: see reference 126.

Although the absolute configuration was undoubtedly determined only for the acrylate-derived cyclopropane **118a**, we suppose that the same facial selectivity with respect to the enolate **119** should operate in the other cases, since the same stereochemical pattern is always observed: mixture of *(Z)*- and *(E)*-isomers, but high *de*(*Z*) and *de*(*E*) values. Therefore, in the present work the assignment of absolute configuration of all the cyclopropanes **118** is based on the presumed *S*-configuration of the fluorinated stereocenter.

f. Cleavage of the chiral auxiliary

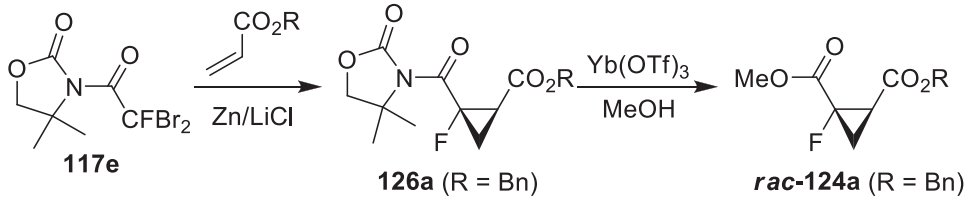
The chiral auxiliary can be removed from **118** easily in either acidic or basic conditions, as shown on the Scheme 58.[179] Enantiomeric excess of the resulting cyclopropanes was determined by chiral HPLC analysis (acid **125b** was converted into the corresponding methyl ester **124b** prior to analysis).



Scheme 58.

[179] Cleavage with $Yb(OTf)_3$ performed by analogy with the LnI_3-catalysed reaction: Fukuzawa, S.-I.; Hongo, Y. *Tetrahedron Lett.* **1998**, *39*, 3521. Cleavage with $LiOH/H_2O_2$ based on: Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363.

The reference racemic compounds were synthesized from the achiral oxazolidinone **117e** according to the Scheme 59.



117e

126a (R = Bn)
126b (R = ^{t}Bu)

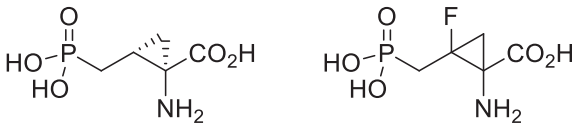
***rac*-124a** (R = Bn)
***rac*-124b** (R = ^{t}Bu)

	Yield of **126**, %	(*Z*)/(*E*)	Yield of *rac*-**124**, %
a	54	18:82	79
b	42	18:82	69

Scheme 59.

5. Synthesis of (*E*)-1-amino-2-fluoro-2-phosphonomethylcyclopropane-carboxylic acid

Overview of the biological activity of 1-amino-2-(phosphonomethyl)cyclopropanecarboxylic acids and their fluorinated analogs was given in the *Section 1c*. Among the cyclopropane-based mGluR III agonists the most active isomer was (1*S*,2*R*)-**25** which is characterized by the *cis*-relationship between amino and phosphonomethyl groups. In the following section we will outline the previous attempts to synthesize its exact fluorinated analog (*E*)-**26** done in our laboratory. Then, two alternative approaches to (*E*)-**26** developed in the course of the present thesis work will be discussed.

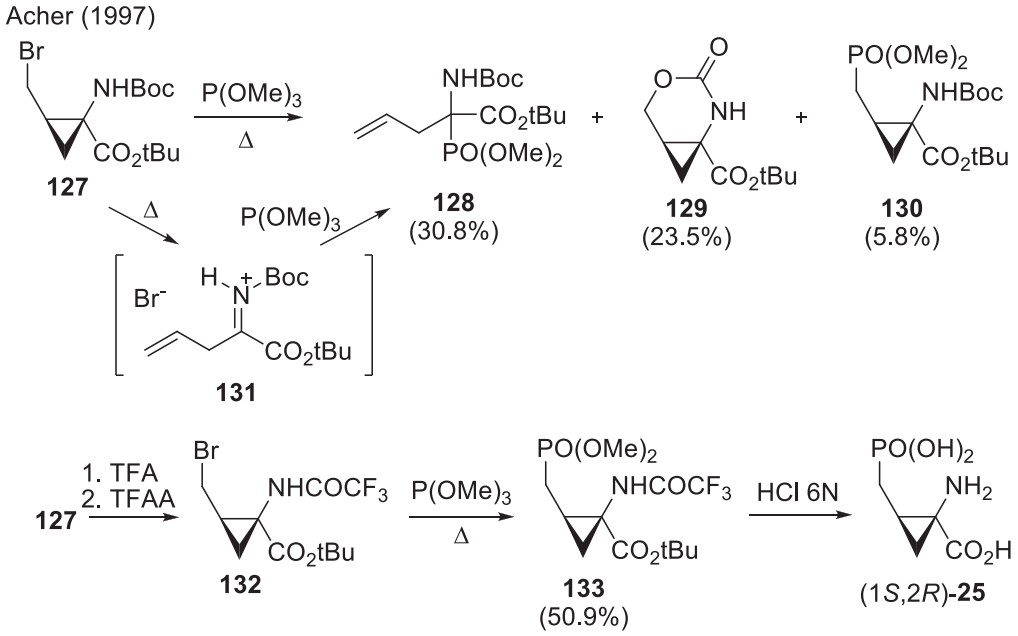


(1*S*,2*R*)-**25** (*E*)-**26**

Figure 15.

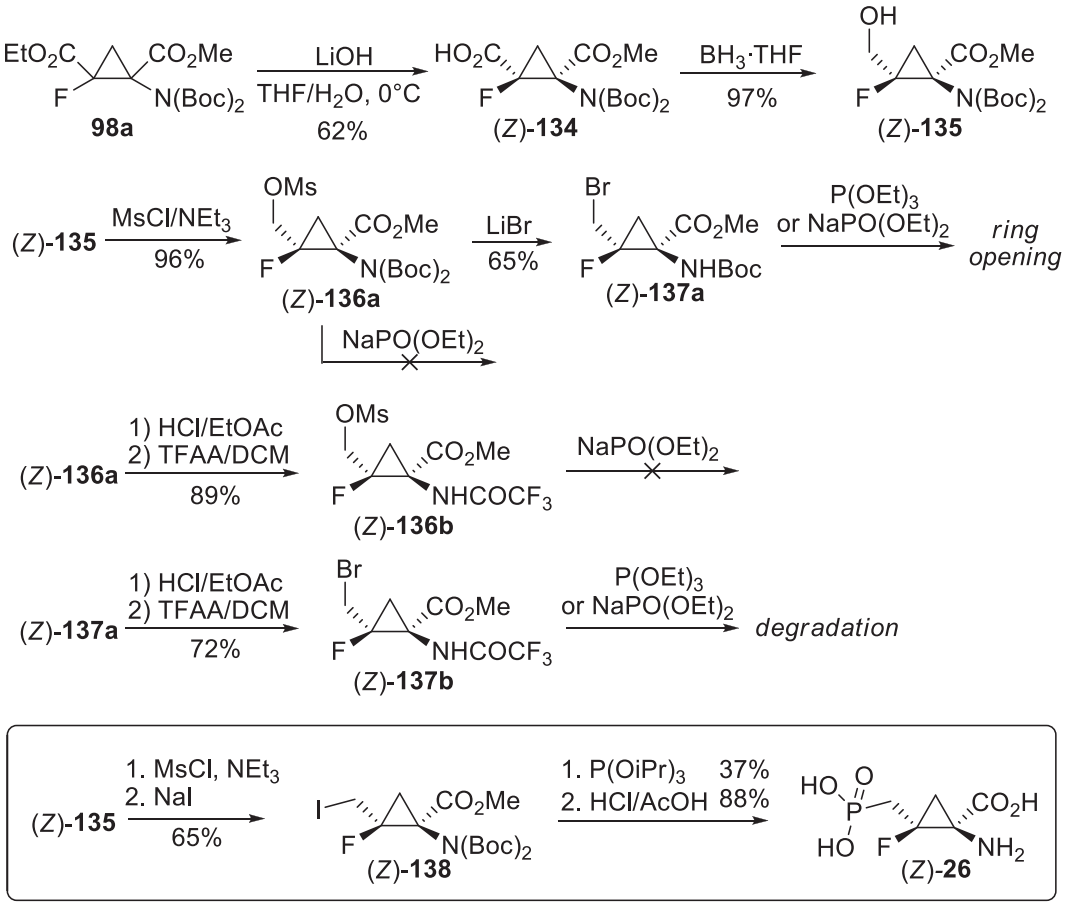
b. Previous work towards the synthesis of (*E*)-1-amino-2-fluoro-2-phosphonomethylcyclopropanecarboxylic acid.

In their synthesis of (1*S*,2*R*)-**25** Acher and co-workers [32] initially used the bromide **131** as a substrate for the Arbuzov reaction. They have obtained however only minor amounts of the desired product **130** accompanied with the products of ring opening (**128**) and cyclization (**129**). According to their hypothesis, the ring opening in **127** proceeds via a carbocationic intermediate **131** that is formed with participation of the nitrogen lone pair. In order to inhibit this fragmentation they decided to reduce the electron density on nitrogen with help of a more electron-withdrawing protecting group and performed the transprotection from Boc to trifluoroacetamide **132** (this should also decrease the rate of intamolecular attack by carbonyl). Resulting bromide was smoothly converted into the cyclopropane **133** with only minor amount of ring-opening by-product.



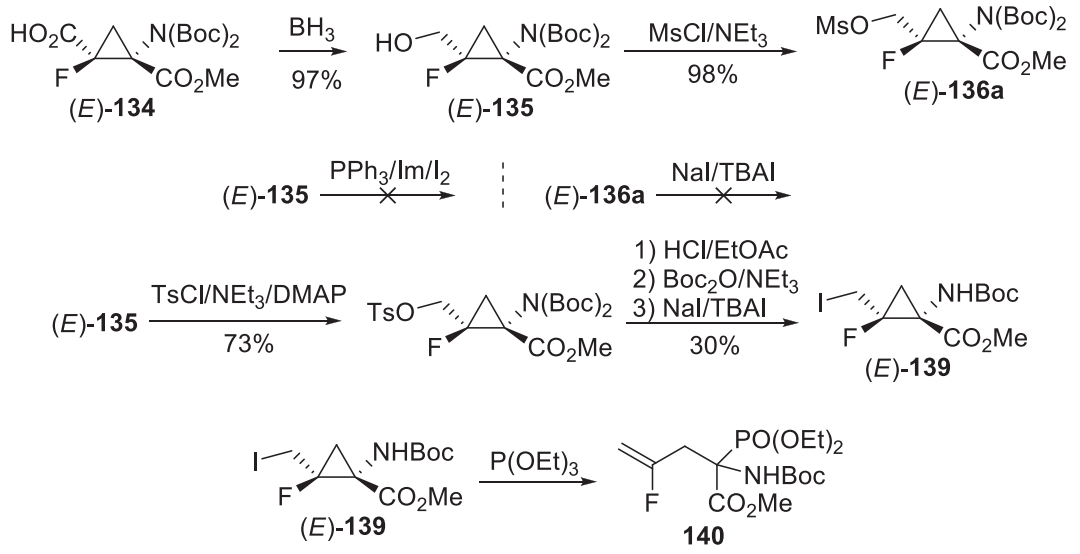
Scheme 60.

The synthesis of (*Z*)-**26** carried out in our laboratory is outlined in the Scheme 61. Cyclopropane **98a** was obtained as a mixture of stereoisomers that was subjected to the regio- and stereoselective saponification. Ethyl ester in **98a** is cleaved selectively under these conditions. (*Z*)-**98a** reacts faster than (*E*)-**98a** due to the steric hidrance of $N(Boc)_2$ group in the (*E*)-isomer. Therefore, pure (*Z*)-isomer of **134** can be selectively produced. Subsequent functionalization of (*Z*)-**134** led to the mesylate (*Z*)-**136a** and to the monoprotected bromide (*Z*)-**137a**. While (*Z*)-**136a** was inert under typical Michaelis-Arbuzov conditions, the bromide (*Z*)-**137** demonstrated the same reactivity as Acher's (*Z*)-**127**, i.e. ring opening. Transprotection of (*Z*)-**136a** and (*Z*)-**137a** was successfully realized, but the compounds (*Z*)-**136b** and (*Z*)-**137b** failed to provide the expected phosphonate. This problem was finally solved by changing the leaving group from bromide to iodide while preserving both Boc groups that serve to lower the electron density on the nitrogen and thus inhibit the ring opening. The iodide (*Z*)-**138** was thus converted into the corresponding phosphonate with moderate yield. The final product (*Z*)-**26** was prepared by total deprotection under acidic conditions.



Scheme 61.

Attempts to apply this reaction sequence to the (*E*)-isomer of **134** were unsuccessful (Scheme 62). Although the carboxylic acid can be reduced into the alcohol (*E*)-**135** and further converted into the corresponding mesylate (*E*)-**136a**, the nucleophilic substitution at the exocyclic position proved to be problematic. All attempts to introduce iodine atom, or perform the Arbuzov or Michaelis-Becker reaction directly with the mesylate failed. This failure apparently arises from the steric effect of voluminous $N(Boc)_2$ group which hinders the exocyclic electrophilic center and thus makes the S_N2 transition state disfavored. In order to overcome this steric effect monodeprotection was done that finally allowed the authors to prepare a less hindered iodide (*E*)-**139**. However, all attempts to introduce the phosphonate group were unsuccessful: ring opening occurred (**140** was identified as the main by-product).



Scheme 62.

c. Functionalization of cyclopropane amino acid core

Since Acher's transprotection approach was not efficient in the case of (*E*)-**135**, in the present project we attempted to inhibit the ring opening by exploiting the stereoelectronic features of the Grob fragmentation that is presumably responsible for the cyclopropane ring opening. For that we wanted to fix the amide moiety in such a conformation (**142**) that its π-system would be nearly orthogonal to the breaking bonds[180] (shown as hashed bonds in Fig. 16). Such a configuration can partially be attained by linking amino and carboxylic functionalities as in **143**. Additional fixation of a leaving group X in the conformation **144** would further inhibit the fragmentation by disturbing the anti-periplanar arrangement of the breaking bonds. An obvious way to attain this conformation is to tether the leaving group with the planar nitrogen atom as in **145**. On the other hand, position of the leaving group in **145** forces the phosphorus nucleophile to approach the reacting center from the vicinity of fluorine atom and cyclopropane CH_2. This fact can potentially make the corresponding transition state more hindered than without a tether.

[180] Parallel arrangement of the breaking bonds and the lone pair (amide π-system in our case) is generally considered as the optimal conformation for concerted Grob fragmentation: Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741.

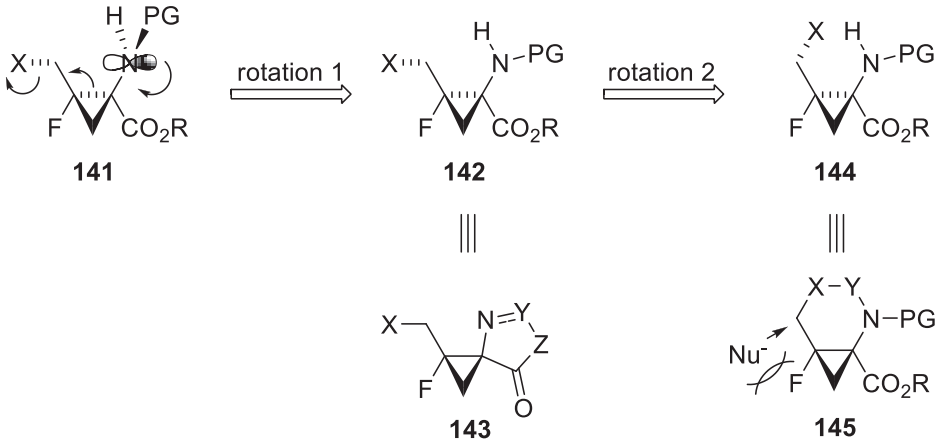
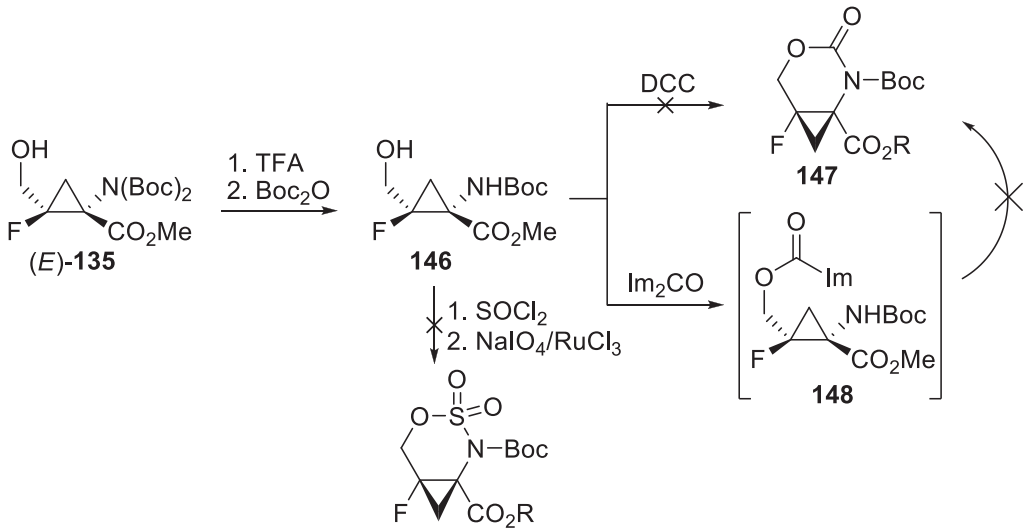


Figure 16.

We prepared the monoprotected alcohol **146** according to the procedure developed earlier in the laboratory. Attempts to introduce an additional cycle (Scheme 63) with DCC or Im_2CO[181] (**147**) were unsuccessful, although in the latter case adduct presumably corresponding to **148** was detected by in situ NMR (hydrolysed upon work-up). Similarly, reaction with $SOCl_2$ followed by oxidation with $NaIO_4/RuCl_3$[182] did not allow us to isolate the corresponding product.

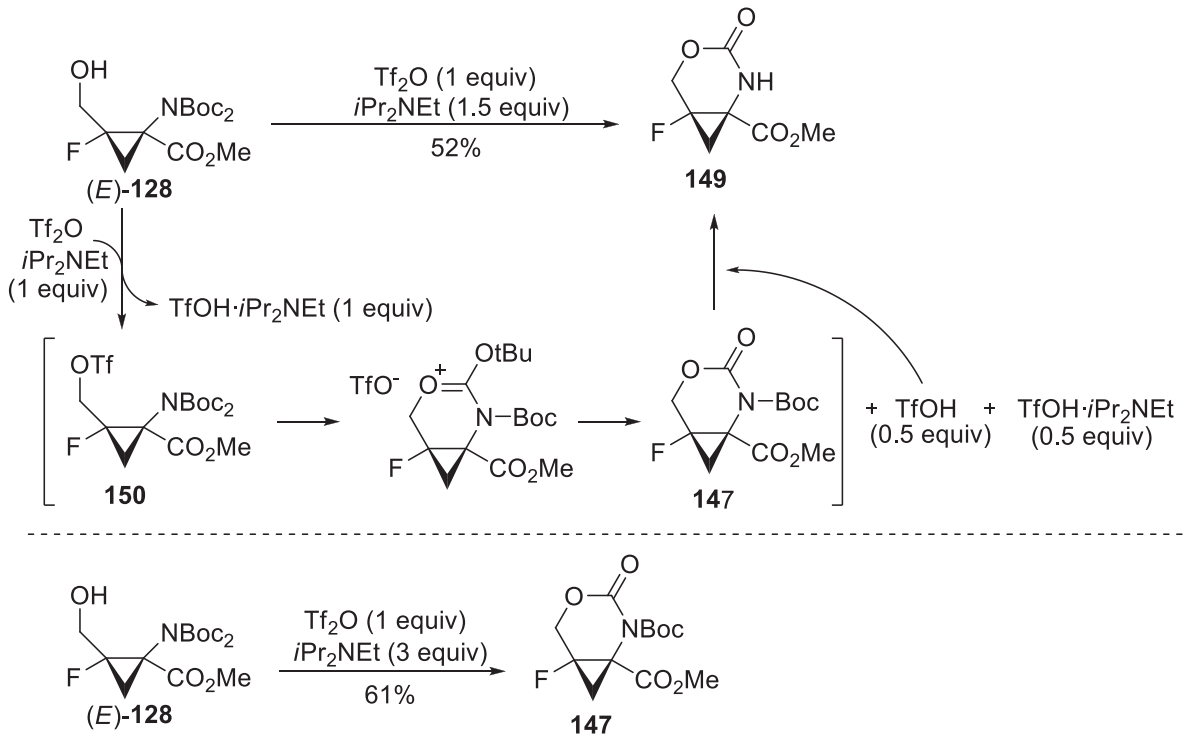


Scheme 63.

Unexpectedly, the bicyclic product **149** of desired type was obtained while the alcohol (*E*)-**135** was treated with Tf_2O and *i*Pr_2NEt in an attempt to prepare the corresponding triflate **150** (Scheme 64). One can hypothesize that the intermediate product of triflation **150** is immediately cyclized with

[181] George, J.H.; Adlington, R.M. *Synlett*. **2008**, 2093.
[182] Moss, T.A.; Alonso, B.; Fenwick, D.R.; Dixon, D.J. *Angew. Chem. Int. Ed.* **2010**, *49*, 568.

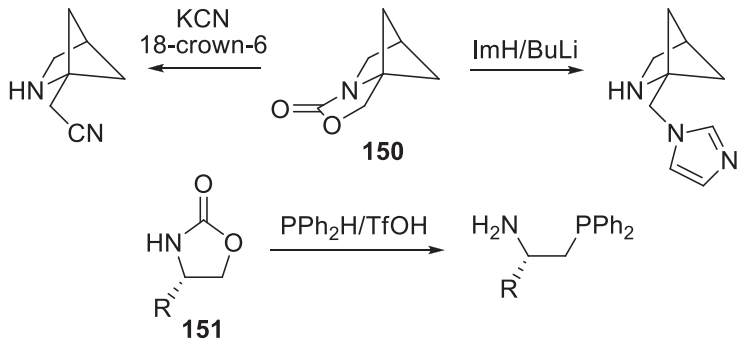
liberation of isobutylene and TfOH. If less than 2 equiv. of base is used, TfOH thus formed is not neutralized and can trigger the cleavage of the second Boc group. In agreement with this proposition, we managed to stop the reaction at the cyclization step and obtain the desired product **147** by simply adding additional *i*Pr_2NEt (3 equiv instead of 1.5 equiv).



Scheme 64.

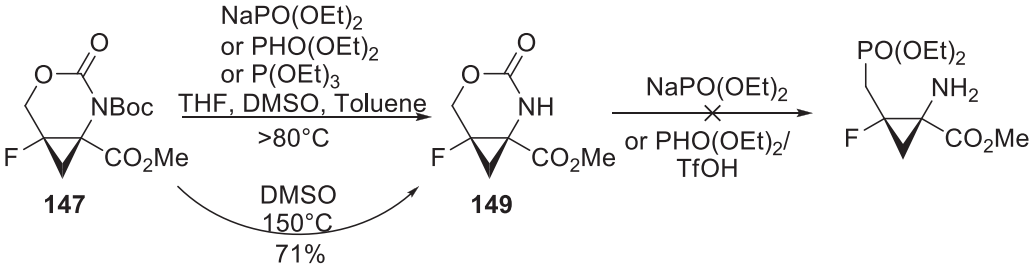
There are few examples of the nucleophilic ring opening in the cyclic carbamates (Scheme 65). J.R. Malpass et al. reported the reactions of tricyclic carbamate **150** with KCN/18-crown-6 and imidazolyllithium.[183] J.J. Gong et al. cleaved the oxazolidinone **151** with diphenylphosphine under acidic conditions.[184]

[183] Malpass, J.R.; Patel, A.B.; Davies, J.W.; Fulford, S.Y. *J. Org. Chem.* **2003**, *68*, 9348.
[184] Gong, J.-J.; Yuan, K.; Song, H.L.; Wu, X.-Y. *Tetrahedron* **2010**, *66*, 2439.



Scheme 65.

Upon treatment of **147** with diethyl phosphite or sodium diethyl phosphite no phosphorus-containing products were detected. Heating the reaction mixture lead to the conversion of **147** into **149** and several other products (Scheme 66). In a control experiment simply heating **147** above 80°C resulted in slow deprotection. Heating to 150°C in DMSO afforded complete conversion of **147** into **149** within 3 min. Meanwhile, compound **149** underwent degradation in the presence of diethyl phosphite under both basic (sodium salt) and acidic (TfOH) conditions: no product with expected P-F spin-spin coupling was detected in the crude mixtures by $\{^1H\}$-^{19}F NMR.



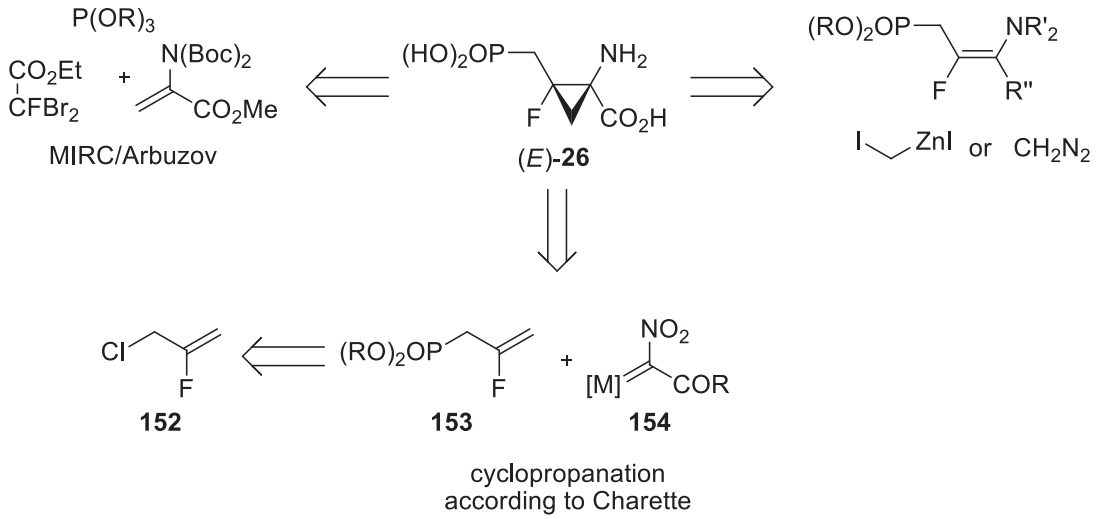
Scheme 66.

Given the difficulties associated with the introduction of a phosphonate group into the fluorinated cyclopropanes we decided to change our strategy and instead of functionalizing the cyclopropane amino acid to perform the cyclopropanation of a phosphorus-containing substrate.

d. Direct cyclopropanation of diethyl 2-fluoroallylphosphonate

Several disconnections can be applied to (*E*)-**26** (Scheme 67). Besides the MIRC cyclopropanation developed in the first part of the present work, at least two evident alternatives exist: Simmons-Smith or diazomethane-based cyclopropanation of a fluorinated enamine and transition metal carbenoid-mediated cyclopropanation of a fluorinated alkene **153** according to the procedure developed by the group of A. Charette. Although the former method allows direct control of the stereochemistry of the

cyclopropanation, the stereocontrolled synthesis of the corresponding alkene is not evidently straightforward. On the other hand, Rh-catalysed cyclopropanation with nitrodiazo compounds **154** was shown to provide different stereoisomers selectively depending on the diazo compound used. [185,186] Overall, the latter approach seemed to be the most easily implemented alternative to the MIRC cyclopropanation.



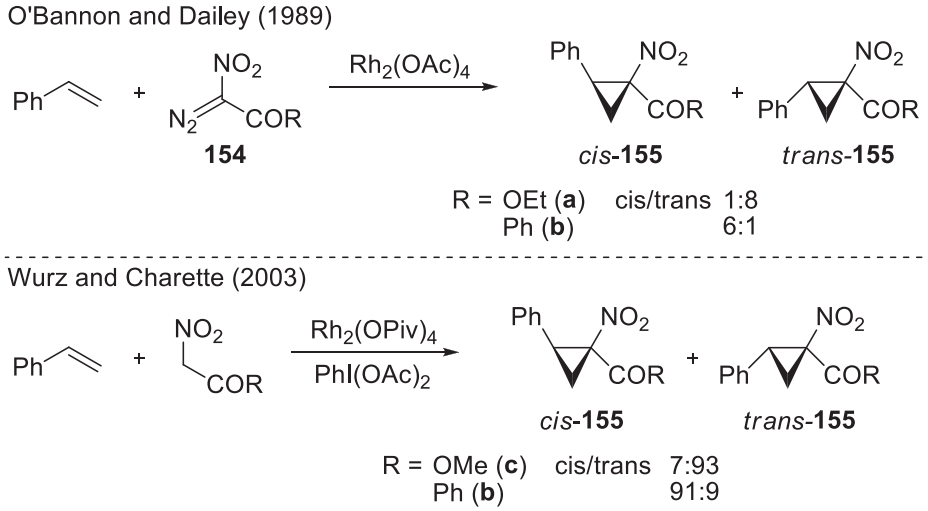
Scheme 67.

Cyclopropanation of fluorinated alkenes with substituted carbenoids has already been studied by several groups (see *Section 2c*). Diazoacetate was successfully added to fluoroalkenes under Rh(II) and Cu(I) catalysis, including the enantioselective Cu(bisoxazoline)-catalysed reaction with α-fluorostyrene developed by Haufe's group (Scheme 17).[85] The most relevant example of cyclopropanation with a diacceptor diazo compound comes from the work by Charette's group dealing with intramolecular addition of cyanoacetate fragment (Scheme 18).[88]

O'Bannon and Dailey described $Rh_2(OAc)_4$-catalysed cyclopropanation with nitrodiazocarbonyl compounds **154** and demonstrated for the first time that the stereoselectivity of this reaction strongly depends on the nature of carbonyl substituent (i.e. ester vs. ketone) for styrene, *cis*-2-butene and cyclohexene (Scheme 68).[185,187] Charette et al. reported a straightforward method of synthesis of diacceptor diazo compounds including **154** and several examples of cyclopropanation of unsymmetrical *gem*-disubstituted alkenes (α-methylstyrene, 2-bromopropene, α-bromostyrene) with moderate

[185] O'Bannon, P.E.; Dailey, W.P.*Tetrahedron Lett*. **1989**, *30*, 4197.
[186] Charette, A.B.; Wurz, R.P.; Ollevier, T.; *Helv. Chim. Acta* **2002**, 4478.
[187] (a) O'Bannon, P.E.; Dailey, W.P. *J. Org. Chem.* **1989**, *54*, 3097; (b) O'Bannon, P.E.; Dailey, W.P. *Tetrahedron Lett*. **1990**, *46*, 7341.

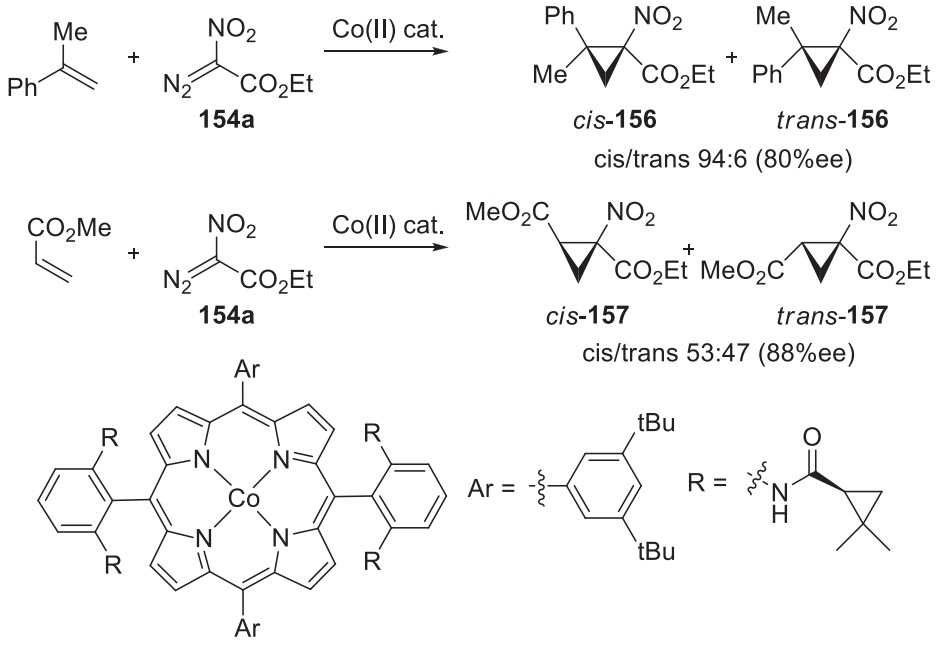
stereoselectivity.[186] The same group used iodonium ylides (generated in situ from alkyl nitroacetate and iodobenzene diacetate) as a source of rhodium carbenoids.[188] On the basis of this methodology Charette's group later developed the enantioselective cyclopropanation catalysed by a copper(bisoxazoline) complex.[189]



Scheme 68.

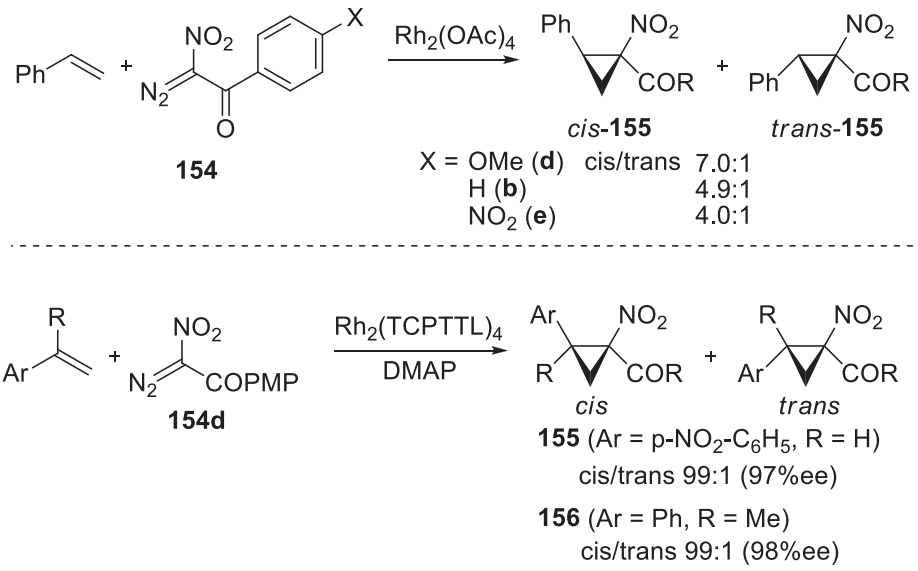
Zhang'group has developed an efficient method of asymmetric cyclopropanation using elaborate Co(II)-porphyrin catalyst (Scheme 69). Their method can be applied to a wide range of electron-rich and electron-deficient alkenes, including acrylates.[190] Noteworthy, the authors assume their reaction to proceed via a radical mechanism,[191] as opposed to the concerted reactions of Cu(I) and Rh(II) carbenoids.

[188] Wurz, R.P.; Charette, A.B.; *Org. Lett.* **2003**, 2327.
[189] (a) Moreau, B.; Charette, A.B. *J. Am. Chem. Soc.* **2005**, *127*, 18014; (b) Moreau, B.; Slberico, D; Lindsay, V.N.G.; Charette, A.B. *Tetrahedron* **2012**, *68*, 3487.
[190] Zhu, S.; Perman, J.A.; Zhang, X.P. *Angew. Chem. Int. Ed*. **2008**, *47*, 8460.
[191] Lu, H.; Dzik, W.I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X.P. *J. Am. Chem. Soc.* **2011**, *133*, 8518.



Scheme 69

More recently, Charette's group developed a highly enantioselective cyclopropanation with diazonitro(p-methoxy)acetophenone **154d** (Scheme 70).[192] Excellent results were obtained with various styrenes, including α-methylstyrene.

