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Synthesis, reactions and structural features of monofluorinated cyclopropanecarboxylates

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Abstract

Monofluorinated cyclopropanecarboxylates are available in racemic or optically active form by transition metal-catalyzed reactions of vinylfluorides with diazoacetates. From α-fluorostyrene and *tert*-butyl diazoacetate in the presence of 2 mol% of an enantiopure bis(oxazoline) copper complex, a 81:19 mixture of *tert*-butyl *trans*- and *cis*-2-fluoro-2-phenylcyclopropanecarboxylates was obtained with high enantiomeric excess (ee) of 93 or 89%, respectively. The corresponding racemic ethylesters were used as starting materials for the synthesis of carboxamides, of the *cis*- and *trans*-isomers of analogues of tranylcypromine, an anti-depressive drug and several of its homologous fluorinated cyclopropylmethyl and cyclopropylethyl amines. Corresponding enantiopure cyclopropylmethanols and several of their derivatives were synthesized also. Solid state structures of a selection of these compounds were examined by X-ray crystallography. Particularly, the *cis*-configurated fluorinated phenylcyclopropane derivatives showed extremely close intermolecular C−H···F−C contacts. The shortest of such distances (2.17 Å) was found in the *N*-(4-bromophenyl)carbamate of (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methanol.

Keywords: Asymmetric synthesis; Transition metal-catalyzed reactions; Enantiopure bis(oxazoline) copper complexes; Cyclopropanation; Vinyl fluorides; Fluorinated cyclopropanecarboxylates; X-ray structural analysis; Close intermolecular C−H···F−C contacts

1. Introduction

Among the structural motifs responsible for biological activity of molecules, the cyclopropyl group is one of the most important. There is a wide variety of naturally occurring cyclopropane derivatives having important biological functions [1–5]. Consequently, such compounds continue to attract much attention in organic synthesis [6–8] as well as in biological, agricultural and medicinal chemistry [1–5,9,10].

On the other hand, it has been demonstrated for numerous compounds that replacement of a C–H moiety with a C–F group can cause dramatic effects on their physicochemical properties and their chemical reactivity [11,12]. Moreover, for biologically active molecules, significant modifications of their physiological properties are connected to selective fluorination in strategic positions [13–22].

Therefore, the development of new synthetic approaches to fluorinated compounds continues to be an important field of research [23–28]. There are several methods for the synthesis of monofluorinated or geminally difluorinated cyclopropanes, which are based mainly on fluorocarbene additions towards olefins [29–31,102]. Accordingly, geminal difluorocyclopropyl methanols [32–36], difluorocyclopropane carboxylic acids and related amino acids were synthesized ([37] and references cited therein). These latter compounds gained particular interest as analogues of some non-fluorinated methano amino acids. Such compounds are currently attracting special attention because of their outstanding biological activity and potential use in conformationally restricted peptides, providing biosynthetic and mechanistic probes [38,39].

Furthermore, 2-fluoro-cyclopropylamines have been synthesized by Curtius degradation of 2-fluorocyclopropanecarboxylic acid [40], which has been synthesized by direct fluorination of *tert*-butyl *cis*-2-(phenylsulfinyl)cyclopropane-1-carboxylate and subsequent reductive desulfonylation [41]. In order to synthesize enantiopure *cis*-2-fluoro-cyclopropylamine, which is a key intermediate in syntheses of antibacterial quinolones, analogous to the highly potent antibiotic ciprofloxacin (Ciprobay®), several methods of de-racemization of the precursor, *cis*-2-fluorocyclopropanecarboxylic acid, have been reported [42,43]. Fluorinated

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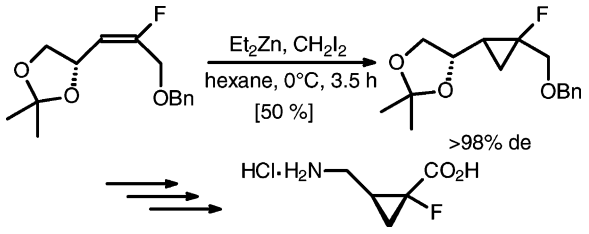
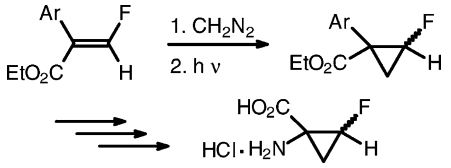


Scheme 1.



Scheme 2.

cyclopropylamines have also been obtained by direct cyclopropanation of enamines with fluorocarbene and subsequent de-racemization [44] or by related auxiliary-directed asymmetric cyclopropanation [45].

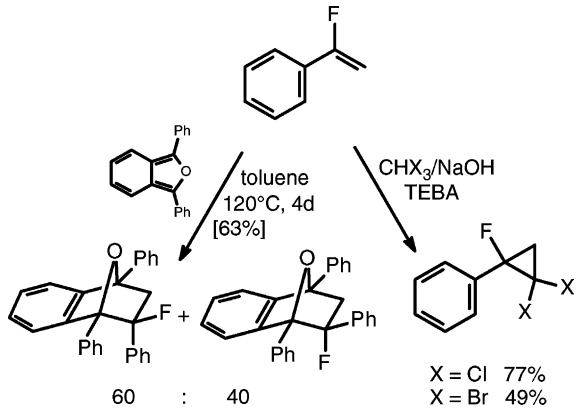
There are also some examples of additions of non-fluorinated carbenes towards fluorinated olefins. Addition of dichlorocarbene towards vinylfluoride yielded 1,1-dichloro-2-fluorocyclopropane [46]. Taguchi and co-workers demonstrated the diastereoselective cyclopropanation of fluorinated allylic alcohol derivatives using the Simmons–Smith reaction [47,48] (Scheme 1) and Sloan and Kirk published a synthesis of a racemic fluorinated ethyl cyclopropanecarboxylate from a β-fluoro-α,β-unsaturated carboxylate and diazomethane [49] (Scheme 2).

