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Organocatalyzed Sulfa-Michael Addition of Thiophenols on Trisubstituted α -Fluoroacrylates, a Straightforward Access to Chiral Fluorinated Compounds

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Abstract: In this manuscript, a simple and efficient sulfa-Michael addition reaction of aryl thiols to trisubstituted α -fluoro- α,β -unsaturated esters both in racemic and, for the first time, in enantioselective version is reported. The commercially available dimer of cinchona derivatives (DHQ)₂PYR was used as catalyst. This strategy showed a great tolerance for various substrates and substituents, providing fair to excellent yields, moderate to excellent diastereoselectivities (2:1 to > 99:1) and low to good enantioselectivities (2 to 87%). The reaction has been applied to the synthesis of fluorinated analogues of Diltiazem and Tiazesim, both therapeutic agents.

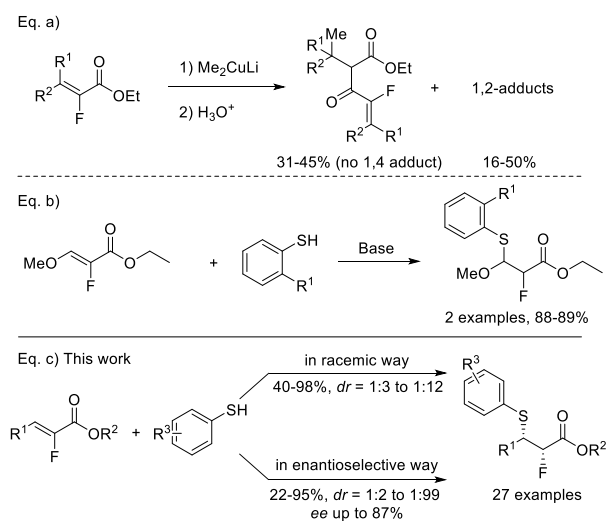
Introduction

Fluorine-containing compounds are widely used in various fields including polymers, pharmaceuticals and agrochemicals.¹ Indeed, due to the highest electronegativity and the small size of the fluorine atom, the incorporation of one or several fluorine atoms into organic compounds often brings unique physical, chemical and biological properties. Considering the importance of chirality as well as the introduction of a fluorinated moiety into organic compounds, the quest for methods to create stereogenic fluorinated carbon centers with high enantioselectivity and catalytic efficiency is highly valuable.² The asymmetric construction of stereogenic fluorinated carbon centers can be achieved by asymmetric direct fluorination or starting from already fluorinated molecules as prochiral sp² substrates. In this context, organocatalysis emerged as a powerful tool in asymmetric synthesis³ and had a large impact on the development of asymmetric and catalytic conjugate additions of various nucleophiles to Michael acceptors for the construction of carbon-carbon and carbon-heteroatom bonds.⁴ In the past few years, part of our research program was dedicated to easy and efficient accesses to 2-fluoroacrylates,⁵ which could serve as Michael acceptor. Surprisingly, whereas the Michael addition is a well-known strategy to obtain highly-functionalized products, only sporadic examples have been reported with

fluoroalkene-type Michael acceptors, while the latter could be a suitable source of fine-fluorinated chemicals. For example, alkyl 2-fluoroacrylates have been used as Michael acceptors since the sixties to the specific synthesis of relevant γ -fluoroglutamic acid.⁶ Other *gem*-fluoro-carbonyl⁷ or -sulfonyl derivatives⁸ have also been submitted to Michael addition in the presence of various nucleophiles but, to our knowledge, no asymmetric reaction as well as no conjugate addition on trisubstituted fluoroalkenes substrates have been reported. Indeed, to the best of our knowledge, the asymmetric 1,4-addition of nucleophiles with β -substituted- α -fluoroacrylates has not been developed yet and only very few examples have been reported in racemic version to date. In an early report, Normant *et al.* studied the addition of lithium dimethylcuprate on α -fluoro- α,β -unsaturated ketones, aldehydes and esters.⁹ Both 1,2- and 1,4-adducts were formed and the ratios depend on the steric hindrance at the β -position of the substrate. Whereas the cuprates are well-known to be 1,4-regioselective,¹⁰ the fluorine atom increased the electrophilicity of the geminal carbonyl moiety allowing the 1,2-adduct formation in non-negligible amount and pointing out the unusual reactivity of fluorinated Michael acceptors. Even more surprisingly, in the case of β -substituted- α -fluoroacrylates, no 1,4-adduct was isolated because the enolate from 1,4-addition underwent a Claisen reaction

to form a dimeric product with concomitant loss of fluorine atom (Scheme 1, Eq a). Later on, in their quest to fluorinated heterocycles, Schlosser et al. reported two examples of 1,4-addition of thiophenols on the 2-fluoro-3-methoxyacrylate, a specially designed Michael acceptor, using a catalytic amount of *t*-BuOK or one equivalent of *n*-BuLi as a base, affording the corresponding 1,4-adduct as a mixture of diastereoisomers in 3:1 to 3:2 ratios and in good yields (Scheme 1, Eq b).¹¹ Considering the dearth of examples for the racemic and asymmetric conjugate addition of nucleophiles with fluoroacrylates, herein we report the Sulfa-Michael Addition (SMA)^{4c,12} of thiophenol derivatives with α -fluoroacrylates both in racemic and enantioselective ways (Scheme 1, Eq. c).

Scheme 1. Conjugate addition on β -substituted- α -fluoroacrylates: state of the art and this work



Two more general points highlighted the relevance of our study, i) sulfur containing-compounds¹³ are very important as biochemical reagents as well as pharmaceutical agents and the one-pot formation of products bearing both sulfur and fluorine atoms could lead to interesting new structures towards biorelevant molecules; ii) whereas the asymmetric SMA reaction is known from a long time and has been studied with a large variety of Michael acceptor,^{4c, 12a} only few organocatalytic studies have been reported with α,β -unsaturated esters substituted in α -¹⁴ or in β -position,¹⁵ and even

less with acrylates substituted in both α and β positions,¹⁶ whereas in the latter two stereogenic centers could be concomitantly formed.

Results and Discussion

We chose the (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (**1a**) as a model Michael-acceptor and the thiophenol as nucleophile to begin our study on SMA reaction. First investigations were carried out in a racemic version. SMA being usually efficiently carried out under basic conditions,^{4c} we decided to consider the low pKa of thiophenol and use the weak base NEt₃ as catalyst. Worthy of note whatever the precaution taken, during the SMA reactions, the oxidation of thiophenol occurred as a side-reaction making the isolation of 1,4-adducts difficult. To minimize the production of disulfide by-products, all the tests were performed in degassed solvents under argon. Traces of 1,4-adducts were identified by ¹⁹F NMR (characteristic doublet of doublet corresponding to two diastereoisomers at -195.0 ppm and -197.0 ppm) when using triethylamine as a catalytic base in dichloromethane; the conversion was not improved when the reaction mixture was heated to reflux for a longer time (Table 1, entries 1-2). Among other solvents tested, acetonitrile appeared as the most suitable one, leading to 50% and 75% conversion at 22°C (room temperature) and 80°C, respectively (Table 1, entries 3-4). 1,4-adduct **3** was isolated in moderate 37% yield due to difficulties to separate product **3** from remaining starting material and disulfide by-products (Table 1, entry 4). The structure of 1,4-adduct was approved by ¹H, ¹³C, ¹⁹F NMR experiments and also by mass spectrometry. Diastereoisomers were obtained in a 77/23 ratio according to ¹⁹F NMR of the crude. The SMA reaction did not proceed in absence of triethylamine (Table 1, entry 5). Noteworthy that the use of sodium thiophenolate instead of the couple thiophenol/triethylamine was totally inefficient.¹⁷ Increasing the amount of thiophenol to 2 equivalents led to an improved 84% yield in 16 hours (Table 1, entry 6). With 2 equivalents of thiophenol, the amount of NEt₃ could be reduced to 0.1 equivalent giving

almost the same isolated yield and *dr* (Table 1, entry 7).

Table 1. Optimization of SMA reactions in racemic version

entry	1a	x	y	2A (x. Equiv.)	Solvent	T °C	Conv. (%) ^a	<i>Dr</i> ^c
1		1.1	0.14		CH ₂ Cl ₂	22 °C	traces	
2 ^d		1.1	0.14		CH ₂ Cl ₂	reflux	traces	
3		1.1	0.14		CH ₃ CN	22 °C	50	
4 ^d		1.1	0.14		CH ₃ CN	80 °C	75 (37)	73:27
5		1.1	-		CH ₃ CN	80 °C	0	
6		2	0.14		CH ₃ CN	80 °C	98 (84)	77:23
7		2	0.1		CH ₃ CN	80 °C	94 (81)	76:24
8		3	0.1		-	80 °C	91 (77)	74:26
9		5	0.1		-	80 °C	100 (89)	76:24
10		10	0.1		-	80 °C	100 (91)	77:23

^aDetermined by ¹⁹F NMR. ^bIsolated yield of mixture of diastereoisomers. ^c*Dr* determined by ¹⁹F NMR of the crude mixture. ^d24h reaction.

We finally found this reaction could be performed in neat thiophenol (Table 1, entries 8-10). Comparing different equivalent of thiophenol, 5 equivalents of thiophenol gave full conversion and 1,4-adducts were isolated in 89% and 76:24 *dr* (Table 1, entry 9). No real improvement was observed with 10 equivalents of thiophenol (Table 1, entry 10). The use of other tertiary amines such as *N,N*-diisopropylethylamine or 1,8-Diazabicyclo-[5.4.0]undéc-7-ène led to lower isolated yields of reaction, while slightly improving the *dr*.¹⁷ Having identified suitable conditions for racemic SMA reactions on α -fluoroacrylates, we rapidly turned our attention to the development of the corresponding asymmetric 1,4-additions screening chiral catalysts and temperatures (Table 2). All the reactions were performed in neat thiophenol according to the previous study. The use of natural cinchona alkaloids,¹⁸ as the cinchonine led to good conversion but no stereodifferentiation (Table 2, entry 1). The use of quinine as catalyst allowed to obtain an enantioselectivity but with low 15% value. Enhancing the catalyst loading to 20 mol% increased the conversion without positive influence on the enantioselectivity. Quinidine gave reverse enantioselectivity compared to quinine, albeit with lower conversion (Table 2, entry 4). The use of aryl ethers of bis-cinchona alkaloids¹⁹ (DHQ)₂PYR

gave full conversion, good diastereoisomeric ratio and allowed to significantly enhance the *ee* value to 66% (Table 2, entry 5).

Table 2. Optimization of asymmetric SMA reaction.