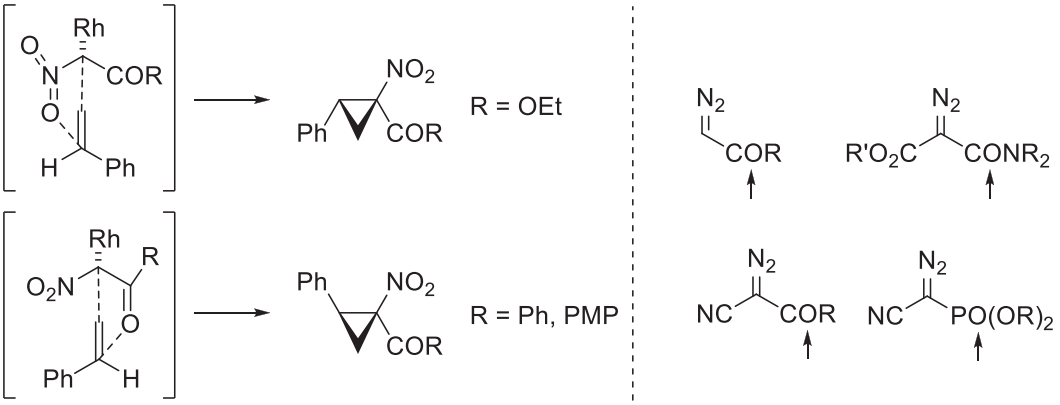


Scheme 70.

Stereochemistry of Rh- and Cu-catalysed cyclopropanation is determined by the *trans*-directing ability of each one of the two acceptor groups (Scheme 71).[192] More basic and more voluminous groups

[192] Lindsay, V.N.G.; Nicolas, C.; Charette, A.B.; *J. Am. Chem. Soc.* **2011**, *133*, 8972.

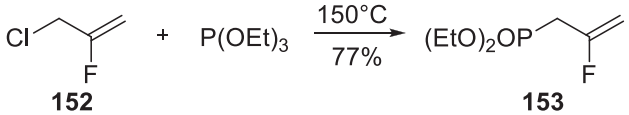
tend to be in *trans*-relationship with the substituent in the monosubstituted alkene. Non-linear acceptor groups (i.e. carbonyl, nitro, but not cyano) are believed to be out of plane of the carbenoid in both the ground state and the transition state of cyclopropanation. In such a conformation, secondary orbital interaction between the oxygen of the *trans*-directing group and the LUMO of alkene creates the repulsion between the *trans*-directing group and the alkene largest substituent. Using aromatic nitrodiazoketones **154b,d,e** with electron-donating and electron-withdrawing substituents Charette's group demonstrated that the Lewis basicity of a *trans*-directing group is a very important factor of stereoselectivity, even when its steric effect remains the same (Scheme 70).



Scheme 71. (*trans*-directing groups are highlighted by small arrows)

Since nitrodiazo compounds have never been used for the cyclopropanation of fluoroalkenes, we could not anticipate the stereoselectivity of this reaction. Therefore we decided to use both ethyl ester (**154a**) and PMP-ketone (**154d**) that are known to react with styrenes and simple alkenes giving the opposite stereoselectivity.

Diethyl 2-fluoroallylphosphonate **153** was synthesized from the commercially available 3-chloro-2-fluoropropene **152** via Arbuzov reaction with triethyl phosphite (Scheme 72). After heating the neat mixture of reagents at 150°C for 2 days, 77% of **153** was isolated via column chromatography.

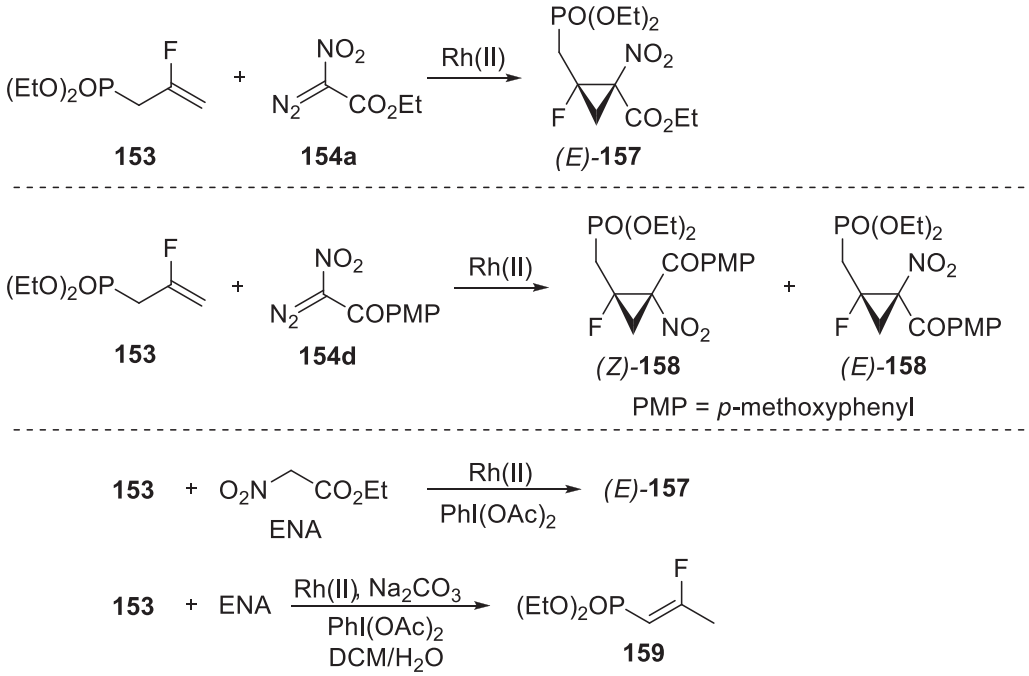


Scheme 72.

Results of cyclopropanation of **153** (Scheme 73) are given in Table 8. The key to the successful cyclopropanation with nitrodiazoester **154a** was the choice of catalyst: rhodium pivalate is greatly superior to rhodium acetate (entry 2 vs. entry 1). In both cases single isomer of cyclopropane **157** was obtained. Iodonium ylide approach[188] (entries 3-5) was inefficient: low yield of cyclopropane was

observed under neutral, solvent-free conditions, while partial double bond migration was the only result of a biphasic reaction in the presence of aqueous base. Iodonium-based methodology gave the same single isomer of **157**.

In the case of nitrodiazoketone **154d** the use of rhodium pivalate instead of rhodium acetate did not result in dramatic improvement (entries 6-7), but almost complete conversion of fluoroalkene was observed upon lowering the temperature to -20°C (entry 9). Mixture of two stereoisomers was obtained (determination of their configuration is discussed below). An attempt to apply Charette's enantioselective method[192] to **153** was unsuccessful: only trace amounts of product were detected (enantiomeric excess was not determined).



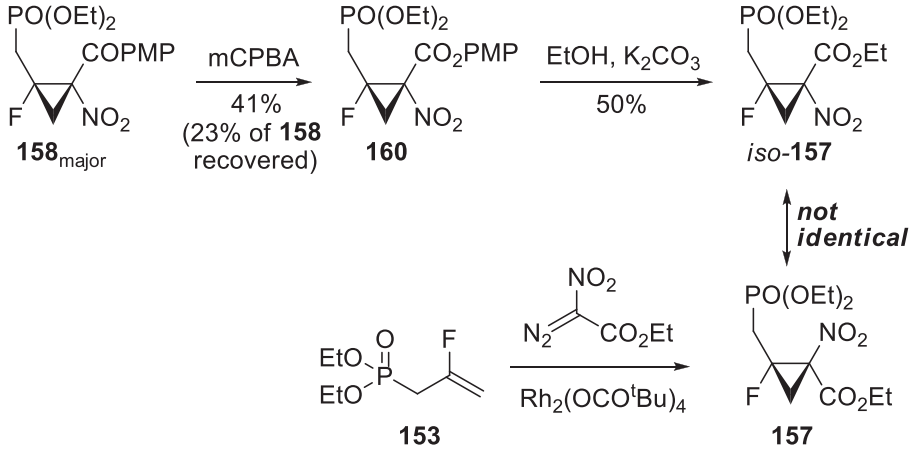
Scheme 73.

Table 8.

Entry	**154**/ENA (equiv)	Catalyst (%)	Solvent ([**153**])	T, °C	Conv. **153**, % by ^{19}F NMR	Yield **157**, % (by ^{19}F)/isol.	(*E*)/(*Z*)
1	**154a** (3)	$Rh_2(OAc)_4$ (2)	DCM (0.6)	rt	20	(11)	100:0
2	**154a** (3)	$Rh_2(OCO^tBu)_4$ (1)	DCM (1.3M)	rt	**100**	**78**	**100:0**
3	ENA (3)	$Rh_2(OCO^tBu)_4$ (2)	DCM (0.07)	40	0	(0)	-
4	ENA (3)	$Rh_2(OCO^tBu)_4$ (2)	DCM/H_2O[a]	rt	50[b]	(0)	
5	ENA (3)	$Rh_2(OCO^tBu)_4$ (2)	no solvent	rt	32	(8)	100:0
6	**154d** (7)	$Rh_2(OAc)_4$ (7)	DCM (0.14M)	rt	25	(3)	-
7	**154d** (5)	$Rh_2(OCO^tBu)_4$ (6)	DCM (0.17M)	rt	29	(14)	18:82
8	**154d** (3)	$Rh_2(OCO^tBu)_4$ (9)	DCM (0.14M)	40	23	(9)	-
9	**154d** (3)	$Rh_2(OCO^tBu)_4$ (5)	DCM (0.17M)	-20	**96**	**87**	**13:87**
10	**154d** (2)	Rh-TCPTTL (2)	Et_2O (0.1M)	-50 to rt	10	(2)	-

[a] Na_2CO_3 (2 equiv); [b] 50% of a by-product is observed (presumably, the conjugated alkene **159**)

Direct determination of stereochemistry of the products **157** and **158** turned out to be unreliable. Chemical shifts of the protons and fluorine in **157** have the values intermediate between those of major and minor isomers of **158**, thus also making difficult to conclude whether the major isomer of **158** has the opposite configuration to **157**, as expected from the work of Dailey[185] and Charette.[186] In order to clarify the relationship between **157** and **158**$_{major}$ we performed the Bayer-Williger oxidation of the latter followed by transesterification with ethanol (Scheme 74). The resulting *iso*-**157** proved to be different from the authentic **157** according to ^{1}H and ^{19}F NMR.



Scheme 74.

Characteristic C-F coupling constants in **157** and **158** are too small to be conclusive, however, they argue for the (*E*)-configuration of **157** and **158**$_{minor}$ according to the trends discussed in the *Section 3e* (Fig. 17).

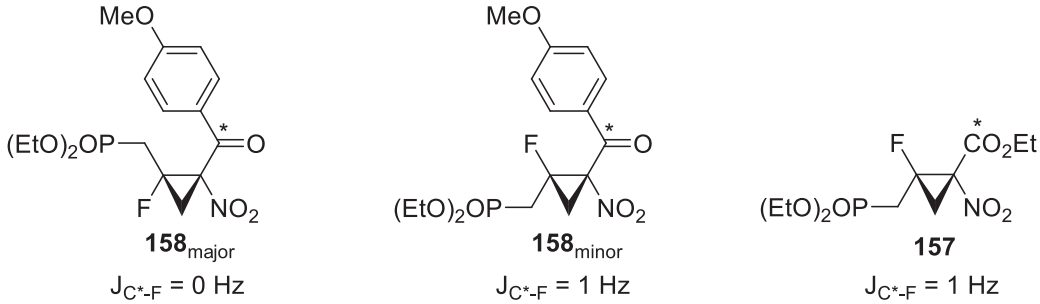


Figure 17.

Both isomers of **158** were analysed by NOESY and ^{1}H-^{19}F HOESY experiments (Fig. 18 and 19). Weak cross-peak is observed in **158**$_{minor}$ between fluorine and an aromatic proton (H_{Ar}) suggesting that these nuclei are located on the same side of the cyclopropane ring. However, analysis of all the NOE correlations indicates that two isomers of **158** exist in different well-defined conformations with the aromatic ring "constrained" between nitro group and the substituents on the same side of cyclopropane. In **158**$_{major}$ the aromatic ring is rotated towards CH_2 of cyclopropane, and H_{Ar} demonstrates NOESY correlation with the protons H(1) and H(2) *on both sides* of cyclopropane. In **158**$_{minor}$ the ring is apparently directed to the opposite side, so that NOE experiments reveal the interaction of H_{Ar} with *both* H(3) and fluorine (that are also located on the opposite sides of cyclopropane). Overall, there seems to be no way to unambiguously determine the relative configuration of two isomers of **158** from NOESY and HOESY experiments. NOESY analysis of **157** revealed no characteristic correlations as well.

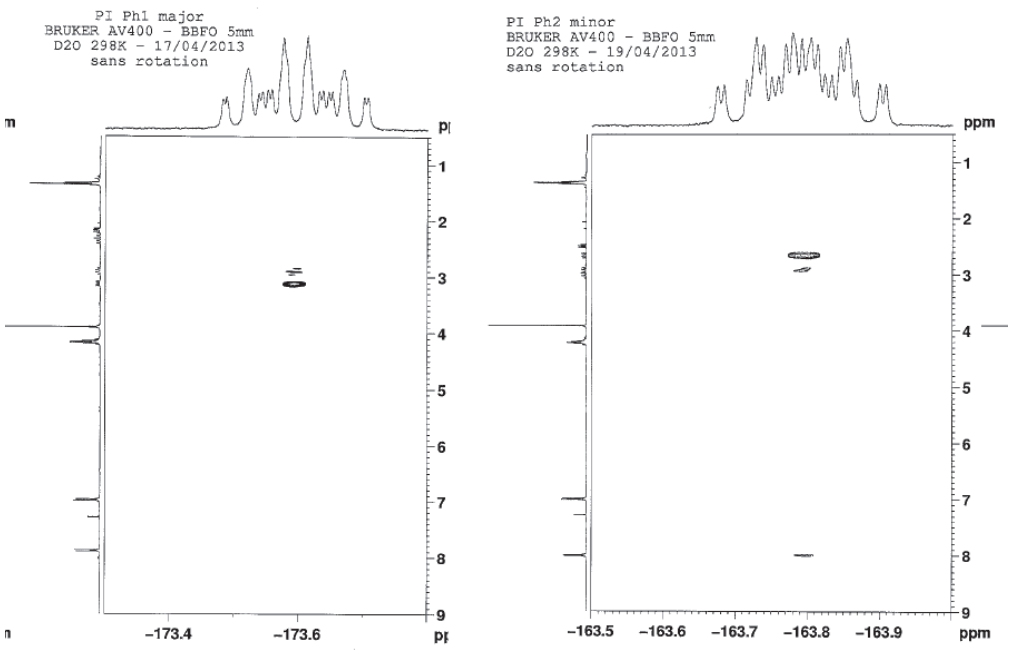


Figure 18. HOESY plots for both isomers of **158**

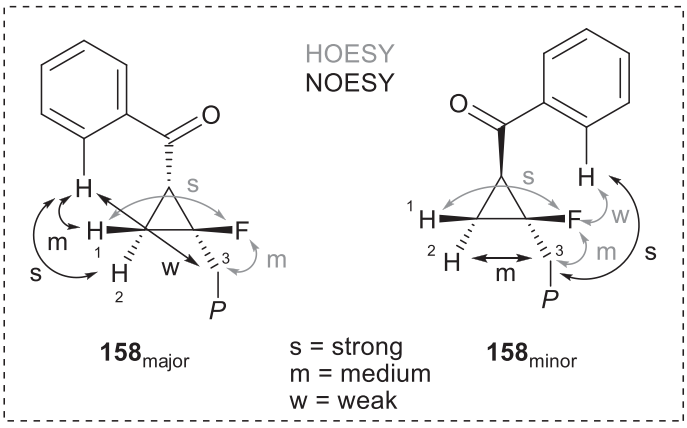
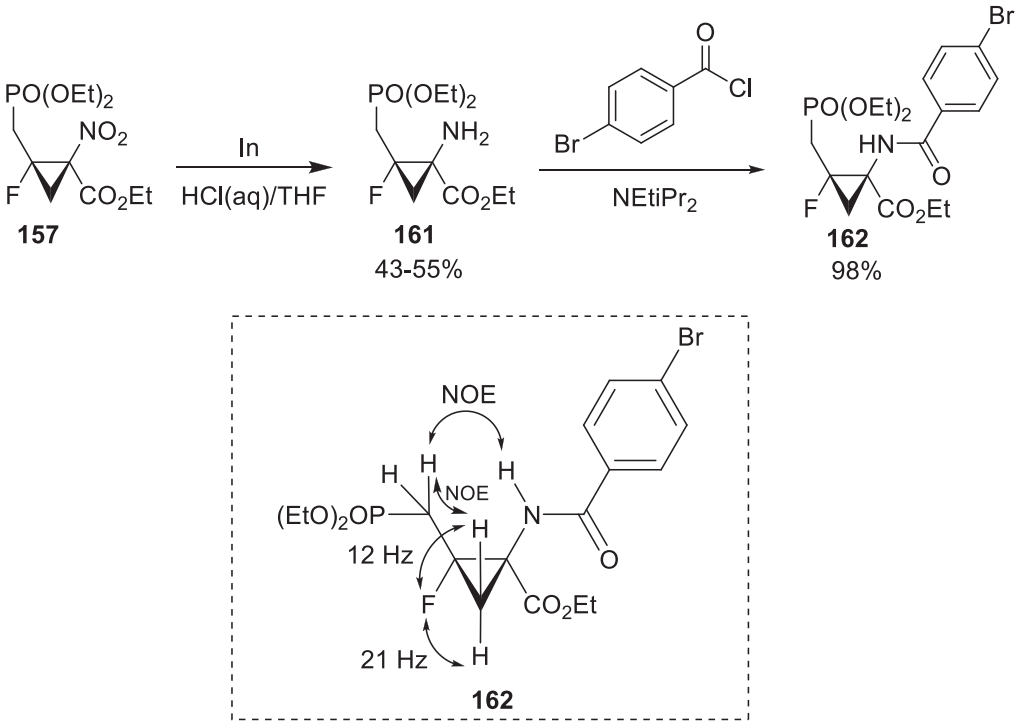


Figure 19. Summary of HOESY and NOESY correlations in **158** (NO_2 groups are omitted for clarity).

To get additional confirmation of the stereochemistry the cyclopropane **157** was reduced according to Charette's procedure[193] and then converted into the corresponding p-bromobenzamide **162**. A weak NOESY cross-peak was observed between NH and exocyclic CH_2 in **162**, thus adding more evidence to our stereochemical hypothesis.

[193] Lindsay, V.N.G.; Fiset, D.; Gritsch, P.J.; Azzi, S.; Charette, A.B.; *J. Am. Chem. Soc.* **2013**, *135*, 1463.



Scheme 75.

Rhodium-catalysed cyclopropanation of **153** with **154a** is characterized by remarkable stereoselectivity (single isomer of **157** is obtained), that is better than for the other alkenes tested so far.[185,186] Moreover, the configuration of **157** and $\mathbf{158}_{major}$ suggests that the fluorine atom is efficiently repulsed by a *trans*-directing group of the carbenoid (similarly to phenyl group in styrene). This effect is more pronounced than in 2-bromopropene and α-bromostyrene, thus indicating at the electronic (orbital/dipole interaction) origin of stereoselectivity, and not the pure steric effect of substituents in the alkene (cf. *dr* values in Fig. 20). Similar trend was observed in the reaction of ethyl diazoacetate with styrene and α-fluorostyrene, although to a lesser extent.[194,85]

[194] Doyle, M.P. *Chem. Rev.* **1986**, *86*, 919.

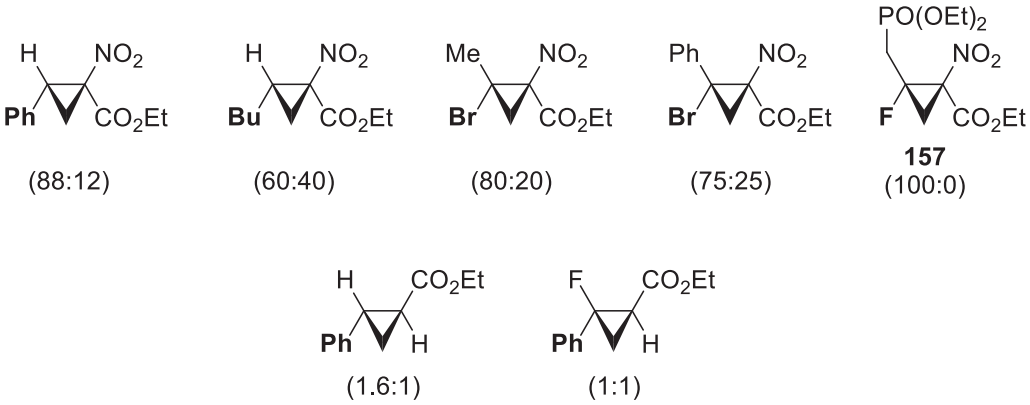
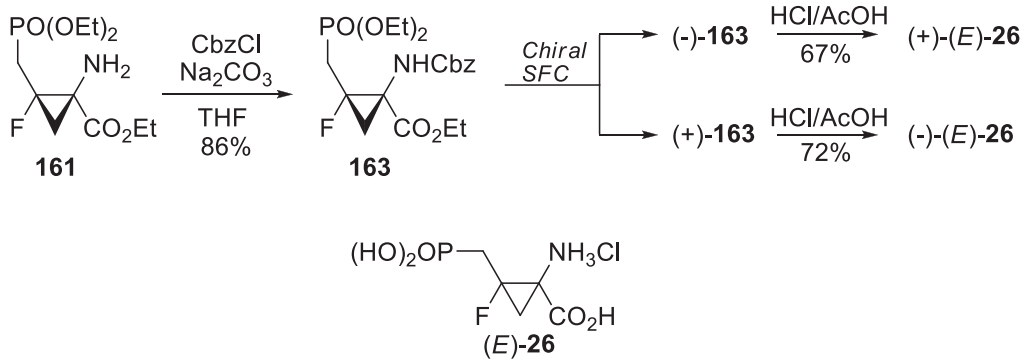


Figure 20.

Amine **161** was further converted into Cbz-derivative **163** that was subjected to separation of enantiomers by chiral SFC. The resulting individual enantiomers (−)-**163** and (+)-**163** were subjected to global deprotection in $HCl_{aq.}$/AcOH to give the desired (+)-(*E*)-**26** and (−)-(*E*)-**26**, respectively, in good yield.



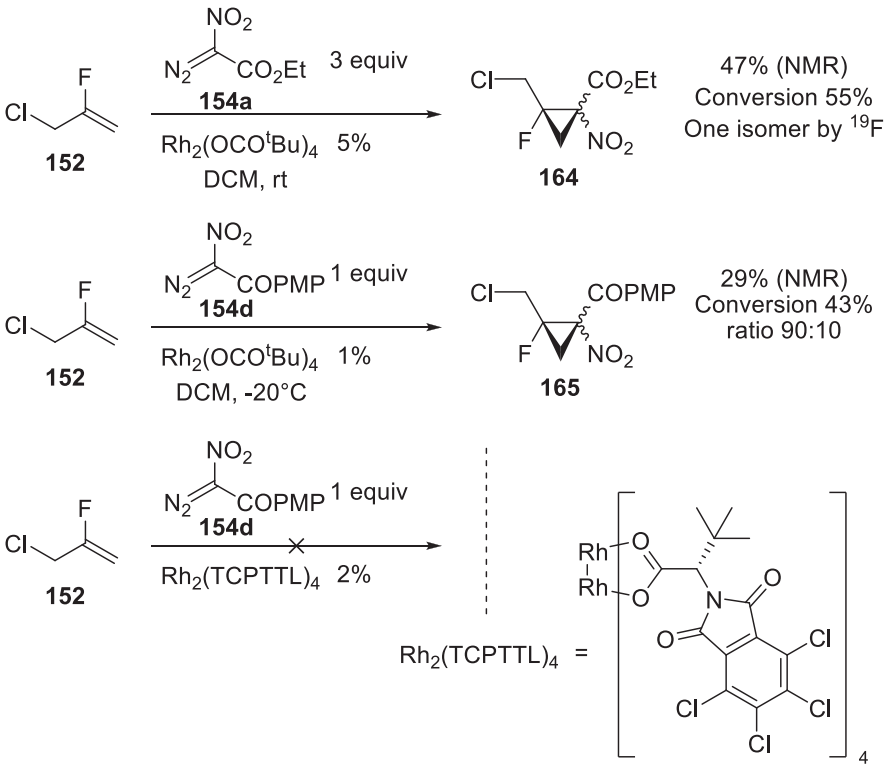
Scheme 76.

The biological tests of (+)-(*E*)-**26** and (−)-(*E*)-**26** against the recombinant mGlu4 are currently underway at the University of Montpellier.

6. Enantioselective cyclopropanation of terminal fluorinated alkenes.

Given the successful preparation of phosphonates **157** and **158**, we attempted to develop an asymmetric synthesis of the similar cyclopropanes according to the method reported by Charette's group[192,195] (Scheme 70). For this project we focused on the commercially available 3-chloro-2-fluoropropene **152** which, once converted to cyclopropane, can be readily functionalized providing a variety of fluorinated amino acids.

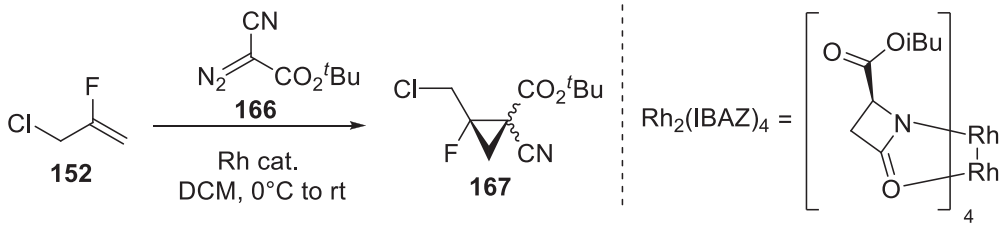
Racemic cyclopropanation of **152** was realized using both diazoester **154a** and diazoketone **154d** with moderate yield in the presence of $Rh_2(OCO^tBu)_4$ (Scheme 77). However, all attempts to catalyse this reaction by $Rh_2(TCPTTL)_4$ under a variety of conditions were unsuccessful (Et_2O, -50°C to rt; Et_2O, -20°C to rt; DCM, -78°C to rt; DCM, -20°C to rt; DCM, rt; toluene, -20°C to rt). Complete degradation of diazo compound was observed with no cyclopropane detected by ^{19}F NMR. $Rh_2(TCPTTL)_4$–catalysed cyclopropanation of the phosphonate **153** also failed as already mentioned in *Section 5d*.



Scheme 77.

[195] As discussed earlier, Cu-catalysed enantioselective cyclopropanation of fluorinated styrenes using ethyl diazoacetate was first reported by Haufe and co-workers in 2000 (see *Section 2c* and ref. 85).

Rhodium carbenoids derived from cyanodiazoesters are considered more electrophilic than those derived from nitrodiazoesters.[196] Since CN group can usually be converted into amino group via Curtius or Hofmann rearrangement, one can substitute the cyanodiazoesters for nitrodiazoesters in the preparation of cyclopropane amino acids. Therefore, we decided to test the more reactive *tert*-butyl cyanodiazoacetate **166** in the cyclopropanation of **152** (Scheme 78). Earlier, Charette has shown that $Rh_2(IBAZ)_4$ provided the highest level of enantioselectivity in the cyclopropanation of alkenes, allenes and alkynes using cyanodiazo compounds including **166**.[193] Our findings were consistent with this observation as can be seen in the Table 9. Notably, inversed *Z/E*-selectivity was observed while using $Rh_2(IBAZ)_4$.



Scheme 78.

Table 9.[a]

Rh catalyst	NMR yield	*dr* of **167** (-173:-189)[b]	*ee*, %[c] (-173)	*ee*, %[c] (-189)
$Rh_2(OCO^tBu)_4$	56	31:69	-	-
$Rh_2(TCPTTL)_4$	42	24:76	35	7
$Rh_2(IBAZ)_4$	30	76:24	99	94

[a] **152**:**166** = 2:1, 2%mol of catalyst, 0°C to rt overnight; [b] Chemical shifts (^{19}F) of individual isomers are given in parentheses (configuration of the isomers was not determined); [c] Enantiomeric excess was determined by chiral GC of the purified product (Supelco β-DEX 120, 130°C).

$Rh_2(IBAZ)_4$–catalysed reaction between **152** and **166** was then tested in different solvents (Table 10). Moderate yields were obtained with most solvents irrespective of the quality thereof. At the same time, good enantioselectivity was observed in most cases. The stereochemical outcome of the reaction strongly depended on the solvent used: the ratio of isomers varied from 33:67 (CCl_4) to 87:13 (propylene carbonate) with the simultaneous decrease in the enantioselectivity of one of the isomers. This variation roughly corresponds to increasing polarity of the corresponding solvent: the highest stereoselectivity was observed in the most polar solvent (propylene carbonate). Further increase in the solvent polarity is

[196] Explanation of this fact is based on the conjugation between the LUMO of carbenoid fragment and π* orbital of cyano group that should lower the LUMO and therefore make the carbenoid more electrophilic. Unlike cyano, the nitro group is rotated orthogonally to the plane of carbenoid, so that this conjugation is minimized. See ref. 193.

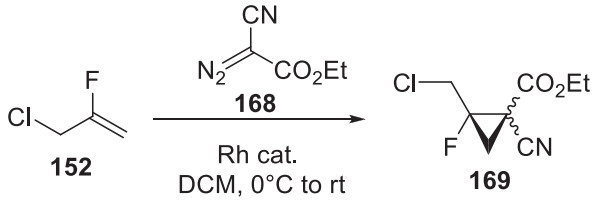
problematic since it will be accompanied by the introduction of the reactive groups that can interfere with the cyclopropanation into the solvent molecules (this is probably the case for acetonitrile). The origin of this solvent effect is not clear, but it is generally postulated that more polar and polarisable solvents better stabilize the polar transition states. Concerning the cyclopropanation of **152**, one can suppose that the transition states leading to the different isomers of **167** are indeed different in their dipole moments. Further studies are needed in order to check whether this solvent effect operates with the non-fluorinated alkenes.

Table 10.[a]

Solvent	NMR yield	*dr* of **167** (-173:-189)[b]	*ee*, %[c] (-173)	*ee*, %[c] (-189)
CCl_4[d]	34	33:67	99	98
Ether[d]	12	40:60		
PhH[e]	36	52:48	99	98
PhCl[d]	27	60:40		
DCM[e]	30	76:24	99	94
DCE[d]	31	77:23		
$PhNO_2$-DCM (7:3)[e]	31	76:24		
Propylene carbonate[e]	24	87:13	99	92
CH_3CN[e]	0	-		
$CHCl_3$[d]	0	-		

[a] **152**:**166** = 2:1, 2%mol of $Rh_2(IBAZ)_4$, -20°C to rt overnight; [b] Chemical shifts (^{19}F) of individual isomers are given in parentheses (configuration of the isomers was not determined); [c] Enantiomeric excess was determined by chiral GC of the purified product (Supelco β-DEX 120, 130°C); [d] Commercial solvent was degassed prior to use; [e] Solvent was distilled over an appropriate drying agent and degassed prior to use.

The influence of the ester bulkiness in **166** was addressed by comparing it with the ethyl cyanodiazoacetate **168** (Table 11). Somewhat higher *dr* was observed for **168** in benzene, but similar *dr* and lower *ee* was observed in DCM compared to **166**. Overall, no advantage of **168** over **166** is observed in terms of the yield and enantioselectivity.



Scheme 79.

Table 11.[a]

Diazo	Catalyst	Solvent	NMR yield	*dr*[b]	*ee*, %[c]	*ee*, %[d]
168	$Rh_2(IBAZ)_4$	PhH	25	67:33	-	-
166	$Rh_2(IBAZ)_4$	PhH	36	52:48	99	98
168	$Rh_2(IBAZ)_4$	DCM	23	76:24	88	84
166	$Rh_2(IBAZ)_4$	DCM	30	76:24	99	94
168	$Rh_2(OCO^tBu)_4$	DCM	49	57:43	-	-
166	$Rh_2(OCO^tBu)_4$	DCM	56	31:69	-	-

[a] **152**:**166** = **152**:**168** = 2:1, 2%mol of $Rh_2(IBAZ)_4$, -20°C to rt overnight; [b] Determined by ^{19}F NMR: -173 ppm : -189 ppm for **166**, -171 ppm : -187 ppm for **168**; [c] Isomer corresponding to -173 ppm (**166**) or -171 ppm (**168**); [d] Isomer corresponding to -189 ppm (**166**) or -187 ppm (**168**).

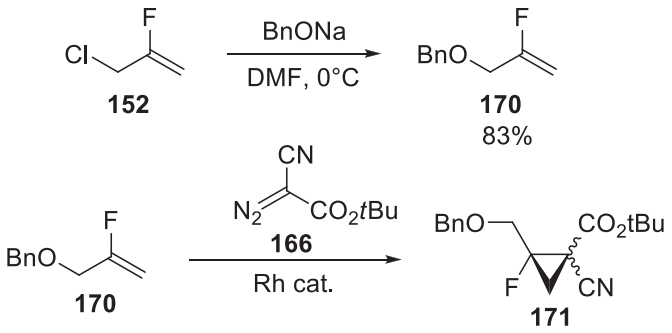
In an attempt to improve the yield of the cyclopropanation we have performed several experiments under different conditions (Table 12). Twofold excess of diazo compound (entry 2) does not result in a better yield, however, excess of fluoroalkene (entry 3) increases the overall yield to 30% (with respect to diazo compound used; equivalent to 15% with respect to the fluoroalkene). Fivefold increase in the catalyst loading (entry 4) slightly improves the yield (23% vs. 16%). Fourfold dilution of the reaction medium (entry 5) slightly decreases the yield, while performing the reaction without any solvent (entry 7) does not affect it at all. The *dr* of **167** is clearly temperature-dependent (entries 1-5 vs. 6-7). Minor increase in stereoselectivity with higher catalyst loading (entries 4 vs. 1) can apparently stem from the lower average temperature of the reaction (bigger portion of diazo compound reacts before the medium is warmed up).

Table 12.

entry	**152**:**166**	$Rh_2(IBAZ)_4$, %	[**166**]	Solvent	T, °C[a]	NMR yield[b]	*dr* of **167**[c] (-173:-189)
1	1:1	0.5	0.2	DCM	-20 to 25	16	71:29
2	1:2	0.5	0.4	DCM	-20 to 25	17	-
3	2:1	2	0.1	DCM	-40 to 25	30	76:24
4	1:1	2.5	0.2	DCM	-20 to 25	23	74:26
5	1:1	0.5	0.05	DCM	-20 to 25	12	72:28
6	2:1	2	0.1	DCM	25	25	67:33
7	1:1	0.5	-	no solvent	25	16	64:36

[a] Warming overnight where applicable; [b] With respect to the limiting reagent; [c] Chemical shifts (^{19}F) of individual isomers are given in parentheses (configuration of the isomers was not determined).

In order to exclude the possible interference from the allylic chlorine atom in **152** we have also prepared and tested the benzyl 2-fluoroallyl ether **170** (Scheme 80, Table 13). Similar yield of cyclopropane **171** was obtained with somewhat lower diastereoselectivity and *ee* of the minor isomer.



Scheme 79.

Table 13.[a]

Catalyst	Solvent	NMR yield	*dr* of **171**[b] (-170:-189)	*ee*, %[c] (-170)	*ee*, %[c] (-189)
$Rh_2(IBAZ)_4$	DCM	17	66:34	>95	74
$Rh_2(OCO^tBu)_4$	DCM	45	18:82	-	-

[a] **166**:**170** = 1:1, 2%mol of catalyst, -20°C to rt overnight; [b] Chemical shifts (^{19}F) of individual isomers are given in parentheses (configuration of the isomers was not determined); [c] Enantiomeric excess was determined by chiral HPLC of the purified product (mixture of 4 isomers).

Although the $Rh_2(IBAZ)_4$–catalysed cyclopropanation of **152** is characterised by a high level of enantioselectivity, all our attempts to improve the yield have been unsuccessful. The only way to slightly increase the yield is by using the large excess of 3-chloro-2-fluoropropene and higher catalyst loading. Since both of these reagents are expensive, the procedure cannot be considered practical in the present state.

Conclusion and perspective

In the course of this project we have developed a one-step Michael-initiated ring closure (MIRC) cyclopropanation leading to monofluorinated cyclopropanes. Efficient generation of an unstable Reformatsky reagent from ethyl dibromofluoroacetate was made possible by the catalytic effect of LiCl. Structurally diverse electron-withdrawing alkenes undergo cyclopropanation with good yields and moderate stereoselectivity.