While continuing our research on reactions of vinyl fluorides [50–57], we became interested in their ability to react in transition metal-catalyzed cyclopropanations [58]. A related method starting from monofluorinated 1,3-dienes has been used by Cottens and Schlosser in the synthesis of fluorinated chrysanthemic acid derivatives, but the reactions suffered from low selectivity and moderate yields [59]. To the best of our knowledge, there have been no previous reports on asymmetric cyclopropanations of prostereogenic fluoroolefins.

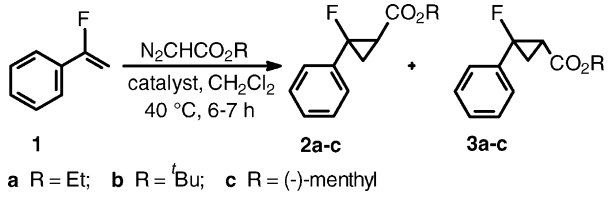
Herein, we report further results on transition metal-catalyzed cyclopropanations of α-fluorostyrene, which provide smooth and efficient entries to racemic or enantiopure monofluorinated phenylcyclopropanecarboxylates. Moreover, the application of compounds prepared by this method for further syntheses of other fluorinated cyclopropanes will be demonstrated. Finally, the solid state structure of some of these compounds, examined by X-ray crystallography, will be discussed in terms of quite short X−H···F−C contacts.

2. Results and discussion

Recently, we have shown that 2-fluoroalkenes, which are readily available from terminal olefins applying a two-step



Scheme 3.



Scheme 4.

sequence consisting of bromofluorination [60,61] with NBS/$Et_3N{\cdot}3HF$ and subsequent HBr elimination from the respective bromofluoro compounds [51,62,63], are valuable building blocks for the synthesis of new fluorinated compounds. Simple vinyl fluorides, such as α-fluorostyrene are weak dienophiles in Diels–Alder reactions and do react solely with very reactive dienes, such as diphenylisobenzofuran [56]. On the other hand, vinyl fluorides are more reactive in electrophilic additions, both in stepwise ones, such as halofluorinations and in dihalogen carbene additions [64] (Scheme 3).

Recently, we demonstrated that α-fluorostyrene (**1**) is a good substrate for metal ion-catalyzed cyclopropanation with ethyl diazoacetate (EDA) [58]. In contrast to the non-fluorinated olefins [65–67], copper salts, particularly $Cu(acac)_2$, are superior to palladium or rhodium salts in this particular reaction [68][1] (Scheme 4; Table 1). However, in all reactions of **1** with EDA 1:1 mixtures of *cis*/*trans* isomeric,[2] fluorinated cyclopropane carboxylates **2** and **3** were formed [58], while with the non-fluorinated counterparts *trans*-selectivity was observed [65–67].

The ratio of diastereomers depends on the steric demand of the ester groups and the nature of the metal/ligand system. While the reactions with copper or rhodium catalysts and EDA gave always 1:1 mixtures (Table 2), the *tert*-butyl- or the (−)-menthyl diazoacetates led to 3:2 mixtures of the diastereomers using rhodium acetate (Table 2).

[1] A related carbene addition to a geminally difluorinated olefin was catalyzed more effectively by $Rh_2(OAc)_4$ compared to $Cu(acac)_2$.

[2] The terms *cis* and *trans* with regard to the phenyl and the carboxyl groups are used to make the diastereoselectivity comparable to the results obtained for non-fluorinated olefins.

Table 1
Cyclopropanation of α-fluorostyrene (**1**) with EDA and different catalysts

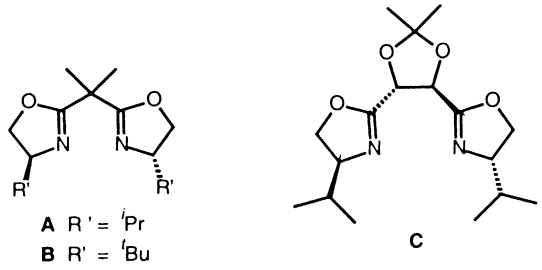
Catalyst	Yield **2a** + **3a** (%, GC)
$Pd(OAc)_2$	11
$PdCl_2$	16
$RhCl_3$	6
$Rh_2(OAc)_4$	25
$CuOTf·(1/2)C_6H_6$	39
$Cu(OAc)_2$	62
$Cu(acac)_2$	93

Table 2
Cyclopropanation of α-fluorostyrene (**1**) with different diazoacetates and rhodium catalysts

	R	Ratio **2**:**3** (GC)	Combined yield (%)
$Rh_2(OAc)_4·2H_2O$	^{t}Bu	64:36	70
$Rh_2(OAc)_4·2H_2O$	(−)-Menthyl	61:39	62

The application of chiral bis(oxazoline) ligands, first used by Masamune and co-workers [69] and Evans et al. [70], for catalytic copper complexes proved to be highly efficient and allowed the asymmetric cyclopropanation of α-fluorostyrene as shown in Table 3. Though this is a very active field of research in non-fluorine series (for recent reviews see [71–73]), there have been no reports on the asymmetric cyclopropanation of prostereogenic vinyl fluorides. We expected this method to be a good approach to a variety of optically active, monofluorinated cyclopropane derivatives.