Catalysts

Cinchonine

Quinine

Quinidine

(DHQ)₂PYR

(DHQD)₂PYR

Entry	Catalyst	X	Conv. (%) ^a	<i>Dr</i> ^c	<i>Ee</i> ^d
1	Cinchonine	10	98	86:14	0
2	Quinine	10	90	83:17	15
3	Quinine	20	96	80:20	15
4	Quinidine	10	85	85:15	-13
5	(DHQ) ₂ PYR	10	100	89:11	66
6	(DHQD) ₂ PYR	10	63	88:12	-72
7	(DHQ) ₂ PYR	5	98	87:13	60
8 ^e	(DHQ) ₂ PYR	10	100	85:15	37
9 ^f	(DHQ) ₂ PYR	10	89 (73)	85:15	70
10 ^g	(DHQ) ₂ PYR	10	42	81:19	73
11 ^{f,h}	(DHQ) ₂ PYR	10	100 (82)	84:16	71

^aDetermined by ¹⁹F NMR. ^bIsolated yield of mixture of diastereoisomers. ^c*Dr* determined by ¹⁹F NMR of the crude mixture. ^dDetermined for major diastereoisomer by HPLC. ^eReaction carried out at 80 °C, 16h of reaction. ^fReaction carried out at 0 °C. ^gReaction carried out at -22 °C. ^h5 days of reaction.

The use of (DHQD)₂PYR gave 72% *ee* but incomplete conversion (Table 2, entry 6). Decrease the catalyst loading to 5 mol% decreased both the conversion and the enantiomeric excess (Table 2, entry 7). The reaction carried out at 80 °C was complete after 16h but gave a low 37% *ee* value (Table 2, entry 8). Decrease the temperature allowed to increase the *ee* value to 70% and 73%, at 0 °C and -20 °C, respectively. Nevertheless, the conversion was lower in these conditions (Table 2, entries 9-10). Finally, carrying out the reaction at 0 °C for 5 days furnished full conversion with 71% of enantiomeric excess.

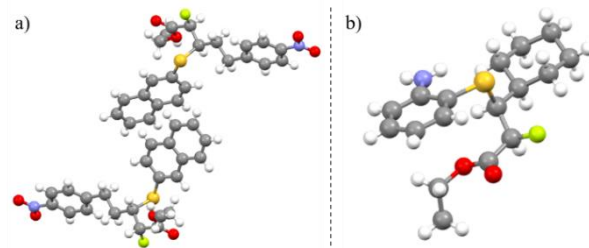
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Noteworthy that we tested more than fifteen catalysts, included other natural or modified cinchona alkaloids, chiral amines and also urea derivatives,²⁰ including the Takemoto's urea^{20a} which was already used successfully in SMA reaction, but the best results were obtained with (DHQ)₂PYR as a catalyst.¹⁷ Other dimers were also tested such as (DHQ)₂PHAL and (DHQ)₂AQN but these catalysts gave lower ees. It is important to note that, in order to increase the enantiomeric excess, we studied the influence of about fifteen solvents on the reaction. None of them was more efficient than the reaction carried out in neat thiophenol.¹⁷ Finally, the use of bulkier ester than methyl or ethyl group such as *iso*-propyl or *tert*-butyl group led to lower yields and ees.¹⁷ (DHQ)₂PYR, giving the best result in terms of conversion, diastereoisomeric and enantiomeric excesses, was selected to study the scope of the reaction with thiophenol acting both as reagent and solvent. With the optimized conditions in hand, the scope of SMA reaction of a variety of thiols on some α -fluoroacrylates was investigated in both racemic and enantioselective ways (Scheme 2). We will first comment briefly about the racemic process before discussing more in details the asymmetric SMA reaction.

Mostly, the racemic way furnished good to excellent yield (61 to 98% yield) whatever the substituent contained in thiol or fluoroacrylate, except for compounds **17**, **21** and **27**, for which the yield is below 50% (40 to 46%). Diastereomeric ratios were obtained in a range from 71:29 to 92:8 with a major diastereoisomer in favor of the *syn*-configuration. This stereoselectivity was ascertained by X-ray analysis of crystals obtained from racemic product **13** (Figure 1, a).^{21a}

For asymmetric reaction, with the (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate **1a**, aryl thiols bearing electron-donating groups, such as methyl (in ortho, meta and para position), methoxy or amino, successfully furnished the desired products **5-9** in good to excellent yields (74-95%) and good to very good diastereoselectivities (81:19 to 95:5). For

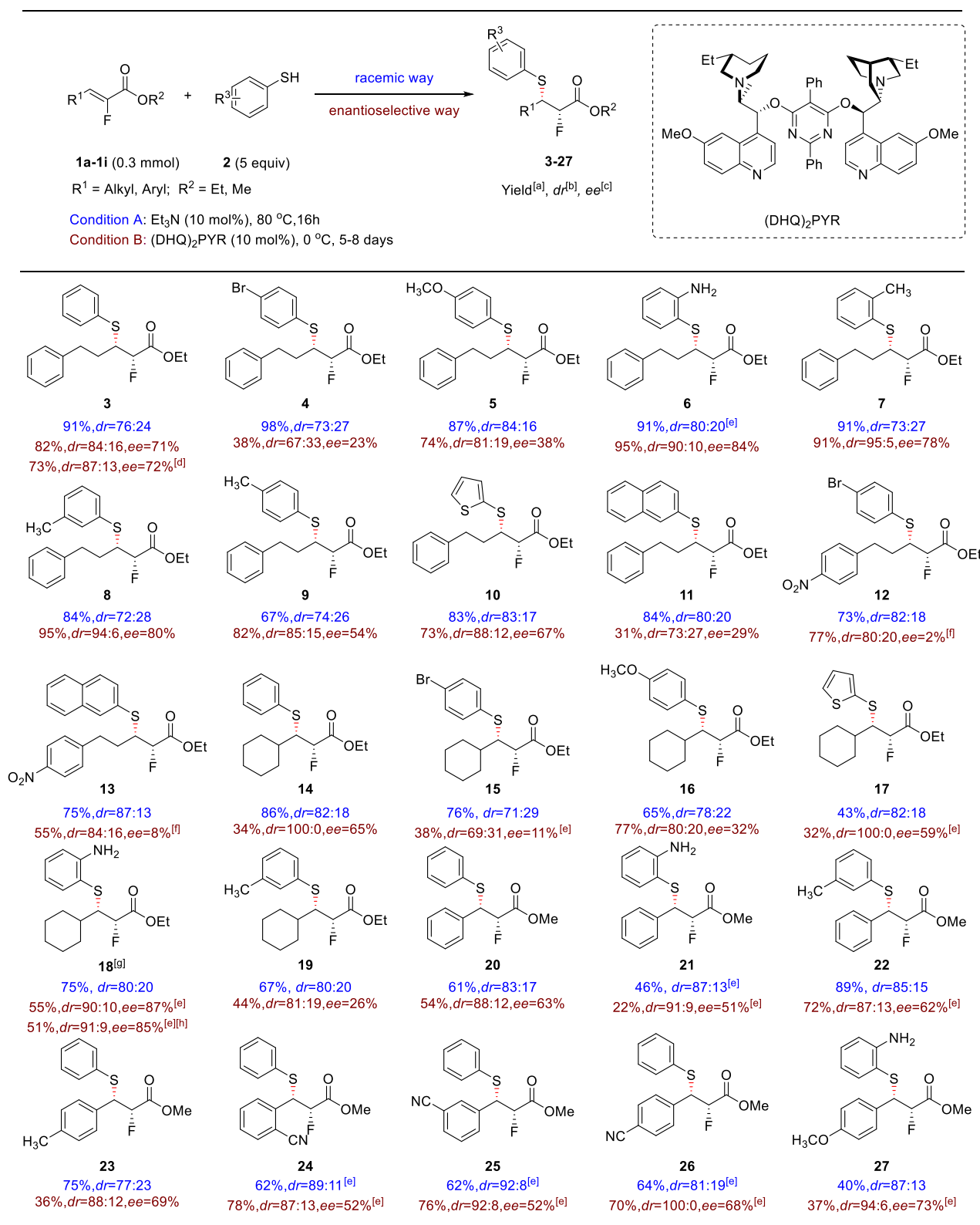
unsubstituted **3** and ortho- or meta-substituted thioaryl **6-8**, good ees were obtained (71 to 84%). However, thioaryl bearing a substituent in para-position **4** (*p*-Br), **5** (*p*-OMe) and **9** (*p*-Me) were obtained in low to fair ee values: 23%, 38% and 54%, respectively. Unfortunately, 2-thionaphthol, which proved to be the best arylthiol in the asymmetric 1,4-addition to cyclic enones,^{19b} furnished the product **11** with only 29% of ee. The substrate scope could be extended to thiophene thiol to give 1,4-adduct **10** in good 73% yields, 88:12 *dr* ratio and 67% of ee. Additions of 4-bromothiophenol and naphthyl thiol to a fluorinated Michael acceptor bearing a nitro-aryl substituent occurred also in good yields and diastereoselectivities, but without enantioselectivities for products **12** and **13**. Usually, diastereomeric ratios were better in enantioselective version of the reaction than in racemic one, except for compounds **4** and **11**. Cyclohexyl α -fluoroacrylate **1c** was also used in the SMA reaction, giving moderate to good yields (32 to 77%), good to complete diastereoselectivities, from 69:31 for **15**, bearing a bromine atom in para position, to 100:0 leading to the formation of a single diastereoisomer for the products **14** and **17**, obtained from thiophenol and thiophene thiol, respectively. As for substrate **1a**, substitution in *para*-position was detrimental for ee giving low value for products **15** and **16**. Substitution in meta-position led also, in this case, to low 26% of ee. Product **18** obtained from 2-aminothiophenol gave the best enantiomeric excess 87%. The X-ray analysis of **18** crystals confirmed the *syn* configuration and revealed that the two stereogenic centers are both in *S*



absolute configurations (Figure 1, b).^{21b}

Figure 1. a) X-ray of major diastereoisomers of **13** obtained in racemic way (mixture of *syn* enantiomers). b) X-ray of major enantiomer of **18**

Scheme 2. Scope of the SMA reaction on α -fluoroacrylates.

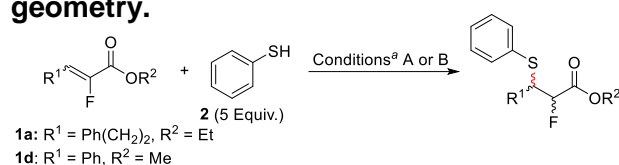


^aIsolated yield of diastereoisomers. ^bDetermined by ¹⁹F NMR of crude mixture. ^cDetermined for major diastereoisomer by HPLC. ^dReaction performed on 1.5 mmol scale of α -fluoroacrylate **1a**. ^eReaction carried out at 22 °C (room temperature). ^fToluene as solvent. ^gAbsolute configuration of **18** was determined by single crystal X-Ray diffractometer; the two stereogenic centres are both in *S* absolute configuration. ^hReaction performed on 1 mmol scale of α -fluoroacrylate **1c**.