Our approach was extended to a novel type of chiral cyclopropanating reagents (N-dibromofluoroacetyl-oxazolidinones) that were used for the synthesis of enantioenriched monofluorinated cyclopropanes. The absolute configuration of the acrylate-derived cyclopropanes was determined and was used as a basis for the stereochemical model of this reaction.

The future development of this project may include:

- studying the scope of the cyclopropanation with $CFBr_2PO(OiPr)_2$
- development of a more Z/E-selective cyclopropanation using alternative metalating agents or Lewis acidic additives
- development of a more stereoselective reaction with oxazolidinones by using alternative metalating agents, given enhanced stability of the chelated metal enolates.
- development of enantioselective version of the reaction (e.g. based on Mukaiyama-Michael addition)

(*E*)-1-amino-2-fluoro-2-(phosphonomethyl)cyclopropanecarboxylic acid ((*E*)-FAP4), the fluorinated analog of a potent mGluR III agonist (1*S*,2*R*)-APCPr, was synthesized via Rh(II)-catalysed cyclopropanation of diethyl 2-fluoroallylphosphonate. Both enantiomers of (*E*)-FAP4 were subjected to the cell culture tests of agonist activity against mGlu4 (University of Montpellier).

The first attempts of the enantioselective $Rh_2(IBAZ)_4$-catalysed cyclopropanation of 2-fluoroallyl compounds revealed high potential of this method for the synthesis of enantiopure monofluorinated diacceptor cyclopropanes. Although high enantioselectivity (up to >99%*ee*) was demonstrated, further studies are needed in order to reach an acceptable level of chemical yield in this reaction.

Experimental part

a. General experimental

All reactions were conducted in oven-dried glassware under argon. NMR spectra were recorded on Bruker DXP 300. Chemical shifts are reported in ppm relative to TMS (^{1}H, ^{13}C), $CFCl_3$ (^{19}F), 85% H_3PO_4 (^{31}P). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier, IR spectra were recorded on a PerkinElmer Spectrum 100. Elemental analyses were performed on a Thermo Flash 2000. Melting points are uncorrected.

THF (Na/benzophenone) and dichloromethane (P_2O_5) were distilled prior to use. Ethyl dibromofluoroacetate (EDBFA, Apollo Scientific), benzyl acrylate (Alfa Aesar), tert-butyl acrylate, acrylonitrile (Aldrich) and dimethyl vinylphosphonate were distilled under reduced pressure prior to use. Non-distilled EDBFA was used in a large-scale preparation of **98a** with no decrease of the yield. DMSO (Acros), TMSCl (Acros), benzyl methacrylate (Aldrich), (S)-4-isopropyloxazolidin-2-one (Aldrich), diethyl benzylidenemalonate (Fluka), 3-chloro-2-fluoropropene (**152**, Apollo Scientific) and the other reagents mentioned below were used without purification.

b. Preparation of the starting materials

Phenyl vinyl sulfone[197] (**97d**), benzyl 2-phenylacrylate[198] (**97g**), methyl 2-(bis(tert-butoxycarbonyl)amino)acrylate[199] (**97a**), tert-butyl 2-(bis(tert-butoxycarbonyl)amino)acrylate[3] (**97i**), dibenzyl fumarate[200] ((*E*)-**97j**), dibenzyl maleate[201] ((*Z*)-**97j**), di(isopropyl) dibromofluoromethylphosphonate,[202] (S)-4-phenyloxazolidin-2-one, (S)-4-tert-butyloxazolidin-2-one,[203] (S)-4-Isopropyl-5,5-dimethyloxazolidin-2-one,[204] ethyl nitrodiazoacetate[186] (**154a**), α-nitro-α-diazo-*para*-methoxyacetophenone[192] (**154d**), *tert*-butyl cyanodiazoacetate[205] (**166**), $Rh_2(OCO^tBu)_4$,[206]

[197] Carr, R.V.C.; Williams, R.V.; Paquette, L.A. *J. Org. Chem.* **1983**, *48*, 4976.
[198] Gerster, M.; Mader, D.; Rotzinger, B.; US2008/269382, 2008.
[199] Ferreira , P.M.T.; Maia , H.L.S.; Monteiro, L.S.; Sacramento, J. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3697.
[200] Madar, D.; Pei, Z.; Pireh, D.; Djuric, S.W.; Wiedeman, P.E.; Yong, H.; Michmerhuizen, M.J.; Kopecka, H.; Li, X.; Longenecker, K.; Sham, H.L.; Stewart, K.D.; Szczepankiewicz, B.G. WO2004/26822 A2, 2004.
[201] Thaqi, A.; Scott, J.L.; McCluskey, A. *Tetrahedron Lett.* **2008**, *49*, 6962.
[202] Burton, D. J.; Flynn, R. M. J. *Fluorine Chem.* **1977**, *10*, 329.
[203] Tietze, L.F., Schneider, C.; Grote, A. *Chem. Eur. J*. **1996**, 2, 139.
[204] Bull, S.D.; Davies, S.G.; Jones, S.; Polywka, M.E.C.; Prasad, R.S.; Sanganee, H.J. *Synlett.* **1998**, 519.
[205] Zhu, S.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc*. **2010**, *132*, 12796.
[206] Cotton, F.A.; Felthouse, T.R. *Inorg. Chem.* **1980**, *19*, 323.

$Rh_2(TCPTTL)_4$,[207] $Rh_2(IBAZ)_4$,[208] were prepared according to the known procedures. 4,4-Dimethyloxazolidin-2-one was prepared according to the known method[209] and distilled at reduced pressure prior to use.

***tert*-Butyl dibromofluoroacetate**

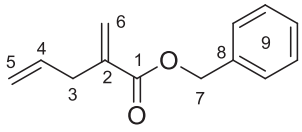
Ethyl dibromofluoroacetate (70 mmol, 9.80 mL) was added at 0 °C to the stirred suspension of NaOH (84 mmol, 3.36 g) in EtOH (60 mL). After one hour the cooling bath was removed and the stirring continued for 12 h at *rt*. The mixture was evaporated under reduced pressure to dryness. The resulting sodium salt was dissolved in a mixture of 2 N HCl and Et_2O (180 mL, 8:10). NaCl was added until saturation, then the aqueous layer was extracted twice with Et_2O (100 mL). Combined organic extracts were dried over $MgSO_4$ and evaporated at rt to give dibromofluoroacetic acid (almost pure by ^{19}F NMR: -64.32 ppm in $CDCl_3$).

The above acid was dissolved in 30 mL CH_2Cl_2, H_2SO_4 (10 drops, 98%) was added and the resulting solution was stirred vigorously in the atmosphere of isobutylene (several drops of H_2SO_4 were added every 2 hours as the reaction slowed down) until the complete conversion detected by ^{19}F NMR. The mixture was poured into a mixture of Et_2O and saturated soln of $NaHCO_3$.The organic layer was washed with brine and evaporated to give a pale-yellow crude product. $NaHCO_3$ (0.5 g) was added and the mixture was stirred at 50 °C for 10 min. The mixture was poured into a mixture of Et_2O and water. The organic layer was washed with brine and evaporated to give the pure tert-butyl ester as a colorless liquid (11.2 g, 55%).

IR (film): 3506, 2984, 2940, 1758, 1473, 1460, 1379, 1372, 1281, 1260, 1153, 1111, 963, 821, 786.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.57 (s); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 27.41 (s, *t*Bu), 82.58 (d, J = 324.6 Hz, CF), 86.58 (s, $tBu_{quat.}$), 160.43 (d, J = 25.9 Hz, CO); **^{19}F NMR** ($CDCl_3$, 282 MHz): -63.83 (s).

Benzyl 2-methylenepent-4-enoate (97f)



2-Methylenepent-4-enoic acid was prepared from diethyl allylmalonate in 56% yield according to the reported procedure[210] and was subjected to benzylation without further purification. To a solution

[207] Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymm*. **2003**, *14*, 817.
[208] Doyle, M.P.; Davies, S.B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.
[209] Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801.

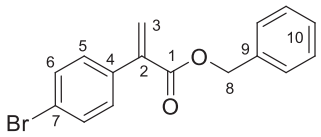
of 2-methylenepent-4-enoic acid (10 mmol, 1.1g) in anhydrous DMF (5 mL) K_2CO_3 (11 mmol, 1.52 g) was added at 0 °C. After stirring at rt for 15 min the mixture was cooled to 0 °C and BnBr (11 mmol, 1.31 mL) was added dropwise. After stirring at rt for 72 h the mixture was poured into a mixture of EtOAc and water (90 mL, 4:5). Organic layer was washed with sat. aqueous solution of $NaHCO_3$ (50 mL), brine (30 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by the column chromatography (0 to 5% EtOAc in cyclohexane) to give 1.79 g (89% yield) of pure **97f**. R_f 0.56 (EtOAc – cyclohexane 1:9).

^{1}H NMR ($CDCl_3$, 300 MHz): 3.09 (br.d, J = 6.7 Hz, 2 H, CH_2-3), 5.08 (br., 1 H, CH_2-5), 5.11-5.13 (m, 1 H, CH_2-5), 5.21 (s, 2 H, CH_2-7), 5.61 (m, 1 H, CH_2-6), 5.86 (m, 1 H, CH-4), 6.26 (br., 1 H, CH_2-6), 7.37 (m, 5 H, Ph). **^{13}C NMR** ($CDCl_3$, 75 MHz): 35.86 (C-3), 66.46 (C-7), 116.94 (C-5), 125.89 (C-6), 128.03, 128.14 and 128.52 (C-9), 135.00 (C-4), 135.98 and 138.88 (C-2 and C-8), 166.70 (C-1).

IR: 3425, 3067, 3035, 2979, 1715, 1630, 1498, 1456, 1431, 1294, 1266, 1246, 1215, 1134, 995, 947, 912, 815, 734, 696.

MS (EI): 202.0 ($[M]^+$).

Benzyl 2-(4-bromophenyl)acrylate (97h)



Prepared analogously to **97g**.[198] BnBr (10.3 mmol, 1.22 mL) was added to the stirred mixture of (4-bromophenyl)acetic acid (10.3 mmol, 2.22 g), K_2CO_3 (11.3 mmol, 1.56 g) and acetone (30 mL). After heating to reflux for 12 h the mixture was partitioned between diethyl ether (100 mL) and water (100 mL). Organic layer was washed with sat. solution of $NaHCO_3$ (50 mL), brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent gave 3.00 g (95%) of benzyl (4-bromophenyl)acetate as a colorless solid. Mixture of the above product (9.67 mmol, 2.95 g), paraformaldehyde (29 mmol, 870 mg), K_2CO_3 (30.9 mmol, 4.26 g) and tetrabutylammonium iodide (0.39 mmol, 143 mg) in 40 mL of toluene was stirred for 20 h at 85 °C under argon (full conversion by ^{1}H NMR at this point). The mixture was poured into 150 mL of diethyl ether, and acidified by 2 N HCl to pH 2. The aqueous layer was extracted with Et_2O (50 mL); the combined extracts were washed with brine (100 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by the column chromatography (0 to 5% EtOAc in cyclohexane) to give 1.47 g (48% yield) of pure **97h**. R_f 0.45 (EtOAc – cyclohexane 1:9).

^{1}H NMR ($CDCl_3$, 300 MHz): 5.27 (s, 2 H, CH_2-8), 5.93 (s, 1 H, CH_2-3), 6.43 (s, 1 H, CH_2-3), 7.30 (d, J = 8.5 Hz, 2 H, CH-5), 7.38 (m, 5 H, CH-10), 7.48 (d, J = 8.5 Hz, 2 H, CH-6); **^{13}C NMR** ($CDCl_3$, 75 MHz): 66.91

[210] Poisson, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 7890.

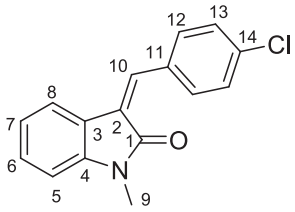
(C-8), 122.44 (C-7), 127.54 (C-3), 128.15, 128.29 and 128.57 (C-10), 129.97 (C-5), 131.22 (C-6), 135.46 (C-4), 135.70 (C-9), 140.14 (C-2), 166.00 (C-1).

IR (neat): 3423, 3088, 3062, 3034, 2940, 1720, 1610, 1584, 1487, 1460, 1393, 1328, 1301, 1270, 1177, 1086, 944, 838, 806, 776, 727.

3-(4-Chlorobenzylidene)-1-methylindolin-2-one (97l).

Prepared from 2-oxyindole and 4-chlorobenzaldehyde analogously to the reported procedure.[211] Mixture of 2-oxyindol (19.1 mmol, 2.54 g), 4-chlorobenzaldehyde (21 mmol, 2.95 g) and piperidine (4 mmol, 0.4 mL) in EtOH (18 mL) was heated to reflux for 2 h and then cooled to room temperature. The precipitate was washed with EtOH and dried in vacuum to afford 3-(4-chlorobenzylidene)indolin-2-one (4.01 g, 82%) as a mixture of isomers. NaH (8.9 mmol, 226 mg, 95%) was added to a solution of the above product (8.56 mmol, 2.19 g) in DMF (15 mL) at rt After the gas evolution ceased, MeI (11.0 mmol, 0.68 mL) was added dropwise. The mixture was stirred overnight (over which time intense color of indolinone anion disappeared). 1 mL of ethanol was added to ensure the absence of NaH, followed by 50 mL of water. The resulting mixture was extracted with ethyl acetate (3×40 mL). Combined extracts were washed with brine (100 mL) and evaporated. Recrystallization from EtOH afforded 2.10 g (91%) of **97l** as a mixture of two stereoisomers (configuration of the exocyclic double bond was assigned based on the known correlation[212] with the chemical shift of the vinylic proton). Pure (Z)-**97l** can be obtained by partial crystallization from EtOH. (E)-**97l**[213] was purified via column chromatography (10 to 20% EtOAc in petroleum ether).

(Z)-isomer:



M.p. 151-152 °C. R_f 0.51 (EtOAc – cyclohexane 3:7).

^{1}H NMR ($CDCl_3$, 300 MHz): 3.27 (s, 3 H, Me), 6.82 (d, J = 7.6 Hz, 1 H, CH-5), 7.06 (d, J = 7.6 Hz, 1 H, CH-7), 7.30 (t, J = 7.6 Hz, 1 H, CH-6), 7.40 and 8.26 (2d, J = 8.6 Hz, 2+2 H, CH-12 and CH-13), 7.46 (s, 1 H, CH-10), 7.51 (d, J = 7.6 Hz, 1 H, CH-8); **^{13}C NMR** ($CDCl_3$, 75 MHz): 25.86 (C-9), 107.89 (C-5), 118.91 (C-8),

[211] Huang, A.; Kodanko, J.J.; Overman, L.E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.
[212] Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477.
[213] Lubkoll, J.; Millemaggi, A.; Perry, A; Taylor, R.J.K. *Tetrahedron* **2010**, *66*, 6606.

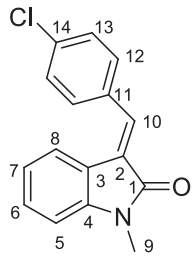
121.84 (C-7), 124.00 (C-2), 126.39 (C-3), 128.39 and 133.20 (C-12 and C-13), 129.04 (C-6), 132.22 and 136.22 (C-11 and C-14), 135.21 (C-10), 142.24 (C-4), 165.93 (C-1).

IR: 3363, 3060, 2929, 1929, 1684, 1605, 1490, 1468, 1412, 1382, 1336, 1298, 1266, 1232, 1122, 1086, 1041, 1009, 910, 828, 785, 744.

Anal. calcd: C 71.25, H 4.48, N 5.19; found: C 71.22, H 4.47, N 5.23.

MS (EI): 269.0 ($[M]^+$).

(E)-isomer:



M.p. 109-110 °C. R_f 0.33 (EtOAc – cyclohexane 3:7).

^{1}H NMR ($CDCl_3$, 300 MHz): 3.29 (s, 3 H, Me), 6.84 (d, J = 7.7 Hz, 1 H, CH-5), 6.90 (t, J = 7.7 Hz, 1 H, CH-7), 7.29 (t, J = 7.7 Hz, 1 H, CH-6), 7.44 and 7.58 (2d, J = 8.5 Hz, 2+2 H, CH-12 and CH-13), 7.57 (d, J = 7.7 Hz, 1 H, CH-8), 7.77 (s, 1 H, CH-10); **^{13}C NMR** ($CDCl_3$, 75 MHz): 26.18 (C-9), 108.31 (C-5), 120.82 (C-2) 121.84 (C-7), 122.65 (C-8), 127.67 (C-3), 128.94 and 130.60 (C-12 and C-13), 130.05 (C-6), 133.37 and 135.34 (C-11 and C-14), 135.49 (C-10), 144.34 (C-4), 168.25 (C-1).

IR (neat): 3397, 3055, 3030, 2968, 2931, 2876, 1911, 1835, 1772, 1710, 1635, 1609, 1487, 1467, 1414, 1379, 1337, 1251, 1064, 1015, 927, 878, 823, 775, 739.

Anal. calcd C 71.25, H 4.48, N 5.19; found: C 69.99, H 4.59, N 5.31.

MS (EI): 269.0 ($[M]^+$).

c. Preparation of the monofluorinated cyclopropanes (98)

2-ethyl 1-methyl 1-di(tert-butoxycarbonyl)amino-2-fluorocyclopropane-1,2-dicarboxylate (98a)

LiCl (3 mmol, 126 mg) and Zn (3 mmol, 196 mg) were placed into an oven-dried 25-mL flask equipped with a septum and a stirring bar, dried at 170 °C (10^{-1} mbar) for 40 min and then flushed with argon. 5 mL of freshly distilled THF, 8 µL of DMSO and 16 µL of TMSCl were added and the mixture was stirred vigorously at 50 °C for 10 min.

EDBFA (2 mmol, 280 μL) was dissolved in 1 mL THF and two drops of this solution were added to the above mixture. The mixture was cooled to 0°, and then **97a** (1 mmol, 301 mg, dissolved in 1 mL of THF under Ar) was added. Finally, the rest of EDBFA solution was added over 40 min. After stirring for additional 10 min mixture was poured into a mixture of ethyl acetate and 0.5 N HCl (50 mL, 3:2). Aqueous layer was extracted with ethyl acetate (10 mL), combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Resulting crude product (*dr* 59:41 by ^{19}F NMR) was purified by the flash column chromatography (10 to 25% EtOAc in cyclohexane). Yield 80% as a mixture of stereoisomers. R_f 0.49 (EtOAc – cyclohexane 3:7).

Large-scale modification:

LiCl (0.25 mol, 10.6 g) and Zn (0.25 mol, 16.4 g) were dried in a 1 L flask equipped with a septum and a stirring bar at 170 °C (10^{-1} mbar) for 60 min (fine powder was obtained after first 30 min of drying). 400 mL of freshly distilled THF, 0.8 mL of DMSO and 1.6 mL of TMSCl were added and the mixture was stirred vigorously at 50 °C for 15 min.

10 drops of EDBFA were added, the mixture was immediately cooled to -5 °C. **97a** (0.1 mol, 30.1 g, dissolved in 50 mL of THF under Ar) was added. EDBFA (0.16 mol, 22 mL) was added over a period of 30 min at -5-0 °C. After stirring for additional 10 min mixture was poured into a mixture of ethyl acetate and 0.5 N HCl (600 mL, 2:1).. Aqueous layer was extracted with ethyl acetate (100 mL), combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Resulting crude product (*dr* 58:42 by ^{19}F NMR) was purified by the column chromatography (EtOAc-cyclohexane 10 to 25%). Yield 37.7 g (93%) as a mixture of stereoisomers.

IR (film): 3445, 1799, 1748, 1371, 1278, 1255, 1159, 1122, 1101, 1027, 855, 785 cm^{-1}

Anal. calcd: C 53.33, H 6.96, N 3.45; found: C 52.95, H 6.64, N 3.71.

MS (ESI): 428.2 ([M+Na]).

Major isomer: rel-(1S,2S)-2-ethyl 1-methyl 1-(bis(tert-butoxycarbonyl)amino)-2-fluorocyclopropane-1,2-dicarboxylate ((*Z*)-**98a**)

^{1}H NMR ($CDCl_3$, 300 MHz): 1.32 (t, J = 7.2 Hz, 3 H, Et), 1.50 (s, 18 H, Boc), 1.90 (dd, J = 9.0 and 20.7 Hz, 1 H, CH_2-cyclo), 2.61 (dd, J = 9.0 and 15.9 Hz, 1 H, CH_2-cyclo), 3.72 (s, 3 H, Me), 4.29 (q, J = 7.2 Hz, 2 H, Et); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) : 14.3 (Et), 22.7 (d, J = 8 Hz, CH_2-cyclo), 28.1 (^{t}Bu), 46.8 (d, J = 10 Hz, $C_{quat.}$-cyclo), 53.1 (Me), 62.6 (Et), 81.4 (d, J = 242 Hz, CF), 83.8 ($C_{quat.}$-^{t}Bu), 151.4 (CO_{Boc}), 164.5 (d, J = 26 Hz, COOEt), 168.0 (d, J = 2 Hz, COOMe); **^{19}F NMR** ($CDCl_3$, 282 MHz): -185.5 (dd, J = 15.9 and 20.7 Hz).

Minor isomer: rel-(1R,2S)-2-ethyl 1-methyl 1-(bis(tert-butoxycarbonyl)amino)-2-fluorocyclopropane-1,2-dicarboxylate ((*E*)-**98a**):

^{1}H NMR ($CDCl_3$, 300 MHz): 1.31 (t, J = 7.2 Hz, 3 H, Et), 1.47 (s, 9 H, Boc), 1.49 (s, 9 H, Boc), 2.06 (dd, J = 8.4 and 9.8 Hz, 1 H, CH_2-cyclo), 2.79 (dd, J = 8.4 and 17.8 Hz, 1 H, CH_2-cyclo), 3.78 (s, 3 H, Me), 4.22 (q, J = 7.2 Hz, 2 H, Et); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.2 (Et), 27.2 (d, J = 9 Hz, CH_2-cyclo), 28.0 (^{t}Bu), 48.5 (d, J = 14 Hz, $C_{quat.}$-cyclo), 53.5 (Me), 62.8 (Et), 81.9 (d, J = 249 Hz, CF), 83.7 ($C_{quat.}$-^{t}Bu), 151.4 (CO_{Boc}), 164.7 (d, J = 35 Hz, COOEt), 166.6 (s, COOMe); **^{19}F NMR** ($CDCl_3$, 282 MHz): -195.5 (dd, J = 9.8 and 17.8 Hz).

2-Benzyl 1-ethyl 1-fluorocyclopropane-1,2-dicarboxylate (98b)

LiCl (3 mmol, 126 mg) and Zn (3 mmol, 196 mg) were placed into an oven-dried 25-mL flask equipped with a septum and a stirring bar, dried at 170 °C (10^{-1} mbar) for 40 min and then flushed with argon. 6 mL of freshly distilled THF, 8 µL of DMSO and 16 µL of TMSCl were added and the mixture was stirred vigorously at 50 °C for 10 min.

EDBFA (2 mmol, 280 µL) was dissolved in 1 mL THF and two drops of this solution were added to the above mixture. The mixture was cooled to -20°. Benzyl acrylate (1 mmol, 108 µL) was added, then the rest of EDBFA solution was added over 40 min. After stirring for additional 10 min mixture was poured into a mixture of ethyl acetate and 0.5 N HCl (50 mL, 3:2). Aqueous layer was extracted with ethyl acetate (10 mL), combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Resulting crude product (*dr* 72:28 by ^{19}F NMR) was purified by the flash column chromatography (EtOAc-cyclohexane 5 to 25%). Yield 80% as a mixture of stereoisomers (*dr* 74:26). R_f 0.57 (20% EtOAc-cyclohexane).

IR (film): 3034, 2985, 2908, 1733, 1456, 1375, 1336, 1307, 1255, 1153, 1016, 947, 908,748, 697 cm^{-1}

HRMS (ESI): calcd for $C_{14}H_{19}NO_4F$ ([M+NH_4]): 284.1298. Found: 284.1314.

Major isomer (E):

^{1}H NMR ($CDCl_3$, 300 MHz): 1.23 (t, J = 7.1 Hz, 3 H, CO_2Et), 1.73 (m, 1 H, CH_2-cycl), 2.01 (ddd, J = 7.1, 9.3, 10.2 Hz, 1 H, CH_2-cycl), 2.51-2.64 (m, 1 H, CH-cycl), 4.16 (m, 2 H, CO_2Et), 5.10 and 5.16 (2d, J = 12.2 Hz, 2 H, CH_2Ph), 7.32-7.38 (m, 5 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.1 (s, CO_2Et), 17.9 (d, $J_{C\text{-}F}$ = 9.9

Hz, CH_2-cycl), 29.0 (d, J_{C-F} = 12.1 Hz, CH-cycl), 62.3 (s, CO_2Et), 67.3 (s, CH_2Ph), 76.9 (d, J_{C-F} = 237.7 Hz, CF), 128.5-128.7 (Ph), 135.4 (s, Ph_{ipso}), 166.7 (s, CO_2Et), 166.7 (d, J_{C-F} = 24.2 Hz, CO_2Bn); **^{19}F NMR** ($CDCl_3$, 282 MHz): -184.4 (ddd, J = 10.2, 17.4, 18.4 Hz)

Minor isomer (Z):

^{1}H NMR ($CDCl_3$, 300 MHz): 1.32 (t, J = 7.1 Hz, 3 H, CO_2Et), 1.78 (m, 1 H, CH_2-cycl), 2.17 (ddd, J = 6.6, 8.1 and 18.6 Hz, 1 H, CH_2-cycl), 2.51-2.64 (m, 1 H, CH-cycl), 4.28 (q, J = 7.2 Hz, 2 H, CO_2Et), 5.16 and 5.23 (2d, J = 12.2 Hz, 2 H, CH_2Ph), 7.32-7.38 (m, 5 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.2 (s, CO_2Et), 18.7 (d, J_{C-F} = 10.5 Hz, CH_2-cycl), 27.8 (d, J_{C-F} = 10.5 Hz, CH-cycl), 62.6 (s, CO_2Et), 67.5 (s, CH_2Ph), 76.4 (d, J_{C-F} = 244.3 Hz, CF), 128.5-128.7 (Ph), 135.4 (s, Ph_{ipso}), 166.7 (s, CO_2Et), 168.1 (d, J_{C-F} = 24.2 Hz, CO_2Bn); **^{19}F NMR** ($CDCl_3$, 282 MHz): -206.0 (ddd, J = 2.1, 9.2 and 18.6 Hz)

Ethyl 2-cyano-1-fluorocyclopropanecarboxylate (98c)

Prepared as described for **98b** on 34 mmol scale (2.22 mL of acrylonitrile, neat EDBFA was added). After aqueous work-up the solvents were removed by fractional distillation. Resulting crude product was purified by short-pass column chromatography (EtOAc-cyclohexane 15 to 25%) and subsequent distillation to yield 2.28 g (47%) of **98c** as a mixture of stereoisomers (*dr* 46:54). R_f 0.52 (20% EtOAc-cyclohexane).

IR (film): 3120, 3045, 2990, 2253, 1742, 1380, 1310, 1180, 1156, 1013, 977, 857, 766, 738, 649 cm^{-1}

Anal.: calcd.: C 53.50, H 5.13; found: C 53.49, H 5.14.

MS (CI): 158 ([M+H]).

Major isomer (Z):

^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (t, J = 7.2 Hz, 3 H, CO_2Et), 1.92 (m, 2 H, CH_2-cyclo), 2.28 (m, 1 H, CH-cyclo), 4.30 (q, J = 7.2 Hz, 2 H, CO_2Et); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 11.72 (d, J = 9.9 Hz, CH-cyclo), 13.90 (s, OEt), 19.67 (d, J = 10.5 Hz, CH_2-cyclo), 63.05 (OEt), 75.17 (d, J = 243.8 Hz, CF), 115.00 (CN), 166.26 (d, J = 23.1 Hz, CO); **^{19}F NMR** ($CDCl_3$, 282 MHz): -199.51 (ddd, J = 2.1, 12.3 and 16.4 Hz).

Minor isomer (E):

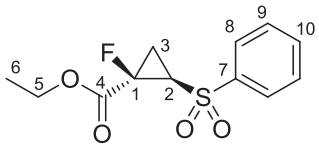
^{1}H NMR (300 MHz, $CDCl_3$): 1.35 (t, J = 7.2 Hz, 3 H, CO_2Et), 1.99 (m, 2 H, CH_2-cyclo), 2.31 (m, 1 H, CH-cyclo), 4.36 (m, 2 H, CO_2Et); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 12.14 (d, $J_{C\text{-}F}$ = 18.2 Hz, CH-cyclo), 13.95 (OEt), 19.26 (d, J = 9.9 Hz, CH_2-cyclo), 63.05 (OEt), 73.92 (d, J = 246.5 Hz, CF), 115.00 (CN), 165.15 (d, J = 23.7 Hz, CO); **^{19}F NMR** ($CDCl_3$, 282 MHz): -189.69 (ddd, J = 10.2, 14.3 and 17.0 Hz).

Ethyl 1-fluoro-2-(phenylsulfonyl)cyclopropanecarboxylate (98d)

Prepared analogously to **98b** using 1.1 equiv of EDBFA. Crude product (*dr* 67:33 by ^{19}F NMR) was purified via column chromatography on silica gel (EtOAc – cyclohexane 1:5 to 1:1).

Major isomer: R_f 0.44 (EtOAc – cyclohexane 1:1), yield 47%. Minor isomer: R_f 0.49 (EtOAc – cyclohexane 1:1), yield 25%

Major isomer (47%): rel-(1R,2R)-ethyl 1-fluoro-2-(phenylsulfonyl)cyclopropanecarboxylate



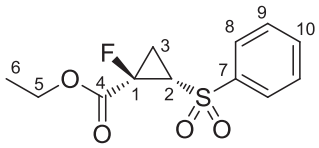
^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (t, J = 7.1 Hz, 3 H, Et), 2.00 (ddd, J = 7.5, 8.7 and 10.3 Hz, 1 H, CH_2-3), 2.50 (ddd, J = 7.5, 7.9 and 18.4 Hz, 1 H, CH_2-3), 3.18 (ddd, J = 2.8, 7.9 and 10.3 Hz, 1 H, CH-2), 4.21 (q, J = 7.1 Hz, Et), 7.57 (m, 2 H, CH-9), 7.68 (m, 1 H, CH-10), 7.95 (d, 7.7 Hz, 2 H, CH-8). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.89 (C-6), 17.98 (d, J = 11.0 Hz, C-3), 43.50 (d, J = 10.5 Hz, C-3), 62.88 (C-5), 74.95 (d, J = 245.4 Hz, C-1), 127.84 (d, J = 1.7 Hz, C-8), 129.39 (C-9), 134.10 (C-10), 139.79 (C-7), 166.52 (d, J = 24.2 Hz, C-4). ^{19}F NMR: -208.03 (ddd, J = 2.8, 8.7 and 18.4 Hz).

IR (film): 3104, 3041, 2986, 1740, 1585, 1448, 1377, 1324, 1296, 1239, 1145, 1087, 998, 948, 906, 858, 756, 729 cm^{-1}

Anal.: calcd.: C 52.93, H 4.81, S 11.78; found: C 52.44, H 5.05, S 11.52.

MS (EI): 272.0 ([M^+]).

Minor isomer (25%): rel-(1R,2S)-ethyl 1-fluoro-2-(phenylsulfonyl)cyclopropanecarboxylate



^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (t, J = 7.2 Hz, 3 H, Et), 2.02 (ddd, J = 8.0, 11.3 and 16.2 Hz, 1 H, CH_2-3), 2.44 (ddd, J = 8.0, 9.0 and 10.5 Hz, 1 H, CH_2-3), 3.23 (ddd, J = 9.0, 11.3, 17.8 Hz, 1 H, CH-2), 4.30 (q, J = 7.2 Hz, 2 H, Et), 7.58 (tm, J = 7.1 Hz, 2 H, CH-9), 7.68 (tm, J = 7.1 Hz, 1 H, CH-10), 7.91 (dm, J = 7.1 Hz, 2 H, CH-8) ; **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.82 (C-6), 18.37 (d, J = 10.5 Hz, C-3), 45.65 (d, J = 13.2 Hz, C-2), 62.92 (C-5), 77.31 (d, J = 239.9 Hz, C-1), 127.72 (C-8), 129.36 (C-9), 134.06 (C-10), 139.81 (C-7), 163.78 (d, J = 25.3 Hz, C-4) ; **^{19}F NMR** ($CDCl_3$, 282 MHz): -180.09 (ddd, J = 10.5, 16.2 and 17.8 Hz).

IR (film): 3068, 3030, 2987, 1746, 1585, 1448, 1375, 1309, 1218, 1149, 1088, 1019, 990, 909, 770, 740 cm^{-1}

Anal.: calcd.: C 52.93, H 4.81, S 11.78; found: C 52.38, H 4.62, S 11.59.

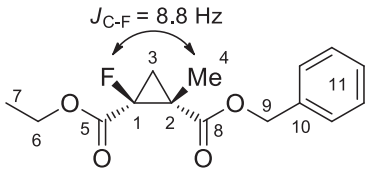
MS (EI): 272.0 ([M^+]).

1-benzyl 2-ethyl 2-fluoro-1-methylcyclopropane-1,2-dicarboxylate (98e)

LiCl (3 mmol, 126 mg) and Zn (3 mmol, 196 mg) were placed into an oven-dried 25-mL flask equipped with a septum and a stirring bar, dried at 170 °C (10^{-1} mbar) for 40 min and then flushed with argon. 6 mL of freshly distilled THF, 8 µL of DMSO and 16 µL of TMSCl were added and the mixture was stirred vigorously at 50 °C for 10 min.

EDBFA (2 mmol, 280 µL) was dissolved in 1 mL THF and two drops of this solution were added to the above mixture. The mixture was cooled to 30 °, and then the **97e** (0.67 mmol, 113 µL) was added. The rest of EDBFA solution was added over 40 min at 30 °. After stirring for additional 10 min mixture was poured into a mixture of ethyl acetate and 0.5 N HCl (50 mL, 3:2). Aqueous layer was extracted with ethyl acetate (10 mL), combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Resulting crude product (*dr* 70:30 by ^{19}F NMR) was purified via column chromatography on silica gel (EtOAc – cyclohexane 1:20 to 1:5). Major isomer : R_f 0.52 (EtOAc – cyclohexane 1:10), yield 40%. Minor isomer: R_f 0.56 (EtOAc – cyclohexane 1:10), yield 23%.

Major isomer (40%): rel-(1R,2S)-1-benzyl 2-ethyl 2-fluoro-1-methylcyclopropane-1,2-dicarboxylate



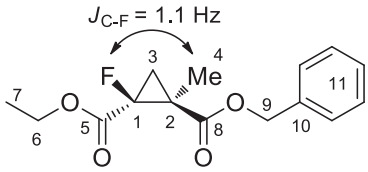
^{1}H NMR (300 MHz, $CDCl_3$): 1.23 (t, J = 7.1 Hz, 3 H, Et), 1.35 (dd, J = 7.2 and 17.5 Hz, 1 H, CH_2-cyclo), 1.54 (d, J = 2.1 Hz, 3 H, Me), 2.10 (dd, J = 7.2 and 10.3 Hz, 1 H, CH_2-cyclo), 4.12 (m, 2 H, Et), 5.08 (d, J = 12.4 Hz, 1 H, CH_2Ph), 5.14 (d, J = 12.4 Hz, 1 H, CH_2Ph), 7.35 (m, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.98 (s, C-7), 15.42 (d, J_{C-F} = 8.8 Hz, C-4), 23.60 (d, J_{C-F} = 9.4 Hz, C-3), 33.74 (d, J_{C-F} = 11.0 Hz, C-2), 62.03 (s, C-6),

67.12 (s, C-9), 78.61 (d, J_{C-F} = 243.2 Hz, C-1), 128.22, 128.30 and 128.50 (C-11), 135.41 (C-10), 167.51 (d, J_{C-F} = 24.8 Hz, C-5), 169.53 (d, J = 1.1 Hz, C-8); **^{19}F NMR** ($CDCl_3$, 282 MHz): -198.3 (ddq, J = 2.1, 10.3 and 17.5 Hz).