As enantiopure ligands for the copper complexes, we used the bis(oxazolines) **A**, **B** and **C**. While the enantioselectivity of the cycloaddition is determined by the topology of the catalyst, its electronic structure is responsible for the completion of the catalytic cycle [74]. The nature of the bridge between the oxazoline rings has a quite weak influence on yield, diastereo- and enantioselectivity (Table 3, entries 1 and 3). In contrast, the substituent R′ attached to the oxazoline ring (isopropyl or *tert*-butyl, respectively) is important (Table 3, entries 1 and 2). While the yield dropped, both the diastereo- and enantioselectivity for the *cis*- and *trans*-isomers increased.



Even better diastereo- and enantioselectivities were found for the reaction of α-fluorostyrene (**1**) with *tert*-butyl diazoacetate (Table 3, entries 2 and 4). Finally, a double stereodifferentiation applying the (−)-menthyl ester showed an almost complete diastereoselectivity for the *cis*-diastereomer.

Scheme 5 illustrates the proposed mechanism of the asymmetric cyclopropanation, shown for the two enantiomers of **3a** [58]. The bis(oxazoline) ligand and the metal carbene are orthogonal to each other. In case of a *si*-attack by the olefin, a steric interaction with the bulky substituent R′ would hinder the turn of the ester group into the plane necessary for cyclopropane formation. This steric repulsion increases with the steric demand of R′. Since such an interaction is absent for the *re*-attack, the latter pathway is favored and the selectivity increases with the size of R′ (Table 3).

In order to prove this mechanistic prediction, the absolute configuration of the fluorinated ethyl *trans*-2-phenylcyclopropanecarboxylate (**3a**) formed, was determined. This ester (89% ee) was hydrolyzed with KOH/MeOH and the formed carboxylic acid **4** was treated with 4-bromoaniline under Schotten–Baumann conditions. Recrystallization gave the corresponding enantiopure 4-bromoanilide (**6**) (Scheme 6).

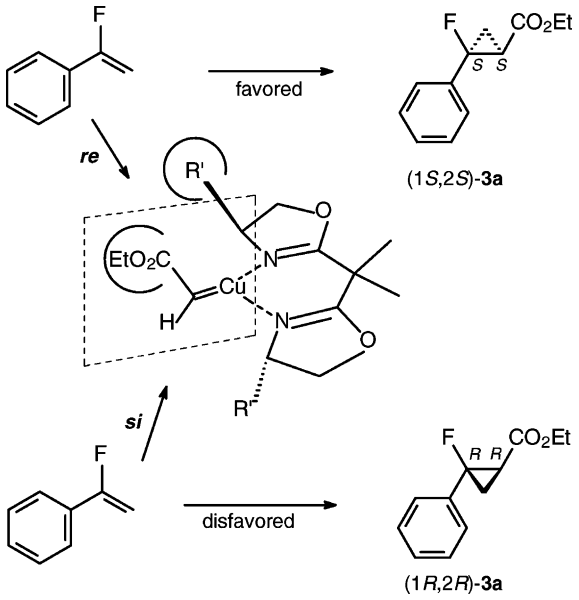
X-ray structure analysis of a single crystal confirmed the configuration of **6** (and therefore, of **3a**) to be (1*S*,2*S*) as expected from the proposed mechanism and assumptions regarding the ligand's configuration [58].

Due to the above-mentioned effects of a fluorine substituent on the properties of compounds, we established pathways to synthesize monofluorinated cyclopropylamines analogous to biogenic amines, such as the racemic *trans*-2-

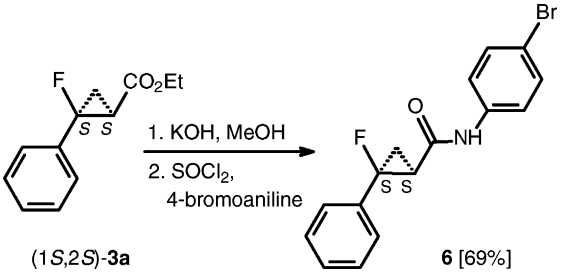
Table 3
Asymmetric cyclopropanation of α-fluorostyrene (**1**) catalyzed by enantiopure copper catalysts

Entry	Ligand	R′	Products	Ratio **2**:**3**	Yield (%)	ee of **2** (%)[a]	ee of **3** (%)[a]
1	**A**	Et	**2a** + **3a**	68:32	81	69	54
2	**B**	Et	**2a** + **3a**	72:28	62	89	80
3	**C**	Et	**2a** + **3a**	66:34	75	70	54
4	**B**	^{t}Bu	**2b** + **3b**	81:19	56	93[b]	89[b]
5	**B**	(−)-Menthyl	**2c** + **3c**	19:81	28[c]	92[d]	>98[d]

[a] The ee of the cyclopropane carboxylates were determined by ^{19}F NMR spectroscopy after hydrolysis and esterification with enantiopure (−)-menthol using DCC.
[b] Determined by chiral GC.
[c] The *cis*-isomer **3c** contains small amounts of the (−)-menthyl esters of maleic and fumaric acids as byproducts.
[d] de.



Scheme 5.