Then, we studied SMA addition on different aryl α -fluoroacrylates (**1d-i**). Generally, with aryl α -fluoroacrylates lower yields, compared to alkyl-fluoroacrylates **1a-c**, were obtained in 1,4-adducts **20-27** (22 to 78%), albeit with very good to excellent diastereoselectivities (87:13 to 100:0). Fair to good *ee* were obtained for these aryl substrates in a range from 51 to 73%. α -Fluorocinnamates bearing a cyano group at the ortho-, meta-, and para-position of phenyl moiety gave the desired products **24-26** in similar results showing no significant substituent effects. Whereas the electronic feature of fluoroacrylates or aryl thiol does not seem to have an impact on the reaction, having a substituent in position para of the aryl thiol implied a lack of stereoselectivity meaning that the approach of the thiol is important in the enantioselective process. A kinetic study showed that the *dr* and *ee* did not evolve from the beginning to the completion of the reaction.¹⁷ To get insight in the influence of the double bond geometry, we synthesized substrates **1a** and **1d** in *E* configuration and submitted them to the SMA reaction. Interestingly, while similar yields and enantiomeric excesses for the major diastereoisomer were achieved, reversed diastereoisomer ratios were obtained starting with (*E*)-fluoroacrylates in place of its (*Z*)-congener, meaning that the face attack does not vary with the geometry of the double bond (Table 3). It has to be noted that for the reaction of (*E*)-**1d**, there was a little amount of (*Z*)-isomer in (*E*)-substrate (*E/Z* ratio: 90:10, (*Z*)-**1d** coming from the synthesis of starting material) explaining the lower *dr* obtained (Table 3, entries 4 and 8). Ninomiya's research group reported the same kind of reversal *dr* depending of double bond configuration with the SMA reaction between thiophenol and α,β -trisubstituted acrylates in the presence of a catalytic amount of base and proposed a concerted process to explain their results.²² In our case, we probably have also a concerted mechanism with the thiol adding preferentially on the *Si* face of the β -position of the alkene, and the concomitant protonation on the opposite *Re* face of the α -position. A substituent in para-position of the aryl-thiol should prevent the stereodifferentiation by

steric hindrance. Two reactions on a larger scale were done with success starting from **1a** (1.5 mmol) and **1c** (1 mmol), furnishing the desired products **3** and **18** in 73% of isolated yield, 87:13 of *dr*, 72% of *ee* and 51% of isolated yield, 91:9 of *dr*, 85% of *ee*, respectively.

Table 3. influence of the double bond geometry.



Entry	Substrate	Cond.	Yield (%) ^[b]	<i>Dr</i> ^[c]	<i>Ee</i> ^[d] (%)
1	(<i>Z</i>)- 1a	A	91	76:24	-
2	(<i>E</i>)- 1a	A	93	26:74	-
3	(<i>Z</i>)- 1d	A	61	87:13	-
4	(<i>E</i>)- 1d ^[e]	A	74	33:67	-
5	(<i>Z</i>)- 1a	B	82	84:16	71
6	(<i>E</i>)- 1a	B	86	14:86	74
7	(<i>Z</i>)- 1d	B	54	88:12	63
8	(<i>E</i>)- 1d ^[e]	B	56	24:76	51

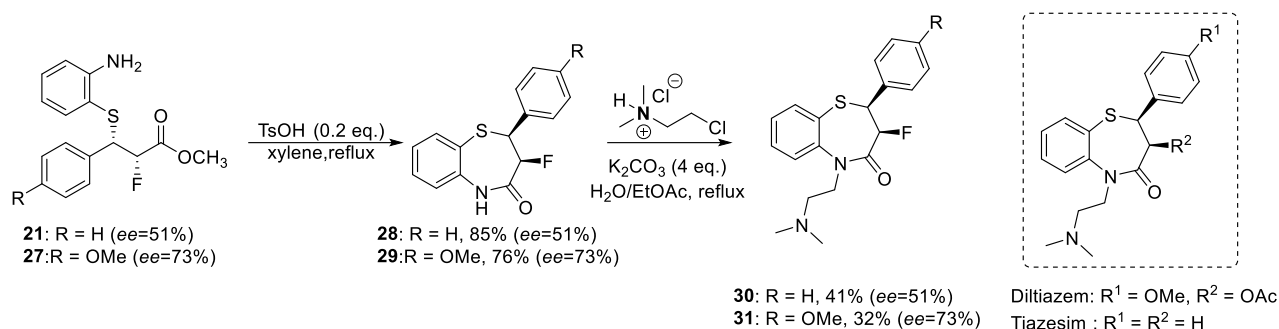
^aConditions A = NEt₃ (10 mol%), 80°C, overnight; Conditions B = (DHQD)₂PYR (10 mol%), 0°C, 8 days. ^bIsolated yield of mixture of diastereoisomers. ^c*Dr* determined by ¹⁹F NMR of the crude mixture. ^dDetermined for major diastereoisomer by HPLC. ^eContaminated with 10% of (*Z*)-**1d**.

Finally, we applied our methodology to the synthesis of fluorinated analogues of biomolecules from both **21** and **27** compounds as starting materials. A two-step synthesis,²³ a cyclisation under acid catalysis followed by an alkylation reaction, allowed to obtain, without variation of *ees*, fluoroanalogues of both Diltiazem, a calcium channel blocker, clinically used since 1974 as an antianginal and antihypertensive agent, and Tiazesim, an antidepressant agent (Scheme 3).²⁴

Conclusion

In summary, we developed a simple and efficient sulfa-Michael addition reaction on β -substituted- α -fluoroacrylates in both racemic, and for the first time, in enantioselective version. This strategy shows great tolerance of various substrates and substituents, providing modest to excellent yields and moderate to good diastereoselectivities in racemic way (40-98%, *dr* = 3:1 to 12:1).

Scheme 3. Synthesis of fluorinated analogues of biomolecules.



In enantioselective way, good levels of reactivity, fair to excellent diastereoselectivities and moderate to good enantioselectivities were achieved by using commercially available (DHQ)₂PYR as catalyst (22-95%, *dr* =2:1 to >99:1, *ee* up to 87%). Two fluorinated analogues of therapeutic agents were successfully synthesized using this SMA strategy. Other Michael addition with fluorinated Michael acceptors are presently under study in our laboratory.

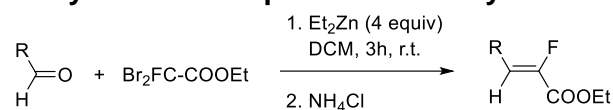
Experimental Section

General Information: Unless otherwise mentioned, all the reagents were purchased from commercial source and used without further purification. All reactions were carried out in oven dried sealed tube under argon. Reaction temperatures were reported as the temperature of the bath surrounding the vessel. The dry solvents used were purified by distillation over the dry agents indicated in brackets and were transferred under argon: THF (Na, benzophenone), CH₂Cl₂ (CaH₂), toluene (Na, benzophenone). Anhydrous DMF, CH₃CN, 1,4-dioxane, Et₂O and DME were purchased from Acros Organics (Solvents Extra Dry over Molecular Sieve, Acroselect). Flash chromatography was carried out using Silicaflash P60 silica gel (40-60 mm); solvents used: PE = petroleum ether, EA = ethyl acetate. Melting points (Mp) were determined on a Fisher Scientific hot stage melting point apparatus and are uncorrected. ¹H, ¹³C and ¹⁹F NMR spectra were recorded using a Bruker Avance-300 spectrometer operating at 300 MHz (¹H), 75 MHz (¹³C) and 282 MHz (¹⁹F), using CDCl₃ as NMR solvent. The chemical

shifts (δ) were calibrated on residual proton and carbon resonances of CDCl₃ (¹H, δ = 7.26 ppm and ¹³C, δ = 77.2 ppm) or relative to external CFCI₃ (¹⁹F, δ = 0.0 ppm). The multiplicity signals were indicated with the common abbreviations: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad) and the combinations thereof. IR spectra were recorded on Perkin Elmer Spectrum 100 FT IR spectrometer. High Resolution Mass Spectra (HRMS) were recorded on a JEOL AccuToF 4G spectrometer coupled to a GC HP Agilent 7890. Enantiomeric excesses (*ee*) were determined by using a SpectraSYSTEM™ HPLC equipped with a P1000XR pump, a UV1000 detector and a Rheodyne injector. See specific conditions detailed for each compound.

General Procedure for Synthesis of Fluoroacrylates.

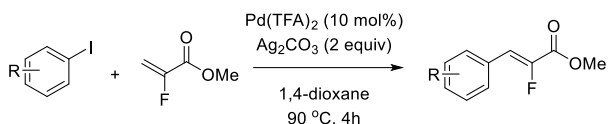
Synthesis of aliphatic fluoroacrylates^{5a}



To an anhydrous CH₂Cl₂ solution (10 mL/mmol of aldehyde) of the appropriate aldehyde (1.0 equiv) and ethyl dibromofluoroacetate (2.0 equiv) was added diethylzinc (1 M in hexane, 4.0 equiv) dropwise under argon. The reaction mixture was stirred during 3 h at 22°C (room temperature) (until *anti* alcohol was not detected by ¹⁹F NMR). The resulting solution was then poured into saturated NH₄Cl, CH₂Cl₂ was evaporated under vacuum, EtOAc was added, and the mixture was stirred for 15 min. The remaining zinc salts were filtered off through a Büchner funnel. The heterogeneous

resulting solution was extracted twice with Et₂O (2×20 mL/mmol of aldehyde), dried over MgSO₄, and concentrated under reduced pressure and then purified by flash silica gel column chromatography.

Synthesis of aromatic fluoroacrylates^{5b}



In a vial was added iodoarene (1.0 equiv), fluoroacrylate (1.5 equiv), Ag₂CO₃ (2.0 equiv) and Pd(TFA)₂ (10 mol%). The vial was then filled with 1,4-dioxane (5 mL/mmol of iodoarene), then was heated to 90 °C (oil bath) for 4 h. The crude was filtrated over celite, washed with EA (3×30 mL/mmol of iodoarene), then solvent were evaporated. The crude was then purified by flash silica gel column chromatography.

General Procedure for Sulfa-Michael Addition of Fluoroacrylates.

a) Racemic pathway:

In an over-dried sealed tube, α-fluoroacrylate 1 (0.3 mmol, 1equiv), thiol 2 (1.5 mmol, 5 equiv) followed by NEt₃ (0.03 mmol, 10 mol%) were introduced, the tube was sealed and then freezed by liquid nitrogen, removed the air under high vacuum and introduced argon. The reaction mixture was stirred at 80 °C (oil bath) for 16 hours and then was cooled to room temperature. The reaction mixture was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc or petroleum ether /CH₂Cl₂).

b) Enantioselective pathway:

In an over-dried sealed tube, α-fluoroacrylate (0.3 mmol, 1equiv), thiol (1.5 mmol, 5 equiv) followed by (DHQ)₂PYR (0.03 mmol, 10 mol%) were introduced, the tube was sealed and then freezed by liquid nitrogen, removed the air under high vacuum and introduced argon. The reaction mixture was stirred at 0 °C or at 22°C (room temperature) for five to eight days. Then the reaction mixture was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc or petroleum ether /CH₂Cl₂).