IR (film): 2986, 2943, 1737, 1498, 1455, 1374, 1348, 1317, 1269, 1181, 1141, 1107, 1017, 976, 916, 745, 697 cm^{-1}

HRMS (ESI): calcd for $C_{15}H_{18}O_4F$ ([M+H]): 281.1189. Found: 281.1203.

Minor isomer (23%): rel-(1S,2S)-1-benzyl 2-ethyl 2-fluoro-1-methylcyclopropane-1,2-dicarboxylate



^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 7.2 Hz, 3 H, Et), 1.46 (d, J = 2.1 Hz, 3 H, Me), 1.63 (dd, J = 7.0 and 10.2 Hz, 1 H, CH_2-cyclo), 2.33 (dd, J = 7.0 and 19.5 Hz, 1 H, CH_2-cyclo), 4.32 (m, 2 H, Et), 5.14 (d, J = 12.5 Hz, 1 H, CH_2Ph), 5.24 (d, J = 12.5 Hz, 1 H, CH_2Ph), 7.36 (m, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.14 (s, C-7), 14.37 (d, J_{C-F} = 1.1 Hz, C-4), 23.40 (d, J_{C-F} = 10.5 Hz, C-3), 32.99 (d, J_{C-F} = 10.5 Hz, C-2), 62.29 (C-6), 67.46 (C-9), 79.58 (d, J_{C-F} = 242.7 Hz, C-1), 128.03, 128.26 and 128.54 (C-11), 135.48 (C-10), 166.94 (d, J_{C-F} = 24.2 Hz, C-5), 168.54 (d, J_{C-F} = 4.4 Hz, C-8); **^{19}F NMR** ($CDCl_3$, 282 MHz): -196.3 (ddq, J = 2.1, 10.2 and 19.5 Hz).

IR (film): 2984, 1728, 1454, 1373, 1306, 1262, 1158, 1114, 1016, 954, 905, 856, 745, 696 cm^{-1}

HRMS (ESI): calcd for $C_{15}H_{18}O_4F$ ([M+H]): 281.1189. Found: 281.1193.

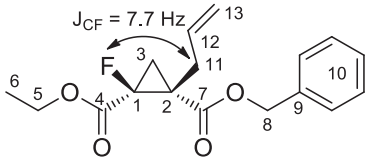
1-benzyl 2-ethyl 1-allyl-2-fluorocyclopropane-1,2-dicarboxylate (98f)

LiCl (3 mmol, 126 mg) and Zn (3 mmol, 196 mg) were placed into an oven-dried 25-mL flask equipped with a septum and a stirring bar, dried at 170 °C (10^{-1} mbar) for 40 min and then flushed with argon. 5 mL of freshly distilled THF, 8 µL of DMSO and 16 µL of TMSCl were added and the mixture was stirred vigorously at 50 °C for 10 min.

EDBFA (2 mmol, 280 µL) was dissolved in 1 mL THF and two drops of this solution were added to the above mixture. The mixture was cooled to 30°, and then **97f** (0.67 mmol, 135 mg, dissolved in 1 mL THF under Ar) was added. The rest of EDBFA solution was added over 40 min at 30°. After stirring for additional 10 min mixture was poured into a mixture of ethyl acetate and 0.5 N HCl (50 mL, 3:2).. Aqueous layer was extracted with ethyl acetate (10 mL), combined extracts were washed with brine, dried over $MgSO_4$ and evaporated.

Crude product (*dr* 73:27 by ^{19}F NMR) was purified via column chromatography on silica gel (EtOAc – cyclohexane 1:20 to 1:2). Major isomer: R_f 0.44 (EtOAc – cyclohexane 3:7), yield 50%. Minor isomer: R_f 0.56 (EtOAc – cyclohexane 3:7), yield 19%.

Major isomer (50%): rel-(1S,2R)-1-benzyl 2-ethyl 1-allyl-2-fluorocyclopropane-1,2-dicarboxylate

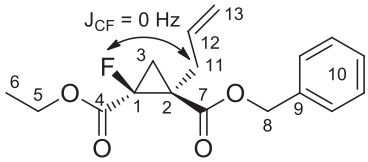


^{1}H NMR ($CDCl_3$, 300 MHz): 1.23 (t, J = 7.1 Hz, 3 H, Et), 1.44 (d, J = 7.3 and 17.5 Hz, 1 H, CH_2-3), 2.11 (ddd, J = 1.1 Hz, 7.3 and 10.0 Hz, 1H, CH_2-3), 2.33 (br.dd, J = 6.5 and 15.1 Hz, 1 H, CH_2-11), 2.83 (br. dd, J = 7.1 and 15.1 Hz, 1 H, CH_2-11), 4.14 (m, 2 H, Et), 5.05-5.15 (m, 4 H, CH_2-8 and CH_2-13), 5.79 (m, 1 H, CH-12), 7.34 (m, 5 H, Ph) ; **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.99 (C-6), 22.51 (d, J = 9.35 Hz, C-3), 34.02 (d, J = 7.7 Hz, C-11), 37.95 (d, J = 10.5 Hz, C-2), 62.13 (C-5), 67.16 (C-7), 78.44 (d, J = 242.6 Hz, C-1), 117.97 (C-13), 128.31, 128.37, 128.47 (C-10), 133.00 (C-12), 135.38 (C-9), 167.43 (d, J = 24.8 Hz, C-4), 168.40 (d, J = 1.7 Hz, C-7) ; **^{19}F NMR** ($CDCl_3$, 282 MHz): -197.27 (ddd, J = 2.0, 10.0 and 17.5 Hz).

IR (film): 3079, 2983, 2919, 1732, 1643, 1499, 1456, 1375, 1322, 1266, 1220, 1179, 1142, 1110, 1016, 992, 920, 860, 736, 697 cm^{-1}

HRMS (ESI): calcd for $C_{17}H_{23}NO_4F$ ([M+NH_4]): 324.1611. Found: 324.1620.

Minor isomer (19%): rel-(1S,2S)-1-benzyl 2-ethyl 1-allyl-2-fluorocyclopropane-1,2-dicarboxylate



^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 7.1 Hz, 3 H, Et), 1,67 (dd, J = 7.1 and 10.2 Hz, 1 H, CH_2-3), 2.34 (dd, J = 7.1 and 19.4 Hz, 1 H, CH_2-3), 2.39 (dd, J = 5.8 and 15.2 Hz, 1 H, CH_2-11), 2.75 (dd, J = 7.1 and 15.2 Hz, 1 H, CH_2-11), 4.30 (q, J = 7.1 Hz, 2 H, Et), 5.01 (br., 1 H, CH_2-13), 5.05 (br.d, J = 8.5 Hz, 1 H, CH_2-13), 5.14 (d, J = 12.4 Hz, 1 H, CH_2-8), 5.23 (d, J = 12.4 Hz, 1 H, CH_2-8), 5.77 (m, 1 H, CH-12), 7.35 (m, 5 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.09 (C-6), 22.26 (d, J = 9.9 Hz, C-3), 31.97 (s, C-11), 37.20 (d, J = 10.5 Hz, C-2), 62.38 (C-5), 67.59 (C-8), 78.93 (d, J = 242.6 Hz, C-1), 117.32 (C-13), 128.19, 128.29 and 128.50 (C-10), 133.50 (C-12), 135.35 (C-9), 167.06 (d, J = 24.2 Hz, C-4), 167.64 (d, J = 5.0 Hz, C-7); ^{19}F NMR: -194.49 (dd, J = 10.2 and 19.4 Hz).

IR (film): 3033, 2984, 1729, 1642, 1456, 1373, 1281, 1215, 1151, 1054, 1016, 917, 858, 746 cm^{-1}

HRMS (ESI): calcd for $C_{17}H_{20}O_4F$ ([M+H]): 307.1346. Found: 307.1357.

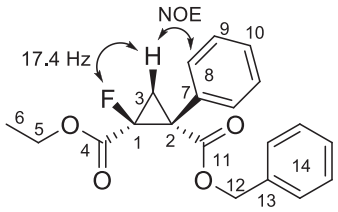
1-benzyl 2-ethyl 2-fluoro-1-phenylcyclopropane-1,2-dicarboxylate (98g)

Prepared analogously to **98f**. Resulting crude product (*dr* 76:24 by ^{19}F NMR) was purified via flash column chromatography on silica gel (EtOAc – cyclohexane 1:10 to 1:2). Yield 76% as a mixture of isomers. R_f 0.50 (EtOAc – cyclohexane 3:7).

IR (film): 3063, 3035, 2983, 1732, 1601, 1499, 1449, 1375, 1304, 1272, 1211, 1147, 1094, 1021, 926, 860, 729 cm^{-1}

HRMS (ESI): calcd for $C_{20}H_{20}O_4F$ ([M+H]): 343.1346. Found: 343.1342.

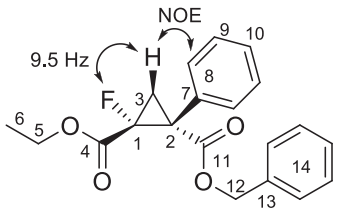
Major isomer: rel-(1S,2S)-1-benzyl 2-ethyl 2-fluoro-1-phenylcyclopropane-1,2-dicarboxylate



$J_{C(7)-F}$ = 3.3 Hz
$J_{C(11)-F}$ = 2.2 Hz

^{1}H NMR ($CDCl_3$, 300 MHz): 1.19 (t, J = 7.2 Hz, 3H, Et), 1.89 (dd, J = 7.2 and 17.4 Hz, 1 H, CH_2-cyclo), 2.37 (dd, J = 7.2 and 10.1 Hz, 1 H, CH_2-cyclo), 4.12 (m, 2 H, Et), 4.99 (dd, 2 H, CH_2Ph), 7.11-7.47 (m, 10 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.04 (s, C-6), 23.07 (d, J_{C-F} = 9.4 Hz, C-3), 43.24 (d, J_{C-F} = 11.6 Hz, C-2), 62.31 (s, C-5), 67.43 (s, C-12), 77.38 (d, J_{C-F} = 243.2 Hz, C-1), 127.94, 128.22, 128.45, 128.57, 128.65 (C-9, C-10, C-14), 130.58 (C-8), 132.27 (d, J_{C-F} = 3.3 Hz, C-7), 135.28 (s, C-13), 167.58 (d, J = 2.2 Hz, C-11), 167.60 (d, J = 24.8 Hz, C-4); **^{19}F NMR** ($CDCl_3$, 282 MHz): -191.65 (dd, J = 10.1 and 17.4 Hz).

Minor isomer: rel-(1S,2R)-1-benzyl 2-ethyl 2-fluoro-1-phenylcyclopropane-1,2-dicarboxylate



$J_{C(7)-F}$ = 0 Hz
$J_{C(11)-F}$ = 3.9 Hz

^{1}H NMR ($CDCl_3$, 300 MHz): 0.82 (t, J = 7.2 Hz, 3 H, Et), 2.18 (dd, J = 7.2 and 9.2 Hz, 1 H, CH_2-cyclo), 2.59 (dd, J = 7.2 and 18.1 Hz, 1 H, CH_2-cyclo), 3.85 (m, 2 H, Et), 5.08 (m, 2 H, CH_2Ph), 7.11-7.47 (m, 10 H,

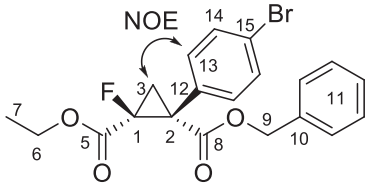
Ph); **$^{13}C\{^1H\}$ NMR** ($CDCl_3$, 75 MHz): 13.52 (C-6), 21.60 (d, J = 10.5 Hz, C-3), 42.36 (d, J = 11.6 Hz, C-2), 61.89 (C-5), 67.73 (C-12), 80.08 (d, J = 241.0 Hz, C-1), 128.09, 128.17, 129.93 and 129.95 (C-8, C-9, C-10, C-14), 133.44 (s, C-7), 135.35 (C-13), 165.71 (d, J = 25.9 Hz, C-4), 166.65 (d, J = 3.9 Hz, C-11); **^{19}F NMR** ($CDCl_3$, 282 MHz): -194.51 (dd, J = 9.2 and 18.1 Hz).

1-benzyl 2-ethyl 1-(4-bromophenyl)-2-fluorocyclopropane-1,2-dicarboxylate (98h)

Prepared analogously to **98f**. Crude product (*dr* 78:22 by ^{19}F NMR) was purified via column chromatography on silica gel (EtOAc – cyclohexane 1:20 to 1:5).

Major isomer: R_f 0.54 (EtOAc – cyclohexane 3:7), yield 61%. Minor isomer: R_f 0.56 (EtOAc – cyclohexane 3:7), yield 19%; m.p. 63-65 °C.

Major isomer (61%): rel-(1S,2S)-1-benzyl 2-ethyl 1-(4-bromophenyl)-2-fluorocyclopropane-1,2-dicarboxylate



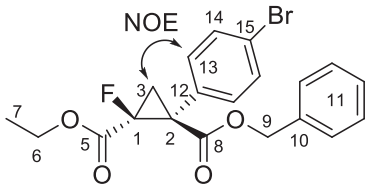
^1H NMR ($CDCl_3$, 300 MHz): 1.26 (t, J = 7.1 Hz, 3 H, Et), 1.92 (dd, J = 7.3 and 17.5 Hz, 1 H, CH_2-cyclo), 2.44 (dd, J = 7.3 and 10.3 Hz, 1 H, CH_2-cyclo), 4.18 (m, 2 H, Et), 5.03 (d, J = 12.4 Hz, 1 H, CH2Ph), 5.08 (d, J = 12.4 Hz, 1 H, CH2Ph), 7.22-7.35 (m, 5 H, Ph), 7.38 (dm, J = 8.6 Hz, 2 H, Ar_{Br}), 7.50 (dm, J = 8.6 Hz, 2 H, Ar_{Br}); **$^{13}C\{^1H\}$ NMR** ($CDCl_3$, 75 MHz): 14.02 (s, C-7), 23.05 (d, J_{C-F} = 9.4 Hz, C-3), 42.53 (d, J_{C-F} = 11.6 Hz, C-2), 62.43 (C-5), 67.65 (C-8), 77.30 (d, J = 243.7 Hz, C-1), 123.04 (C-15), 128.06, 128.36, 128.51 (C-11), 131.35 (d, J = 3.3 Hz, C-12), 131.78 and 132.24 (C-13 and C-14), 135.09 (C-10), 167.10-167.42 (2d, C-5 and C-8); **^{19}F NMR** ($CDCl_3$, 282 MHz): -191.20 (dd, J = 10.3 and 17.5 Hz).

IR (film): 2983, 1732, 1589, 1489, 1456, 1394, 1375, 1282, 1211, 1148, 1090, 1010, 956, 913, 826, 737, 713, 697 cm^{-1}

Anal. calcd.: C 57.02, H 4.31; found: C 56.86, H 4.42.

MS (ESI): 421.1 ([M+H]).

Minor isomer (19%): rel-(1S,2R)-1-benzyl 2-ethyl 1-(4-bromophenyl)-2-fluorocyclopropane-1,2-dicarboxylate



^{1}H NMR ($CDCl_3$, 300 MHz): 0.98 (t, J = 7.1 Hz, 3 H, Et), 2.23 (d, J = 7.3 and 9.2 Hz, 1 H, CH_2-cyclo), 2.68 (d, J = 7.3 and 17.7 Hz, 1 H, CH_2-cyclo), 3.99 (m, 2 H, Et), 5.16 (m, 2 H, CH_2Ph), 7.22 (d, J = 8.12 Hz, 2 H, Ar_{Br}), 7.22-7.33 (m, 5 H, Ph), 7.43 (d, J = 8.12 Hz, 2 H, Ar_{Br}); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.64 (s, C-7), 21.66 (d, $J_{C\text{-}F}$ = 9.9 Hz, C-3), 41.75 (d, $J_{C\text{-}F}$ = 11.6 Hz, C-2), 62.14 (C-5), 67.97 (C-8), 79.89 (d, J = 243.2 Hz, C-1), 122.36 (C-15), 127.71, 128.25 and 128.51 (C-11), 131.42 (C-14), 131.63 (d, J = 1.7 Hz, C-13), 132.51 (d, J = 1.1 Hz, C-12), 135.11 (C-10), 165.46 (d, J = 25.3 Hz, C-5), 166.15 (d, J = 3.3 Hz, C-8); **^{19}F NMR** ($CDCl_3$, 282 MHz): -194.53 (dd, J = 9.2 and 17.7 Hz).

IR (neat): 3447, 3125, 3062, 2990, 2947, 2881, 1732, 1589, 1490, 1455, 1380, 1347, 1323, 1253, 1213, 1109, 1075, 1009, 955, 913, 854, 826, 739, 699, 607 cm^{-1}

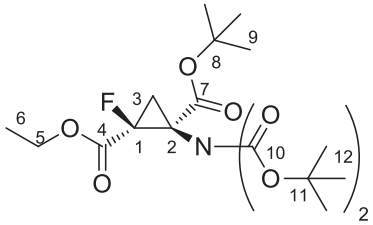
Anal. calcd.: C 57.02, H 4.31; found: C 56.99, H 4.30.

MS (ESI): 421.0 ([M+H]).

1-butyl 2-ethyl 1-(bis(tert-butoxycarbonyl)amino)-2-fluorocyclopropane-1,2-dicarboxylate (98i)

Prepared analogously to **98a** (small scale procedure). Resulting crude product (*dr* 84:16 by ^{19}F NMR) was purified via column chromatography (5 to 25% of EtOAc in cyclohexane). Major isomer: R_f 0.55 (EtOAc – cyclohexane 3:7), yield 63%; m.p. 48-50 °C. Minor isomer: R_f 0.52 (EtOAc – cyclohexane 3:7), oil, yield 10%.

Major isomer (63%): rel-(1S,2S)-1-*tert*-butyl 2-ethyl 1-(bis(tert-butoxycarbonyl)amino)-2-fluorocyclopropane-1,2-dicarboxylate



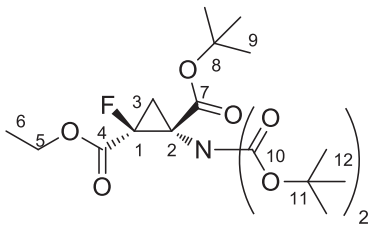
^{1}H NMR ($CDCl_3$, 300 MHz): 1.33 (t, J = 7.1 Hz, 3 H, Et), 1.44 and 1.52 (2s, 27 H, tBu), 1.83 (dd, J = 8.8 and 21.0 Hz, 1 H, CH_2-cyclo), 2.53 (dd, J = 8.8 and 15.9 Hz, 1 H, CH_2-cyclo), 4.29 (q, J = 7.1 Hz, 2 H, Et); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.99 (C-6), 26.36 (d, J = 8.3 Hz, C-3), 27.81 (br, C-9 and C-13), 46.69 (d, J =

9.9 Hz, C-2), 62.18 (C-5), 81.60 (d, C-1), 82.56 and 83.20 (br., C-8 and C-11), 151.01 (br,, C-11), 151.00 (C-10), 163.95 (d, J = 25.9 Hz, C-4), 166.04 (d, J = 2.8 Hz, C-7); **^{19}F NMR** ($CDCl_3$, 282 MHz): -186.07 (dd, J = 15.9 and 21.0 Hz).

IR (neat): 3430, 3125, 2981, 2938, 1796, 1744, 1721, 1454, 1394, 1373, 1339, 1281, 1256, 1146, 1089, 1032, 928, 913, 847, 790, 752, 709, 683, 614, 566.

HRMS (ESI): calcd for $C_{21}H_{34}NO_8FNa$ ([M+Na]): 470.2166. Found: 470.2152.

Minor isomer (10%): rel-(1R,2S)-1-*tert*-butyl 2-ethyl 1-(bis(tert-butoxycarbonyl)amino)-2-fluorocyclopropane-1,2-dicarboxylate



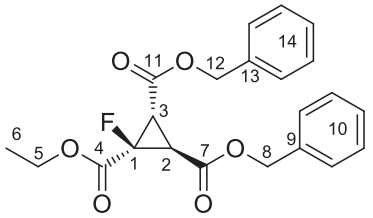
^{1}H NMR ($CDCl_3$, 300 MHz): 1.30 (t, J = 7.1 Hz, 3 H, Et), 1.46 and 1.49 (3s, 27 H, tBu), 1.98 (dd, J = 8.2 and 10.5 Hz, 1 H, CH_2-cyclo), 2.70 (dd, J = 8.2 and 17.7 Hz, 1 H, CH_2-cyclo), 4.22 (m, 2 H, Et); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.91 (C-6), 27.02 (d, J = 8.8 Hz, C-3), 27.72, 27.85 and 27.96 (C-9 and C-13), 48.64 (d, J = 13.8 Hz, C-2), 62.34 (C-5), 81.64 (d, J = 248.1 Hz, C-1), 82.98 and 83.12 (C-8 and C-11), 150.89 (d, J = 2.2 Hz, C-10), 151.00 (C-10), 164.44 (s, C-7), 165.78 (d, J = 25.3 Hz, C-4); **^{19}F NMR** ($CDCl_3$, 282 MHz): -196.47 (dd, J = 10.5 and 17.7 Hz).

IR (film): 3117, 2978, 2934, 1799, 1733, 1480, 1458, 1394, 1368, 1345, 1277, 1252, 1152, 1115, 1095, 1071, 1029, 934, 902, 843, 784, 735, 679, 579.

HRMS (ESI): calcd for $C_{21}H_{34}NO_8FNa$ ([M+Na]): 470.2166. Found: 470.2159.

***rel*-(2S,3S)-2,3-dibenzyl 1-ethyl 1-fluorocyclopropane-1,2,3-tricarboxylate (98j)**

Prepared analogously to **98b** starting from either dibenzyl fumarate or diethyl maleate using 1.1 equiv of EDBFA. Resulting crude product (only one isomer by ^{19}F NMR) was purified via flash column chromatography (20 to 40% of EtOAc in cyclohexane). Yield 66% (from dibenzyl fumarate) or 61% (from diethyl maleate). R_f 0.46 (EtOAc – cyclohexane 3:7).



^{1}H NMR ($CDCl_3$, 300 MHz): 1.23 (t, J = 7.2 Hz, 3 H, Et), 3.12 (dd, J = 4.1 and 8.6 Hz, 1 H, CH-2), 3.33 (dd, J = 8.6 and 19.5 Hz, 1 H, CH-3), 4.17 (m, 2 H, Et), 5.12 (d, J = 12.2 Hz, 1 H, CH_2-12), 5.17 (d, J = 12.2 Hz, 1 H, CH_2-12), 5.17 (d, J = 12.2 Hz, 1 H, CH_2-8), 5.23 (d, J = 12.2 Hz, 1 H, CH_2-8), 7.33-7.41 (m, 10 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.79 (C-6), 30.95 (d, J = 9.4 Hz, C-2), 32.84 (d, J = 11.6 Hz, C-3), 62.80 (C-5), 67.58 (C-12), 67.79 (C-8), 77.25 (d, J = 252.5 Hz, C-1), 128.41, 128.46, 128.51, 128.56 (C-10 and C-14), 134.75 and 134.84 (C-9 and C-13), 164.47-164.82 (m, C-4, C-7 and C-11); **^{19}F NMR** ($CDCl_3$, 282 MHz): -193.94 (dd, J = 4.1 and 19.5 Hz).

IR (film): 3463, 3034, 2984, 1734, 1592, 1499, 1455, 1373, 1338, 1283, 1187, 1135, 1051, 1015, 908, 856, 799, 739, 695.

HRMS (ESI): calcd. for $C_{22}H_{22}O_6F$ ([M+H]): 401.1400. Found: 401.1397.

Triethyl 2-fluoro-3-phenylcyclopropane-1,1,2-tricarboxylate (98k)

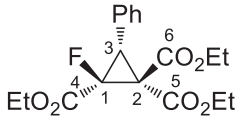
Prepared analogously to **98b**, except stirring for additional 2 h at rt after addition of EDBFA is finished. Purified by flash column chromatography. Yield 72% as a mixture of isomers. R_f 0.40 (EtOAc – cyclohexane 3:7).

IR (film): 3480, 2983, 2944, 2910, 1739, 1608, 1504, 1469, 1450, 1392, 1370, 1332, 1294, 1237, 1215, 1173, 1151, 1091, 1049, 1008, 919, 856, 748, 697.

Anal. calcd. C 61.36, H 6.01; found: C 61.33, H 6.34.

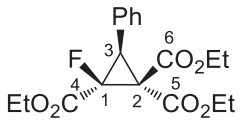
MS (EI): 352.2 ([M^+]).

Major isomer: rel-(2S,3R)-triethyl 2-fluoro-3-phenylcyclopropane-1,1,2-tricarboxylate



^{1}H NMR ($CDCl_3$, 300 MHz): 1.05, 1.23 and 1.33 (3t, 7.1, 7.1 and 7.3 Hz, 9 H, 3Et), 4.00-4.40 (m, 7 H, 3Et, CH-3), 7.25-7.40 (m, 5 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.53, 13.73 and 13.93 (Et), 39.69 (d, J = 11.6 Hz, C-3), 46.34 (d, J = 12.1 Hz, C-2), 79.69 (C-1), 127.81 and 129.46 (Ph), 129.92 (Ph-ipso), 163.10-163.99 (m, C-5 and C-6), 164.53 (d, J = 29.7 Hz, C-5); **^{19}F NMR** ($CDCl_3$, 282 MHz): -186.45 (d, J = 21.5 Hz).

Minor isomer: rel-(2S,3S)-triethyl 2-fluoro-3-phenylcyclopropane-1,1,2-tricarboxylate

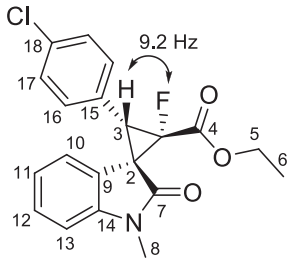


^{1}H NMR ($CDCl_3$, 300 MHz): 1.02, 1.31 and 1.37 (3t, 7.2 Hz, 9 H, 3Et), 3.71 (d, J = 7.6 Hz, 1 H, CH-3), 4.00-4.40 (m, 6 H, 3Et), 7.25-7.40 (m, 5 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.61, 13.89 and 13.99 (Et), 35.96 (d, J = 8.3 Hz, C-3), 45.02 (d, J = 8.3 Hz, C-2), 62.37 and 62.92 (Et), 79.56 (d, J = 258.1 Hz, C-1), 127.50-128.46 (Ph), 129.77 (Ph-ipso), 162.51-163.99 (m, C-5 and C-6), 166.16 (d, J = 25.3 Hz, C-4); **^{19}F NMR** ($CDCl_3$, 282 MHz): -203.82 (d, J = 7.2 Hz).

Ethyl 3-(4-chlorophenyl)-2-fluoro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxylate (98l)

Prepared analogously to **98a** using 1.1 equiv EDBFA. Both E and Z isomers of **97l** (or mixture thereof) can be used with the same stereochemical outcome, but the best yield is observed with (Z)-**97l**. Crude product (*dr* 53:36:7:4) was purified via column chromatography (5 to 35% of EtOAc in cyclohexane) to give three isomers. **98l**: yield 38% as a colorless solid (m.p. 132 °C); R_f 0.32 (EtOAc – cyclohexane 3:7). **98l'** (additionally recrystallized from hexane – DCM to remove the traces of starting material): yield 27% as a colorless solid (m.p. 86-88 °C); R_f 0.42 (EtOAc – cyclohexane 3:7). **98l"**: yield 5% as a colorless solid (m.p. 131-132 °C); R_f 0.52 (EtOAc – cyclohexane 3:7).Crystals of **98l** suitable for X-Ray analysis were grown from hexane-CH_2Cl_2 (slow evaporation at rt).

Major isomer (38%): rel-(1S,2R,3S)-ethyl 3-(4-chlorophenyl)-2-fluoro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxylate (**98l**)



$J_{C(9)-F}$ = 2.8 Hz
$J_{C(15)-F}$ = 2.8 Hz
$J_{C(10)-F}$ = 5.5 Hz

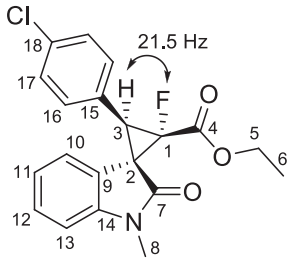
^{1}H NMR ($CDCl_3$, 300 MHz): 1.37 (t, J = 7.1 Hz, 3 H, Et), 3.29 (s, 3 H, NMe), 4.05 (d, 9.5 Hz, 1 H, CH-3), 4.38 (q, J = 7.1 Hz, 2 H, Et), 6.20 (br.d, J = 9.2 Hz, 1H, CH-10), 6.82 (dt, J = 0.9 and 7.6 Hz, 1 H, CH-11), 6.91 (d, J = 7.8 Hz, 1 H, CH-13), 7.12 (d, J = 8.5 Hz, 2 H, CH-16), 7.27 (dt, J = 0.9 and 7.6Hz, 1 H, CH-12), 7.29 (d, J = 8.5 Hz, 2 H, CH-17); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz):13.97 (C-6), 26.65 (C-8), 35.65 (d, J = 6.6 Hz, C-3), 41.23 (d, J = 11.6 Hz, C-2), 62.66 (C-5), 83.98 (d, J = 242.7 Hz, C-1), 108.2 (C-13), 120.84 (d, J = 2.8 Hz, C-9), 121.89 (C-11), 125.24 (d, J = 5.5 Hz, C-10), 126.62 (d, J = 1.7 Hz, C-15), 128.14 (C-12), 128.70 (C-17),

132.01 (C-16), 133.99 (C-18), 144.20 (C-14), 163.43 (d, J = 27.5 Hz, C-4), 171.02 (s, C-7); **^{19}F NMR** ($CDCl_3$, 282 MHz): -195.90 (d, J = 9.2 Hz).

IR (neat): 3059, 2983, 2938, 1746, 1713, 1613, 1495, 1471, 1374, 1346, 1279, 1254, 1215, 1147, 1127, 1086, 1016, 852, 806, 749, 724, 690.

HRMS (ESI): calcd for $C_{20}H_{18}NO_3FCl$ ([M+H]): 374.0959. Found: 374.0953.

Second isomer (27%): rel-(1S,2S,3R)-ethyl 3-(4-chlorophenyl)-2-fluoro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxylate (**98l'**)



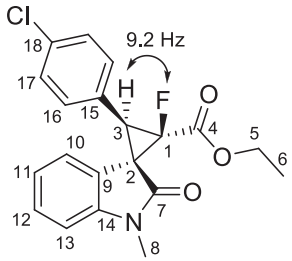
$J_{C(9)-F}$ = 1.7 Hz
$J_{C(15)-F}$ = 0 Hz

^{1}H NMR ($CDCl_3$, 300 MHz): 1.20 (t, J = 7.1 Hz, 3 H, Et), 3.35 (s, 3 H, NMe), 4.17 (m, 2 H, Et), 4.24 (br.d, J = 21.5 Hz, 1 H, CH-3), 6.72 (d, J = 7.7 Hz, 1 H, CH-10), 6.88 (t, J = 7.7 Hz, 1 H, CH-11), 6.93 (d, J = 7.7 Hz, 1 H, CH-13), 7.02 (d, J = 8.3 Hz, 2 H, CH-16), 7.28 (d, J = 8.3 Hz, 2 H, CH-17), 7.31 (t, J = 7.7 Hz, 1 H, CH-12); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.91 (C-6), 26.91 (C-8), 39.00 (d, J = 11.6 Hz, C-3), 42.23 (d, J = 11.0 Hz, C-2), 62.23 (C-5), 82.99 (d, J = 259.7 Hz, C-1), 108.00 (C-13), 120.89 (d, J = 1.7 Hz, C-9), 121.57 (C-11), 126.79 (C-10), 127.02 (C-15), 128.23 (C-17), 128.35 (C-12), 131.24 (C-16), 133.72 (s, C-18), 144.39 (C-14), 163.62 (d, J = 24.8 Hz, C-4), 169.94 (d, J = 1.1 Hz, C-7); **^{19}F NMR** ($CDCl_3$, 282 MHz): -185.15 (d, J = 21.5 Hz).

IR (neat): 3056, 2961, 2931, 1716, 1610, 1495, 1471, 1370, 1347, 1317, 1270, 1252, 1174, 1155, 1129, 1089, 1016, 988, 859, 812, 752, 715.

HRMS (ESI): calcd for $C_{20}H_{18}NO_3FCl$ ([M+H]): 374.0959. Found: 374.0961.

Third isomer (5%): rel-(1S,2R,3R)-ethyl 3-(4-chlorophenyl)-2-fluoro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxylate (**98l"**)



$J_{C(9)-F}$ = 0 Hz
$J_{C(15)-F}$ = 1.7 Hz

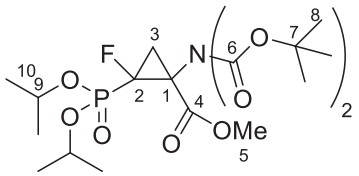
^{1}H NMR ($CDCl_3$, 300 MHz): 1.29 (t, J = 7.2 Hz, 3 H, Et), 3.23 (s, 3 H, NMe), 3.97 (d, 9.2 Hz, 1 H, CH-3), 4.30 (q, J = 7.2 Hz, 2 H, Et), 6.90 (d, J = 7.6 Hz, 1H, CH-13), 7.06 (dt, J = 0.9 and 7.6 Hz, 1 H, CH-11), 7.32 (s, 4 H, CH-16 and CH-17), 7.34 (m, 2 H, CH-10 and CH-12); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 14.04 (C-6), 26.54 (C-8), 37.86 (d, J = 7.2 Hz, C-3), 40.09 (d, J = 9.4 Hz, C-2), 62.96 (C-5), 84.37 (d, J = 261.4 Hz, C-1), 107.97 (C-13), 122.03 (C-11), 122.65 (C-12), 124.15 (C-9), 127.40 (d, J = 1.7 Hz, C-15), 128.40 (C-10), 128.54 (C-17), 131.44 (d, J = 2.2 Hz, C-16), 133.86 (C-18), 143.90 (C-14), 164.80 (d, J = 24.8 Hz, C-4), 167.48 (C-7); **^{19}F NMR** ($CDCl_3$, 282 MHz): -203.88 (d, J = 9.2 Hz).

IR (neat): 3420, 3060, 2976, 2939, 1742, 1716, 1613, 1492, 1473, 1281, 1184, 1075, 1015, 830, 747.

HRMS (ESI): calcd for $C_{20}H_{18}NO_3FCl$ ([M+H]): 374.0959. Found: 374.0954.

Methyl 1-(bis(tert-butoxycarbonyl)amino)-2-(diisopropoxyphosphoryl)-2-fluorocyclopropane-carboxylate

Prepared analogously to **98b**, except stirring for additional 1 h at rt. The crude product (*dr* 85:15) was purified by the column chromatography (Et_2O – petroleum ether 3:7) to give the pure major isomer (yield 71%) as a colorless oil.



HRMS (ESI+): calcd for $C_{21}H_{38}NO_9FP$ ($[M+H]^+$): 498.2268; found: 498.2254.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.33 (d, J = 6.2 Hz, 6 H, CH_3-10), 1.36 (dd, J = 1.6 and 6.1 Hz, 6 H, CH_3-10), 1.49 (s, 18 H, CH_3-8), 1.77 (ddd, J = 5.4, 8.7 and 25.1 Hz, 1 H, CH_2-3, F-*cis*), 2.48 (ddd, J = 8.9, 9.9 and 18.9 Hz, 1 H, CH_2-3, F-*trans*), 3.73 (s, 3 H, CH_3-5), 4.81 (m, 2 H, CH-9); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 23.25 (m, C-10), 23.89 (d, J = 2.8 Hz, C-10), 27.61 (C-8), 27.89 (d, J = 8.3 Hz, C-3), 45.91 (d, J = 8.8 Hz, C-1), 52.43 (C-5), 72.04 (d, J = 6.6 Hz, C-9), 72.24 (d, J = 6.6 Hz, C-9), 80.77 (dd, J = 228.9 and 249.8 Hz, C-2), 82.89 (C-7), 151.27 (br. C-6), 167.52 (t, 2 Hz, C-4); **^{19}F NMR** ($CDCl_3$, 282 MHz): -188.08 (ddd, J = 19.4, 25.5 and 77.7 Hz); **^{31}P NMR** ($CDCl_3$, 121 MHz): 9.45 (d, J = 77 Hz).