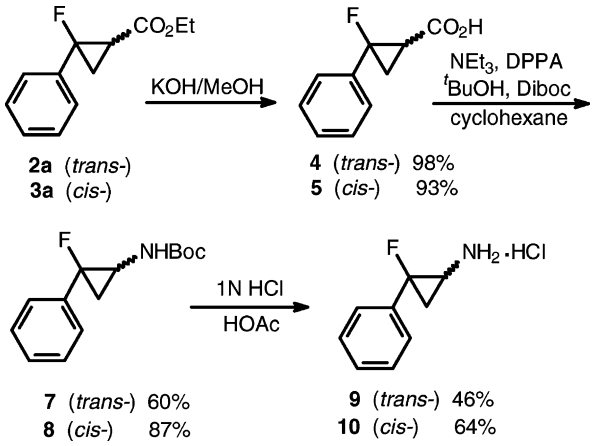
Scheme 6.

phenylcyclopropylamine (Tranylcypromine®), which is an anti-depressive drug.

Saponification of the racemic, diastereopure fluorinated ethyl *cis*- and *trans*-2-phenylcyclopropylcarboxylates **2a** and **3a** gave the corresponding cyclopropanecarboxylic acids **4** and **5**, which subsequently served as precursors for the fluorinated analogues **9** and **10** of tranylcypromine (Scheme 7). Curtius-type degradation of **4** and **5**, and reaction of the intermediary isocyanates with *tert*-butanol gave the Boc-protected fluorinated cyclopropylamines **7** and **8**. Deprotection with HCl in HOAc led to the hydrochlorides of both diastereomers of the fluorinated analogues **9** and **10** of the 2-phenylcyclopropylamines.

The homologues (**13** and **14**) of **9** and **10** were synthesized as shown in Scheme 8. The diastereopure carboxylic acids **4** and **5**, were transformed to the corresponding acid chlorides, which were treated without isolation with ammonia to give the carboxamides **11** and **12**. These compounds were reduced with borane in THF. After work-up, the hydrochlorides **13** and **14** of the corresponding amines were obtained by treatment with dry HCl gas.[3] The structures

[3] Complete synthetic details and spectroscopic data will be published in combination with results of biological studies.



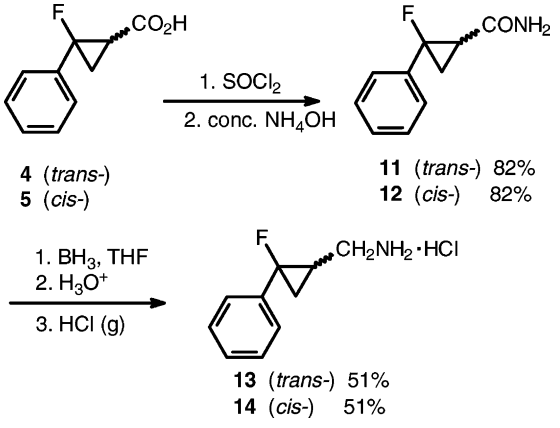
Scheme 7.

of some of these compounds were proved by X-ray crystallography.

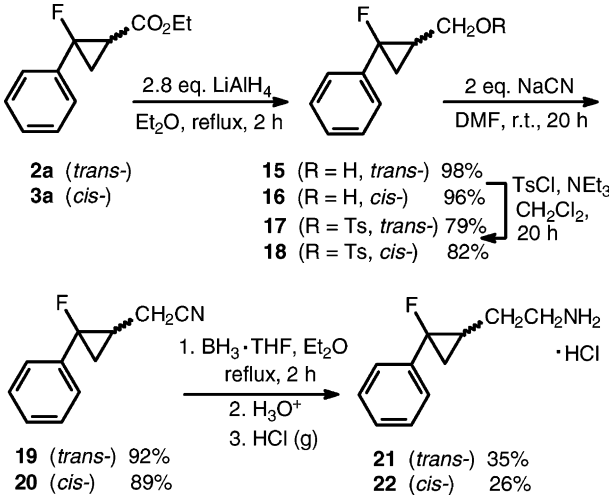
The corresponding cyclopropylethyl amines have been synthesized by a classical homologation methodology. Reduction of carboxylic esters **2a** and **3a** gave the cyclopropylmethanol derivatives **15** and **16**, which were tosylated to give **17** and **18**. Subsequent nucleophilic substitution led to the nitriles **19** and **20**, which were reduced with BH_3 in THF and the formed amines were precipitated as hydrochlorides **21** and **22** (Scheme 9) (see footnote 3).

Having a series of these fluorinated phenylcyclopropanes in hands, we observed that it is very easy to assign the relative configuration of such compounds by ^{19}F NMR spectroscopy. Fluorocyclopropane itself has a ^{19}F NMR chemical shift of -218.0 ppm relative to $CFCl_3$. The *trans*-diastereomeric compounds of this series showed chemical shifts in a quite narrow range of 7 ppm between -187 and -194 ppm. The *cis*-diastereomers on the other hand, exhibited a high field shift in a range of -162 to -152 ppm compared to the *trans*-isomers (Scheme 10).