Characterization Data for Products:

(2*S*,3*S*)-ethyl 2-fluoro-5-phenyl-3-(phenylthio)pentanoate (**3**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat thiophenol (1.5 mmol, 165 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 84:16. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 82% yield (major: 67 mg as a colorless oil; minor: 14 mg as a colorless oil). 71% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 6.810 min, *t* (major) = 7.507 min.]. The reaction performed on 1.5 mmol of (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate led to 73% of isolated yield (major: 304 mg, major and minor mixture: 59 mg), *dr*:87:13 and ee: 72% (major diastereoisomer). The racemic product has been obtained following the procedure **a** (the same scale) in 91% yield (major: 80 mg as a colorless oil; minor: 11 mg as a colorless oil) with *dr* = 76:24. [α]_D²⁰ = -18.0 (c 1.23, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.37 – 7.34 (m, 2H), 7.22 – 7.05 (m, 8H), 4.97 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.13 – 3.89 (m, 2H), 3.49 – 3.33 (m, 1H), 2.92 – 2.68 (m, 2H), 2.09 – 1.91 (m, 2H), 1.12 (t, 3H, J_{H-H} = 9.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -197.0 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 28.2 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.9 (d, ²J_{C-F} = 22.5 Hz), 140.7, 133.8, 132.9, 129.0, 128.5, 128.5, 127.6, 126.2, 90.5 (d, ¹J_{C-F} = 195.0 Hz), 61.7, 50.5 (d, ²J_{C-F} = 22.5 Hz), 33.4, 33.2, 14.0. IR: 2980, 1761, 1737, 1475, 1266, 1212, 1103, 1024, 745, 692, 557, 491 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₉H₂₂FO₂S: 333.1325, found: 333.1319.

(2*S*,3*R*)-ethyl 2-fluoro-5-phenyl-3-(phenylthio)pentanoate (**anti-3**). (*E*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat thiophenol (1.5 mmol, 165 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 14:86. The crude was purified by silica gel

column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 86% yield (major: 39 mg as a colorless oil; major and minor mixture: 47 mg). 74% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 230 nm, t (minor) = 5.340 min, t (major) = 5.803 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 93% yield (major: 72 mg as a colorless oil; minor: 21 mg as a colorless oil) with *dr* = 26:74.

¹H NMR (300 MHz, CDCl₃): δ 7.40 – 7.37 (m, 2H), 7.25 – 7.09 (m, 8H), 4.80 (dd, 1H, ²*J*_{H-H} = 48.0 Hz, *J*_{H-H} = 6.0 Hz), 4.07 (q, 2H, *J*_{H-H} = 6.0 Hz), 3.42 – 3.31 (m, 1H), 2.94 – 2.70 (m, 2H), 1.94 – 1.87 (m, 2H), 1.13 (t, 3H, *J*_{H-H} = 9.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -195.7 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 22.6 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.1 (d, ²*J*_{C-F} = 22.5 Hz), 140.8, 133.2, 132.9, 129.2, 128.5, 127.9, 126.2, 90.3 (d, ¹*J*_{C-F} = 195.0 Hz), 61.8, 49.5 (d, ²*J*_{C-F} = 15.0 Hz), 32.8, 30.6, 14.1.

(2*S*,3*S*)-ethyl 3-((4-bromophenyl)thio)-2-fluoro-5-phenylpentanoate (**4**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 4-bromobenzenethiol (1.5 mmol, 281 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 67:33. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 38% yield (major: 38 mg as a white solid; minor: 9 mg as a white solid). 23% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 98/2, flow = 1 mL/min, λ = 254 nm, t (minor) = 9.810 min, t (major) = 11.183 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 98% yield (major: 107 mg as a white solid; minor: 13 mg as a white solid) with *dr* = 73:27.

$[\alpha]_D^{20}$ = -6.1 (c 1.09, CDCl₃); Mp 54-56 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.34 – 7.31 (m, 2H), 7.22 – 7.06 (m, 7H), 4.97 (dd, 1H, ²*J*_{H-F} = 51.0 Hz, *J*_{H-H} = 3.0 Hz), 4.13 – 4.02 (m, 2H), 3.41 – 3.29 (m, 1H), 2.85 – 2.73 (m, 2H), 2.07 – 1.93

(m, 2H), 1.17 (t, 3H, *J*_{H-H} = 6.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -197.2 (dd, ²*J*_{F-H} = 51.0 Hz, ³*J*_{F-H} = 31.0 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.8 (d, ²*J*_{C-F} = 22.5 Hz), 140.4, 134.5, 132.8, 132.0, 128.6, 128.5, 126.3, 122.0, 90.6 (d, ¹*J*_{C-F} = 187.5 Hz), 61.8, 50.4 (d, ²*J*_{C-F} = 15.0 Hz), 33.3, 33.1, 14.1. IR: 2920, 1757, 1474, 1209, 1091, 815, 695, 585, 478 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₉H₂₁BrFO₂S: 411.0430, found: 411.0429.

(2*S*,3*S*)-ethyl 2-fluoro-3-((4-methoxyphenyl)thio)-5-phenylpentanoate (**5**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 4-methoxybenzenethiol (1.5 mmol, 210 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 81:19. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 49/1 to 19/1, v/v) affording two diastereoisomers in 74% yield (major: 71 mg as a colorless oil; minor: 9 mg as a colorless oil; major and minor mixture: 12 mg). 38% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 8.783 min, t (major) = 9.857 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 87% yield (major: 78 mg as a colorless oil; minor: 19 mg as a colorless oil) with *dr* = 84:16.

$[\alpha]_D^{20}$ = -10.4 (c 0.57, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.36 – 7.33 (m, 2H), 7.19 – 7.06 (m, 5H), 6.75 – 6.73 (m, 2H), 4.92 (d, 1H, ²*J*_{H-F} = 48.0 Hz), 4.16 – 4.01 (m, 2H), 3.71 (s, 3H), 3.27 – 3.17 (m, 1H), 2.89 – 2.70 (m, 2H), 1.99 – 1.88 (m, 2H), 1.17 (t, 3H, *J*_{H-H} = 6.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -197.1 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 28.2 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.1 (d, ²*J*_{C-F} = 30.0 Hz), 159.9, 140.9, 136.2, 128.6, 128.5, 126.2, 123.4, 114.5, 90.8 (d, ¹*J*_{C-F} = 187.5 Hz), 61.7, 55.4, 51.1 (d, ¹*J*_{C-F} = 22.5 Hz), 33.2, 33.0, 14.1. IR: 2940, 1760, 1455, 1494, 1245, 1026, 829, 699, 525, 493 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₂₀H₂₄FO₃S: 363.1430, found: 363.1426.

(2*S*,3*S*)-ethyl 3-((2-aminophenyl)thio)-2-fluoro-5-phenylpentanoate (**6**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 2-aminobenzenethiol (1.5 mmol, 188 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 90:10. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 95% yield (major: 89 mg as a yellow oil; major and minor mixture: 11 mg). 84% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 230 nm, *t* (minor) = 11.380 min, *t* (major) = 15.850 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 91% yield (major: 61 mg as a yellow oil; major and minor mixture: 34 mg) with *dr* = 80:20.

[α]_D²⁰ = +13.4 (c 1.08, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.30 – 7.02 (m, 7H), 6.63 – 6.56 (m, 2H), 4.92 (d, 1H, ²*J*_{H-F} = 48.0 Hz), 4.32 (s, 2H), 4.10 – 3.95 (m, 2H), 3.36 (d, 1H, *J* = 27 Hz), 2.85 – 2.75 (m, 2H), 2.07 – 1.91 (m, 2H), 1.15 (t, 3H, *J*_{H-H} = 6.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -196.0 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 25.4 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.1 (d, ²*J*_{C-F} = 22.5 Hz), 149.2, 140.7, 137.3, 130.5, 128.5, 128.4, 126.2, 118.4, 115.1, 114.9, 89.8 (d, ¹*J*_{C-F} = 187.5 Hz), 61.8, 49.6 (d, ²*J*_{C-F} = 15.0 Hz), 33.2, 32.9, 14.0. IR: 3468, 3371, 2925, 1754, 1607, 1479, 1216, 1103, 1022, 857, 747, 699, 454 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₉H₂₃FNO₂S: 348.1434, found: 348.1426.

(2*S*,3*S*)-ethyl 2-fluoro-5-phenyl-3-(*o*-tolylthio)pentanoate (**7**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 2-methylbenzenethiol (1.5 mmol, 186 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 95:5. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 91% yield (major: 78 mg as a colorless oil; major and minor mixture: 16 mg). 78% *ee* was obtained for the major

diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 5.793 min, *t* (major) = 6.470 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 91% yield (major: 68 mg as a colorless oil; major and minor mixture: 26 mg) with *dr* = 73:27.

[α]_D²⁰ = +29.4 (c 0.68, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.24 – 7.06 (m, 9H), 4.98 (d, 1H, ²*J*_{H-F} = 48.0 Hz), 4.08 – 3.83 (m, 2H), 3.57 – 3.45 (m, 1H), 2.84 – 2.75 (m, 2H), 2.34 (s, 3H), 2.15 – 1.97 (m, 2H), 1.10 (t, 3H, *J*_{H-H} = 9.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -196.5 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 28.2 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.8 (d, ²*J*_{C-F} = 22.5 Hz), 140.6, 140.1, 133.3, 132.3, 130.4, 128.5, 128.5, 127.4, 126.5, 126.2, 90.0 (d, ¹*J*_{C-F} = 187.5 Hz), 61.7, 49.7 (d, ²*J*_{C-F} = 22.5 Hz), 33.5, 33.2, 20.9, 13.9. IR: 2935, 1761, 1736, 1454, 1299, 1212, 1025, 747, 699, 558, 438 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₂₀H₂₄FO₂S: 347.1481, found: 347.1480.

(2*S*,3*S*)-ethyl 2-fluoro-5-phenyl-3-(*m*-tolylthio)pentanoate (**8**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 3-methylbenzenethiol (1.5 mmol, 186 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 94:6. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 95% yield (major: 86 mg as a colorless oil; major and minor mixture: 13 mg). 80% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 6.873 min, *t* (major) = 7.530 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 84% yield (major: 66 mg as a colorless oil; major and minor mixture: 21 mg) with *dr* = 72:28.

[α]_D²⁰ = -18.8 (c 0.89, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.23 – 6.97 (m, 9H), 4.97 (d, 1H, ²*J*_{H-F} = 48.0 Hz, *J*_{H-H} 3.0 Hz), 4.12 – 3.93 (m, 2H), 3.47 – 3.34 (m, 1H), 2.91 – 2.69 (m, 2H), 2.23 (s, 3H), 2.06 – 1.89 (m, 2H), 1.13 (t, 3H, *J*_{H-H} = 9.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃):

δ -196.8 (dd, $^2J_{F-H} = 48.0$ Hz, $^3J_{F-H} = 28.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.0 (d, $^2J_{C-F} = 22.5$ Hz), 140.7, 138.7, 133.5, 133.3, 129.7, 128.8, 128.5, 128.4, 126.2, 90.5 (d, $^1J_{C-F} = 187.5$ Hz), 61.7, 50.4 (d, $^2J_{C-F} = 22.5$ Hz), 33.4, 33.1, 21.3, 14.0. IR: 2933, 1762, 1737, 1454, 1299, 1212, 1025, 749, 698, 557, 432 cm^{-1} . HRMS (API⁺) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{FO}_2\text{S}$: 347.1481, found: 347.1479.