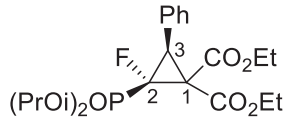
Diethyl 2-(diisopropoxyphosphoryl)-2-fluoro-3-phenylcyclo-propane-1,1-dicarboxylate (111k)

Prepared analogously to **98b**, except stirring for additional 3 h at -20 °C and then overnight at rt. The crude product (*dr* 65:35) was purified by the column chromatography (Et_2O – petroleum ether 3:7) to give 68% (mixture of stereoisomers 63:37) as a colorless oil. R_f 0.39 (Et_2O – petroleum ether 8:2).

IR (neat):2982, 2937, 1743, 1501, 1468, 1449, 1387, 1376, 1242, 1176, 1153, 1102, 1085, 1059, 988, 887, 863, 834, 770, 746.

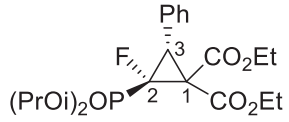
HRMS (ESI): calcd for $C_{21}H_{31}O_7FP$ ([M+H]): 445.1791. Found: 445.1795.

Major isomer: *rel*-(2S,3S)-diethyl 2-(diisopropoxyphosphoryl)-2-fluoro-3-phenylcyclo-propane-1,1-dicarboxylate



^{1}H NMR ($CDCl_3$, 300 MHz): 1.12-1.45 (m, 18 H, Me), 3.91 (dd, J = 7.6 and 27.0 Hz, 1 H, CH-3), 4.13-4.35 (m, 4 H, CH_2-ethyl), 4.59 (m, 1 H, CH-*i*Pr), 4.93 (m, 1 H, CH-*i*Pr), 7.23-7.36 (m, 3 H, Ph), 7.55 (br.d, J = 7.8 Hz, 2 H, Ph-ortho); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.76 and 14.03 (Et), 23.30 (d, J = 6.1 Hz, CH_3-*i*Pr), 23.53 (d, J = 5.0 Hz, CH_3-*i*Pr), 23.94 (d, J = 3.9 Hz, CH_3-*i*Pr), 24.28 (d, J = 2.8 Hz, CH_3-*i*Pr), 38.73 (d, J = 12.1 Hz, CH-3), 45.47 (d, J = 12.7 Hz, C-1), 61.91 and 62.90 (CH_2-Et), 72.43 (d, J = 6.6 Hz, CH-*i*Pr), 72.84 (d, J = 6.6 Hz, CH-*i*Pr), 79.83 (dd, J = 222.8 and 245.4 Hz, C-2), 127.56 (Ph_p), 127.77 (Ph_m), 130.07 (br., Ph_o), 130.3 (m, Ph_{ipso}), 163.03 (d, J = 3.9 Hz, CO), 164.25 (d, J = 4.4 Hz, CO); **^{19}F NMR** ($CDCl_3$, 282 MHz): -188.74 (dd, J= 27.0 and 80.7 Hz).

Minor isomer: *rel*-(2S,3R)-diethyl 2-(diisopropoxyphosphoryl)-2-fluoro-3-phenylcyclo-propane-1,1-dicarboxylate



^{1}H NMR ($CDCl_3$, 300 MHz): 1.04 (t, J = 7.1 Hz, 3H, CH_3-ethyl), 1.12-1.45 (m, 15 H, CH_3-Et and CH_3-*i*Pr), 3.55 (t, J = 11.3 Hz, 1 H, CH-3), 4.05 (q, J = 7.1 Hz, 2 H, CH_2-Et), 4.13-4.35 (m, 2 H, CH_2-Et), 4.78-4.98 (m, 2 H, CH-*i*Pr), 7.23-7.36 (m, 5 H, Ph); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz): 13.72 and 13.90 (Et), 23.78 (d, J = 5.5 Hz, CH_3-*i*Pr), 24.00 (d, J = 5.0 Hz, CH_3-*i*Pr), 24.07 (d, J = 3.9 Hz, CH_3-*i*Pr), 24.12 (d, J = 3.3 Hz, CH_3-*i*Pr), 33.37 (dd, J = 2.2 and 8.3 Hz, CH-3), 42.99 (d, J = 8.3 Hz, C-1), 61.75 and 62.63 (CH_2-Et), 72.93 (d, J = 6.6 Hz, CH-*i*Pr), 73.12 (d, J = 6.6 Hz, CH-*i*Pr), 78.33 (dd, J = 225.0 and 259.7 Hz, C-2), 127.67 (Ph_p), 128.29 (Ph_m),

129.67 (d, J = 2.2 Hz, Ph_o), 130.3 (m, Ph_{ipso}), 162.92 (br., CO), 164.92 (d, J = 3.3 Hz, CO); **^{19}F NMR** ($CDCl_3$, 282 MHz): -209.78 (dd, J = 11.3 and 73.6 Hz).

d. Optimization of conditions for the cyclopropanation of 2-alkyl and 2-aryl-substituted acrylates

Reaction with benzyl methacrylate (3 equiv EDBFA, Zn/LiCl, THF) was carried out at different temperatures after Zn activation (2 mol % TMSCl/DMSO in THF at 50 °C for 10 min for all reactions). Conversion of EDBFA was close to 100% in all the cases. Conversion of benzyl methacrylate and yield of cyclopropane were measured by ^{1}H NMR of the crude mixtures after aqueous work-up using DMF as an internal standard. *De* values were measured by ^{19}F NMR. Reactions with all the other 2-substituted acrylates were carried out in the optimized conditions (30 °C).

e. Evidence for cis-trans isomerization of 3l under cyclopropanation conditions[214]

LiCl (0.75 mmol, 32 mg) and Zn (0.75 mmol, 49 mg) were placed into an oven-dried 10-mL flask equipped with a septum and a stirring bar, dried at 170 °C (10^{-1} mbar) for 40 min and then flushed with argon. 2 mL of freshly distilled THF, 2 µL of DMSO and 4 µL of TMSCl were sequentially added and the mixture was stirred vigorously at 50 °C for 10 min.

Anhydrous $ZnBr_2$ (0.25 mmol, 56 mg) was dissolved under argon in 1 mL of THF and two drops of this solution were added to the above mixture. The mixture was cooled to 0°. (Z)-**97l** (0.25 mmol, 68 mg, dissolved in 0.5 mL THF) was added. After 1 min and 10 min of stirring two aliquots were taken (0.1 mL, poured into a mixture of EtOAc and saturated soln of $NaHCO_3$). The rest of $ZnBr_2$ solution was added in one portion, then the third aliquot was taken in the above manner after another 10 min. The three above aliquots showed 4%, 11% and 43% of the (E)-isomer respectively. For comparison, small amount of (Z)-**97l** was stirred with unactivated Zn metal and LiCl in THF at 0° for 0.5h. After similar aqueous work-up (EtOAc/sat. soln of $NaHCO_3$) no isomerization was observed by ^{1}H NMR.

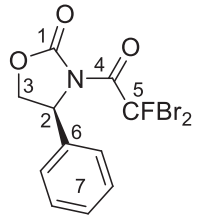
[214] In a similar experiment performed with dibenzyl maleate ((*Z*)-**3j**) no sign of dibenzyl fumarate ((*E*)-**3j**) formation was detected by ^{1}H NMR of aliquots, despite the gradual decrease of the vinylic proton signal.

f. Synthesis of N-dibromofluoroacetyl-oxazolidinones

Dibromofluoroacetyl chloride. Ethyl dibromofluoroacetate (70 mmol, 9.8 mL) was added at 0°C to the solution of NaOH (84 mmol, 3.36 g) in a mixture of ethanol and water (9:1, 100 mL). The resulting mixture was stirred at 0 °C for 1 h, then at room temperature overnight. Solvents were removed in vacuum, the residue was washed with ether (100 mL), taken up in ether (100 mL) and evaporated to dryness. The resulting white solid (sodium dibromofluoroacetate) was dissolved in a stirred mixture of ether (100 mL) and 2 N aqueous HCl (100 mL). Solid NaCl was added to saturation. Organic layer was separated, aqueous layer was extracted with ether (2×50 mL). Combined organic extracts were dried over $MgSO_4$ and evaporated to give dibromofluoroacetic acid as a yellow liquid. $SOCl_2$ (40 mL) was slowly added followed by several drops of DMF. The resulting mixture was heated to reflux for 30 h and then distilled to give 10.8 g of $CFBr_2COCl$ (60% from ethyl dibromofluoroacetate) as a yellow liquid (b.p. 113-115 °C, d = 2.21).

General procedure for the synthesis of N-dibromofluoroacetyl-oxazolidinones (117a-e). BuLi (1.05 equiv) was added dropwise to a solution of oxazolidinone (1 equiv, 0.2 M) in THF at -78 °C. After stirring for 30 min $CFBr_2COCl$ (1.1 equiv) was added. The mixture was stirred at -78 °C for 10 min and then slowly warmed to 0 °C. Ice-cold water was added and the mixture was extracted with ether. Organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. N-dibromofluoroacetyl-oxazolidinones **117a,b,d,e** were purified via short-pass column chromatography (ether – petroleum ether 1:9 to 1:4). **117c** was recrystallized from ether – petroleum ether.

(S)-N-dibromofluoroacetyl-4-phenyloxazolidin-2-one (117a). Yield 46% as a colorless solid (m.p. 161-162 °C)



$[\alpha]_D^{23}$ = -58.5° (c 1.0, $CHCl_3$)

R_f 0.34 (30% EtOAc in petroleum ether).

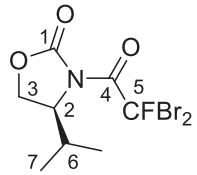
HRMS (ESI): calcd for $C_{11}H_9NO_3FBr_2$: 379.8933; found: 379.8937.

^{1}H NMR ($CDCl_3$, 300 MHz): 4.36 (dd, J = 4.2 and 8.9 Hz, 1 H, CH_2-3), 4.82 (dd, J = 8.7 and 8.9 Hz, CH_2-3), 5.51 (dd, J = 4.2 and 8.7 Hz, CH-2), 7.34-7.45 (m, 5 H, CH-7). **^{13}C NMR** ($CDCl_3$, 75 MHz): 59.69 (C-2),

70.42 (C-3), 83.33 (d, J = 321.9 Hz, C-5), 125.73, 129.31 and 129.44 (C-7), 137.13 (C-6), 149.96 (C-1), 159.62 (d, J = 28.1 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -60.78 (br.s).

IR (neat): 3563, 3403, 3039, 2977, 2917, 1795, 1706, 1496, 1473, 1461, 1384, 1333, 1299, 1197, 1121, 1084, 1058, 958, 862, 816.

(S)-N-dibromofluoroacetyl-4-isopropyloxazolidin-2-one (117b). Yield 72% as a yellowish oil.



$[\alpha]_D^{26}$ **=** +29.5° (c 1.0, $CHCl_3$)

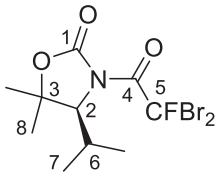
R_f 0.41 (30% EtOAc in petroleum ether).

Anal. calcd: C 27.69, H 2.90, N 4.04; found: C 27.71, H 3.04, N 4.06.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.96 (m, 6 H, CH_3-7), 2.42 (m, 1 H, CH-6), 4.30 (dd, J = 2.9 and 9.1 Hz, 1 H, CH_2-3), 4.43 (dd, 8.2 and 9.1 Hz, 1 H, CH_2-3), 4.53 (m, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 14.81 and 17.76 (C-7), 28.08 (C-6), 60.44 (C-2), 63.86 (C-3), 83.23 (d, J = 320.2 Hz, C-5), 150.08 (C-1), 160.00 (d, J = 27.5 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -59.31 (br.s).

IR (neat): 2962, 2880, 1797, 1746, 1706, 1486, 1419, 1387, 1369, 1315, 1247, 1193, 1106, 1054, 1018, 942, 813, 771.

(S)-N-dibromofluoroacetyl-4-isopropyl-5,5-dimethyloxazolidin-2-one (117c). Yield 82% as colorless to slightly yellowish crystals (m.p. 63-66°C).



$[\alpha]_D^{26}$ **=** +31.1° (c 1.0, $CHCl_3$)

R_f 0.47 (30% EtOAc in petroleum ether).

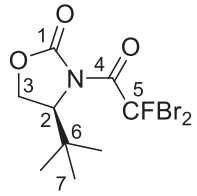
HRMS (ESI): calcd for $C_{10}H_{14}NO_3FBr_2Na$: 395.9222; found 395.9216.

Anal. calcd: C 32.03, H 3.76, N 3.73; found: C 32.03, H 3.94, N 3.69.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.05 (d, J = 6.9 Hz, 3 H, CH_3-7), 1.08 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.47 (s, 3 H, CH_3-8), 1.55 (s, 3 H, CH_3-8), 2.25 (m, 1 H, CH-6), 4.22 (d, J = 3.6 Hz, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.71 (C-7), 21.25 (C-8), 21.47 (C-7), 28.79 (C-8), 29.73 (C-6), 68.80 (C-2), 83.14 (d, J = 318.6 Hz, C-5), 83.64 (C-3), 149.70 (C-1), 160.67 (d, J = 26.4 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -57.79 (br.s).

IR (neat): 3385, 2975, 2930, 1781, 1700, 1465, 1361, 1324, 1277, 1121, 1069, 955, 864, 811, 773.

(S)-N-dibromofluoroacetyl-4-*tert*-butyloxazolidin-2-one (117d). Yield 88% as a colorless solid (m.p. 46-48°C).



$[\alpha]_D^{26}$ = +20.6° (c 1.0, $CHCl_3$)

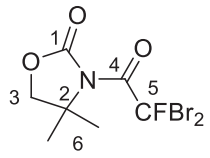
R_f 0.44 (30% EtOAc in petroleum ether).

Anal. calcd: C 29.94, H 3.35, N 3.88; found C 29.97, H 3.33, N 3.68.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.99 (s, 9 H, CH_3-7), 4.36 (dd, J = 1.7 and 9.3 Hz, 1 H, CH_2-3), 4.41 (dd, J = 7.1 and 9.3 Hz, 1 H, CH_2-3), 4.52 (dd, J = 1.7 and 7.1 Hz, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 25.43 (C-7), 36.38 (C-6), 63.07 (C-2), 65.46 (C-3), 83.44 (d, J = 320.8 Hz, C-5), 150.48 (C-1), 160.64 (d, J = 27.5 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -57.90 (br.s).

IR (neat): 2969, 1795, 1752, 1703, 1488, 1479, 1383, 1368, 1330, 1286, 1215, 1183, 1118, 1081, 1068, 1007, 967.

3-(2,2-dibromo-2-fluoroacetyl)-4,4-dimethyloxazolidin-2-one (117e). Prepared according to the general procedure (page S2) on a 6 mmol scale. The product was purified by the column chromatography (10-30% Et_2O in petroleum ether) and subsequent recrystallization from Et_2O – petroleum ether. Yield 77% as a colorless solid.



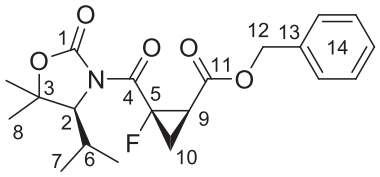
^{1}H NMR ($CDCl_3$, 300 MHz): 1.61 (s, 6 H, CH_3-6), 4.15 (s, 2 H, CH_2-3). **^{13}C NMR** ($CDCl_3$, 75 MHz): 23.57 (C-6), 62.96 (C-2), 75.75 (C-3), 84.82 (d, J = 327.4 Hz, C-5), 150.46 (C-1), 161.49 (d, J = 27.0 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -61.46.

g. Asymmetric synthesis of cyclopropanes

General procedure for the cyclopropanation of Michael acceptors. LiCl (1.5 mmol, 64 mg) and Zn (1 mmol, 65 mg) were placed into an oven-dried 10-mL flask equipped with a septum and a stirring bar, dried at 170 °C (10^{-1} mbar) for 40 min and then flushed with argon. Freshly distilled THF (2.5 mL), DMSO (2 µL) and TMSCl (6 µL) were added and the mixture was stirred vigorously at 50 °C for 10 min and then cooled to -20 °C.

Oxazolidinone (0.5 mmol) and a Michael acceptor (0.6 mmol) were dissolved in THF (1 mL) under argon and the resulting solution was added dropwise to the above mixture. After stirring for 1 h at -20 °C the mixture was poured into ethyl acetate and water with ice (50 mL, 3:2). The resulting biphasic solution was filtered through paper and the organic phase was separated. Aqueous layer was extracted with ethyl acetate (10 mL), combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Resulting crude product was analysed by ^{19}F NMR before being subjected to the column chromatography.

(1R,2S)-benzyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclo-propanecarboxylate (*(E)*-118a). Purified by the column chromatography (5-15% ethyl acetate in cyclohexane). Recrystallization from EtOAc – hexane resulted in the pure *(E)*-**118a** (65%, single isomer by ^{19}F NMR) as large colorless crystals (m.p. 110-113°C).



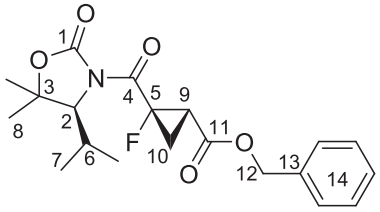
R_f 0.32 (20% EtOAc in petroleum ether).

Anal. calcd. C 63.65, H 6.41, N 3.71; found C 63.61, H 6.63, N 3.68.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.89 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.08 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.42 (s, 3H, CH_3-8), 1.52 (s, 3H, CH_3-8), 1.76 (m, 1 H, CH_2-10), 1.96 (m, 1 H, CH_2-10), 2.16 (m, 1 H, CH-6), 2.74 (m, 1 H, CH-9), 4.02 (d, J = 2.6 Hz, 1 H, CH-2), 5.13 (s, 2 H, CH_2-12), 7.34 (m, 5 H, CH-14). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.36 (C-7), 16.94 (d, J = 9.4 Hz, C-10), 21.28 (C-7 and C-8), 28.33 (d, J = 13.2 Hz, C-9), 28.47 (C-8), 29.81 (C-6), 67.00 (C-12), 67.87 (C-2), 81.19 (d, J = 236.6 Hz, C-5), 83.80 (C-3), 128.07, 128.20 and 128.47 (C-14), 135.35 (C-13), 152.17 (C-1), 162.77 (d, J = 25.3 Hz, C-4), 169.93 (s, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -184.59 (dt, J = 11.2 and 18.4 Hz).

IR (neat): 2979, 1783, 1725, 1700, 1459, 1435, 1372, 1282, 1164, 1119, 1072, 970, 852, 749, 736.

(1S,2S)-benzyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropane-carboxylate (*(Z)*-118a). Purified by the column chromatography (5-15% ethyl acetate in cyclohexane). Yield 14% (*de* 84% by ^{19}F NMR) as a colorless oil.



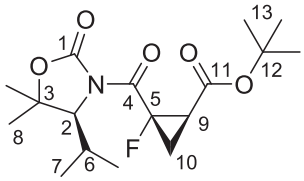
R_f 0.23 (20% EtOAc in petroleum ether).

Anal. calcd. C 63.65, H 6.41, N 3.71; found C 63.59, H 6.41, N 3.75.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.99 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.05 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.44 (s, 3H, CH_3-8), 1.54 (s, 3H, CH_3-8), 1.79 (ddd, J = 7.4, 10.1 and 10.2 Hz, 1 H, CH_2-10), 2.14-2.29 (m, 2 H, CH-6 and CH_2-10), 2.61 (ddd, J = 3.1, 8.3 and 10.1 H, CH-9), 4.03 (d, J = 3.4 Hz, 1 H, CH-2), 5.18 (d, J = 12.2 Hz, 1 H, CH_2-12), 5.26 (d, J = 12.2 Hz, 1 H, CH_2-12), 7.31-7.41 (m, 5 H, CH-14). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.96 (C-7), 17.36 (d, J = 10.5 Hz, C-10), 21.29 (C-7), 21.51 (C-8), 25.90 (d, J = 10.5 Hz, C-9), 28.71 (C-8), 29.36 (C-6), 67.22 (C-12), 67.82 (C-2), 79.33 (d, J = 247.6 Hz, C-5), 83.74 (C-3), 128.26 and 128.50 (C-14), 135.46 (C-13), 151.51 (C-1), 166.65 (d, J = 26.4 Hz, C-4), 166.68 (d, J = 1.7 Hz, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -198.05 (ddd, J = 3.1, 10.2 and 19.4 Hz).

IR (neat): 2975, 1788, 1738, 1700, 1455, 1362, 1326, 1274, 1216, 1159, 1119, 1071, 916, 745.

(1R,2S)-*tert*-butyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropanecarboxylate (*(E)*-118b). Purified by the column chromatography (5-15% ethyl acetate in cyclohexane). Yield 61% (*de* 94% by ^{19}F NMR) as a colorless solid (m.p. 87-88°C)



R_f 0.58 (30% EtOAc in petroleum ether).

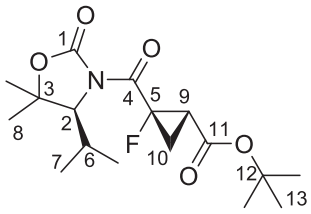
Anal. calcd. C 59.46, H 7.63, N 4.08; found C 59.35, H 7.86, N 4.09.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.95 (d, J = 6.9 Hz, 3 H, CH_3-7), 1.10 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.41 and 1.51 (2s, 6 H, CH_3-8), 1.42 (s, 9 H, CH_3-13), 1.65 (ddd, J = 7.4, 11.1 and 18.5 Hz, 1 H, CH_2-10), 1.86 (m, 1 H, CH_2-10), 2.19 (m, 1 H, CH-6), 2.57 (ddd, J = 8.5, 11.1 and 18.6 Hz,1 H, CH-9), 4.00 (d, J = 2.5 Hz, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.47 (C-7), 16.49 (d, J = 9.4 Hz, C-10), 21.23 and 21.29 (2 s, C-7 and C-8),

27.91 (C-13), 28.47 (C-8), 29.56 (d, J = 12.7 Hz, C-9), 29.74 (C-6), 68.03 (C-2), 81.24 (d, J = 234.4 Hz, C-5), 81.61 (C-13), 83.72 (C-3), 152.25 (C-1), 163.27 (d, J = 25.3 Hz, C-4), 169.27 (C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -185.42 (dt, J = 12.3 and 19.4 Hz).

IR (neat): 3112, 2975, 1781, 1713, 1446, 1366, 1283, 1150, 1122, 1073, 974, 842, 731.

(1S,2S)-*tert*-butyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropanecarboxylate (*(Z)*-118b). Purified by the column chromatography (DCM – pentane 1:1 to 9:1). Yield 8% (*de* 76% by ^{19}F NMR) as a colorless oil.



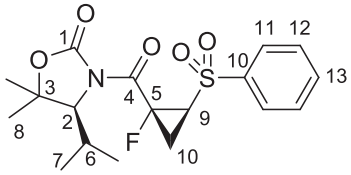
R_f 0.49 (30% EtOAc in petroleum ether).

HRMS: calcd for $C_{17}H_{26}NO_5FNa$: 366.1693; found: 366.1711.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.99 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.05 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.43 and 1.52 (2s, 6 H, CH_3-8), 1.48 (s, 9 H, CH_3-13), 1.71 (dt, J = 7.3 and 10.0 Hz, 1 H, CH_2-10), 2.09 (m, 1 H, CH_2-10), 2.19 (m, 1 H, CH-6), 2.43 (m, 1 H, CH-9), 4.02 (d, J = 3.4 Hz, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.77 (d, J = 10.5 Hz, C-10), 16.98 (C-7), 21.26 and 21.52 (2 s, C-7 and C-8), 27.25 (d, J = 10.5 Hz, C-9), 27.29 (C-13), 28.68 (C-8), 29.39 (C-6), 67.91 (C-2), 79.13 (d, J = 246.0 Hz, C-5), 81.90 (C-12), 83.61 (C-3), 151.52 (C-1), 165.63 (d, J = 2.2 Hz, C-11), 167.09 (d, J = 26.4 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -199.30 (ddd, J = 3.1, 10.2 and 20.4 Hz).

IR (neat): 2974, 2921, 1780, 1723, 1467, 1365, 1313, 1277, 1221, 1170, 1151, 1120, 1094, 1072, 956, 913.

(S)-3-((1R,2S)-1-fluoro-2-(phenylsulfonyl)cyclopropanecarbonyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one (*(E)*-118c). Purified by the column chromatography (10-20% ethyl acetate in cyclohexane). Yield 17% (single isomer by ^{19}F NMR) as a colorless solid (m.p. 135-137°C).



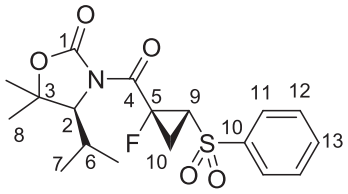
R_f 0.22 (30% EtOAc in petroleum ether).

Anal. calcd. C 56.38, H 5.78, N 3.65; found C 56.41, H 5.93, N 3.51.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.11 (d, J = 6.9 Hz, 3 H, CH_3-7), 1.17 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.44 and 1.56 (2 s, 6 H, CH_3-8), 1.83 (ddd, J = 8.5, 11.1 and 17.5 Hz, 1 H, CH_2-10), 2.24 (m, 2 H, CH_2-10 and CH-6), 3.46 (ddd, J = 9.1, 11.1 and 17.3 Hz, 1 H, C-9), 4.09 (d, J = 2.3 Hz, 1 H, CH-2), 7.56 (m, 2 H, CH-12), 7.66 (m, 1 H, CH-13), 7.92 (m, 2 H, CH-11). **^{13}C NMR** ($CDCl_3$, 75 MHz):16.24 (d, J = 11.0 Hz, C-10), 16.49 (C-7), 21.23 and 21.31 (C-7 and C-8), 28.58 (C-8), 30.09 (C-6), 45.78 (d, J = 12.1 Hz, C-9), 68.28 (C-2), 80.48 (d, J = 243.8 Hz, C-5), 83.98 (C-3), 127.95 (C-11), 129.28 (C-12), 133.98 (C-13), 139.59 (C-10), 151.71 (C-1), 161.41 (d, J = 25.3 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz):-176.28 (dt, J = 11.2 and 17.4 Hz).

IR (neat): 3100, 3051, 2968, 1782, 1700, 1449, 1370, 1321, 1280, 1226, 1153, 1073, 982, 949, 750.

(S)-3-((1R,2R)-1-fluoro-2-(phenylsulfonyl)cyclopropanecarbonyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one (*(Z)*-118c). Purified by the column chromatography (10-20% ethyl acetate in cyclohexane). Yield 62% (single isomer by ^{19}F NMR) as a colorless solid (m.p. 133-134°C).



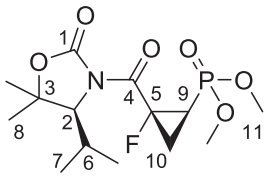
R_f 0.13 (30% EtOAc in petroleum ether).

Anal. calcd. C 56.38, H 5.78, N 3.65; found C 56.35, H 5.82, N 3.62.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.78 (d, J = 6.8 Hz, 6 H, CH_3-7), 1.39 and 1.48 (2 s, 6 H, CH_3-8), 1.95 (m, 1 H, CH_2-10), 2.04 (m, 1 H, CH-6), 2.71 (ddd, J = 8.3, 8.4 and 20.6 Hz, 1 H, CH_2-10), 3.45 (m, 1 H, CH-9), 4.02 (d, J = 3.7 Hz, 1 H, C-2), 7.55 (m, 3 H, CH-12), 7.65 (m, 1 H, CH-13), 7.97 (m, 2 H, CH-11). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.65 (C-7), 18.67 (d, J = 10.5 Hz, C-10), 21.10 (C-7), 21.47 (C-8), 28.98 (C-8), 29.22 (C-6), 41.65 (d, J = 11.0 Hz, C-9), 67.10 (C-2), 77.95 (d, J = 249.2 Hz, C-5), 83.71 (C-3), 127.87 (d, J = 1.7 Hz, C-11), 129.17 (C-12), 133.84 (C-13), 140.06 (C-10), 150.99 (C-1), 166.59 (d, J = 26.4 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz):-198.92 (ddd, J = 3.1, 9.2 and 20.4 Hz).

IR (neat): 3048, 2971, 2938, 1794, 1706, 1450, 1370, 1321, 1280, 1242, 1223, 1152, 1119, 1072, 996, 962, 925, 853, 756.

Dimethyl (1S,2R)-2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropylphosphonate (*(E)*-118d). Purified by the column chromatography (ethyl acetate – cyclohexane 1:1 to 1:0). Yield 7% (*de* 86% by ^{19}F NMR) as a colorless solid (m.p. 85-88°C).



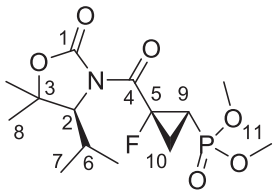
R_f 0.26 (70% EtOAc in petroleum ether).

Anal. calcd. C 47.86, H 6.60, N 3.99; found C 47.87, H 6.92, N 4.04.

^{1}H NMR ($CDCl_3$, 300 MHz):1.05 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.13 (d, J = 7.1 Hz, 3 H, CH_3-7), 1.42 and 1.54 (2 s, 6 H, CH_3-8), 1.61-1.77 (m, 1 H, CH_2-10), 1.84-2.08 (m, 2 H, CH_2-10 and CH-9), 2.21 (m, 1 H, CH-6), 3.74 (d, J = 11.0 Hz, 3 H, CH_3-11), 3.78 (d, J = 11.1 Hz, 3 H, CH_3-11), 4.03 (d, J = 2.4 Hz, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.40 (dd, J = 6.1 and 11.6 Hz, C-10), 16.32 (C-7), 19.82 (dd, J = 12.1 and 192.0 Hz, C-9), 21.19 (C-7), 21.31 (C-8), 28.51 (C-8), 29.92 (C-6), 52.70 (d, J = 6.1 Hz, C-11), 53.42 (d, J = 6.1 Hz, C-11), 68.24 (C-2), 79.75 (dd, J = 2.2 and 236.6 Hz, C-5), 83.92 (C-3), 152.12 (C-1), 163.12 (dd, J = 3.9 and 26.4 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz):-179.90 (m). **^{31}P NMR** ($CDCl_3$, 121 MHz): 23.14 (d, J = 5.9 Hz).

IR (neat): 3100, 2970, 1786, 1708, 1466, 1371, 1311, 1263, 1172, 1121, 1061, 1033, 845, 795, 773, 730.

Dimethyl (1R,2R)-2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropylphosphonate (*(Z)*-118d). Purified by the column chromatography (ethyl acetate – cyclohexane 1:1 to 1:0). Yield 55% (single isomer by ^{19}F NMR) as a colorless oil.



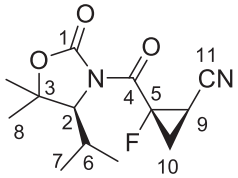
R_f 0.14 (70% EtOAc in petroleum ether).

HRMS calcd for $C_{14}H_{24}NO_6FP$: 352.1325; found: 352.1326.

^{1}H NMR ($CDCl_3$, 300 MHz):0.99 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.02 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.43 and 1.52 (2 s, 6 H, CH_3-11), 1.68-1.81 (m, 1 H, CH_2-10), 2.00 (m, 1 H, CH-9), 2.01-2.22 (m, 2 H, CH-6 and CH_2-10), 3.78 (d, J = 11.1 Hz, 3 H, CH_3-11), 3.80 (d, J = 11.1 Hz, 3 H, CH_3-11), 4.10 (d, J = 3.5 Hz, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.87 (C-7), 17.26 (dd, J = 12.7 and 190.4 Hz, C-9), 17.94 (dd, J = 5.5 and 10.5 Hz, C-10), 21.28 (C-7), 21.56 (C-8), 28.88 (C-8), 29.41 (C-6), 52.78 (dd, J = 6.1 Hz, C-11), 53.08 (dd, J = 6.1 Hz, C-11), 67.49 (C-2), 78.89 (dd, J = 6.6 and 243.7 Hz, C-5), 83.63 (C-3), 151.37 (C-1), 167.29 (d, J = 27.5 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -193.98 (m). **^{31}P NMR** ($CDCl_3$, 121 MHz): 23.07 (d, J = 7.2 Hz).

IR (neat): 2969, 1785, 1703, 1467, 1362, 1318, 1257, 1171, 1027, 953, 831, 775.

(1R,2S)-2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropanecarbonitrile (*(E)*-118e). Purified by the column chromatography (10-30% of ethyl acetate in cyclohexane). Yield 34% (single isomer by ^{19}F NMR) as a colorless solid (m.p. 124-125°C).



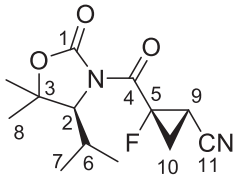
R_f 0.45 (30% EtOAc in petroleum ether).

Anal. calcd C 58.20, H 6.39, N 10.44; found C 58.03, H 6.44, N 10.33.

^{1}H NMR ($CDCl_3$, 300 MHz):1.05 (d, J = 6.9 Hz, 3 H, CH_3-7), 1.11 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.45 and 1.56 (CH_3-8), 1.85 (ddd, J = 7.9, 11.1 and 17.4 Hz, 1 H, CH_2-10), 2.08 (ddd, J = 7.9, 8.5 and 11.2 Hz, 1 H, CH_2-10), 2.24 (m, 1 H, CH-6), 2.46 (ddd, J = 8.5, 11.1 and 15.3 Hz, 1 H, CH-9), 4.01 (d, J = 2.8 Hz, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 12.10 (d, J = 16.5 Hz, C-9), 16.24 (d, J = 10.5 Hz, C-10), 16.68 (C-7), 21.39 and 21.42 (C-7 and C-8), 28.44 (C-8), 29.60 (C-6), 68.44 (C-2), 79.09 (d, J = 251 Hz, C-5), 84.42 (C-3), 116.17 (C-11), 151.66 (C-1), 162.41 (d, J = 24.2 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -184.71 (ddd, J = 11.2, 15.3 and 17.4 Hz).

IR (neat): 3133, 3079, 2979, 2252, 2240, 1785, 1700, 1470, 1373, 1311, 1289, 1224, 1174, 1122, 1075, 954, 942, 758.

(1S,2S)-2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropanecarbonitrile (*(Z)*-118e). Purified by the column chromatography (10-30% of ethyl acetate in cyclohexane). Yield 36% (single isomer by ^{19}F NMR) as a colorless oil.



R_f 0.38 (30% EtOAc in petroleum ether).

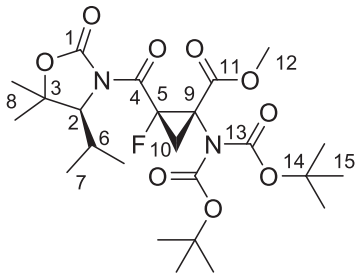
Anal. calcd C 58.20, H 6.39, N 10.44; found C 58.03, H 6.44, N 10.33.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.98 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.02 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.43 and 1.54 (CH_3-8), 1.85 (ddd, 8.0, 11.0 and 11.2 Hz, 1 H, CH_2-10), 2.07 (td, J = 8.0 and 19.8 Hz, 1 H, CH_2-10), 2.18 (m, 1 H, CH-6), 2.42 (ddd, J = 2.6, 8.0, 11.0 Hz, CH-9), 4.08 (d, J = 3.3 Hz, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 9.91 (d, J = 11.0 Hz, C-9), 16.80 (C-7), 19.19 (d, J = 11.0 Hz, C-10), 21.31 and 21.47 (C-7 and C-8),

28.86 (C-8), 29.33 (C-6), 67.41 (C-2), 77.18 (d, J = 248.7 Hz, C-5), 84.09 (C-3), 115.21 (d, J = 3.9 Hz, C-11), 151.28 (C-1), 165.08 (d, J = 24.8 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -189.88 (ddd, J = 2.6, 11.2 and 19.8 Hz).

IR (neat): 3115, 2977, 2253, 1784, 1704, 1466, 1362, 1326, 1276, 1173, 1120, 965, 915, 771.

(1S,2S)-methyl 1-(bis(tert-butoxycarbonyl)amino)-2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropanecarboxylate (*(Z)*-118f). Purified by the column chromatography (10-30% ethyl acetate in cyclohexane). Yield 56% (single isomer by ^{19}F NMR) as a colorless oil.



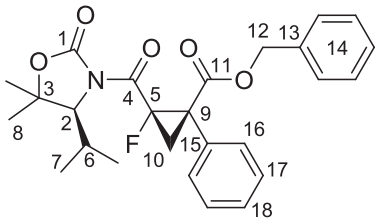
R_f 0.40 (30% EtOAc in petroleum ether).