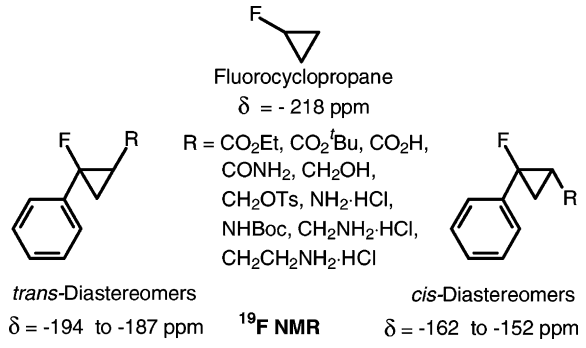
There are also significant differences between the *cis*- and the *trans*-configurated compounds in the ^1H NMR spectra. Most significantly, there is only one large $^3J_{HF}$ in the *trans*-compound indicating the relative *cis*-configuration



Scheme 8.



Scheme 9.



Scheme 10.

of fluorine and one of the vicinal hydrogens. In contrast, two large $^3J_{HF}$ are found in the *cis*-compounds indicating the relative *cis*-configuration of fluorine to two vicinal hydrogens. Moreover, there are $^3J_{CF}$ couplings of about 7–11 Hz to the γ-carbon atoms only, in most of the *trans*-compounds.

Besides the synthetic aspects, it is also interesting to gain insights into the structure of such fluorinated compounds. During the past years, there has been an enormous interest in the question, whether or not a fluorine substituent in organic compounds can function as a hydrogen bridge acceptor with acidic X–H bonds, such as O–H, N–H or even C–H moieties.

A hydrogen bridge in organic compounds is a particular type of a chemical bond, which is formed between a covalently bound hydrogen atom and a free electron pair of an electronegative atom. In terms of macroscopic properties of a compound, hydrogen bridges do influence the physical properties, such as the melting point, the boiling point as well as the dipole moment [75]. Moreover, hydrogen bridges contribute to the formation of particular crystal structures and to the arrangement of supramolecular ensembles [76]. Most importantly, hydrogen bridges determine the active conformation of enzymes and the interactions of substrates and their receptors in the body [75–83] and can be applied to steer selectivity in organic synthesis (non-covalent synthesis [84]). While the 'inorganic' fluoride ion is known as a very strong proton acceptor [85], the 'organic' C–F group seems to be rarely involved in hydrogen bonding compared to C–O or C–N moieties. Recently, the question, whether or not C–F groups can function as hydrogen bridge acceptors have been discussed quite controversially [86–92].

Dunitz and Taylor [89] defined a X−H···F−C distance <2.3 Å and an X−H···F angle >90° as criteria for a "real" hydrogen bridge. They analyzed almost 6000 C–F bonds in more than 1200 crystal structures of fluorinated, organic (excluding organometallic) compounds found in the Cambridge Crystallographic Data Collection (CCDC) and identified only 37 (0.6%) which meet these criteria. Among these compounds, only two were identified by these authors as exhibiting true hydrogen bridges. Thus, it seems extremely rare that C–F moieties act as hydrogen bond acceptors.

On the other hand, Howard et al. identified 40 monofluorinated compounds from the same source in 1996 having X−H···F−C contacts (X = O, N) <2.35 Å [88]. Recently, several close intermolecular X−H···F−C contacts below these limits were described [93–95]. Other authors regarded a distance of about the sum of the van der Waals radii (2.67 Å) [96] or even longer as hydrogen bridges [97,98]. Furthermore, a quite short intramolecular N−H···F−C distance of 2.27 Å has been found for *N*-(fluoroacetyl)phenylglycine in the crystalline state recently [99]. This interest in short X−H···F−C contacts led us to examine the X-ray structures[4] of several of the crystalline, fluorinated 2-phenylcyclopropane derivatives.[5]

As expected, the two diastereomeric racemic carboxylic acids formed dimers in the crystalline state. There are strong hydrogen bridges between the two acid groups, but there are also C−H···F−C distances, which are close to the sum of the van der Waals radii, namely 2.62 Å to the C–H of the cyclopropane ring and 2.65 Å to an aromatic hydrogen, in the case of the racemic *trans*-compound **4** (Fig. 1).

Due to the different crystal type, the structure of the enantiopure *trans*-configurated carboxylic acid (*S*,*S*)-**4** revealed a shorter contact to the C–H of the cyclopropane ring (2.39 Å), while the distance to the aromatic hydrogen became longer compared to the racemate (Fig. 2).

In the corresponding *p*-bromocarboxamide **6**, which was prepared in order to assign the absolute configuration of the carboxylic acid (*S*,*S*)-**4** (Fig. 2), an even shorter contact of

[4] A detailed discussion of the X-ray structures of these compounds will be matter of a separate future paper. The H atoms in the studied compounds (presented in Figs. 1–8) have been calculated into their idealized positions and the C–H, O–H and N–H distances have been normalized to their neutron diffraction distances during the refinements, e.g. C–H to 1.08 Å, O–H and N–H to 1.00 Å, using the SHELXL command AFIX.

[5] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 145029–145031 and 170381–170385. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk

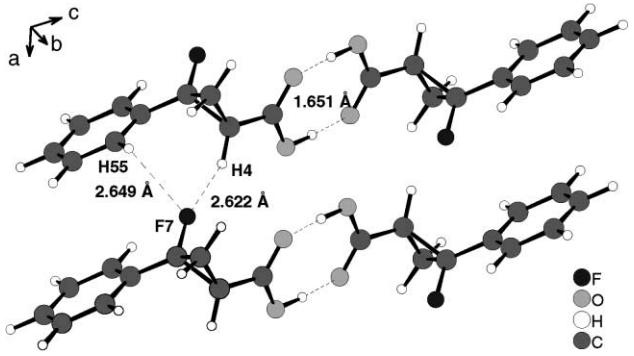


Fig. 1. *trans*-(±)-2-Fluoro-2-phenylcyclopropanecarboxylic acid (**4**).