(2*S*,3*S*)-ethyl 2-fluoro-5-phenyl-3-(*p*-tolylthio)pentanoate (**9**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 4-methylbenzenethiol (1.5 mmol, 186 mg) at 0 °C for 5 days according to the general procedure **b**. ^{19}F NMR of crude product showed $dr = 85:15$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 82% yield (major: 77 mg as a colorless oil; minor: 8 mg as a colorless oil). 54% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 7.347 min, t (major) = 8.143 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 67% yield (major: 31 mg as a colorless oil; minor: 9 mg as a colorless oil; major and minor mixture: 30 mg) with $dr = 74:26$.

$[\alpha]_{\text{D}}^{20} = -14.0$ (c 0.84, CDCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.28 – 7.00 (m, 9H), 4.94 (d, 1H, $^2J_{H-F} = 48.0$ Hz), 4.13 – 3.97 (m, 2H), 3.40 – 3.25 (m, 1H), 2.92 – 2.68 (m, 2H), 2.24 (s, 3H), 2.03 – 1.91 (m, 2H), 1.15 (t, 3H, $J_{H-H} = 6.0$ Hz). ^{19}F NMR (282 MHz, CDCl_3): δ -196.8 (dd, $^2J_{F-H} = 48.0$ Hz, $^3J_{F-H} = 28.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.0 (d, $^2J_{C-F} = 22.5$ Hz), 140.8, 137.9, 133.5, 129.7, 129.7, 128.5, 128.5, 126.2, 90.6 (d, $^1J_{C-F} = 187.5$ Hz), 61.7, 50.7 (d, $^2J_{C-F} = 15.0$ Hz), 33.2, 33.2, 21.1, 14.0. IR: 2920, 1762, 1737, 1493, 1300, 1211, 1104, 1020, 811, 749, 699, 556, 496 cm^{-1} . HRMS (API⁺) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{FO}_2\text{S}$: 347.1481, found: 347.1481.

(2*S*,3*S*)-ethyl 2-fluoro-5-phenyl-3-(thiophen-2-ylthio)pentanoate (**10**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred

in neat thiophene-2-thiol (1.5 mmol, 174 mg) at 0 °C for 5 days according to the general procedure **b**. ^{19}F NMR of crude product showed $dr = 88:12$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 73% yield (major: 41 mg as a yellow oil; major and minor mixture: 33 mg). 67% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 6.183 min, t (major) = 7.050 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 83% yield (major: 60 mg as a yellow oil; major and minor mixture: 24 mg) with $dr = 83:17$.

$[\alpha]_{\text{D}}^{20} = -15.7$ (c 0.69, CDCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.33 – 7.31 (m, 1H), 7.24 – 7.10 (m, 6H), 6.92 – 6.89 (m, 1H), 4.91 (dd, 1H, $^2J_{H-F} = 48.0$ Hz, $J_{H-H} = 6.0$ Hz), 4.20 – 4.08 (m, 2H), 3.21 – 3.14 (m, 1H), 2.95 – 2.73 (m, 2H), 1.99 – 1.91 (m, 2H), 1.21 (t, 3H, $J_{H-H} = 6.0$ Hz). ^{19}F NMR (282 MHz, CDCl_3): δ -196.5 (dd, $^2J_{F-H} = 48.0$ Hz, $^3J_{F-H} = 25.4$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 167.9 (d, $^2J_{C-F} = 22.5$ Hz), 140.7, 136.5, 130.8, 130.6, 128.6, 128.5, 127.6, 126.2, 90.4 (d, $^1J_{C-F} = 195.0$ Hz), 61.8, 52.4 (d, $^2J_{C-F} = 15.0$ Hz), 33.1, 32.5, 32.4, 14.1. IR: 2940, 1760, 1737, 1216, 1023, 847, 749, 698, 493 cm^{-1} . HRMS (API⁺) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{20}\text{FO}_2\text{S}_2$: 339.0889, found: 339.0899.

(2*S*,3*S*)-ethyl 2-fluoro-3-(naphthalen-2-ylthio)-5-phenylpentanoate (**11**). (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat naphthalene-2-thiol (1.5 mmol, 240 mg) at 0 °C for 8 days according to the general procedure **b**. ^{19}F NMR of crude product showed $dr = 73:27$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 31% yield (major: 27 mg as a colorless oil; major and minor mixture: 8 mg). 29% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 7.777 min, t (major) = 8.900 min.]. The racemic product has been obtained following the procedure **a** (the same

scale) in 84% yield (major: 80 mg as a colorless oil; major and minor mixture: 16 mg) with $dr = 80:20$.

$[\alpha]_D^{20} = -7.7$ (c 0.57, CDCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.80 – 7.65 (m, 4H), 7.41 – 7.38 (m, 3H), 7.21 – 7.06 (m, 5H), 5.01 (d, 1H, $^2J_{\text{H-F}} = 48.0$ Hz), 4.06 – 3.86 (m, 2H), 3.60 – 3.46 (m, 1H), 2.95 – 2.72 (m, 2H), 2.12 – 2.00 (m, 2H), 1.07 (t, 3H, $J_{\text{H-H}} = 6.0$ Hz). $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ -196.8 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 167.9 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 140.8, 133.5, 132.4, 131.6, 131.1, 129.8, 128.6, 128.5, 127.7, 127.4, 126.6, 126.4, 126.3, 90.5 (d, $^1J_{\text{C-F}} = 187.5$ Hz), 61.7, 50.3 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 33.4, 33.2, 14.0. IR: 2933, 1760, 1736, 1497, 1454, 1212, 1103, 1023, 858, 814, 744, 699, 475 cm^{-1} . HRMS (API⁺) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{FO}_2\text{S}$: 383.1481, found: 383.1477.

(2S,3S)-ethyl 3-((4-bromophenyl)thio)-2-fluoro-5-(4-nitrophenyl)pentanoate (**12**). (*Z*)-ethyl 2-fluoro-5-(4-nitrophenyl)pent-2-enoate (0.3 mmol, 80.1 mg), 4-bromobenzenethiol (1.5 mmol, 283.5 mg) with $(\text{DHQ})_2\text{PYR}$ (0.03 mmol, 26.4 mg) were stirred in toluene at 0 °C for 8 days according to the general procedure **b**. $^{19}\text{F NMR}$ of crude product showed $dr = 80:20$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 77% yield (major: 72 mg as a yellow oil; major and minor mixture: 33 mg). 2% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 99/1, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 125.503 min, t (major) = 115.393 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 73% yield (major: 75 mg as a yellow oil; major and minor mixture: 24 mg) with $dr = 82:18$.

$[\alpha]_D^{20} = -0.34$ (c 0.87, CDCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.07 (d, 2H, $J_{\text{H-H}} = 9.0$ Hz), 7.37 – 7.34 (m, 2H), 7.27 – 7.19 (m, 4H), 4.98 (dd, 1H, $^2J_{\text{H-F}} = 48.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.21 – 4.01 (m, 2H), 3.43 – 3.28 (m, 1H), 3.03 – 2.77 (m, 2H), 2.14 – 1.91 (m, 2H), 1.19 (t, 3H, $J_{\text{H-H}} = 6.0$ Hz). $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ -196.4 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 167.6 (d, $^2J_{\text{C-F}} = 30.0$ Hz),

148.3, 146.7, 134.7, 132.3, 132.2, 129.2, 123.9, 122.4, 90.5 (d, C-F , = 187.5 Hz), 62.0, 50.6 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 33.0, 32.9, 14.1. IR: 2940, 1759, 1737, 1599, 1516, 1343, 1068, 852, 817, 698, 479 cm^{-1} . HRMS (API⁻) m/z : $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{BrFNO}_4\text{S}$: 455.0202, found: 455.0193.

(2S,3S)-ethyl 2-fluoro-3-(naphthalen-2-ylthio)-5-(4-nitrophenyl)pentanoate (**13**). (*Z*)-ethyl 2-fluoro-5-(4-nitrophenyl)pent-2-enoate (0.3 mmol, 80.1 mg), naphthalene-2-thiol (1.5 mmol, 240 mg) with $(\text{DHQ})_2\text{PYR}$ (0.03 mmol, 26.4 mg) were stirred in toluene at 0 °C for 8 days according to the general procedure **b**. $^{19}\text{F NMR}$ of crude product showed $dr = 84:16$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 55% yield (major: 47 mg as a yellow solid; major and minor mixture: 23 mg). 8% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 35.240 min, t (major) = 45.267 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 75% yield (major: 71 mg as a yellow solid; major and minor mixture: 25 mg) with $dr = 87:13$.

$[\alpha]_D^{20} = -2.2$ (c 0.68, CDCl_3); Mp 86 – 88 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.00 (d, 2H, $J_{\text{H-H}} = 9.0$ Hz), 7.84 (s, 1H), 7.76 – 7.65 (m, 3H), 7.45 – 7.40 (m, 3H), 7.20 – 7.18 (m, 2H), 5.02 (dd, 1H, $^2J_{\text{H-F}} = 48.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.16 – 3.93 (m, 2H), 3.59 – 3.44 (m, 1H), 3.07 – 2.82 (m, 2H), 2.19 – 1.97 (m, 2H), 1.13 (t, 3H, $J_{\text{H-H}} = 6.0$ Hz). $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ -196.0 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 167.7 (d, $^2J_{\text{C-F}} = 30.0$ Hz), 148.5, 146.6, 133.5, 132.6, 131.9, 130.6, 129.8, 129.8, 129.3, 128.8, 127.7, 127.4, 126.9, 126.7, 123.8, 90.5 (d, $^1J_{\text{C-F}} = 187.5$ Hz), 61.9, 50.4 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 33.1, 33.0, 14.0. IR: 2925, 1764, 1490, 1222, 1109, 1027, 830, 523, 468 cm^{-1} . HRMS (API⁻) m/z : $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{22}\text{FNO}_4\text{S}$: 427.1254, found: 427.1254.

(2S,3S)-ethyl 3-cyclohexyl-2-fluoro-3-(phenylthio)propanoate (**14**). (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg), with $(\text{DHQ})_2\text{PYR}$ (0.03 mmol, 26.4 mg)

were stirred in neat benzenethiol (1.5 mmol, 165 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 100:0. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 34% yield (32 mg as a colorless oil). 65% *ee* was obtained for it [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 6.607 min, *t* (major) = 7.450 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 86% yield (major: 61 mg as a colorless oil; major and minor mixture: 19 mg) with *dr* = 82:18.

[α]_D²⁰ = -5.6 (c 0.32, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.39 – 7.36 (m, 2H), 7.22 – 7.13 (m, 3H), 5.20 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.10 – 3.81 (m, 2H), 3.34 – 3.19 (m, 1H), 2.14 (d, 1H, J_{H-H} = 15.0 Hz), 1.84 – 1.53 (m, 5H), 1.21 – 1.13 (m, 5H), 1.07 (t, 3H, J_{H-H} = 6.0 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ -197.9 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 36.7 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.6 (d, ²J_{C-F} = 30.0 Hz), 135.7, 132.0, 128.9, 127.1, 89.3 (d, ¹J_{C-F} = 187.5 Hz), 61.6, 57.9 (d, ²J_{C-F} = 15.0 Hz), 40.7, 31.1, 30.8, 26.2, 26.1, 13.9. IR: 2925, 1763, 1735, 1440, 1214, 1102, 1024, 746, 691, 537, 481 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₇H₂₄FO₂S: 311.1481, found: 311.1491.