HRMS calcd for $C_{24}H_{37}N_2O_9FNa$: 539.2381; found 539.2365.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.98 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.03 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.42 (s, 3 H, CH_3-8), 1.46 (s, 18 H, CH_3-15), 1.52 (s, 3 H, CH_3-8), 2.02 (dd, J = 9.7 and 24.6 Hz, 1 H, CH_2-10), 2.17 (m, 1 H, CH-6), 2.50 (dd, J = 9.7 and 17.4 Hz, 1 H, CH_2-10), 3.71 (s, 3 H, CH_3-12), 4.06 (d, J = 3.5 Hz, 1 H, CH-2). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.84 (C-7), 21.23 and 21.29 (C-7 and C-8), 27.78 (C-15), 28.49 (C-8), 29.25 (C-6), 29.30 (d, J = 8.8 Hz, C-10), 44.98 (d, J = 9.9 Hz, C-9), 52.79 (C-12), 66.90 (C-2), 82.75 (d, J = 243.2 Hz, C-5), 83.15 (br, C-14), 83.93 (C-3), 150.94 and 151.41 (br, C-13), 151.66 (C-1), 160.18 (d, J = 25.9 Hz, C-4), 169.09 (d, J = 2.8 Hz, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -181.24 (dd, J = 17.4 and 24.6 Hz).

IR (neat): 2981, 1789, 1756, 1713, 1458, 1436, 1369, 1275, 1154, 1100, 921, 853, 766.

(1S,2S)-benzyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)-1-phenylcyclopropanecarboxylate (*(E)*-118g). Purified by the column chromatography (3-15% ethyl acetate in cyclohexane). Yield 41% (*de* 88% by ^{19}F NMR) as a colorless oil.



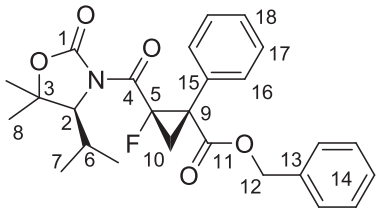
R_f 0.51 (30% EtOAc in petroleum ether).

HRMS calcd for $C_{26}H_{28}NO_5FNa$: 476.1849; found 476.1848.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.95 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.11 95 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.41 (s, 3 H, CH_3-8), 1.53 (s, 3 H, CH_3-8), 2.09 (dd, J = 7.5 and 20.2 Hz, 1 H, CH_2-10), 2.22 (m, 1 H, CH-6), 2.50 (7.5 and 12.0 Hz, CH_2-10), 4.03 (d, 2.5 Hz, CH-2), 5.02 (d, J = 12.9 Hz, CH_2-12), 5.12 (d, J = 12.9 Hz, CH_2-12), 7.12-7.39 (m, 8 H, CH-14, CH-17 and CH-18), 7.73 (d, J = 7.2 Hz, CH-16). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.62 (C-7), 21.31 and 21.41 (C-7 and C-8), 23.28 (d, J = 8.3 Hz, C-10), 28.48 (C-8), 29.78 (C-6), 41.26 (d, J = 12.7 Hz, C-9), 67.17 (C-12), 68.34 (C-2), 83.88 (d, J = 242.1 Hz, C-5), 83.98 (C-3), 127.24, 127.86, 128.10 and 128.32 (C-14, C-17 and C-18), 131.25 (C-16), 132.67 (d, J = 2.8 Hz, C-15), 135.48 (C-13), 152.16 (C-1), 163.90 (d, J = 26.4 Hz, C-4), 170.30 (d, J = 1.7 Hz, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -186.40 (dd, J = 12.0 and 20.2 Hz).

IR (neat): 2976, 1787, 1700, 1498, 1450, 1369, 1299, 1218, 1169, 1120, 1072, 953, 858, 734.

(1R,2S)-benzyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)-1-phenylcyclopropanecarboxylate (*(Z)*-118g). Purified by the column chromatography (3-15% ethyl acetate in cyclohexane). Yield 33% (single isomer by ^{19}F NMR) as a colorless oil.



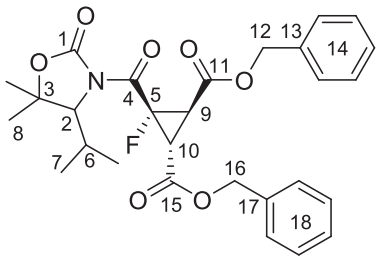
R_f 0.47 (30% EtOAc in petroleum ether).

Anal. calcd C 68.86, H 6.22, N 3.09; found C 68.86, H 6.60, N 3.12.

^{1}H NMR ($CDCl_3$, 300 MHz): 0.63 (d, J = 7.0 Hz, 3 H, CH_3-7), 0.78 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.41 (s, 3 H, CH_3-8), 1.50 (s, 3 H, CH_3-8), 2.00 (m, 1 H, CH-6), 2.48-2.61 (m, 2 H, CH_2-10), 3.74 (d, J = 2.6 Hz, CH-2), 5.17 (d, J = 12.8 Hz, CH_2-12), 5.27 (d, J = 12.8 Hz, CH_2-12), 7.25-7.30 (m, 8 H, CH-14, CH-17 and CH-18), 7.61 (d, J = 7.4 Hz, CH-16). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.72 (C-7), 19.31 (d, J = 11.0 Hz, C-10), 21.11 and 21.27 (C-7 and C-8), 28.26 (C-8), 29.58 (C-6), 41.50 (d, J = 10.5 Hz, C-9), 67.67 (C-12), 68.89 (C-2), 84.18 (C-3), 84.36 (d, J = 253.7 Hz, C-5), 127.46, 127.84, 128.13, 128.26 and 128.36 (C-14, C-17 and C-18), 130.85 and 130.86 (C-16), 132.68 (d, J = 1.1 Hz, C-15), 133.65 (C-13), 152.15 (C-1), 163.93 (d, J = 25.9 Hz, C-4), 166.65 (d, J = 2.8 Hz, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -188.18 (dd, J = 11.3 and 18.4 Hz).

IR (neat): 2975, 1788, 1730, 1700, 1496, 1452, 1366, 1274, 1120, 1070, 952, 929, 742.

Dibenzyl 3-fluoro-3-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropane-1,2-dicarboxylate (*(E)*-118h). Purified by the column chromatography (3-15% ethyl acetate in cyclohexane) to give a mixture of inseparable isomers (78:17:5). Yield 79% as a colorless oil.



(relative configuration is given)

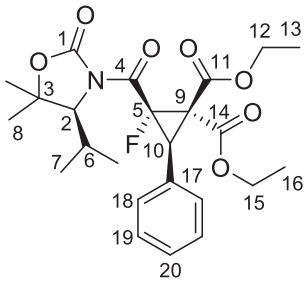
R_f 0.43 (30% EtOAc in petroleum ether).

HRMS calcd for $C_{28}H_{30}NO_7FNa$: 534.1904; found 534.1910.

^{1}H NMR ($CDCl_3$, 300 MHz):0.99 (d, J = 6.7 Hz, 3 H, CH_3-7), 1.04 (d, J = 7.0 Hz, 3 H, CH_3-7), 1.32 and 1.51 (2 s, 6 H, CH_3-8), 2.15 (m, 1 H, CH-6), 3.09 (dd, J = 5.3 and 8.1 Hz, 1 H, CH-10), 3.49 (dd, J = 8.1 and 19.5 Hz, 1 H, CH-9), 4.21 (d, J = 3.3 Hz, 1 H, CH-2), 5.10 (s, 2 H, CH_2-16), 5.15 (d, J = 12.3 Hz, 1 H, CH_2-12), 5.30 (d, J = 12.3 Hz, 1 H, CH_2-12), 7.35-7.38 (m, 10 H, CH-14 and CH-18). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.63 (C-7), 21.31 (C-8), 21.58 (C-7), 28.59 (C-8), 29.63 (C-6), 30.49 (d, J = 8.8 Hz, C-10), 33.18 (d, J = 12.1 Hz, C-9), 66.14 (C-2), 67.61 and 67.65 (C-12 and C-16), 81.90 (d, J = 250.4 Hz, C-5), 83.90 (C-3), 128.15-128.56 (C-14 and C-18), 134.76 and 134.99 (C-13 and C-17), 151.64 (C-1), 161.64 (d, J = 26.4 Hz, C-4), 164.88 (d, J = 2.2 Hz, C-11), 168.21 (d, J = 1.7 Hz, C-15).

IR (neat): 3064, 3035, 2975, 1786, 1726, 1708, 1499, 1455, 1364, 1317, 1276, 1168, 1136, 1120, 1073, 911, 737.

(2S,3R)-diethyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)-3-phenylcyclopropane-1,1-dicarboxylate (***(E)*-118i**) Purified by the column chromatography (3-15% ethyl acetate in cyclohexane). Yield 42% (single isomer by ^{19}F NMR) as a colorless solid (m.p. 139-140°C).



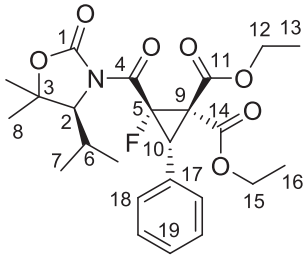
R_f 0.49 (30% EtOAc in petroleum ether).

HRMS calcd for $C_{24}H_{30}NO_7FNa$: 486.1904; found 486.1902.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.08 (m, 6 H, CH_3-7), 1.18 (t, J = 7.1 Hz, 3 H, CH_3-13), 1.36 (t, 7.1 Hz, 3 H, CH_3-16), 1.40 and 1.53 (2 s, 6 H, CH_3-8), 2.24 (m, 1 H, CH-6), 3.97-4.48 (m, 6 H, CH-2, CH-10, CH_2-12 and CH_2-15), 7.26-7.31 (m, 3 H, CH-19 and CH-20), 7.36-7.38 (m, 2 H, CH-18). **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.87 (C-13), 14.11 (C-16), 16.92 and 20.68 (C-7), 21.45 and 28.67 (C-8), 29.86 (C-6), 38.54 (d, J = 13.8 Hz, C-10), 46.64 (d, J = 12.7 Hz, C-9), 62.04 (C-12), 62.73 (C-15), 68.11 (C-2), 81.47 (d, J = 243.7 Hz, C-5), 83.58 (C-3), 126.60 (C-20), 127.86 and 129.52 (C-18 and C-19), 130.29 (d, J = 1.7 Hz, C-17), 151.92 (C-1), 162.33 (d, J = 27.5 Hz, C-4), 163.97 (d, J = 3.3 Hz, C-14), 164.46 (s, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -176.13 (d, J = 24.5 Hz).

IR (neat): 2989, 2942, 1789, 1709, 1367, 1305, 1245, 1173, 1066, 1004, 915, 779, 750.

(2S,3S)-diethyl 2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)-3-phenylcyclopropane-1,1-dicarboxylate (*(Z)*-118i). Purified by the column chromatography (3-15% ethyl acetate in cyclohexane). Yield 24% (single isomer by ^{19}F NMR) as a colorless oil.



R_f 0.40 (30% EtOAc in petroleum ether).

HRMS calcd for $C_{24}H_{30}NO_7FNa$: 486.1904; found 486.1910.

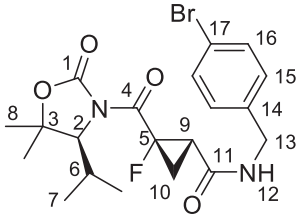
^{1}H NMR ($CDCl_3$, 300 MHz): 1.00-1.05 (m, 6 H, CH_3-7 and CH_3-16), 1.13 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.30 (t, J = 7.1 Hz, 3 H, CH_3-13), 1.46 and 1.54 (2 s, 6 H, CH_3-8), 2.22 (m, 1 H, CH-6), 3.61 (d, J = 10.5 Hz, 1 H, CH-10), 4.01-4.13 (m, 3 H, CH-2 and CH_2-15), 4.25 (q, J = 7.1 Hz, 2 H, CH_2-12), 7.27-7.39 (m, 5 H, CH-18 and C-19). **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.69 (C-16), 13.95 (C-13), 16.56 (C-7), 21.41 and 21.46 (C-7 and C-8), 28.62 (C-8), 29.84 (C-6), 35.40 (d, J = 8.3 Hz, C-10), 43.94 (d, J = 9.9 Hz, C-9), 61.49 (C-15), 62.63 (C-12), 68.06 (C-2), 84.01 (C-3), 84.30 (d, J = 250.9 Hz, C-5), 127.69 and 128.16 (C-19), 129.67 (d, J = 2.8 Hz, C-18), 130.54 (C-17), 151.82 (C-1), 161.94 (d, J = 1.1 Hz, C-14), 162.91 (d, J = 27.0 Hz, C-4), 167.12 (s, C-11). **^{19}F NMR** ($CDCl_3$, 282 MHz): -197.97 (d, J = 10.5 Hz).

IR (neat): 2981, 1793, 1722, 1703, 1365, 1272, 1243, 1174, 1121, 1073, 1012, 857, 752.

h. Transformations of cyclopropanes

(1S,2S)-N-(4-bromobenzyl)-2-fluoro-2-((S)-4-isopropyl-5,5-dimethyl-2-oxooxazolidine-3-carbonyl)cyclopropanecarboxamide (121)

Pd/C (10%, 3.0 mg) was added to a solution of (*Z*)-**118a** (43.3 mg, 0.115 mmol) in MeOH (2 mL). The mixture was stirred under hydrogen for 30 min, filtered and evaporated to give the corresponding carboxylic acid in quantitative yield (33 mg). The latter was dissolved in DMF (2 mL) under argon and cooled to 0 °C. HATU (0.125 mmol, 48 mg) was added, followed by DIPEA (0.173 mmol, 30 μL). After stirring for 10 min a solution of *p*-bromobenzylamine in DMF (0.138 mmol, 26 mg, 0.5 mL DMF) was added. The resulting mixture was stirred at *rt* overnight, poured into a mixture of EtOAc – water (20 mL, 1:1). Aqueous layer was extracted with EtOAc (10 mL). Combined extracts were washed with water (10 mL), 0.5 N HCl (10 mL), saturated soln of $NaHCO_3$ (10 mL), brine and dried over $MgSO_4$. At this point ^{19}F NMR analysis of the crude product indicated the presence of two isomers with a ratio of 92:8. After short-path column chromatography (10 to 30% of EtOAc in petroleum ether) and recrystallization from EtOAc – hexane pure **6** (only major isomer by ^{19}F NMR) was obtained as a colorless crystalline solid (m.p. 141-143 °C). Yield 42.2 mg (81%). X-ray quality crystals were obtained via slow evaporation of EtOAc – hexane solution of this material.



R_f 0.10 (30% EtOAc in petroleum ether).

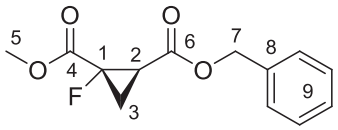
^{1}H NMR ($CDCl_3$, 300 MHz): 0.97 (d, J = 6.8 Hz, 3 H, CH_3-7), 1.09 (d, J = 7 Hz, 3 H, CH_3-7), 1.48 and 1.56 (2s, 3 H, CH_3-8), 1.83-1.98 (m, 2 H, CH_2-10), 2.24 (m, 1 H, CH-6), 2.35 (m, 1 H, CH-9), 3.90 (d, J = 3.1 Hz, CH-2), 4.45 (m, 2 H, CH2-13), 7.19 and 7.43 (2 d, J = 8.2 Hz, 2 H, CH-15 and CH-16). **^{13}C NMR** ($CDCl_3$, 75 MHz): 13.58 (d, J = 11.0 Hz, C-10), 17.07 (C-7), 21.22 (C-7), 21.56 (C-8), 28.39 (C-8), 28.95 (d, J = 11.6 Hz, C-9), 29.36 (C-6), 43.33 (C-13), 69.35 (C-2), 78.94 (d, J = 241.5 Hz, C-5), 84.93 (C-3), 121.11 (C-17), 129.32 and 131.62 (C-15 and C-16), 137.11 (C-14), 152.85 (C-1), 164.68 (d, J = 3.3 Hz, C-11), 166.23 (d, J = 25.9 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -196.04 (ddd, J = 4.1, 11.2 and 17.4 Hz).

IR (neat): 3327, 2991, 2978, 1783, 1702, 1658, 1550, 1488, 1398, 1362, 1328, 1277, 1175, 1121, 1071, 998, 779.

Yb(OTf)$_3$-catalysed methanolysis of *(E)*-118a.

(1S,2R)-2-benzyl 1-methyl 1-fluorocyclopropane-1,2-dicarboxylate ((*E*)-124a)

Solution of *trans*-**3a** (0.1 mmol, 37.7 mg) and Yb(OTf)$_3$ (0.02 mmol, 12 mg) in MeOH (1 mL) was stirred at 50 °C for 1.5 h, evaporated, then the residue was solubilized in a mixture of ethyl acetate and water. Organic layer was washed with brine, dried over $MgSO_4$ and evaporated. ^{19}F NMR analysis of the crude mixture showed no epimerization of cyclopropane. The mixture was purified by the column chromatography (20-30% of ether in petroleum ether) to give 23.5 mg (93%) of **4** as a colorless oil. Elution with ethyl acetate resulted in recuperation of the chiral auxiliary **1c** (14.9 mg, 95%, $[\alpha]_D^{26}$ **=** +15.6° (c 0.8, $CHCl_3$).



R$_f$ 0.50 (30% EtOAc in petroleum ether).

HRMS calcd for $C_{13}H_{14}O_4F$: 253.0876; found: 253.0877.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.76 (ddd, J = 7.2, 11.1 and 17.7 Hz, 1 H, CH_2-3), 2.02 (m,1 H, CH_2-3), 2.58 (ddd, J = 9.3, 11.1 and 18.5 Hz, 1 H, CH-2), 3.67 (s, 3 H, CH_3-5), 5.10 (d, J = 12.2 Hz, 1 H, CH_2-7), 5.17 (d, J = 12.2 Hz, 1 H, CH_2-7), 7.36 (m, 5 H, CH-9). **^{13}C NMR** ($CDCl_3$, 75 MHz): 17.82 (d, J = 9.9 Hz, C-3), 28.90 (d, J = 12.7 Hz, C-2), 52.73 (C-5), 67.25 (C-7), 76.80 (d, J = 237.2 Hz, C-1), 128.43, 128.52 and 128.55 (C-9), 135.31 (C-8), 166.51 (d, J = 1.1 Hz, C-6), 167.00 (d, J = 24.8 Hz, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -184.96 (ddd, J = 10.2, 17.7 and 18.5 Hz).

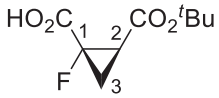
IR (neat):3035, 2957, 1746, 1499, 1440, 1387, 1347, 1255, 1156, 1041, 975, 903, 822, 781.

Basic cleavage of the chiral auxiliary in *(E)*-118b.

(1S,2R)-2-(tert-butoxycarbonyl)-1-fluorocyclopropanecarboxylic acid ((*E*)-125b).

Solution of LiOH (0.25 mmol, 6.0 mg, 3 mL H_2O) was added at rt to the solution of trans-**3b** (0.124 mmol, 42.5 mg) and H_2O_2 (0.74 mmol, 35% in water, 64 μL) in a mixture of THF and water (2.2 mL, 85:15). The mixture was stirred at rt for 20 min, cooled to 0°C and treated with a solution of Na_2SO_3 (0.87 mmol, 109 mg, 0.6 mL H_2O). The mixture was evaporated to one third of the initial volume, diluted with water to ca. 15 mL, extracted with EtOAc (3×10 mL). Organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. After short-path chromatography on silica gel (EtOAc) pure **1c** was obtained in 89% yield, $[\alpha]_D^{26}$ **=** +16.1° (c 0.5, $CHCl_3$).

Aqueous phase was acidified with 1 N HCl to pH 1, extracted with EtOAc (2×10 mL). Combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The residue was taken up in DCM (10 mL), filtered and evaporated to give pure acid (*E*)-**125b** (22.1 mg, 87%) as a colorless oil.



R_f 0.12 (EtOAc).

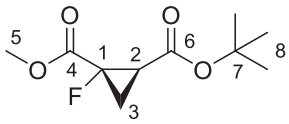
HRMS calcd for $C_9H_{13}O_4FNa$: 227.0696; found 227.0688.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.45 (s, 9 H, ^{t}Bu), 1.82 (ddd, J = 7.2, 11.5 and 18.4 Hz, 1 H, CH_2-3), 1.93 (ddd, J = 7.2, 9.4 and 17.1 Hz, 1 H, CH_2-3), 2.55 (ddd, J = 9.4, 11.1 and 18.4 Hz, 1 H, CH-2), 9.88 (br.s, 1 H, CO_2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): 19.02 (d, J = 9.9 Hz, C-3), 27,84 (^{t}Bu), 30.49 (d, J = 12.1 Hz, C-2), 76.16 (d, J = 235.5 Hz, C-1), 83.31 (^{t}Bu), 167.27 (COO^{t}Bu), 171.37 (d, J = 24.8 Hz, COOH). **^{19}F NMR** ($CDCl_3$, 282 MHz): -183.23 (br.s).

IR (neat): 2983, 1717, 1429, 1369, 1257, 1149, 1047, 1028, 909, 838, 804.

(1S,2R)-2-tert-butyl 1-methyl 1-fluorocyclopropane-1,2-dicarboxylate ((*E*)-124b).

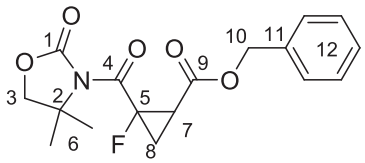
For determination of enantiomeric excess the acid (*E*)-**125b** was converted into the corresponding methyl ester (*E*)-**124b** according to the following procedure: (Trimethylsilyl)diazomethane (0.14 mmol, 0.07 mL of 2 M solution in hexane) was added dropwise to a solution of 5 (0.064 mmol, 13.0 mg) in toluene – MeOH (1 mL, 4:1) at 0 °C. After stirring for 3 h at rt the mixture was poured into EtOAc – water (30 mL, 1:1). Organic layer was washed with saturated solution of $NaHCO_3$ (10 mL), brine (10 mL) and dried over $MgSO_4$. After evaporation, the crude product was purified by column chromatography (10% EtOAc in pentane) to give 9.1 mg (65%) of (*E*)-**124b** as a colorless oil.



^{1}H NMR ($CDCl_3$, 300 MHz): 1.43 (s, 9 H, CH_3-9), 1.67 (ddd, J = 7.1, 11.0 and 17.5 Hz, 1 H, CH_2-3), 1.92 (ddd, J = 7.1, 9.4 and 10.1 Hz, 1 H, CH_2-3), 2.47 (ddd, J = 9.4, 11.1 and 19.4 Hz, 1 H, CH-2), 3.80 (s, 3 H, CH_3-5). **^{13}C NMR** ($CDCl_3$, 75 MHz): 17.58 (d, J = 9.9 Hz, C-3), 27.87 (C-8), 30.10 (d, J = 11.6 Hz, C-2), 52.70 (C-5), 76.99 (d, J = 236.0 Hz, C-1), 81.88 (C-7), 165.61 (d, J = 1.1 Hz, C-6), 167.26 (d, J = 24.2, C-4). **^{19}F NMR** ($CDCl_3$, 282 MHz): -184.96 (ddd, J = 10.1, 17.5 and 19.4 Hz).

i. Synthesis of racemic cyclopropanes

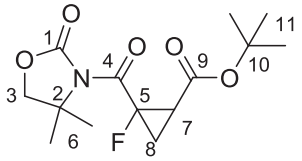
Benzyl 2-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-fluorocyclopropanecarboxylate (*(E)*-126a). Prepared from **117e** according to the general procedure of cyclopropanation. *Z/E* ratio of a crude product: 18:82 (by ^{19}F NMR). Pure *(E)*-**126a** was separated by the column chromatography (15-30% EtOAc in petroleum ether). Yield 54% as a colorless oil.



^{1}H NMR ($CDCl_3$, 300 MHz): 1.46 and 1.58 (2 s, 6 H, CH_3-6), 1.74 (ddd, J = 7.5, 11.1 and 19.9 Hz, 1 H, CH_2-8), 2.00 (ddd, J = 7.5, 8.6 and 11.5 Hz, 1 H, CH_2-8), 2.71 (ddd, J = 8.6, 11.1 and 19.0 Hz, 1 H, CH-7), 4.01 (m, 2 H, CH_2-3), 5.10 (br.s, 2 H, CH_2-10), 7.34 (m, 5 H, CH-12). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.97 (d, J = 9.4 Hz, C-8), 23.82 and 24.05 (C-6), 28.71 (d, J = 12.7 Hz, C-7), 60.54 (C-2), 67.01 (C-10), 75.43 (C-3), 81.34 (d, J = 238.2 Hz, C-5), 128.22 and 128.49 (C-12), 135.41 (C-11), 152.22 (C-1), 163.30 (d, J = 24.8 Hz, C-4), 169.52 (C-9). **^{19}F NMR** ($CDCl_3$, 282 MHz): -184.99 (ddd, J = 11.5, 19.0 and 19.9 Hz).

***rel*-(1S,2R)-2-benzyl 1-methyl 1-fluorocyclopropane-1,2-dicarboxylate (*Rac*-124a)** was prepared by the methanolysis of *(E)*-**126a**: $Yb(OTf)_3$ (0.02 mmol, 12 mg) was added to a solution of *(E)*-**126a** in MeOH (0.1 mmol, 33.5 mg, 1 mL MeOH). After stirring at *rt* for 1.5 h (complete conversion by TLC) the mixture was evaporated to dryness and the residue was subjected to the column chromatography (10% EtOAc in petroleum ether). Yield 19.8 mg (79%) as a colorless oil. Spectral data were found to be identical to optically pure **125a**.

***Tert*-butyl 2-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-fluorocyclopropanecarboxylate (*(E)*-126b)**. Prepared from **117e** according to the general procedure of cyclopropanation. *Z/E* ratio of a crude product: 18:82 (by ^{19}F NMR). *(E)*-**126b** was separated by the column chromatography (10-20% EtOAc in petroleum ether). Yield 42% as a colorless solid.



^{1}H NMR ($CDCl_3$, 300 MHz): 1.41 (s, 9 H, CH_3-11), 1.57 and 1.61 (2 s, 6 H, CH_3-6), 1.65 (ddd, J = 7.4, 11.0 and 17.9 Hz, 1 H, CH_2-8), 1.92 (ddd, J = 7.4, 8.8 and 11.4 Hz, 1H, CH_2-8), 2.56 (ddd, J = 8.8, 11.0 and

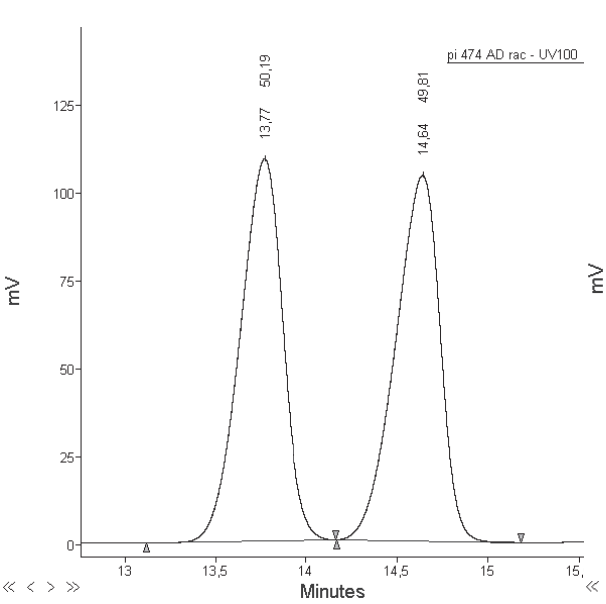
19.6 Hz, 1 H, CH-7), 4.06 (m, 2 H, CH_2-3). **^{13}C NMR** ($CDCl_3$, 75 MHz): 16.46 (d, J = 9.4 Hz, C-8), 23.81 and 24.22 (C-6), 27.80 (C-11), 29.87 (d, J = 12.1 Hz, C-7), 60.57 (C-2), 75.40 (C-3), 81.50 (d, J = 237.7 Hz, C-5), 81.71 (C-10), 152.22 (C-1), 163.55 (d, J = 25.3 Hz, C-4), 168.95 (C-9). **^{19}F NMR** ($CDCl_3$, 282 MHz): -185.92 (ddd, J = 11.4, 17.9 and 19.6 Hz).

***rel*-(1S,2R)-2-tert-butyl 1-methyl 1-fluorocyclopropane-1,2-dicarboxylate (*rac*-124b)** was prepared by the methanolysis of *(E)*-**126b**: $Yb(OTf)_3$ (0.02 mmol, 12 mg) was added to a solution of *(E)*-**126b** in MeOH (0.080 mmol, 24.0 mg, 1 mL MeOH). After stirring at *rt* for 1.5 h (complete conversion by TLC) the mixture was evaporated to dryness and the residue was subjected to the column chromatography (10% EtOAc in pentane). Yield 12.1 mg (69%) as a colorless oil. Spectral data were found to be identical to (*E*)-**124b** prepared by the esterification of (*E*)-**125b**.

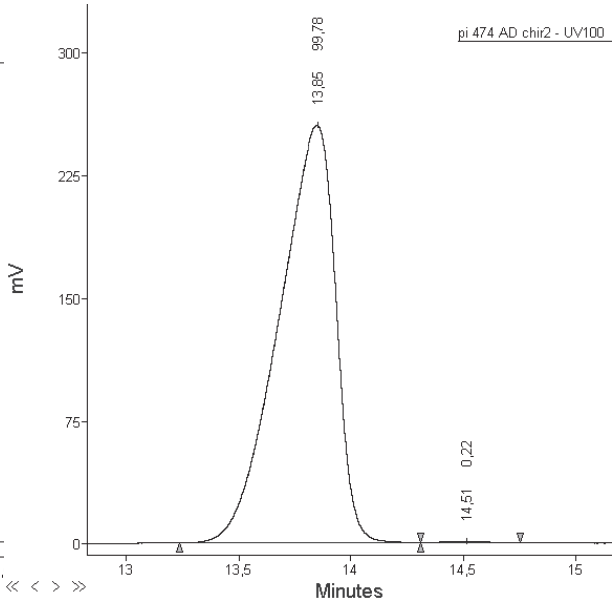
j. HPLC traces of (*E*)-124 and (*E*)-124b

Compound (*E*)-**124**: CHIRALPAK AD-H; heptane – isopropanol 98.6:1.4; flow rate 1.0 mL/min; UV detector: 230 nm.

Rac-**124:**

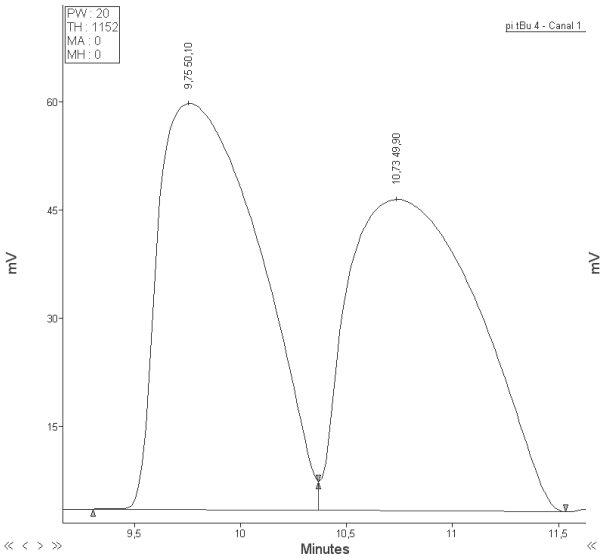


Chiral **124:** *ee* > 99%

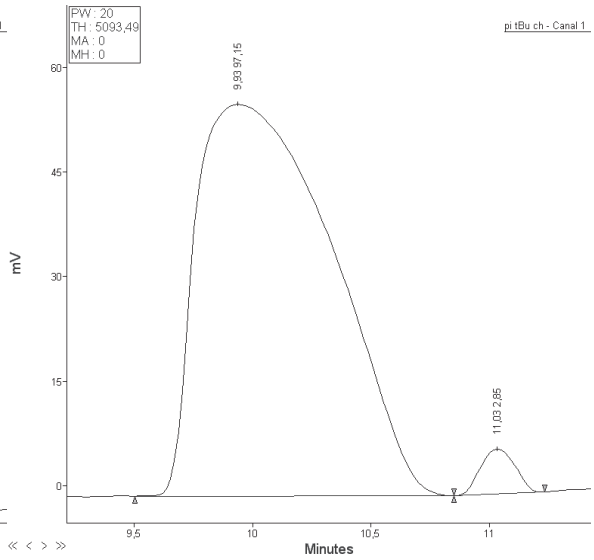


Compound (*E*)-**124b**: CHIRALPAK AD-H; heptane – isopropanol 99.7:0.3; flow rate 1.0 mL/min; UV detector: 210 nm.

rac-**124b**



Chiral **124b**: *ee* 94%

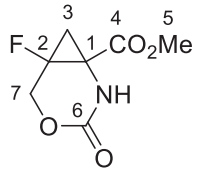


k. Synthesis of (E)-1-amino-2-fluoro-2-phosphonomethylcyclopronane-carboxylic acid

Starting (*E*)-**128** was prepared according to the method developed earlier in our laboratory.[33]

Methyl 6-fluoro-3-oxo-4-oxa-2-azabicyclo[4.1.0]heptane-1-carboxylate (149)

NEt_3 (0.3 mmol, 52 µL) was added to a stirred solution of (*E*)-**128** (0.2 mmol, 69 mg) in DCM (1 mL) at -80°C, followed by Tf_2O (0.2 mmol, 34 µL). The mixture was allowed to warm up slowly to rt. A mixture of EtOAc (10 mL) and water (10 mL) was added with stirring. The organic layer was separated, the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. Column chromatography on silica afforded 20 mg (52%) of the pure carbamate **149**.



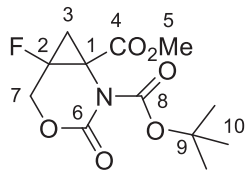
^{1}H NMR ($CDCl_3$, 300 MHz): 1.74 (dd, J = 8.0 and 8.5 Hz, 1 H, CH_2- cyclopropane), 2.56 (ddd, J = 1.0, 8.0 and 18.4 Hz, 1 H, CH_2-cyclopropane), 3.83 (s, 3 H, Me), 4.37 (dd, J = 12.6 and 16.8 Hz, 1 H, CH_2O), 4.82 (dd, J = 12.6 and 13.4 Hz, 1 H, CH_2O), 6.38 (br.s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): 26.87 (d, J = 11.6 Hz, C-3), 41.93 (d, J = 10.5 Hz, C-1), 53.46 (s, C-5), 69.10 (d, J = 28.1 Hz, C-7), 77.68 (d, J = 249.2 Hz, C-2), 153.43 (s, C-6), 166.12 (d, J = 2.8 Hz, C-4).

^{19}F NMR ($CDCl_3$, 282 MHz): -195.66 (m).

Methyl 6-fluoro-3-oxo-4-oxa-2-(*tert*-butoxycarbonyl)-2-azabicyclo[4.1.0]heptane-1-carboxylate (147).

NEt*i*Pr_2 (0.6 mmol, 105 µL) was added to a stirred solution of (*E*)-**128** (0.2 mmol, 69 mg) in DCM (2 mL) at -95°C, followed by Tf_2O (0.2 mmol, 34 µL). The mixture was allowed to warm up slowly to rt. A mixture of DCM (5 mL) and water (2 mL) was added with stirring. The organic phase was separated, filtered through a pad of $MgSO_4$ and evaporated. Column chromatography on silica afforded 35 mg (61%) of the pure N-Boc-carbamate **147**.



HRMS (ESI+) calcd for $C_{12}H_{17}NO_6F$ ($[M+H]^+$): 290.1040, found 290.1028; calcd for $C_{12}H_{16}NO_6FK$ ($[M+K]^+$): 328.0599, found 328.0602.

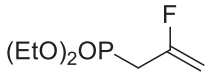
^{1}H NMR ($CDCl_3$, 300 MHz): 1.49 (s, 9 H, Boc), 1.70 (dd, J = 8.0 and 8.9 Hz, 1 H, CH_2-cyclopropane), 2.83 (dd, J = 8.0 and 16.6 Hz, 1 H, CH_2-cyclopropane), 3.81 (s, 3 H, CO_2Me), 4.19 (dd, J = 13.8 and 29.6 Hz, 1 H, CH_2O), 4.90 (dd, J = 13.9 and 19.9 Hz, 1 H, CH_2O).