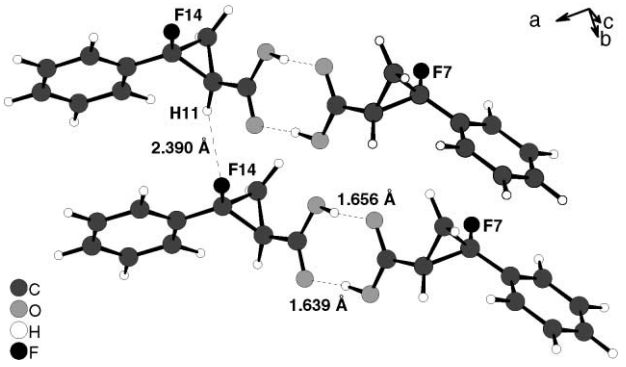


Fig. 2. (1*S*,2*S*)-2-Fluoro-2-phenylcyclopropanecarboxylic acid, (*S*,*S*)-**4**.

2.35 Å was found to one C–H group of the cyclopropane ring (Fig. 3).

For the *cis*-configurated carboxylic acid **5**, two different short distances of 2.41 or 2.28 Å, were found to one of the methylene hydrogens of the cyclopropane ring (Fig. 4).

It is known in the literature, that methylene hydrogens of cyclopropanes are quite acidic and can form intermolecular hydrogen bridges towards oxygen functions of an imide (particularly C−H···O=C distances of 2.27 or 2.37 Å) [100]. Thus, we obtained very similar C−H···F−C distances.

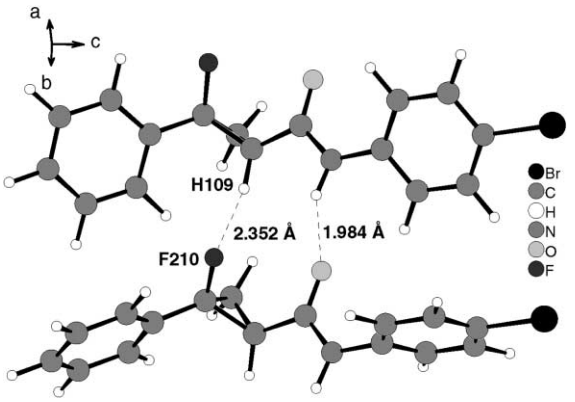


Fig. 3. (1*S*,2*S*)-2-Fluoro-2-phenylcyclopropanecarbox(4-bromophenyl)amide (**6**).

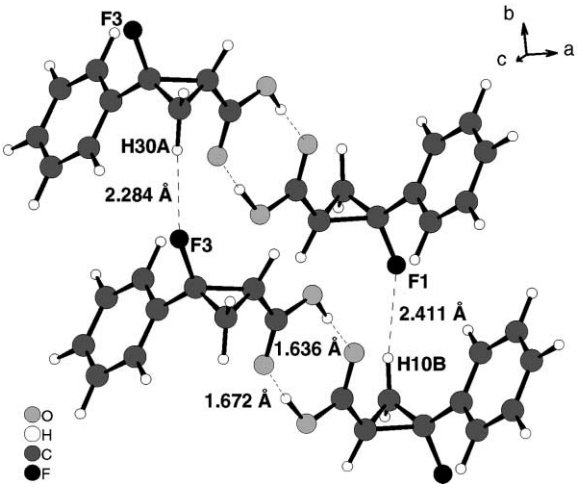


Fig. 4. *cis*-(±)-2-Fluoro-2-phenylcyclopropanecarboxylic acid (**5**).

The structures of the two diastereomeric carboxamides **11** and **12** are quite different in crystalline state. The *trans*-compound **11** shows a symmetric arrangement of the dimers (1.92 Å for the N−H···O=C) and an intermolecular C−H···F−C distance to one of the methylene hydrogens of the cyclopropane ring, which is longer (2.76 Å) than the sum of the van der Waals radii (Fig. 5).

On the other hand, the *cis*-isomer **12** crystallized in a much more complicated structure. There are no very short C−H···F−C contacts and no clear dimeric moieties, but a ''network'' of hydrogen bridges and short contacts of one of the N–H bonds to a carbonyl oxygen were found. Three different hydrogen bridges of this type have been identified, one is 1.96 Å, the second is 1.91 Å and the shortest is 1.88 Å. Surprisingly, there are also three different and very short distances between a C–F group and the second amide hydrogen. There is one of 2.10 Å, another one of 2.09 Å and the third one is even as short as 2.07 Å. These, to the best of our knowledge [89,101], are the shortest intermolecular contacts ever observed for monofluorinated compounds, which can be considered as real hydrogen bridges, because

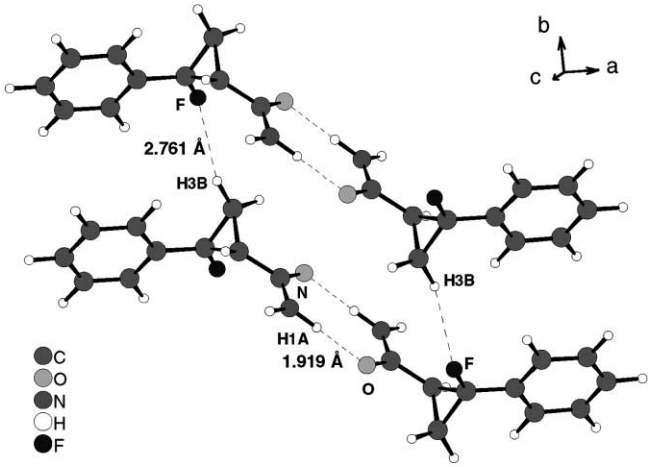


Fig. 5. *trans*-(±)-2-Fluoro-2-phenylcyclopropanecarboxamide (**11**).