(2*S*,3*S*)-ethyl 3-((4-bromophenyl)thio)-3-cyclohexyl-2-fluoropropanoate (**15**). (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 4-bromobenzenethiol (1.5 mmol, 283.5 mg) at 0 °C for 8 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 69:31. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 38% yield (major: 24 mg as a white solid; major and minor mixture: 20 mg). 11% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 5.987 min, *t* (major) = 6.587 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 76% yield (major: 62 mg as a

white solid; major and minor mixture: 24 mg) with *dr* = 71:29.

[α]_D²⁰ = +2.5 (c 1.02, CDCl₃); Mp 31 – 33 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.33 – 7.23 (m, 4H), 5.20 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.15 – 3.90 (m, 2H), 3.28 – 3.13 (m, 1H), 2.09 (d, 1H, J_{H-H} = 12.0 Hz), 1.82 – 1.59 (m, 5H), 1.18 – 0.98 (m, 8H). ¹⁹F NMR (282 MHz, CDCl₃): δ -197.7 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 33.8 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.6 (d, ²J_{C-F} = 30.0 Hz), 134.7, 133.7, 121.3, 89.3 (d, ¹J_{C-F} = 195.0 Hz), 61.8, 58.0 (d, ²J_{C-F} = 22.5 Hz), 40.5, 31.0, 30.7, 26.1, 26.1, 14.0. IR: 2920, 1753, 1472, 1299, 1216, 817, 595, 466, 483 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₇H₂₃BrFO₂S: 389.0586, found: 389.0596.

(2*S*,3*S*)-ethyl 3-cyclohexyl-2-fluoro-3-((4-methoxyphenyl)thio)propanoate (**16**). (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 4-methoxybenzenethiol (1.5 mmol, 210 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 80:20. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 77% yield (major: 60 mg as a white solid; major and minor mixture: 19 mg). 32% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 8.557 min, *t* (major) = 10.183 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 65% yield (major: 47 mg as a white solid; major and minor mixture: 19 mg) with *dr* = 78:22.

[α]_D²⁰ = -5.4 (c 0.61, CDCl₃); Mp 57 – 58 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.35 – 7.33 (m, 2H), 6.76 – 6.73 (m, 2H), 5.17 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 2.4 Hz), 4.17 – 3.91 (m, 2H), 3.72 (s, 3H), 3.14 – 3.00 (m, 1H), 2.15 (d, 1H, J_{H-H} = 6.0 Hz), 1.81 – 1.58 (m, 5H), 1.18 – 1.01 (m, 8H). ¹⁹F NMR (282 MHz, CDCl₃): δ -197.9 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 36.7 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.8 (d, ²J_{C-F} = 22.5 Hz), 159.4, 135.2, 125.5, 114.4, 89.4 (d, ¹J_{C-F} = 187.5 Hz), 61.6, 58.7 (d, ²J_{C-F} = 15.0 Hz), 55.3, 40.2, 31.1, 30.7, 26.2, 26.2, 14.0. IR: 2926, 1763, 1590, 1490, 1222, 1026, 830, 594, 522,

473 cm⁻¹. HRMS (API⁺) m/z: [M+H]⁺ calcd for C₁₈H₂₆FO₃S: 341.1587, found: 341.1581.

(2*S*,3*S*)-ethyl 3-cyclohexyl-2-fluoro-3-(thiophen-2-ylthio)propanoate (**17**). (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat thiophene-2-thiol (1.5 mmol, 174 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 100:0. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 32% yield (30 mg as a yellow oil). 59% *ee* was obtained for it [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 6.583 min, t (major) = 8.433 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 43% yield (major: 30 mg as a yellow oil; major and minor mixture: 11 mg) with *dr* = 82:18.

[α]_D²⁰ = -8.3 (c 0.06, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.29 – 7.26 (m, 1H), 7.09 – 7.08 (m, 1H), 6.89 – 6.86 (m, 1H), 5.17 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.26 – 4.02 (m, 2H), 3.11 – 2.96 (m, 1H), 2.19 (d, 1H, J_{H-H} = 12.0 Hz), 1.83 – 1.63 (m, 5H), 1.22 – 1.05 (m, 8H). ¹⁹F NMR (282 MHz, CDCl₃): δ -198.3 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 33.8 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.5 (d, ²J_{C-F} = 22.5 Hz), 135.4, 133.2, 130.0, 127.3, 89.1 (d, ¹J_{C-F} = 195.0 Hz), 61.7, 60.4 (d, ²J_{C-F} = 15.0 Hz), 39.8, 31.1, 30.5, 26.2, 26.1, 14.1. IR: 2925, 1762, 1736, 1448, 1216, 1024, 847, 700, 533, 495 cm⁻¹. HRMS (API⁺) m/z: [M+H]⁺ calcd for C₁₅H₂₂FO₂S₂: 317.1045, found: 317.1051.

(2*S*,3*S*)-ethyl 3-((2-aminophenyl)thio)-3-cyclohexyl-2-fluoropropanoate (**18**). (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 2-aminobenzenethiol (1.5 mmol, 188.0 mg) at room temperature for 8 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 90:10. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 55% yield (major: 45 mg as a yellow solid, major and minor mixture: 9 mg). 87% *ee* was

obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 16.160 min, t (major) = 22.437 min.]. The reaction performed on 1 mmol of (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate led to 51% of isolated yield (major: 132 mg, major and minor mixture: 34 mg), *dr*:91:9 and *ee*: 85% (major diastereoisomer). The racemic product has been obtained following the procedure **a** (the same scale) in 75% yield (major: 38 mg as a yellow solid; minor: 11 mg as a yellow solid; major and minor mixture: 19 mg) with *dr* = 80:20.

[α]_D²⁰ = +24.1 (c 0.22, CDCl₃); Mp 112 – 113 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.28 (d, 1H, J_{H-H} = 6.0 Hz), 7.03 – 6.98 (m, 1H), 6.61 – 6.56 (m, 2H), 5.09 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.29 (s, 2H), 4.05 – 3.94 (m, 1H), 3.80 – 3.69 (m, 1H), 3.35 – 3.21 (m, 1H), 2.02 – 1.88 (m, 2H), 1.74 – 1.61 (m, 4H), 1.26 – 1.04 (m, 8H). ¹⁹F NMR (282 MHz, CDCl₃): δ -196.1 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 33.8 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.7 (d, ²J_{C-F} = 30.0 Hz), 148.7, 136.5, 129.8, 118.4, 116.7, 115.0, 88.7 (d, ¹J_{C-F} = 187.5 Hz), 61.6, 56.7 (d, ²J_{C-F} = 15.0 Hz), 40.9, 31.0, 30.5, 30.5, 26.4, 26.3, 26.2, 13.9. IR: 3445, 3351, 2925, 1748, 1613, 1480, 1233, 737, 602, 454 cm⁻¹. HRMS (API⁺) m/z: [M+H]⁺ calcd for C₁₇H₂₅FNO₂S: 326.1590, found: 326.1594.

(2*S*,3*S*)-ethyl 3-cyclohexyl-2-fluoro-3-(*m*-tolylthio)propanoate (**19**). (*Z*)-ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 3-methylbenzenethiol (1.5 mmol, 186.3 mg) at 0 °C for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 81:19. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 44% yield (major: 35 mg as a colorless oil, major and minor mixture: 8 mg). 26% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 7.013 min, t (major) = 7.820 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 67% yield (major: 54 mg as a

colorless oil; major and minor mixture: 11 mg) with $dr = 80:20$.

$[\alpha]_D^{20} = -20.3$ (c 0.10, CDCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.19 – 7.15 (m, 2H), 7.11 – 7.05 (m, 1H), 6.96 – 6.93 (m, 1H), 5.19 (dd, 1H, $^2J_{\text{H-F}} = 51.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.11 – 3.81 (m, 2H), 3.34 – 3.19 (m, 1H), 2.24 (s, 3H), 2.13 (d, 1H, $J_{\text{H-H}} = 12.0$ Hz), 1.71 – 1.60 (m, 5H), 1.20 – 1.01 (m, 8H). $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ -197.7 (dd, $^2J_{\text{F-H}} = 51.0$ Hz, $^3J_{\text{F-H}} = 33.8$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.6 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 138.6, 135.5, 132.4, 128.9, 128.7, 127.9, 89.3 (d, $^1J_{\text{C-F}} = 187.5$ Hz), 61.6, 57.8 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 40.8, 31.1, 30.8, 26.2, 26.1, 21.3, 13.9. IR: 2925, 1764, 1735, 1600, 1449, 1213, 1102, 1025, 856, 776, 690, 541, 436 cm^{-1} . HRMS (API⁺) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{FO}_2\text{S}$: 325.1638, found: 325.1647.

(2S,3S)-methyl 2-fluoro-3-phenyl-3-(phenylthio)propanoate (**20**). (*Z*)-methyl 2-fluoro-3-phenylacrylate (0.3 mmol, 54.4 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat benzenethiol (1.5 mmol, 165.0 mg) at 0 °C for 8 days according to the general procedure **b**. $^{19}\text{F NMR}$ of crude product showed $dr = 88:12$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 54% yield (major: 40 mg as a white solid, major and minor mixture: 7 mg). 63% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 6.530 min, t (major) = 7.053 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 61% yield (major: 42 mg as a white solid, major and minor mixture: 11 mg) with $dr = 83:17$.

$[\alpha]_D^{20} = +101.4$ (c 0.67, CDCl_3); Mp 52 - 53 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.31 – 7.22 (m, 7H), 7.18 – 7.14 (m, 3H), 5.16 (dd, 1H, $^2J_{\text{H-F}} = 48.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.60 (dd, 1H, $^3J_{\text{H-F}} = 28.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 3.61 (s, 3H). $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ -194.2 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 167.9 (d, $^2J_{\text{C-F}} = 30.0$ Hz), 137.8, 133.6, 132.9, 128.9, 128.7, 128.4, 128.4, 126.2, 127.7, 91.3 (d, $^1J_{\text{C-F}} = 187.5$ Hz), 55.8 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 52.6. IR: 2947, 1755, 1438,

1225, 1087, 1001, 736, 701, 688, 540, 467 cm^{-1} . HRMS (API⁺) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{FO}_2\text{S}$: 291.0855, found: 291.0859.