^{13}C NMR ($CDCl_3$, 75 MHz): 27.68 (d, J = 12.1 Hz, C-3), 27.81 (s, C-10), 45.43 (d, J = 11.0 Hz, C-1), 53.41 (s, C-5), 71.92 (d, J = 25.3 Hz, C-7), 81.62 (d, J = 248.2 Hz, C-2), 84.89 (s, C-9), 149.50 and 149.80 (s, C-6 and C-8), 164.80 (d, J = 3.3 Hz, C-4).

^{19}F NMR ($CDCl_3$, 282 MHz): -190.71 (m).

Diethyl 2-fluoroallylphosphonate (153)

Microwave tube equipped with a stirring bar was charged with 3-chloro-2-propene (10 mmol, 0.90 mL) and triethyl phosphite (12 mmol, 2.1 mL), sealed with a septum and purged with nitrogen. The mixture was stirred at 150°C for 3 days, then cooled to rt and directly deposed onto the silica column (attempt to purify the product via distillation in vacuo was not successful: phosphorus-containing by-product was detected). Elution with petroleum ether – EtOAc (1:2 to 0:1) afforded pure phosphonate **153** as a colorless liquid. Yield 1.51 g (77%).



HRMS (ESI+) calcd for $C_7H_{14}NO_3FPNa$ ($[M+Na]^+$): 219.0562, found 219.0560.

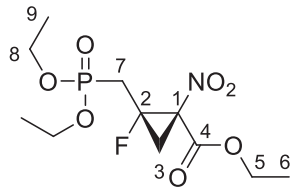
^{1}H NMR ($CDCl_3$, 300 MHz): 1.32 (t, J = 7.1 Hz, 6 H, CH_3), 2.77 (dd, J = 18.1 and 21.4 Hz, 2 H, CH_2P), 4.14 (m, 4 H, CH_2O), 4.48 (ddd, J = 3.4, 4.1 and 48.3 Hz, 1 H, vinyl), 4.72 (ddd, J = 3.4, 3.6 and 16.5 Hz, 1 H, vinyl).

^{13}C NMR (CD_3CN, 75 MHz): 16.62 and 16.70 (2s, CH_3), 30.81 (dd, J = 30.3 and 139.8 Hz, CH_2P), 63.11 (d, J = 6.1 Hz, CH_2O), 94.19 (dd, J = 9.9 and 18.7 Hz, CH_2-vinyl), 159.60 (dd, J = 12.1 and 255.3 Hz, CF).

^{19}F NMR ($CDCl_3$, 282 MHz): -90.1 (m). **^{31}P NMR** ($CDCl_3$, 121 MHz): 22.3 (s).

***Rel*-(1*S*,2*S*)-ethyl 2-((ethoxy(methoxymethyl)phosphoryl)methyl)-2-fluoro-1-nitrocyclopropane-carboxylate (157)**

Oven-dried tube equipped with a stirring bar was charged with $Rh_2(OCO^tBu)_4 \cdot 2H_2O$ (0.03 mmol, 20 mg) and **153** (4.37 mmol, 856 mg), sealed with a septum and filled with nitrogen. DCM (2 mL) was added. Solution of **154a** (12.6 mmol, 2.00 g) in DCM (1 mL) was added dropwise at rt maintaining the moderate gas evolution (over 10-15 min). The resulting burgundy mixture was stirred overnight (very slow gas evolution continues after the addition of diazo compound is finished). The mixture was poured into EtOAc (30 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (10 mL). Combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Column chromatography on silica (eluent: PE-EtOAc 1:1 to 0:1) afforded the desired cyclopropane 157 as a colorless oil. Yield 1.11 g (78%).



HRMS (ESI+) calcd for $C_{11}H_{19}NO_7FPNa$ ($[M+Na]^+$): 350.0781, found 350.0770.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.33 (t, 7.1 Hz, 9 H, CH_3-6 and CH_3-9), 2.27 (ddd, J = 16.1, 20.2 and 30.5 Hz, 1 H, CH_2-7), 2.36 (dd, J = 9.5 and 14.0 Hz, 1 H, CH_2-3), 2.59 (ddd, J = 1.4, 9.6 and 20.0 Hz, 1 H, CH_2-3), 2.79 (ddd, J = 1.5, 16.1 and 33.0 Hz, 1 H, CH_2-7), 4.15 (m, 4 H, CH_2-8), 4.35 (m, 2H, CH_2-5).

^{13}C NMR ($CDCl_3$, 75 MHz): 13.85 (s, C-6), 16.30 (m, C-9), 25.80 (dd, J_{CP} = 5.0 Hz, J_{CF} = 11.0, C-3), 27.95 (dd, J_{CF} = 23.1 Hz, J_{CP} = 143.2 Hz, C-7), 62.52 (m, C-8), 63.59 (s, C-5), 71.72 (m, C-1), 79.55 (dd, J_{CP} = 7.7 Hz, J_{CF} = 239.9 Hz, C-2), 160.30 (d, J_{CF} = 1.1 Hz, C-4).

^{19}F NMR ($CDCl_3$, 282 MHz): -169.45 (m, J_{FP} = 3.0 Hz).

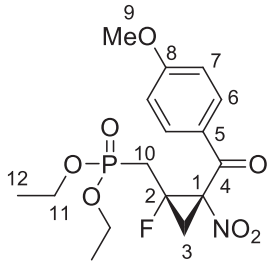
^{31}P NMR ($CDCl_3$, 121 MHz): 21.94 (d, J_{PF} = 3.0 Hz).

Diethyl (1-fluoro-2-(4-methoxybenzoyl)-2-nitrocyclopropyl)methylphosphonate (158)

Oven-dried tube equipped with a stirring bar was charged with $Rh_2(OCO^tBu)_4 \cdot 2H_2O$ (0.022 mmol, 14.5 mg) and **153** (0.5 mmol, 98 mg), sealed with a septum and filled with nitrogen. DCM (1 mL) was added. Solution of **154d** (1.5 mmol, 332 mg) in DCM (1 mL) was added dropwise at -20°C over a period of 50 min. The resulting brown mixture was allowed to warm slowly (over 2 h) to *ca* 0°C. ^{19}F NMR analysis indicated 96% conversion at this stage. The mixture was poured into EtOAc (30 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (10 mL). Combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Individual isomers were obtained via column chromatography on silica gel (eluent: PE-EtOAc 1:3 to 0:1).

HRMS (ESI+) calcd for $C_{16}H_{21}NO_7FPNa$ ($[M+Na]^+$): 412.0937, found 412.0932.

Major isomer: 99 mg (51%), colorless oil.



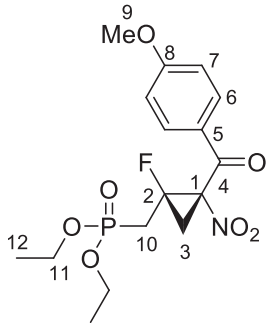
^{1}H NMR ($CDCl_3$, 300 MHz): 1.32 (t, J = 7.0 Hz, 6 H, CH_3-12), 2.15 (dd, J = 9.7 and 13.8 Hz, 1 H, CH_2-3, F-*trans*), 2.29 (m, 1 H, CH_2-10), 2.90 (m, 1 H, CH_2-10), 3.10 (dd, J = 9.7 and 20.9 Hz, 1 H, CH_2-3, F-*cis*), 3.88 (s, 3 H, CH_3-9), 4.14 (m, 4 H, CH_2-11), 6.95 (d, J = 8.9 Hz, 2 H, CH-7), 7.85 (d, J = 8.9 Hz, 2 H, CH-7).

^{13}C NMR ($CDCl_3$, 75 MHz): 16.27-16.37 (2d, C-12), 24.86 (dd, J = 3.3 and 11.6 Hz, C-3), 29.52 (dd, J = 23.1 and 141.4 Hz, C-10), 55.64 (C-9), 62.29-62.51 (2d, C-11), 72.45 (dd, J = 10.5 and 13.8 Hz, C-1), 78.72 (dd, J = 7.7 and 241.0 Hz, C-2), 114.5 (s, C-7), 127.10 (d, J = 1.1 Hz, C-5), 131.22 (s, C-6), 164.79 (C-8), 184.44 (br.s, C-4).

^{19}F NMR ($CDCl_3$, 282 MHz): -173.7 (m, J_{F-P} = 2 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): 22.63.

Minor isomer: 15 mg (8%), colorless oil.



^{1}H NMR ($CDCl_3$, 300 MHz): 1.33 (m, 6 H, CH_3-12), 2.47 (dd, J = 9.4 and 15.2 Hz, 1 H, CH_2-3, F-*trans*), 2.64 (dd, J = 9.4 and 20.8 Hz, 1 H, CH_2-3, F-*cis*), 2.90 (m, 2 H, CH_2-10), 3.89 (s, 3 H, CH_3-9), 4.19 (m, 4 H, CH_2-11), 6.97 (d, J = 9.0 Hz, 2 H, CH-7), 7.98 (d, J = 9.0 Hz, 2 H, CH-6).

^{13}C NMR ($CDCl_3$, 75 MHz): 16.29 (d, J = 2.8 Hz, C-12), 16.37 (d, J = 2.8 Hz, C-12), 25.30 (dd, J = 6.1 and 9.9 Hz, C-3), 26.98 (dd, J = 22.6 and 143.1 Hz, C-10), 55.60 (s, C-9), 62.55 (2d, C-11), 72.85 (dd, J = 10.5 and 17.6 Hz, C-1), 81.11 (dd, J = 8.3 and 233.8 Hz, C-2), 114.15 (s, C-7), 128.03 (s, C-5), 131.88 (s, C-6), 164.57 (s, C-8), 181.96 (d, J = 1.1 Hz, C-4).

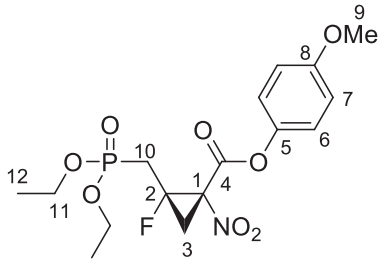
^{19}F NMR ($CDCl_3$, 282 MHz): -163.8 (m, J_{F-P} = 4 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): 22.39.

4-Methoxyphenyl 2-((diethoxyphosphoryl)methyl)-2-fluoro-1-nitrocyclopropanecarboxylate (160).

(Modified from Charette.[192] Phosphate buffered saline was used according to the reported procedure, however, NaCl-free buffer solution is expected to ensure the homogeneity of the reaction mixture)

mCPBA (*ca* 0.5 g) was washed with PBS several times, then with water and dried in vacuo. **158**$_{major}$ (0.085 mmol, 33 mg) was dissolved in DCM (0.5 mL). iPrOH (0.5 mL), then PBS (pH 7.4, 0.1 mL) were added (small drops of aqueous phase are not dissolved). Solid dried mCPBA (0.42 mmol, 73 mg) was added to the solution. The resulting mixture was stirred at 50°C for 8 h (no progress after first 5 h by TLC). The mixture was poured into EtOAc (10 mL)/$Na_2S_2O_3$ (semisaturated, 10 mL). Organic phase was washed with $NaHCO_3$ (sat., 5 mL), brine, dried over Na_2SO_4 and evaporated. 77% conversion was observed by ^{19}F NMR at this stage. Column chromatography on silica gel (PE-EtOAc 1:1 to 1:3) afforded 14 mg (41%) of **160** as a colorless oil.



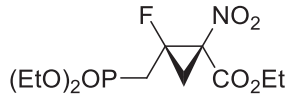
^{1}H NMR ($CDCl_3$, 300 MHz): 1.34 (m, 6 H, CH-12), 2.21 (dd, J = 9.6 ad 16.7 Hz, 1 H, CH_2-3), 2.60-2.93 (m, 3 H, CH_2-3 and CH_2-10), 3.80 (s, 3 H, CH_3-9), 4.17 (m, 4 H, CH_2-11), 6.89 (d, J = 9.1 Hz, 2 H, CH-7), 7.10 (d, J = 9.1 Hz, 2 H, CH-6).

^{19}F NMR ($CDCl_3$, 282 MHz): -168.17 (m, J_{F-P} = 4 Hz).

^{31}P NMR ($CDCl_3$, 121 MHz): 22.05.

Preparation of *iso*-157 via transesterification of 160.

Solution of **160** (0.018 mmol, 7.1 mg) in absolute ethanol (1 mL) was added under nitrogen to the ground K_2CO_3 (3 mg). The resulting suspension was stirred for 10 min (complete conversion by TLC). The mixture was diluted with EtOAc (10 mL) and 5% citric acid (10 mL). Organic phase was separated, washed with brine, dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography to give 4.9 mg (85%) of the ethyl ester *iso*-**157** which was clearly different from the authentic **157** according to ^{1}H NMR.



HRMS (ESI+) calcd for $C_{11}H_{19}NO_7FPNa$ ($[M+Na]^+$): 350.0781, found 350.0784.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (m, 9 H, Et), 2.10 (dd, J = 10.5 and 17.8 Hz, 1 H, CH_2-cyclo), 2.56-2.90 (m, 3 H, CH_2P, CH_2-cyclo), 4.17 (m, 4 H, POEt), 4.32 (m, 2 H, CO_2Et).

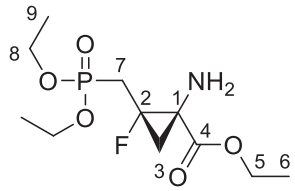
^{19}F NMR ($CDCl_3$, 282 MHz): -169.19.

^{31}P NMR ($CDCl_3$, 121 MHz): 21.77.

Ethyl 1-amino-2-((diethoxyphosphoryl)methyl)-2-fluorocyclopropanecarboxylate (161)

(According to Charette's method[193])

In powder (30 mmol, 3.5 g) was added at once to the stirred solution of 157 (1.53 mmol, 500 mg) in THF (7 mL) and 2N HCl (25 mL) at rt. After stirring for 40 min (complete by TLC after 30 min) the mixture was neutralized with conc. $NaHCO_3$, then solid NaCl was added to saturation. The mixture was extracted with EtOAc (3×30 mL). Combined extracts were dried over Na_2SO_4, filtered and evaporated. The whole procedure was repeated once more and the crude products of these two experiments were combined. Pure amine **161** was obtained via column chromatography on silica gel (EtOAc-EtOH 5% to 15%). Yield 497 mg (55%).



HRMS (ESI+) calcd for $C_{11}H_{22}NO_5FP$ ($[M+H]^+$): 298.1220, found 298.1217.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.20 (dd, J = 7.4 and 12.0 Hz, 1 H, CH_2-3, F-*trans*), 1.27 (t, J = 7.1 Hz, 3 H, CH_3-6), 1.33 (t, J = 7.1 Hz, 6 H, CH_3-9), 2.20 (dd, J = 7.4 and 21.9 Hz, 1 H, CH_2-3, F-*cis*), 2.25 (br.s, NH), 2.42-2.80 (m, 2 H, CH_2-7), 4.08-4.24 (m, 6 H, CH_2-5 and CH_2-8).

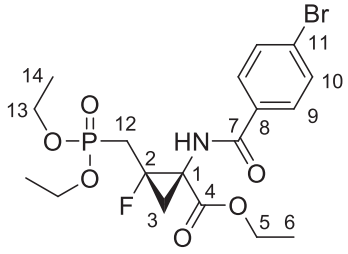
^{13}C NMR ($CDCl_3$, 75 MHz): 14.10 (s, C-6), 16.30 (2d, C-9), 24.20 (dd, J = 8.8 and 11.0 Hz, C-3), 27.77 (dd, J = 22.6 and 143.1 Hz, C-7), 43.02 (dd, J = 8.8 and 11.6 Hz, C-1), 61.57 (s, C-5), 61.92 (d, 6.1 Hz, C-8), 81.70 (dd, J = 8.8 and 230.0 Hz, C-2), 170.96 (d, J = 2.8 Hz, C-4).

^{19}F NMR ($CDCl_3$, 282 MHz): -180.73 (m).

^{31}P NMR ($CDCl_3$, 121 MHz): 26.27 (J_{P-F} = 4 Hz).

Ethyl 1-(4-bromobenzamido)-2-((diethoxyphosphoryl)methyl)-2-fluorocyclopropanecarboxylate (162)

Solution of 4-bromobenzoyl chloride (0.15 mmol, 33 mg) in DCM (0.8 mL) was added at -50°C to the stirred solution of **161** (0.1 mmol, 30 mg) and NEt*i*Pr$_2$ (0.2 mmol, 35 mg) in DCM (1.0 mL). The cooling bath was removed and the mixture was stirred at rt overnight. Saturated solution of $NaHCO_3$ (5 mL) was added. The mixture was extracted with EtOAc (2×10 mL). The extracts were washed with brine, dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, PE-EtOAc 1:1 to 0:1) afforded 47 mg (98%) of the pure amide **162** as a colorless oil.



HRMS (ESI+) calcd for $C_{18}H_{25}NO_6FPBr$ ($[M+H]^+$): 480.0587, found 480.0573.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.21 (t, J = 7.1 Hz, 3 H, CH_3-6), 1.35 (m, 6 H, CH_3-14), 1.40 (dd, J = 9.0 Hz, 12.0 Hz, 1 H, CH_2-3), 1.94-2.18 (m, 1 H, CH_2-12), 2.74 (ddd, J = 5.3, 8.1 and 21.1 Hz, 1 H, CH_2-3, F-*cis*), 2.89-3.03 (m, 1 H, CH_2-12), 4.10-4.25 (m, 6 H, CH_2-5 and CH_2-13), 7.56 (d, J = 8.6 Hz, 2 H, CH-10), 7.81 (d, J = 8.6 Hz, 2 H, CH-9).

^{13}C NMR ($CDCl_3$, 75 MHz): 14.11 (C-6), 16.29 (d, J = 6.1 Hz, C-14), 26.57 (dd, J = 11.0 and 15.4 Hz, C-3), 30.59 (dd, J = 23.1 and 142.5 Hz, C-12), 42.11 (dd, J = 5.5 and 12.7 Hz, C-1), 61.98 (C-5), 62.27 (d, J = 7.2 Hz, C-13), 63.44 (dd, J = 2.2 and 6.6 Hz, C-13), 79.63 (dd, J = 9.4 and 232.2 Hz, C-2), 126.67 (C-11), 129.01 (C-10), 131.73 (C-9), 132.05 (C-8), 166.78-166.87 (m, C-4 and C-7).

^{19}F NMR ($CDCl_3$, 282 MHz): -181.29 (m).

^{31}P NMR ($CDCl_3$, 121 MHz): 25.97 (J_{P-F} = 4 Hz).

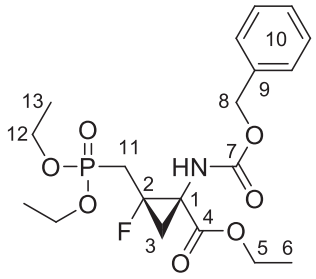
Ethyl 1-(benzyloxycarbonylamino)-2-((diethoxyphosphoryl)methyl)-2-fluorocyclopropanecarboxylate (163)

Solution of **161** (1.54 mmol, 457 mg) in THF (5 mL) was added to dry Na_2CO_3 (3.08 mmol, 326 mg) under nitrogen. CbzCl (1.85 mmol, 0.26 mL) was added dropwise and the resulting mixture was stirred at rt for 4 h. 5% citric acid (10 mL) was added. The resulting solution was extracted with EtOAc (3×20 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography (silica gel, PE-EtOAc 1:1 to 0:1) to give **163** (570 mg, 86%) as a colorless oil.

Individual enantiomers of **163** were obtained via preparative chiral SCF chromatography.

(+)-**163**: $[\alpha]_D^{22}$ = +31.0° (c = 0.98)

(−)-**163**: $[\alpha]_D^{22}$ = −30.9° (c = 0.87)



HRMS (ESI+) calcd for $C_{19}H_{28}NO_7FP$ ([M+H]$^+$): 432.1587, found 432.1588.

^{1}H NMR ($CDCl_3$, 300 MHz): 1.19 (t, J = 7.1 Hz, 3 H, CH_3-6), 1.32 (m, 4 H, CH_3-13), 1.37 (m, 1 H, CH_2-3), 2.02-2.25 (m, 1 H, CH_2-12), 2.56 (ddd, J = 4.4, 7.5 and 21.1 Hz, 1 H, CH_2-3, F-*cis*), 2.68-2.83 (m, 1 H, CH_2-11), 4.07-4.19 (m, 6 H, CH_2-5 and CH_2-12), 5.03-5.15 (m, 2 H, CH_2-8), 7.03 (br.s., NH), 7.33 (m, 5 H, CH-10).

^{13}C NMR ($CDCl_3$, 75 MHz): 13.99 (C-6), 16.17 and 16.25 (C-13), 25.96 (br.m, C-3), 29.72 (dd, J = 23.1 and 143.1 Hz, C-11), 42.55 (br.m, C-1), 61.87 (C-5), 62.10 (d, J = 6.6 Hz, C-12), 62.74 (d, J = 6.1 Hz, C-12), 66.82 (C-8), 80.23 (br.d, J = 234 Hz, C-2), 127.96, 128.00 and 128.34 (C-10), 136.11 (C-9), 156.25 (C-7), 167.43 (C-4).

^{19}F NMR ($CDCl_3$, 282 MHz): -181.5 (br.s.).

^{31}P NMR ($CDCl_3$, 121 MHz): 25.28.

1-amino-2-fluoro-2-(phosphonomethyl)cyclopropanecarboxylic acid hydrochloride ((*E*)-26)

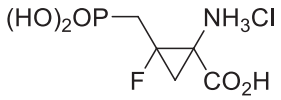
The following method was applied to both enantiomers of **163**.

Cyclopropane **163** (0.464 mmol, 200 mg) was dissolved in 2 mL of AcOH. 2 mL of concentrated aqueous HCl was added. The mixture was stirred at 80°C for 115 hours. The resulting yellow solution was evaporated to dryness, dissolved in 1N HCl (20 mL), washed with ether (10 mL), then DCM (10 mL). Evaporation of the aqueous phase gave the colorless solid that was solubilized in a minimum amount of water and subjected to the ion-exchange chromatography on Dowex 50WX8 (washed excessively with 1N HCl, then H_2O before use). The resin was washed with H_2O (100 mL), then with 1N HCl. Fractions containing the desired product were concentrated giving the yellowish solid that was further lyophilized overnight. Yield: (+)-**26**, 77.9 mg (67%); (−)-**26**, 83.3 mg (72%).

(+)-**26**: $[\alpha]_D^{22}$ = +39.8° (c = 0.63)

(−)-**26**: $[\alpha]_D^{22}$ = −39.0° (c = 0.70)

HRMS (ESI+) calcd for $C_5H_{10}NO_5FP$ ([M+H]$^+$): 214.0281, found 214.0274.



^{1}H NMR (D_2O, 300 MHz): 1.79 (dd, J = 9.6 and 12.2 Hz, 1 H, CH_2-cyclo), 2.28-2.55 (m, 3 H, CH_2-cyclo, CH_2P).

^{13}C NMR (D_2O, 75 MHz, CH_3CN as a reference): 23.05 (br. s, CH_2-cyclo), 29.74 (dd, J = 23.1 and 133.7 Hz, CH_2P), 41.30 (dd, J = 8.8 and 14.3 Hz, C-NH_2), 78.99 (dd, J = 7.7 and 234.9 Hz, CF), 168.23 (s, CO_2H).

^{19}F NMR (D_2O, 282 MHz): -177.06 (m, J_{FP} = 5 Hz).

^{31}P NMR (D_2O, 121 MHz): 17.32.

l. Studies on the enantioselective cyclopropanation

Determination of enantiomeric excess

Crude **167**, **169** or **171** were purified via column chromatography on silica gel (PE-EtOAc 10-20%) before subjecting to chiral chromatography. **167** and **169** were analysed via chiral GC (Supelco β-DEX 120, 130°C).

General procedure for enantioselective cyclopropanation of 152

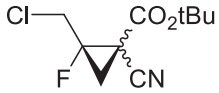
Relative quantities of reagents are and other conditions are given in Tables 9-13.

Oven-dried tube equipped with a stirring bar was charged with $Rh_2(IBAZ)_4$, sealed with a septum and filled with nitrogen. **152** (0.2 mmol, 18 μL) was introduced, followed by DCM. Solution of **166** in DCM was added dropwise at the given temperature. The resulting burgundy mixture was allowed to warm slowly to rt. Internal standard ($PhCF_3$) was added and the mixture was analysed by ^{19}F NMR. The mixture was either evaporated (in the case of volatile solvents) or partitioned in EtOAc-water. In the latter case, the organic layer was washed with brine, dried over $MgSO_4$ and evaporated. Pure cyclopropane **167** was obtained after column chromatography on silica gel (PE-EtOAc 10 to 20%) as an inseparable mixture of isomers and was subjected to chiral GC analysis.

***tert*-butyl 2-(chloromethyl)-1-cyano-2-fluorocyclopropanecarboxylate (167)**

Oven-dried tube equipped with a stirring bar was charged with $Rh_2(OCO^tBu)_4 \cdot 2H_2O$ (0.005 mmol, 3 mg), sealed with a septum and filled with nitrogen. **152** (1.0 mmol, 90 μL) was introduced, followed by DCM (0.5 mL). Solution of **166** (0.5 mmol, 70 mg) in DCM (0.5 mL) was added dropwise at -20°C. The resulting grey mixture was allowed to warm to rt overnight. The mixture was poured into EtOAc/H_2O,

the organic layer was washed with brine and evaporated. Pure cyclopropane **167** was obtained via column chromatography (PE-EtOAc 10 to 20%) as an inseparable mixture of isomers (56:44). Yield 40 mg (34%).



HRMS (ESI+) calcd for $C_{10}H_{14}NO_2FCl$ ($[M+H]^+$): 234.0697, found 234.0697.

Major isomer (presumably trans-CN/F):

^{1}H NMR ($CDCl_3$, 300 MHz): 1.53 (s, 9 H, tBu), 1.84 (dd, J = 7.9 and 11.5 Hz, 1 H, CH_2-cyclo, F-*trans*), 2.58 (dd, J = 7.9 and 18.1 Hz, 1 H, CH_2-cyclo, F-*cis*), 4.01 (m, 2 H, CH_2Cl).

^{13}C NMR ($CDCl_3$, 75 MHz): 24.50 (d, J = 10.5 Hz, CH_2-cyclo), 26.78 (d, J = 15.4 Hz, C(CN)CO_2tBu), 27.75 (CH_3), 44.57 (d, J = 23.1 Hz, CCl), 82.53 (d, J = 247.6 Hz, CF), 85.41 (tBu_{quat}), 115.28 (d, J = 2 Hz, CN), 159.76 (CO_2tBu).

^{19}F NMR ($CDCl_3$, 282 MHz): -187.99.

Minor isomer (presumably cis-CN/F):

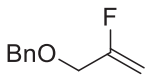
^{1}H NMR ($CDCl_3$, 300 MHz): 1.54 (s, 9 H, tBu), 2.14 (dd, J = 7.7 and 14.4 Hz, 1 H, CH_2-cyclo, F-*trans*), 2.24 (dd, J = 7.7 and 18.4 Hz, 1 H, CH_2-cyclo, F-*cis*), 3.92 (dd, J = 13.1 and 30.5 Hz, 1 H, CH_2Cl), 4.17 (dd, J = 13.1 and 14.9 Hz, 1 H, CH_2Cl).

^{13}C NMR ($CDCl_3$, 75 MHz): 25.65 (d, J = 11.0 Hz, C(CN)CO_2tBu), 26.92 (d, J = 9.4 Hz, CH_2-cyclo), 27.67 (CH_3), 41.47 (d, J = 22.0 Hz, CCl), 83.68 (d, J = 241.5 Hz, CF), 85.71 (tBu_{quat}), 114.07 (d, J = 5 Hz, CN), 162.66 (CO_2tBu)

^{19}F NMR ($CDCl_3$, 282 MHz): -171.78.

((2-fluoroallyloxy)methyl)benzene (169)

NaH (4 mmol, 101 mg, 95%) was added to a stirred solution of BnOH (4 mmol, 0.42 mL) in DMF (5 mL) at 0°C. After stirring for 30 min the mixture was cooled to -20°C. Solution of 3-chloro-2-fluoropropene (3 mmol, 284 mg) in DMF (1 mL) was added slowly. The mixture was allowed to warm to rt and stirred for 2 h. Water (10 mL) was added. The mixture was extracted with ether (2×20 mL), the extracts were washed with brine, dried over $MgSO_4$ and evaporated. Column chromatography on silica (eluent: PE-ether 10:1 to 3:1) afforded 415 mg (83%) of **169** as a colorless liquid.



HRMS (EI) calcd for C10H11FO: 166.079393; found: 166.080006.

^{1}H NMR ($CDCl_3$, 300 MHz): 3.93 (d, J = 13.0 Hz, 2 H, CH_2-allyl), 4.47 (s, 2 H, CH_2Ph), 4.50 (dd, J = 2.9 and 48.5 Hz, 1 H, CH_2-vinyl), 4.69 (dd, J = 2.9 and 16.6 Hz, 1 H, CH_2-vinyl), 7.21-7.28 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$, 75 MHz): 67.99 (d, J = 33.0 Hz, CH_2-allyl), 72.09 (CH_2Ph), 92.54 (d, J = 17.1 Hz, CH_2-vinyl), 127.57, 127.62 and 128.24 (Ph), 137.40 (Ph-*ipso*), 162.15 (d, J = 259.7 Hz, CF).

^{19}F NMR ($CDCl_3$, 282 MHz): -105.58.

***Tert*-butyl 2-(benzyloxymethyl)-1-cyano-2-fluorocyclopropanecarboxylate (171)**

Prepared from **169** similarly to **167**. Isolated yield of $Rh_2(OCO^tBu)_4$-catalysed cyclopropanation 41%.

HRMS (ESI+) calcd for $C_{17}H_{21}NO_3F$ ($[M+H]^+$): 306.1505, found 306.1506

major isomer

^{1}H NMR ($CDCl_3$, 300 MHz): 1.51 (s, 9 H, tBu), 1.80 (dd, J = 7.6 and 11.9 Hz, 1 H, CH_2-cyclo, F-*trans*), 2.46 (dd, J = 7.6 and 18.9 Hz, 1 H, CH_2-cyclo, F-*cis*), 4.00 (m, 2 H, CH_2O), 4.67 (s, 2 H, CH_2Ph), 7.32-7.38 (m, 5 H, Ph).

^{19}F NMR ($CDCl_3$, 282 MHz): -188.53.

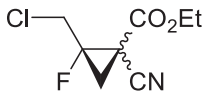
minor isomer

^{1}H NMR ($CDCl_3$, 300 MHz): 1.46 (s, 9 H, tBu), 2.00-2.13 (m, 2 H, CH_2-cyclo), 3.95 (m, 2 H, CH_2O), 4.56 (m, 2 H, CH_2Ph), 7.32-7.38 (m, 5 H, Ph).

^{19}F NMR ($CDCl_3$, 282 MHz): -170.23.

Ethyl 2-(chloromethyl)-1-cyano-2-fluorocyclopropanecarboxylate (169)

Prepared similarly to **167**. Isolated yield of $Rh_2(OCO^tBu)_4$-catalysed cyclopropanation 35%.



HRMS (ESI+) calcd for $C_8H_{10}NO_2FCl$ ($[M+H]^+$): 206.0384, found 206.0384.

major isomer:

^{1}H NMR ($CDCl_3$, 300 MHz): 1.37 (t, J = 7.1 Hz, 3 H, CH_3), 2.21 (dd, J = 7.8 and 14.6 Hz, 1 H, CH_2-cyclo), 2.31 (ddd, J = 0.9, 7.7 and 18.3 Hz, 1 H, CH_2-cyclo), 3.92 (ddd, J = 0.9, 13.1 and 29.6 Hz, 1 H, CH_2P), 4.17 (dd, J = 13.1 and 15.9 Hz, 1 H, CH_2P), 4.34 (m, 2 H, CH_2O).

^{19}F NMR ($CDCl_3$, 282 MHz): -171.50 (m).

minor isomer:

^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 7.1 Hz, 3 H, CH_3), 1.92 (dd, J = 8.0 and 11.7 Hz, 1 H, CH_2-cyclo), 2.66 (ddd, J = 1.2, 7.9 and 18.0 Hz, 1 H, CH_2-cyclo), 3.99 (ddd, J = 1.3, 13.3 and 21.4 Hz, 1 H, CH_2P), 4.05 (dd, J = 13.3 and 20.2 Hz, 1 H, CH_2P), 4.31 (m, 2 H, CH_2O).

^{19}F NMR ($CDCl_3$, 282 MHz): -187.13 (m).

Résumé de thèse en français

Introduction

Depuis plusieurs décennies, le fluor occupe une place privilégiée en chimie organique. Trois principales caractéristiques distinctes de l'atome du fluor expliquent cet engouement et cette intense activité de recherche. Premièrement, le fluor est le plus petit hétéroatome accessible pour un chimiste organicien. Deuxièmement il est en l'élément le plus électronégatif, il a un effet significatif sur le dipôle électrostatique et sur la distribution locale des charges au sein d'une molécule. Ce fort effet électronique accompagné par une perturbation stérique minimale résultante lors de l'introduction d'un atome de fluor a conduit aux développements de nombreuses applications des composés organofluorés en chimie thérapeutique. Finalement, en raison de la forte liaison carbone-fluor, les composés organiques fluorés sont thermiquement et chimiquement stables, propriété qui peut être illustrée par la popularité du polymère PTFE, mais aussi par les effets plus subtils du fluor sur la stabilité métabolique des molécules bioactives. En plus de cela, les molécules fortement fluorées démontrent une forte affinité vers les molécules perfluorées - phénomène se trouvant dans la base de la "fluorous chemistry".

Compte tenu des effets spécifiques du fluor sur les propriétés des composés organiques, il n'est pas surprenant que de nombreux efforts aient été dirigés vers le développement de nouvelles méthodes de synthèse de composés organofluorés. Néanmoins, le problème de l'incorporation sélective des atomes de fluor et des groupes fluorés n'est pas complètement résolu à ce jour.

Les petits cycles fluorés, en particulier, les cyclopropanes constituent une classe spéciale au sein des composés aliphatiques organiques fluorés. Le cyclopropane a une structure rigide unique, ce qui en fait un motif de choix pour la préparation de molécules d'intérêt biologique. Aussi, certains cyclopropanes sont des intermédiaires importants dans la synthèse de diverses classes de composés.

Du point de vue de la synthèse, les cyclopropanes partiellement fluorés ne représentent pas un objectif simple. L'utilisation des méthodes usuelles de fluoration, substitution nucléophile ou déprotonation suivie d'une addition d'électrophile, sont défavorisées du fait de la structure particulière de ces cycles. En conséquence, les atomes de fluor sont rarement introduits sur un motif cyclopropane préformé, mais plutôt simultanément (par exemple dans le cas de cyclopropanation avec des carbènes fluorés) ou avant l'étape de cyclisation.

Les cyclopropanes fluorés les plus abondants sont les difluorocyclopropanes géminaux, généralement synthétisés via une cycloaddition [2 +1] entre un difluorocarbène et une double liaison carbone-carbone. En revanche, les monofluorocyclopropanes sont des espèces moins accessibles et le

développement de nouvelles méthodes de synthèse sont nécessaires afin d'explorer le potentiel de cette classe de composés.

Le présent manuscrit contient deux parties : la première partie concerne le développement de nouvelles méthodes de synthèse de cyclopropanes monofluorés avec un carbone quaternaire fluoré à partir des alcènes pauvres en électrons ; la deuxième partie est consacrée à la synthèse d'un acide aminé fluorocyclopropanique agoniste potentiel de mGluR groupe 3.

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Développement d'une nouvelle méthode de synthèse de cyclopropanes monofluorés

De nombreuses méthodes de synthèse de cyclopropanes sont connues. La substitution nucléophile intramoléculaire (y compris les réactions à plusieurs étapes comme la "Michael-Initiated Ring Closure", MIRC) et les additions [2+1] de carbènes ou carbénoïdes métalliques sur des alcènes sont largement utilisées.[215] Parmi les autres méthodes puissantes on trouve la cycloisomérisation d'énynes,[216] la réaction de Kulinkovich,[217] la γ-substitution électrophile.