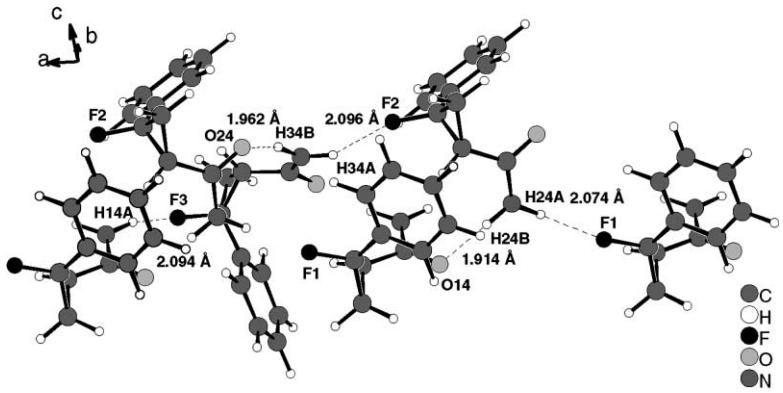


Fig. 6. *cis*-(±)-2-Fluoro-2-phenylcyclopropanecarboxamide (**12**).

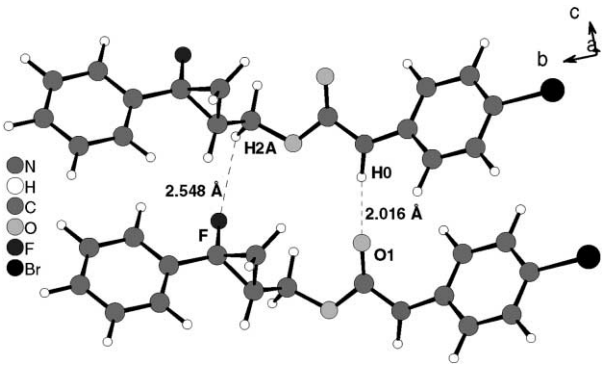


Fig. 7. *N*-(4-Bromophenyl)carbamate of (1*R*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methanol (**24**).

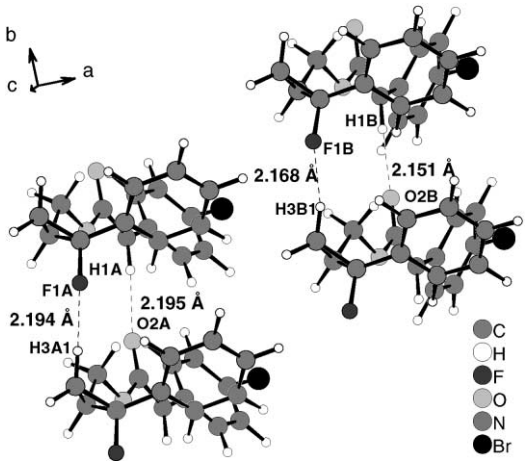
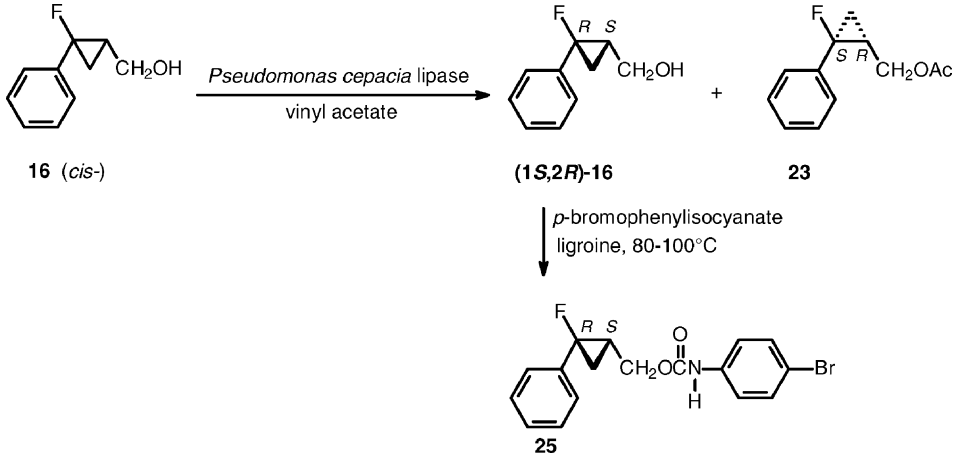


Fig. 8. *N*-(4-Bromophenyl)carbamate of (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methanol (**25**).

also the bond angles of 158–167° meet the criteria of Dunitz and Taylor [89] (Fig. 6).

After reduction of the diastereopure esters **2a** and **3a** to the corresponding cyclopropyl methanols **15** and **16** and enzyme-catalyzed (*Pseudomonas cepacia* lipase (PCL)) resolution of the racemates, we synthesized the corresponding enantiopure *p*-bromophenylcarbamates **24** and **25** in order to determine the absolute configuration. In Scheme 11, the sequence is shown for the *cis*-isomer **25** (see footnote 3).