(2S,3R)-methyl 2-fluoro-3-phenyl-3-(phenylthio)propanoate (**anti-20**). (*E*)-methyl 2-fluoro-3-phenylacrylate (0.3 mmol, 54.4 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat benzenethiol (1.5 mmol, 165.0 mg) at 0 °C for 8 days according to the general procedure **b**. $^{19}\text{F NMR}$ of crude product showed $dr = 24:76$. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 56% yield (major and minor mixture: 49 mg as a white solid). 51% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 95/5, flow = 1 mL/min, $\lambda = 230$ nm, t (minor) = 6.773 min, t (major) = 7.453 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 74% yield (major: 30 mg as a white solid; major and minor mixture: 34 mg) with $dr = 33:67$.

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.38 – 7.34 (m, 2H), 7.25 – 7.19 (m, 8H), 5.09 (dd, 1H, $^2J_{\text{H-F}} = 48.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.56 (dd, 1H, $^3J_{\text{H-F}} = 28.0$ Hz, $J_{\text{H-H}} = 6.0$ Hz), 3.54 (s, 3H). $^{19}\text{F NMR}$ (282 MHz, CDCl_3): δ -195.0 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 26.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.0 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 135.5, 133.5, 132.9, 129.2, 128.9, 128.8, 128.6, 128.4, 128.4, 89.2 (d, $^1J_{\text{C-F}} = 195.0$ Hz), 54.6 (d, $^2J_{\text{C-F}} = 15.0$ Hz), 52.4.

(2S,3S)-methyl 3-((2-aminophenyl)thio)-2-fluoro-3-phenylpropanoate (**21**). (*Z*)-methyl 2-fluoro-3-phenylacrylate (0.3 mmol, 54.4 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 2-aminobenzenethiol (1.5 mmol, 188.0 mg) at room temperature for 4 days according to the general procedure **b**. $^{19}\text{F NMR}$ of crude product showed $dr = 91:9$. The crude was purified by silica gel column chromatography (DCM/PE, from 5/1 to 2/1, v/v) affording two diastereoisomers in 22% yield (major: 16 mg as a yellow solid, major and minor mixture: 4 mg). 51% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, $\lambda = 254$ nm, t (minor) = 11.947 min, t

(major) = 14.737 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 46% yield (major: 34 mg as a yellow solid, major and minor mixture: 8 mg) with *dr* = 87:13.

$[\alpha]_D^{20} = +111.2$ (c 1.02, CDCl_3); Mp 77 – 79 °C; ^1H NMR (300 MHz, CDCl_3): δ 7.24 – 7.21 (m, 5H), 7.10 – 7.00 (m, 2H), 6.62 – 6.47 (m, 2H), 5.13 (dd, 1H, $^2J_{\text{H-F}} = 48.0$, $J_{\text{H-H}} = 3.0$ Hz), 4.48 (dd, 1H, $^3J_{\text{H-F}} = 28.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.23 (s, 2H), 3.56 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -194.2 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.1 (d, $^2J_{\text{C-F}} = 30.0$ Hz), 149.2, 138.1, 137.5, 130.8, 128.6, 128.3, 128.3, 128.1, 118.3, 115.0, 89.5 (d, $^1J_{\text{C-F}} = 195.0$ Hz), 54.0 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 52.5. IR: 3432, 3327, 2951, 1755, 1609, 1217, 1101, 751, 698, 530, 457 cm^{-1} . HRMS (API⁺) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{FNO}_2\text{S}$: 306.0964, found: 306.0964.

(2S,3S)-methyl 2-fluoro-3-phenyl-3-(*m*-tolylthio)propanoate (**22**). (*Z*)-methyl 2-fluoro-3-phenylacrylate (0.3 mmol, 54.4 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 3-methylbenzenethiol (1.5 mmol, 186.3 mg) at room temperature for 5 days according to the general procedure **b**. ^{19}F NMR of crude product showed *dr* = 87:13. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 72% yield (major: 50 mg as a colorless oil, major and minor mixture: 16 mg). 62% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 6.750 min, *t* (major) = 7.183 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 89% yield (major: 45 mg as a colorless oil, major and minor mixture: 37 mg) with *dr* = 85:15.

$[\alpha]_D^{20} = +113.0$ (c 0.70, CDCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.31 – 7.20 (m, 5H), 7.07 – 6.94 (m, 4H), 5.15 (dd, 1H, $^2J_{\text{H-F}} = 48.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 4.59 (dd, 1H, $^3J_{\text{H-F}} = 28.0$ Hz, $J_{\text{H-H}} = 3.0$ Hz), 3.60 (s, 3H), 2.18 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -194.1 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.0 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 138.7, 138.0, 133.5, 133.3, 129.8, 128.8, 128.7, 128.6, 128.4,

128.4, 128.1, 91.3 (d, $^1J_{\text{C-F}} = 187.5$ Hz), 55.7 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 52.5, 21.2. IR: 2960, 1765, 1741, 1437, 1219, 1101, 774, 692, 544, 436 cm^{-1} . HRMS (API⁺) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{FO}_2\text{S}$: 305.1012, found: 305.1024.

(2S,3S)-methyl 2-fluoro-3-(*p*-tolylthio)-3-(*p*-tolyl)propanoate (**23**). (*Z*)-methyl 2-fluoro-3-(*p*-tolyl)acrylate (0.3 mmol, 58.3 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat benzenethiol (1.5 mmol, 151.5 mg) at 0 °C for 8 days according to the general procedure **b**. ^{19}F NMR of crude product showed *dr* = 88:12. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 36% yield (major: 29 mg as a white solid, major and minor mixture: 4 mg). 69% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 6.490 min, *t* (major) = 7.410 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 75% yield (major: 51 mg as a white solid; major and minor mixture: 17 mg) with *dr* = 77:23.

$[\alpha]_D^{20} = +129.6$ (c 0.57, CDCl_3); Mp 82 - 84 °C; ^1H NMR (300 MHz, CDCl_3): δ 7.27 – 7.24 (m, 2H), 7.17 – 7.13 (m, 4H), 7.05 – 7.03 (m, 2H), 5.12 (dd, 1H, $^2J_{\text{H-F}} = 48.0$ Hz, $J_{\text{H-H}} = 6.0$ Hz), 4.57 (dd, 1H, $^3J_{\text{H-F}} = 28.0$ Hz, $J_{\text{H-H}} = 6.0$ Hz), 3.60 (s, 3H), 2.24 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -194.0 (dd, $^2J_{\text{F-H}} = 48.0$ Hz, $^3J_{\text{F-H}} = 28.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.0 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 138.0, 134.8, 133.8, 132.8, 129.4, 128.9, 128.3, 128.2, 127.8, 91.5 (d, $^1J_{\text{C-F}} = 195.0$ Hz), 55.5 (d, $^2J_{\text{C-F}} = 22.5$ Hz), 52.6, 21.2. IR: 2927, 1739, 1434, 1269, 1085, 1008, 741, 570, 413 cm^{-1} . HRMS (API⁺) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{FO}_2\text{S}$: 305.1012, found: 305.1009.

(2S,3S)-methyl 3-(2-cyanophenyl)-2-fluoro-3-(*p*-tolylthio)propanoate (**24**). (*Z*)-methyl 3-(2-cyanophenyl)-2-fluoroacrylate (0.3 mmol, 61.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat benzenethiol (1.5 mmol, 151.5 mg) at room temperature for 5 days according to the general procedure **b**. ^{19}F NMR of crude product showed *dr* = 87:13. The crude

was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 78% yield (major: 56 mg as a white solid, major and minor mixture: 14 mg). 52% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 12.513 min, t (major) = 13.350 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 62% yield (major: 43 mg as a white solid; major and minor mixture: 16 mg) with *dr* = 89:11.

$[\alpha]_D^{20}$ = +3.0 (c 1.03, CDCl₃); Mp 71 – 72 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.74 – 7.71 (m, 1H), 7.56 – 7.51 (m, 2H), 7.35 – 7.29 (m, 3H), 7.20 – 7.18 (m, 3H), 5.20 (dd, 1H, ²*J*_{H-F} = 48.0 Hz, *J*_{H-H} = 3.0 Hz), 5.12 (dd, 1H, ³*J*_{H-F} = 28.0 Hz, *J*_{H-H} = 3.0 Hz), 3.64 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -195.8 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 28.0 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.0 (d, ²*J*_{C-F} = 22.5 Hz), 141.4, 133.4, 133.2, 132.8, 132.1, 130.0, 129.9, 129.2, 128.6, 128.5, 117.0, 112.1, 89.9 (d, ¹*J*_{C-F} = 195.0 Hz), 53.0 (d, ²*J*_{C-F} = 15.0 Hz), 52.8. IR: 2947, 2224, 1732, 1438, 1283, 1106, 1016, 743, 692, 555, 491 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₇H₁₅FNO₂S: 316.0808, found: 316.0814.

(2*S*,3*S*)-methyl 3-(3-cyanophenyl)-2-fluoro-3-(phenylthio)propanoate (**25**). (*Z*)-methyl 3-(3-cyanophenyl)-2-fluoroacrylate (0.3 mmol, 61.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat benzenethiol (1.5 mmol, 151.5 mg) at room temperature for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 92:8. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 76% yield (major: 60 mg as a colorless oil, major and minor mixture: 8 mg). 52% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 50.573 min, t (major) = 54.183 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 62% yield (major: 54 mg as a colorless

oil; major and minor mixture: 5 mg) with *dr* = 92:8.

$[\alpha]_D^{20}$ = +85.8 (c 1.15, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.56 – 7.48 (m, 3H), 7.37 – 7.32 (m, 1H), 7.23 – 7.16 (m, 5H), 5.16 (dd, 1H, ²*J*_{H-F} = 48.0 Hz, *J*_{H-H} = 3.0 Hz), 4.60 (dd, 1H, ³*J*_{H-F} = 28.0 Hz, *J*_{H-H} = 3.0 Hz), 3.69 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -195.4 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 28.0 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.5 (d, ²*J*_{C-F} = 22.5 Hz), 139.7, 133.4, 133.0, 132.9, 132.4, 132.0, 131.8, 129.5, 129.2, 128.5, 118.4, 112.8, 90.7 (d, ¹*J*_{C-F} = 195.0 Hz), 55.2 (d, ²*J*_{C-F} = 15.0 Hz), 52.8. IR: 2953, 2231, 1763, 1438, 1221, 1102, 1008, 801, 739, 690, 528, 479 cm⁻¹. HRMS (API⁺) *m/z*: [M+H]⁺ calcd for C₁₇H₁₅FNO₂S: 316.0808, found: 316.0808.

(2*S*,3*S*)-methyl 3-(4-cyanophenyl)-2-fluoro-3-(phenylthio)propanoate (**26**). (*Z*)-methyl 3-(4-cyanophenyl)-2-fluoroacrylate (0.3 mmol, 61.6 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat benzenethiol (1.5 mmol, 151.5 mg) at room temperature for 5 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr*=100:0. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 70% yield (66 mg as a white solid). 68% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 21.380 min, t (major) = 23.313 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 64% yield (major: 51 mg as a white solid; major and minor mixture: 9 mg) with *dr* = 81:19.