Dans le domaine des cyclopropanes fluorés, les méthodes suivantes ont été utilisées : l'ajout de carbènes fluorés (notamment difluorocarbène) ; la réaction de Simmons-Smith utilisant les fluoroalcènes ou carbénoïdes fluorés ; l'addition (y compris catalysée par des métaux de transition) des composés diazo sur des fluoroalcènes ; la fluoration de précurseurs insaturés des cyclopropanes ; la cyclisation nucléophile intramoléculaire.[218]

Dans ce projet, nous avons essayé de mettre au point une méthode générale pour la synthèse de cyclopropanes monofluorés hautement fonctionnalisés à l'aide d'un "building-block" fluoré facilement disponible. En tant que tel, nous avons choisi le dibromofluoroacetate d'éthyle commercial ($CFBr_2CO_2Et$, EDBFA) qui possède une fonction ester, groupe approprié pour une fonctionnalisation ultérieure. La métallation de l'EDBFA conduirait à un intermédiaire organométallique α-carbonylé qui serait suffisamment nucléophile pour effectuer l'addition 1,4 sur les accepteurs de Michael. La substitution nucléophile intramoléculaire conduirait ensuite au cyclopropane monofluoré.

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[215] (a) Lebel, H.; Marcoux, J.F.; Molinaro, C.; Charette, A.B. *Chem. Rev*. **2003**, *103*, 977; (b) Donaldson, W.A. *Tetrahedron* **2001**, *57*, 8589.

[216] (a) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; (b) Shu, X.Z.; Shu, D.; Schienebecka, C.M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698.

[217] (a) Kulinkovich, O.G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; (b) Cha, J.K.; Kulinkovich, O.G., *Org. React.* **2011**, *77*, 1; (c) Haym, I.; Brimble, M.A. *Org. Biomol. Chem*. **2012**, *10*, 7649.

[218] (a) Brahms, D.L.S.; Dailey, W.P. *Chem. Rev.* **1996**, *96*, 1585. (b) Taguchi, T.; Okada, M. *J. Fluorine Chem.* **2000**, *105*, 279; (c) Dolbier, W.R., Battiste, M.A. *Chem. Rev.* **2003**, *103*, 1071; (d) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. Eur. J.* **2012**, *18*, 14904.

Notre laboratoire a déjà appliqué avec succès la réaction MIRC à partir de l'EDBFA pour la synthèse d'un acide aminé fluorocyclopropanique protégé **1a** (Schéma 1). Le produit de cyclopropanation a été utilisé pour la synthèse d'une variété d'agonistes des récepteurs mGluR III. Cependant, la réaction n'a pu être appliquée à d'autres accepteurs de Michael. La polymérisation des alcènes pauvres en électrons dans les conditions de réaction a été identifiée comme la cause probable de cet échec.

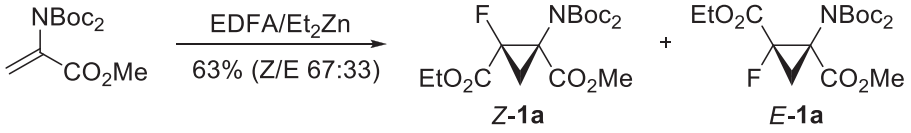


Schéma 1.

Le résultat principal de ce travail a été la découverte d'un effet catalytique de LiCl sur la métallation de l'EDBFA par le zinc métallique. Cette réaction a eu lieu dans des conditions très douces (température en dessous de 0°C). De bons rendements en cyclopropanes **1** ont été obtenus. D'un point de vue global, notre travail manifeste de l'utilité potentielle du système sélectif Zn/LiCl pour la génération in situ des réactifs de Reformatsky hautement instables (**2**), qui sont inaccessibles par la méthode classique en deux étapes de la réaction de Reformatsky.

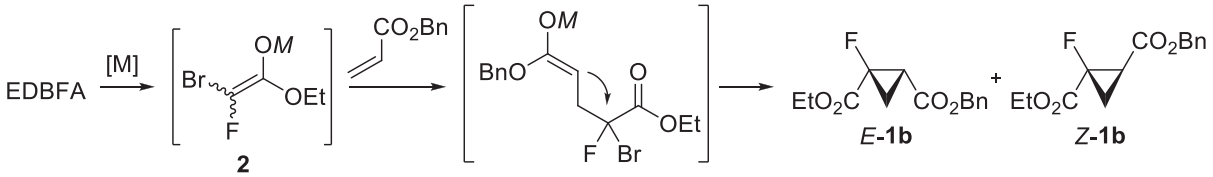
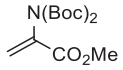
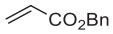
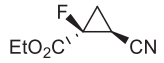
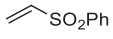
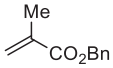
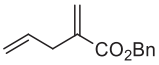
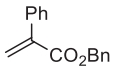
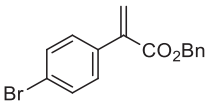
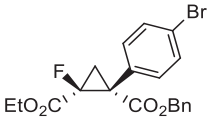
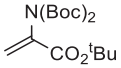
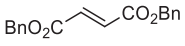
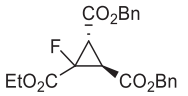
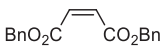
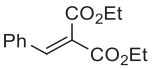
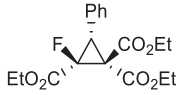
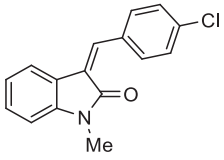
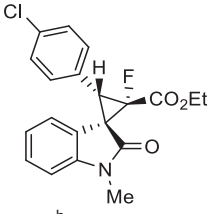


Schéma 2.

Les limites de notre réaction de cyclopropanation sont illustrées par le Tableau 1. Divers esters α,β-insaturés, un nitrile (entrée 3), un sulfonate (entrée 4) et un amide (entrée 13) peuvent être transformés en cyclopropane fluoré correspondant. Des alcènes mono-, di-et tri-substitués sont des substrats appropriés. Des mélanges de diastéréoisomères ont été obtenus dans la plupart des cas.

Tableau 1. Scope de cyclopropanation avec Zn/LiCl

entrée	alcène	**1** produit majoritaire montré		T, °C	equiv de EDBFA	Rendement	*dr*[a]
1		**a**		0 -5	2 1.6	78 93[b]	59:41
2		**b**		-20	2	80	72:28
3		**c**		-20	2	47	53:47
4		**d**		-20	1.1	72	67:33
5		**e**		30	3	61	70:30
6		**f**		30	3	68	73:27
7		**g**		30	3	76	76:24
8		**h**		30	3	80	78:22
9		**i**		-20	2	73	84:16
10		**j**		-20	1.1	66	100:0
11				-20	1.1	61	100:0
12		**k**		-20 to rt	2	72	69:31
13		**l**		0	1.1	70	53:36:7:4

[a] par ^{19}F RMN d'un mélange réactionnel; [b] 0.10 mol d'accepteur de Michael a été utilisée.

Cyclopropanation asymétrique.

Après avoir mis au point une nouvelle méthode de synthèse de cyclopropanes monofluorés, nous nous sommes concentrés sur le développement d'une version asymétrique de celle-ci.

Plusieurs dibromofluoroacetyl-oxazolidinones **3** ont été préparées en trois étapes à partir de l'EDBFA (Schéma 3). L'acide dibromofluoroacétique a été préparé par hydrolyse basique de l'EDBFA et ensuite transformé en chlorure d'acyle correspondant. L'acylation des oxazolidinones chiraux donne les produits **3**.

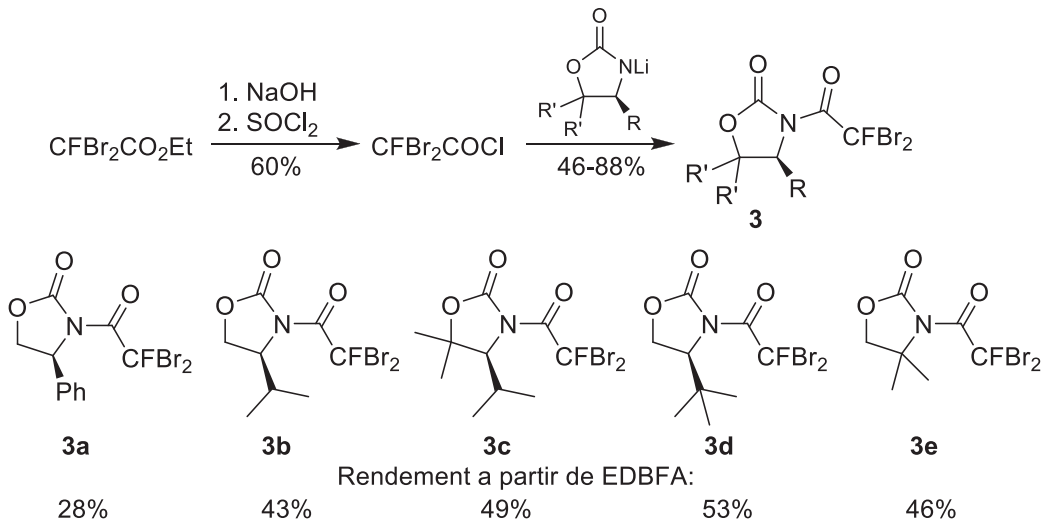


Schéma 3.

Toutes les oxazolidinones ont été testées dans la réaction de cyclopropanation de l'acrylate de benzyle dans les conditions optimisées pour l'EDBFA (Schéma 4, Tableau 2). Deux tendances opposées sont observées : l'augmentation de la taille de la chaîne latérale dans le composé **3** induit une sélectivité (*E*)/(*Z*) plus faible mais au contraire une augmentation l'excès diastéréoisomérique. Étant donné les valeurs de *de* élevées et la meilleure stabilité du composé **3c**, nous avons décidé d'utiliser ce réactif pour toutes les études de cyclopropanation.

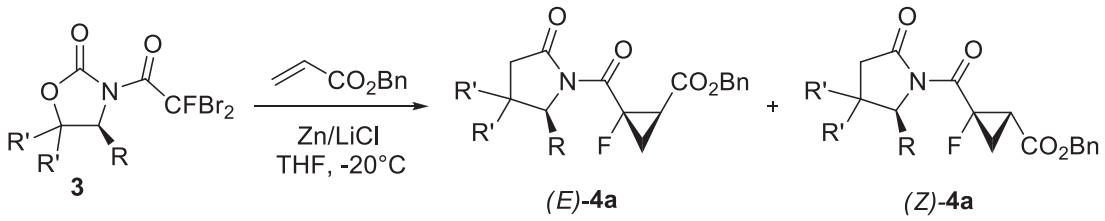


Schéma 4.

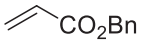
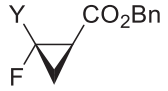
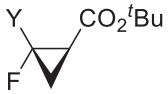
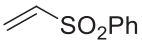
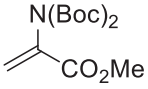
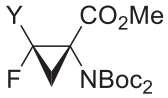
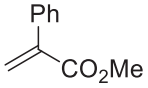
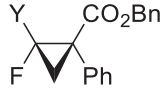
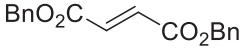
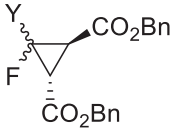
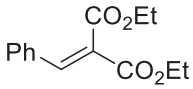
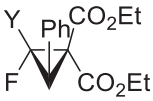
Tableau 2.

3	(*Z*):(*E*)	*de*(*Z*)	*de*(*E*)
a	3:97	52	68
b	16:84	84	86
c	21:79	84	93
d	27:73	86	88
e	18:82	-	-

De même que l'EDBFA, l'oxazolidinone fluorée **3c** peut être utilisée dans la réaction de cyclopropanation d'une variété d'accepteurs de Michael (Tableau 3). La réaction a lieu avec les différents accepteurs de Michael monosubstitués: l'ester (entrées 1,2), le sulfonate (entrée 3), le phosphonate (entrée 4) ou le nitrile (entrée 5), conduisant aux cyclopropanes fluorés attendus avec de

bons rendements. Les alcènes di- et tri-substitués réagissent également avec des bons rendements et généralement avec le même niveau de diastéréosélectivité (entrées 6-9).

Tableau 3. Scope de cyclopropanation asymétrique.

entrée	alcène	produit majoritaire (**4**)		rendement **4**, %[b]	(*Z*):(*E*)[a]	*de*[a] (rendement[b]) *Z*-**4**	*de*[a] (rendement[b]) *E*-**4**
1			**a**	79	21:79	84 (14)	93 (65[c])
2			**b**	69	16:84	76 (8)	94 (61)
3			**c**	79	78:22	88 (62[c])	92 (17[c])
4			**d**	62	85:15	>94 (55[c])	80 (7)
5			**e**	70	50:50	94 (36[c])	>94 (34[c])
6			**f**	78	73:27	80 (56[c])	84
7			**g**	74	45:55	>90 (33[c])	>92 (41)
8			**h**	79	5:95[d]	-	64
9			**i**	66	36:64	>94 (24[c])	>94 (42[c])

[a] déterminé par ^{19}F RMN du produit brut; [b] rendement isolé; [c] seul isomère par ^{19}F RMN de produit isolé; [d]ratio *E/Z* concerne la stéréochimie des groupements ester.

Afin de déterminer la configuration absolue des isomères du composé **4a** nous avons envisagé la préparation de monocristaux pour l'analyse RX. Alors que l'isomère majoritaire (*E*)-**4a** a été facilement cristallisé à partir de mélange d'isomères brut, nous avons dû modifier l'isomère minoritaire (*Z*)-**4a** en deux étapes selon la Schéma 5.

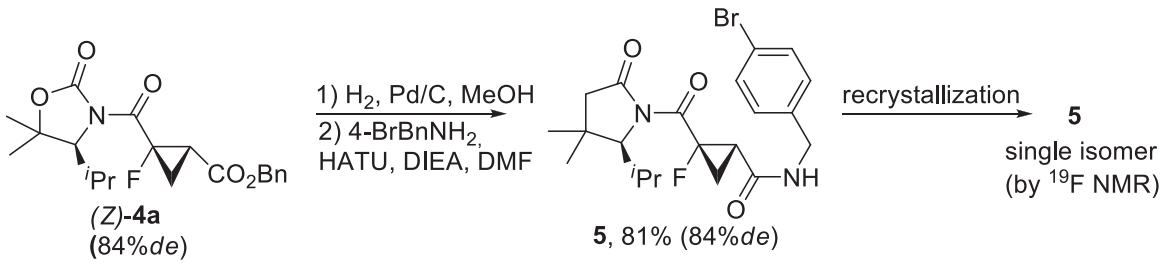


Schéma 5.

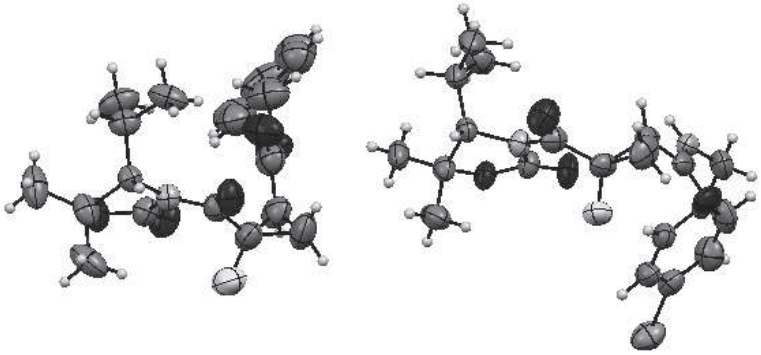


Figure 1. Structures RX de (*E*)-**4a** and **5**.

Les résultats de l'analyse RX nous ont permis d'attribuer la configuration *S* au stéréocentre fluoré des deux isomères du composé **4a** (*Z* et *E*). Par conséquent, les deux isomères majoritaires sont issus de la cyclisation non-stéréosélective du même intermédiaire (*R*)-**6a** (Schéma 6). Étant donné que l'addition 1,4 sur l'acrylate est très stéréosélective et résulte en un seul intermédiaire non-cyclisé (*R*)-**6a**, on peut définir la réelle structure moléculaire de l'intermédiaire **7** comme montré sur le Schéma 6, en accord avec le mécanisme standard de la réaction aldol d'Evans.[219]

[219] Evans , D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

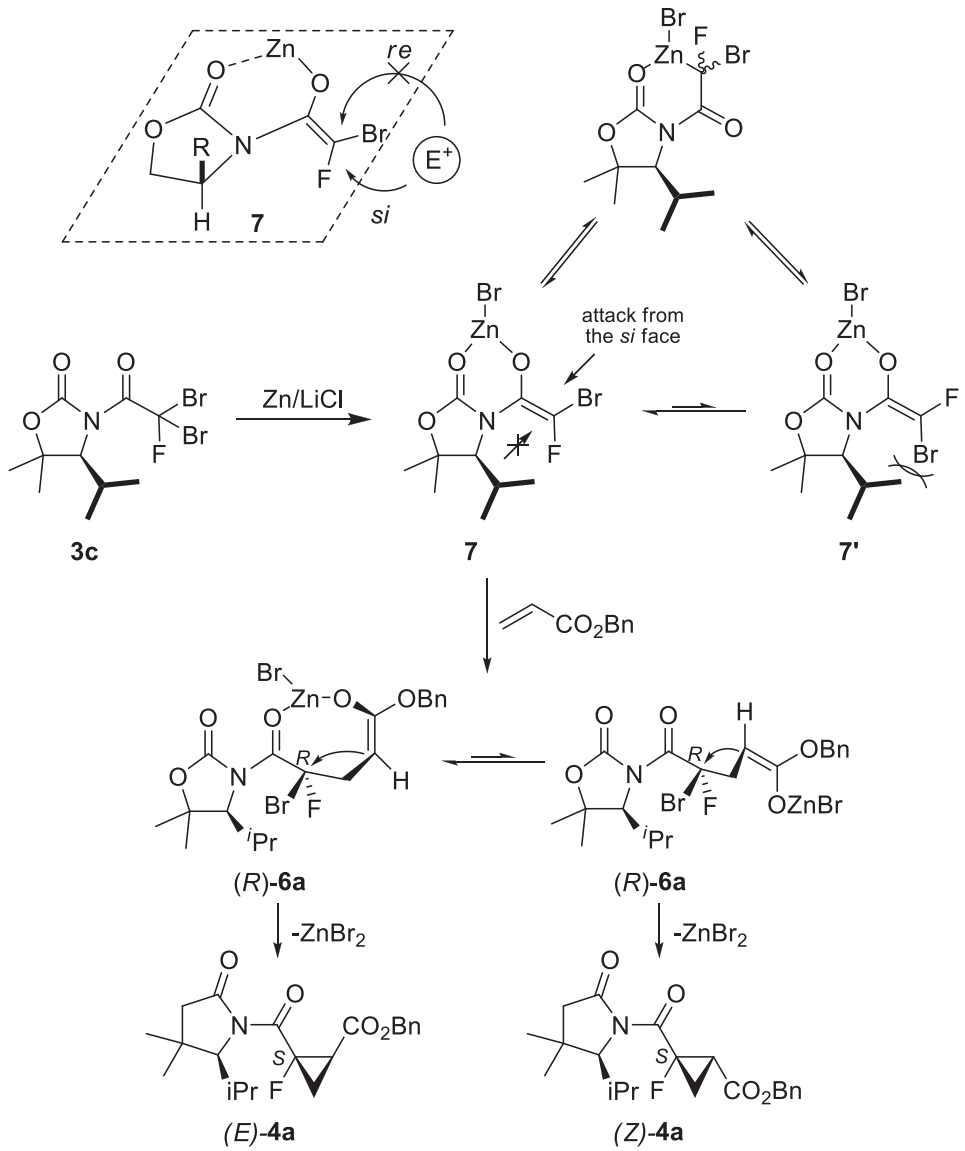


Schéma 6.

Synthèse de l'analogue fluoré de (Z)-APCPr (agoniste de mGluR III)

Les agonistes sélectifs des mGluRs (récepteurs métabotropiques de glutamate) du groupe III peuvent potentiellement être utilisés pour le traitement de certaines maladies neurologiques: anxiété,[220] douleurs neuropathiques,[221] trauma de cerveau[222] et la maladie de Parkinson.[223]

[220] Meldrum, B.S. *J. Nutrition* **2000**, *130*, 1007S.
[221] Chen, S.-R.; Pan, H.-L. *J. Pharmacol. Exp. Ther.* **2005**,*312*, 120.
[222] Bruno, V.; Battaglia, G.; Copani, A.; D'Onofrio, M.; Di Iorio, P.; De Blasi, A.; Melchiorri, D.; Flor, P.J.; Nicoletti, F.; *J. Cereb. Blood Flow Metab.* **2001**, *21*, 1013.
[223] Conn, P.J.; Battaglia, G.; Marino, M.J.; Nicoletti, F. *Nat. Rev. Neurosci.* **2005**, *6*, 787.

Les ligands sélectifs pour le groupe III des mGluRs sont souvent caractérisés par un groupe acide additionnel[224] sur la chaîne latérale de glutamate (phosphonate ou deuxième carboxylate) (Fig. 2). Le ligand standard *L*-AP4 (**8**) est un agoniste sélectif du groupe III, mais pas des différents types du groupe III: mGluR4 (EC_{50} dans les rats 0.5-1 μM), mGluR6 (EC_{50} dans les rats 0.6-0.9 μM) et mGluR8 (EC_{50} dans les rats 0.6-0.7 μM). Certains agonistes spécifiques ont été rapportés: *homo*-AMPA (mGluR6, 58 μM), DCPG[225] (mGluR8, 31 nM), mais aucun agoniste sélectif des types mGluR4 et mGluR7. En revanche, les modulateurs allostériques sélectifs pour mGluR4 (VU0003423,[226] VU0359516[227]) et mGluR7 (AMN082[228]) sont connus.

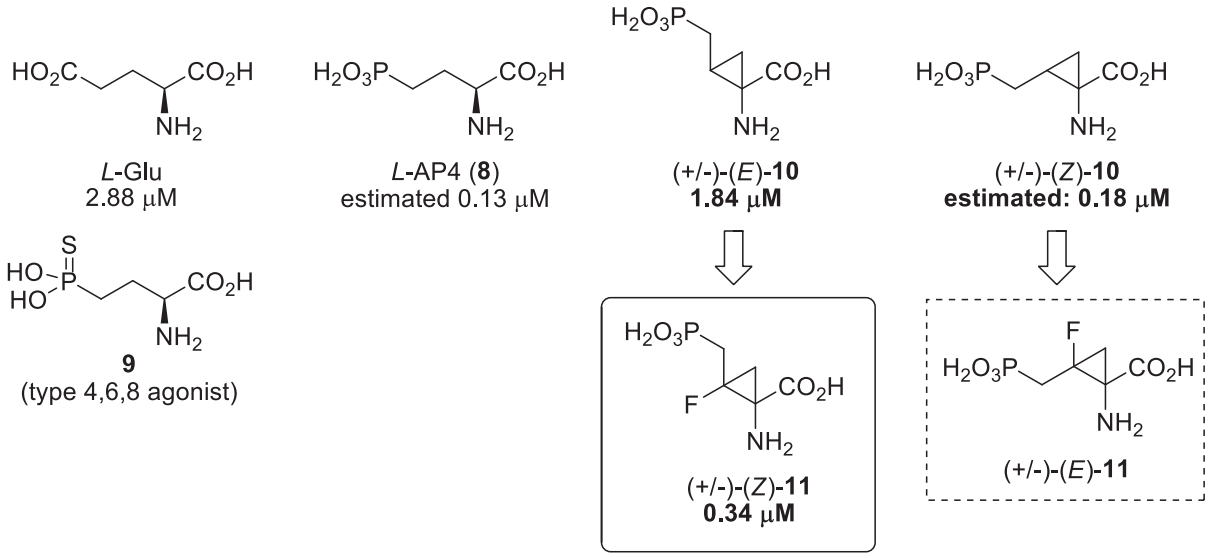


Figure 2.

Certains analogues du *L*-AP4 avec une conformation restreinte, incorporant des unités de type cyclopropane, cyclobutane ou cyclopentane, ont été préparés, mais la plupart de ces molécules ont été moins actives que le *L*-AP4. Une seule exception a été l'analogue (1S,2R)-APCPr ((*Z*)-**10**) [229,230] qui a démontré le même niveau d'activité et de sélectivité que *L*-AP4.

[224] Discussion sur l'importance des groupes acidiques additionnels: Selvam, C.; Goudet, C.; Oueslati, N.; Pin, J.P.; Acher, F.C. *J. Med. Chem.* **2007**, *50*, 4656.

[225] Thomas, N.K.; Wright, R.A.; Howson, P.A.; Kingston, A.E.; Schoepp, D.D.; Jane, D.E. *Neurophamacology* **2001**, *40*, 311.

[226] Niswender, C.M.; Johnson, K.A.; Weaver, C.D.; Jones, C.K.; Xiang, Z.; Luo, Q.; Rodriguez, A.L.; Marlo, J.E.; de Paulis, T.; Thompson, A.D.; Days, E.L.; Nalywajko, T.; Austin, C.A.; Williams, M.B.; Ayala, J.E.; Williams, R.; Lindsley, C.W.; Conn, P.J. *Mol. Pharmacol.* **2008**, *74*, 1345.

[227] Zhou, Y.; Niswender, C.M.; Luo, Q.; Conn, P.J.; Lindsley, C.W.; Hopkins, C.R. *ACS Chem. Neurosci.* **2010**, *1*, 411.

[228] Mitsukawa, K.; Yamamoto, R.; Ofner, S.; Nozulak, J.; Pescott, O.; Lukic, S.; Stoehr, N.; Mombereau, C.; Kuhn, R.; McAllister, K.H.; van der Putten, H.; Cryan, J.F.; Flor, P.J. *Proc. Natl. Acad. Sci USA* **2005**, *102*, 18712.

[229] Synthèse de APCPr racémique les etudes électrophysiologiques: Kroona, H.B.; Peterson, N.L.; Koerner, J.F.; Johnson, R.L. *J. Med. Chem.* **1991**, *34*, 1692.

La compatibilité du motif cyclopropane avec l'activité agoniste dans **10** et les effets positifs de l'augmentation de l'acidité Illustrée par le thiophosphonate **9** ont motivé notre groupe à préparer l'analogue fluoré du composé **10** afin de développer des agonistes plus puissants et d'étudier les effets de la fluoration sur la sélectivité envers les différents types de mGluR. Le phosphonate (*Z*)-**11** (l'analogue le plus proche de **10**) a démontré la meilleure activité agoniste de la série, étant 5 fois plus actif que le stéréoisomère correspondant et 10 fois plus puissant que le glutamate. Cependant, l'activité biologique la plus élevée dans la série non fluorée est associée à l'isomère (*Z*)-**10** (équivalent à (*E*)-**11** dans la série fluorée). Dans ce projet nous avons donc effectué la synthèse de l'analogue (*E*)-**11**.

Notre première approche pour la synthèse de (*E*)-**11** en utilisant la méthodologie MIRC (décrite ci-dessus) a échoué, nous nous sommes donc concentrés sur la cyclopropanation directe du fluoroallylphosphonate **12** catalysée par le Rh(II). Le composé **12** a été synthétisé à partir du 3-chloro-2-fluoropropène commercial **13** via la réaction d'Arbuzov avec le triéthylphosphite (Schéma 7). La cyclopropanation de **12** avec deux composés diazo a été effectuée avec succès.

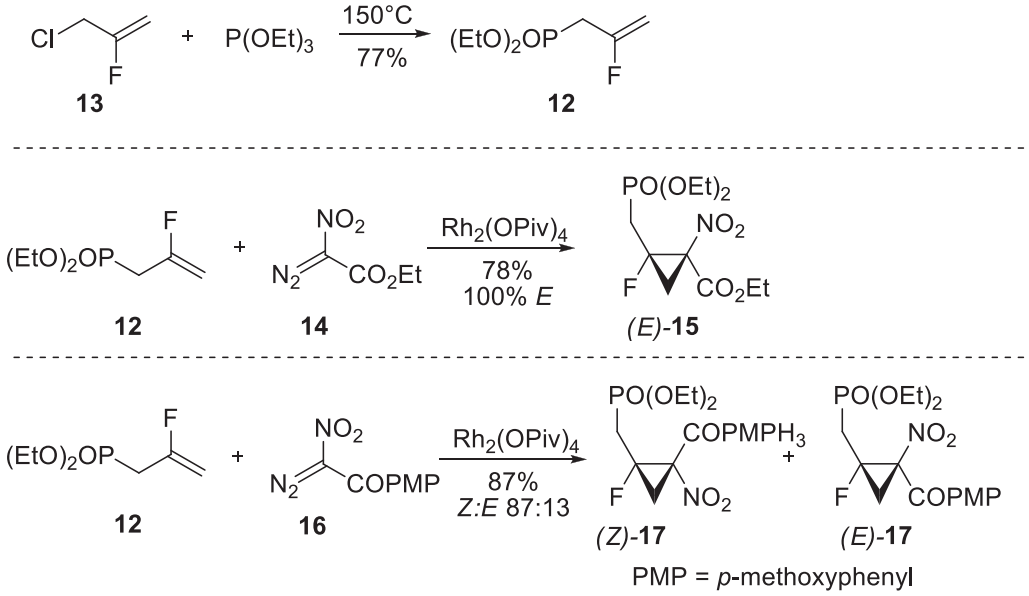


Schéma 7.

Le nitrocyclopropane **15** a été ensuite réduit en amine **18** qui a été protégée par un groupement Cbz. Les énantiomères du produit **19** ainsi obtenu ont été séparé par SFC chiral (Schéma 8). Les énantiomères (−)-**19** et (+)-**19** ont ensuite été déprotégés avec un mélange $HCl_{aq.}$/AcOH pour fournir les composés (+)-(*E*)-**11** et (−)-(*E*)-**11** avec de bons rendements. Les tests biologiques de (+)-(*E*)-**11** et (−)-(*E*)-**11** sont actuellement en cours à l'Université de Montpellier.

[230] Synthèse des isomèrs individuels de APCPr et les études d'activité agoniste: Sibille, P.; Lopez, S.; Brabet, I.; Valenti, O.; Oueslati, N.; Gaven, F.; Goudet, C.; Bertrand, H.-O.; Neyton, J.; Marino, M.J.; Amalric, M.; Pin, J.-P.; Acher, F.C. *J. Med. Chem*. **2007**, *50*, 3585.

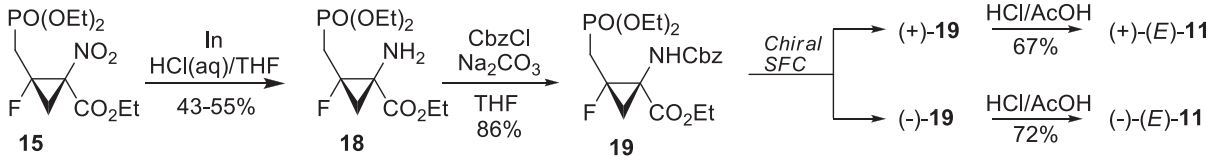


Schéma 8.

Cyclopropanation énantiosélective de composés 2-fluoroallyle catalysée par le Rh(II)

Compte tenu de la réussite de la préparation des phosphonates **15** et **17**, nous avons tenté de mettre au point une synthèse asymétrique des cyclopropanes selon la méthode décrite par le groupe de Charette.[231] Pour ce projet, nous nous sommes concentrés sur le 3-chloro-2-fluoropropène **13** qui, une fois transformé en cyclopropane, peut être facilement fonctionnalisé menant à divers acides aminés fluorés.

Les carbénoïdes de rhodium dérivés de cyanodiazoesters sont généralement considérés plus réactifs que ceux dérivés de nitrodiazoesters.[232] Le groupe nitrile peut généralement être converti en un groupe amino via le réarrangement de Hofmann ou de Curtius, on peut donc substituer les nitrodiazoesters par des cyanodiazoesters dans la préparation d'acides aminés cyclopropaniques. Nous avons donc décidé de tester le plus réactif cyanodiazoacetate de tert-butyle **20** dans la cyclopropanation de **13** (Schéma 9).

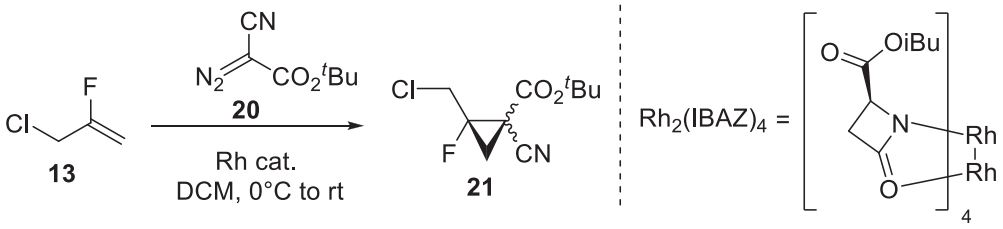


Schéma 9.

Tableau 10.[a]

Solvant	Rendement par RMN	*dr* de **21** (-173:-189)[b]	*ee*, %[c] (-173)	*ee*, %[c] (-189)
CCl_4[d]	34	33:67	99	98
Ether[d]	12	40:60		
PhH[e]	36	52:48	99	98
PhCl[d]	27	60:40		
DCM[e]	30	76:24	99	94
DCE[d]	31	77:23		
$PhNO_2$-DCM (7:3)[e]	31	76:24		
Propylene carbonate[e]	24	87:13	99	92

[231] Lindsay, V.N.G.; Nicolas, C.; Charette, A.B.; *J. Am. Chem. Soc.* **2011**, *133*, 8972.
[232] Lindsay, V.N.G.; Fiset, D.; Gritsch, P.J.; Azzi, S.; Charette, A.B.; *J. Am. Chem. Soc.* **2013**, *135*, 1463.

CH_3CN[e]	0	-	
$CHCl_3$[d]	0	-	

[a] **13**:**20** = 2:1, 2%mol de $Rh_2(IBAZ)_4$, -20°C à ta; [b] Déplacements chimiques (^{19}F) des isomères sont donnés entre parenthèses; [c] L'excès énantiomerique a été détermine par GC chiral d'un produit purifié (Supelco β-DEX 120, 130°C); [d] Solvant commercial a été dégazé avant usage; [e] Solvant a été distillé et dégazé avant usage.

Bien que la cyclopropanation de **13** catalysée par $Rh_2(IBAZ)_4$ soit caractérisée par un haut niveau d'énantiosélectivité, tous nos efforts pour améliorer le rendement ont été infructueux. Le seul moyen d'augmenter légèrement le rendement est d'utiliser un large excès de 3-chloro-2-fluoropropène et d'augmenter le chargement en catalyseur. Compte tenu du prix important de ces deux réactifs, la réaction ne peut pas être considérée pratique actuellement.

Conclusion et perspectives

Dans le cadre de ce projet, nous avons développé la cyclopropanation de type MIRC menant à des cyclopropanes monofluorés. La génération efficace d'un réactif de Reformatsky instable à partir du dibromofluoroacetate d'éthyle a été rendue possible par l'effet catalytique de LiCl. Une variété d'alcènes pauvres en électronsont été engagésdans cette réaction de cyclopropanation avec de bons rendements et une stéréosélectivité modérée.

Notre approche a été appliquée à un nouveau type de réactifs chiraux de cyclopropanation (N-dibromofluoroacetyl-oxazolidinones) qui ont été utilisés pour la synthèse de cyclopropanes monofluorés énantioenrichis. La configuration absolue des cyclopropanes dérivés d'acrylate a été déterminée et utilisée pour la formation du modèle stéréochimique de cette réaction.

Les futurs développements de ce projet peuvent inclure:

- les études de cyclopropanation avec $CFBr_2PO(OiPr)_2$
- le développement de la cyclopropanation Z/E-sélective en utilisant des agents de métallation différents ou des acides de Lewis
- le développement d'une version plus stéréosélective de la réaction de cyclopropanantion avec les oxazolidinones en utilisant des agents de métallation différents
- le développement de la réaction énantiosélective (e.g. basé sur l'addition de Mukaiyama-Michael)

L'acide (*E*)-1-amino-2-fluoro-2-(phosphonométhyl)cyclopropanecarboxylique, analogue fluoré d'agoniste potentiel de mGluR III (APCPr), a été synthétisé via la cyclopropanation du 2-fluoroallylphosphonate de diéthyle catalysée par le Rh(II).

Les premiers essais de cyclopropanation énantiosélective catalysée par $Rh_2(IBAZ)_4$ de composés 2-fluoroallyle ont démontré le grand potentiel de cette méthode pour la synthèse des cyclopropanes monofluorés possédant deux groupes électro-attracteurs. Malgré une haute énantiosélectivité (jusqu'à >99%*ee*) de cette réaction, des études additionnelles sont nécessaires afin d'atteindre un niveau acceptable de rendement.