While the *trans*-isomer **24** showed a C−H···F−C contact, which is only slightly shorter than the sum of the van der Waals radii (2.55 Å, Fig. 7), in the *cis*-diastereomer **25** significantly shorter distances were found (Fig. 8). One is 2.19 Å and the other one is 2.17 Å. These are the shortest contacts of this type found so far.



Scheme 11.

3. Experimental

Synthesis and complete spectroscopic data of compounds **1–10** have been published [58]. Synthesis and complete spectroscopic data of compounds **11–25** will be published in combination with results of biological studies.

X-ray crystal data sets were collected with Nonius CAD4 or KappaCCD diffractometers.

Compound (*S*,*S*)-**4** (CCDC 170381): $C_{10}H_9FO_2$, f.w. = 180.17, $T = 223(2)$ K, $\lambda = 1.54178$ Å. Monoclinic $P2_1$, $a = 12.054(1)$ Å, $b = 5.609(1)$ Å, $c = 12.994(1)$ Å, $\beta = 94.56(1)^\circ$, $V = 875.75(18)$ Å^3, $Z = 4$, $D_c = 1.367$ Mg/m^3, refl. coll. 3932, of which independent 1969 [R(int) = 0.0238]. Full-matrix least-squares refinement on F^2 with 238 parameters, $S = 1.086$, final R indices [$I > 2\sigma(I)$]; $R1 = 0.0378$, $wR2 = 0.1011$; R indices (all data), $R1 = 0.0398$, $wR2 = 0.1036$, absolute structure parameter = 0.11(17), extinction coefficient = 0.0116(17), largest diff. peak and hole = 0.237/(−0.304) e Å^{-3}.

Compound **11** (CCDC 170382): $C_{10}H_{10}FNO$, f.w. = 179.19, $T = 223(2)$ K, $\lambda = 1.54178$ Å. Monoclinic $P2_1/c$, $a = 17.620(3)$ Å, $b = 5.251(1)$ Å, $c = 9.720(1)$ Å, $\beta = 93.68(1)^\circ$, $V = 897.5(2)$ Å^3, $Z = 4$, $D_c = 1.326$ Mg/m^3, refl. coll. 1944, of which independent 1825 [R(int) = 0.0210]. Full-matrix least-squares refinement on F^2 with 118 parameters, $S = 0.967$, final R indices [$I > 2\sigma(I)$]; $R1 = 0.0525$, $wR2 = 0.1247$; R indices (all data), $R1 = 0.1432$, $wR2 = 0.1675$, largest diff. peak and hole = 0.155/(−0.186) e Å^{-3}.

Compound **12** (CCDC 170383): $C_{10}H_{10}FNO$, f.w. = 179.19, $T = 198(2)$ K, $\lambda = 0.71073$ Å. Triclinic $P1$, $a = 9.241(1)$ Å, $b = 9.859(2)$ Å, $c = 15.262(3)$ Å, $\alpha = 78.06(1)^\circ$, $\beta = 80.61(1)^\circ$, $\gamma = 78.47(1)^\circ$, $V = 1322.1(4)$ Å^3, $Z = 6$, $D_c = 1.350$ Mg/m^3, refl. coll. 8389, of which independent 3429 [R(int) = 0.1654], Full-matrix least-squares refinement on F^2 with 352 parameters, $S = 1.034$, final R indices [$I > 2\sigma(I)$]; $R1 = 0.0906$, $wR2 = 0.1525$; R indices (all data), $R1 = 0.1950$, $wR2 = 0.11902$, largest diff. peak and hole = 0.235/(−0.266) e Å^{-3}.

Compound **24** (CCDC 179384): $C_{17}H_{15}BrFNO_2$, f.w. = 364.21, $T = 198(2)$ K, $\lambda = 0.71073$ Å. Orthorhombic $P2_12_12$, $a = 8.840(1)$ Å, $b = 34.535(1)$ Å, $c = 5.054(1)$ Å, $V = 1542.9(4)$ Å^3, $Z = 4$, $D_c = 1.568$ Mg/m^3, refl. coll. 8237, of which independent 3553 [R(int) = 0.0510]. Full-matrix least-squares refinement on F^2 with 199 parameters, $S = 1.017$, final R indices [$I > 2\sigma(I)$]; $R1 = 0.0469$, $wR2 = 0.0895$; R indices (all data), $R1 = 0.0823$, $wR2 = 0.1019$, absolute structure parameter = −0.030(12), largest diff. peak and hole = 0.364/(−0.619) e Å^{-3}.

Compound **25** (CCDC 170385): $C_{17}H_{15}BrFNO_2$, f.w. = 364.21, $T = 198(2)$ K, $\lambda = 0.71073$ Å. Monoclinic $P2_1$, $a = 16.186(1)$ Å, $b = 5.348(1)$ Å, $c = 18.294(1)$ Å, $\beta = 93.91(1)^\circ$, $V = 1579.9(3)$ Å^3, $Z = 4$, $D_c = 1.531$ Mg/m^3 Refl. coll. 9847, of which independent 7096 [R(int) = 0.0429]. Full-matrix least-squares refinement on F^2 with 397 parameters, $S = 1.056$, final R indices [$I > 2\sigma(I)$]; $R1 = 0.0616$, $wR2 = 0.0909$; R indices (all data), $R1 = 0.1260$, $wR2 = 0.1108$, absolute structure parameter = 0.002(11), largest diff. peak and hole = 0.428/−0.599 e Å^{-3}.

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