$[\alpha]_D^{20}$ = +168.8 (c 0.32, CDCl₃); Mp 79 – 80 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.54 – 7.38 (m, 4H), 7.23 – 7.16 (m, 5H), 5.17 (dd, 1H, ²*J*_{H-F} = 48.0 Hz, *J*_{H-H} = 3.0 Hz), 4.61 (dd, 1H, ³*J*_{H-F} = 28.0 Hz, *J*_{H-H} = 3.0 Hz), 3.70 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -195.3 (dd, ²*J*_{F-H} = 48.0 Hz, ³*J*_{F-H} = 28.0 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.5 (d, ²*J*_{C-F} = 30.0 Hz), 143.3, 133.4, 132.4, 132.4, 129.3, 129.3, 129.2, 126.5, 118.4, 112.1, 90.6 (d, ¹*J*_{C-F} = 195.0 Hz), 55.6 (d, ²*J*_{C-F} = 15.0 Hz), 52.9. IR: 2967, 2237, 1767, 1441, 1214, 1096, 1003, 836, 745, 570,

437 cm⁻¹. HRMS (API⁺) m/z: [M+H]⁺ calcd for C₁₇H₁₅FNO₂S: 316.0808, found: 316.0790.

(2*S*,3*S*)-methyl 3-(2-aminophenyl)thio)-2-fluoro-3-(4-methoxyphenyl)propanoate (**27**).

(*Z*)-methyl 2-fluoro-3-(4-methoxyphenyl)acrylate (0.3 mmol, 63.1 mg), with (DHQ)₂PYR (0.03 mmol, 26.4 mg) were stirred in neat 2-aminobenzenethiol (1.5 mmol, 188.0 mg) at room temperature for 3 days according to the general procedure **b**. ¹⁹F NMR of crude product showed *dr* = 94:6. The crude was purified by silica gel column chromatography (DCM/PE, from 5/1 to 2/1, v/v) affording two diastereoisomers in 37% yield (major: 30 mg as a yellow solid, major and minor mixture: 7 mg). 73% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 16.977 min, t (major) = 23.033 min.]. The racemic product has been obtained following the procedure **a** (the same scale) in 40% yield (major: 35 mg as a yellow solid, major and minor mixture: 5 mg) with *dr* = 87:13.

[α]_D²⁰ = +183.2 (c 2.20, CDCl₃); Mp 80 – 82 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.18 – 6.99 (m, 4H), 6.76 – 6.73 (m, 2H), 6.62 – 6.59 (m, 1H), 6.52 – 6.47 (m, 1H), 5.09 (dd, 1H, ²J_{H-F} = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.44 (dd, 1H, ³J_{H-F} = 28.0 Hz, J_{H-H} = 3.0 Hz), 4.25 (s, 2H), 3.71 (s, 3H), 3.54 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -193.9 (dd, ²J_{F-H} = 48.0 Hz, ³J_{F-H} = 28.0 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.1 (d, ²J_{C-F} = 22.5 Hz), 159.3, 149.2, 137.5, 130.8, 130.1, 129.5, 129.5, 118.3, 115.2, 115.0, 113.9, 91.0 (d, ¹J_{C-F} = 195.0 Hz), 55.3, 53.4 (d, ²J_{C-F} = 22.5 Hz), 52.5. IR: 3354, 2953, 1754, 1605, 1511, 1480, 1243, 1102, 1023, 827, 743, 534, 435 cm⁻¹. HRMS (ESI⁺) m/z: [M+H]⁺ calcd for C₁₇H₁₉FNO₃S: 336.1070, found: 336.1062.

(2*S*,3*S*)-3-fluoro-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**28**).

Compound **21** (0.35 mmol, 106.8 mg,) with *p*-TsOH (0.07 mmol, 6.9 mg) were added into 2 mL xylene and the resulting mixture was heated to reflux overnight. After completion of the reaction, the solvent was removed in vacuo and the crude mixture was purified by column chromatography (petroleum ether/EtOAc,

from 5/1 to 4/1, v/v) to give the desired product (**28**) in 85% yield (81 mg, white solid). 51% *ee* [determined by HPLC, AD-H column, Hept/*i*-PrOH: 80/20, flow = 1 mL/min, λ = 254 nm, t (minor) = 10.467 min, t (major) = 14.543 min.] [α]_D²³ = +126.1 (c 0.80, CDCl₃); Mp 161 – 163 °C; ¹H NMR (300 MHz, CDCl₃): δ 9.39 (s, 1H), 7.74 (d, 1H, J_{H-H} = 6.0 Hz), 7.59 – 7.58 (m, 2H), 7.45 – 7.35 (m, 4H), 7.27 – 7.21 (m, 2H), 5.36 – 5.18 (m, 2H). ¹⁹F NMR (282 MHz, CDCl₃): δ -190.5 (dd, ²J_{F-H} = 47.9 Hz, ³J_{F-H} = 8.5 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.6 (d, ²J_{C-F} = 22.5 Hz), 140.3, 135.3, 135.3, 134.8, 130.6, 129.3, 128.8, 128.5, 126.7, 126.5, 123.1, 88.8 (d, ¹J_{C-F} = 195.0 Hz), 56.3 (d, ²J_{C-F} = 15.0 Hz). IR: 3188, 3072, 2961, 2903, 1687, 1474, 1306, 1075, 768, 736, 717, 696, 524, 463 cm⁻¹. HRMS (API⁺) m/z: [M+H]⁺ calcd for C₁₅H₁₃FNOS: 274.0702, found: 274.0707.

(2*S*,3*S*)-3-fluoro-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**29**).

Compound **27** (0.2 mmol, 67.0 mg,) with *p*-TsOH (0.04 mmol, 3.9 mg) were added into 1.2 mL xylene and the resulting mixture was heated to reflux overnight. After completion of the reaction, the solvent was removed in vacuo and the crude mixture was purified by column chromatography (petroleum ether/EtOAc, from 5/1 to 3/1, v/v) to give the desired product **29** in 76% yield (46 mg, white solid). 73% *ee* [determined by HPLC, AD-H column, Hept/*i*-PrOH: 80/20, flow = 1 mL/min, λ = 254 nm, t (minor) = 13.940 min, t (major) = 21.507 min.] [α]_D²³ = +122.2 (c 0.54, CDCl₃); Mp 165 – 166 °C; ¹H NMR (300 MHz, CDCl₃): δ 9.00 (s, 1H), 7.63 (d, 1H, J_{H-H} = 9.0 Hz), 7.41 – 7.30 (m, 3H), 7.18 – 7.11 (m, 2H), 6.81 – 6.75 (m, 2H), 5.22 – 5.04 (m, 2H), 3.71 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -190.4 (ddd, ²J_{F-H} = 47.9 Hz, ³J_{F-H} = 8.5 Hz, ⁴J_{F-H} = 2.8 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.3 (d, ²J_{C-F} = 22.5 Hz), 160.0, 140.3, 134.8, 130.5, 130.5, 126.8, 123.1, 113.9, 88.4 (d, ¹J_{C-F} = 195.0 Hz), 55.6 (d, ²J_{C-F} = 22.5 Hz), 55.3. IR: 3189, 3076, 2923, 2856, 1684, 1513, 1475, 1306, 1250, 1083, 1027, 785, 764, 652, 490, 410 cm⁻¹. HRMS (API⁺) m/z: [M+H]⁺ calcd for C₁₆H₁₅FNO₂S: 304.0808, found: 304.0812.

(2*S*,3*S*)-5-(2-(dimethylamino)ethyl)-3-fluoro-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**30**).

To a solution of compound **28** (0.25 mmol, 68.5 mg) in ethyl acetate (1.5 mL) was added 2-dimethylaminoethyl chloride hydrochloride (72.0 mg, 0.50 mmol), followed by potassium carbonate (138.0 mg, 1.0 mmol) and H₂O (15 μ L). After the mixture was stirred for 24 h under reflux, it was cooled to room temperature. The mixture was dried over Na₂SO₄ then the crude mixture was purified by column chromatography (DCM/MeOH, 10/1 to 8/1, v/v) to give the desired product **30** in 41% yield (35 mg, white solid). 51% ee, [determined by HPLC, luxcell 2 column, Hept/*i*-PrOH: 80/20, flow = 1 mL/min, λ = 254 nm, t (minor) = 16.503 min, t (major) = 19.920 min.]

$[\alpha]_D^{20}$ = +144.9 (c 0.31, CDCl₃); Mp 165 – 166 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.84 – 7.73 (m, 1H), 7.59 – 7.28 (m, 8H), 5.43 – 4.90 (m, 2H), 4.53 – 4.26 (m, 1H), 3.85 – 3.71 (m, 1H), 2.79 – 2.45 (m, 2H), 2.29 (s, 6H). ¹⁹F NMR (282 MHz, CDCl₃): δ -189.3 (d, ²J_{F-H} = 47.9 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 166.5 (d, ²J_{C-F} = 22.5 Hz), 145.1, 135.5, 131.1, 129.9, 128.9, 128.5, 128.4, 128.2, 128.1, 127.6, 124.7, 86.2 (d, ¹J_{C-F} = 187.5 Hz), 56.7, 55.0 (d, ²J_{C-F} = 22.5 Hz), 47.8, 45.6. IR: 3064, 2939, 2765, 1681, 1441, 1179, 1088, 856, 766, 602, 591, 428 cm⁻¹. HRMS (ESI⁺) m/z: [M+H]⁺ calcd for C₁₉H₂₂FN₂O₂S: 345.1437, found: 345.1449.

(2*S*,3*S*)-5-(2-(dimethylamino)ethyl)-3-fluoro-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**31**).

To a solution of compound **29** (0.15 mmol, 45.0 mg) in ethyl acetate (1.0 mL) was added 2-dimethylaminoethyl chloride hydrochloride (43.2 mg, 0.30 mmol), followed by potassium carbonate (82.8 mg, 0.6 mmol) and H₂O (10 μ L). After the mixture was stirred for 24 h under reflux, it was cooled to room temperature. The mixture was dried over Na₂SO₄ then the crude mixture was purified by column chromatography (DCM/MeOH, 9/1 to 8/1, v/v) to give the desired product **31** in 32% yield (18 mg, colorless oil). 73% ee, [determined by HPLC, luxcell 2 column, Hept/*i*-PrOH: 80/20, flow = 1.2 mL/min, λ = 254 nm, t (minor) = 18.370 min, t (major) = 23.353 min.]

$[\alpha]_D^{20}$ = +126.4 (c 0.47, CDCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.72 – 7.64 (m, 1H), 7.43 – 7.35 (m, 3H), 7.23 – 7.19 (m, 2H), 6.86 – 6.75 (m, 2H), 5.28 – 4.78 (m, 2H), 4.45 – 4.17 (m, 1H), 3.74 (s, 3H), 3.71 – 3.62 (m, 1H), 2.71 – 2.32 (m, 2H), 2.21 (s, 6H). ¹⁹F NMR (282 MHz, CDCl₃): δ -189.2 (d, ²J_{F-H} = 47.9 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 166.6 (d, ²J_{C-F} = 22.5 Hz), 160.0, 145.0, 135.4, 131.0, 129.4, 128.2, 127.6, 124.6, 113.9, 86.1 (d, ¹J_{C-F} = 187.5 Hz), 56.6, 55.3, 54.5 (d, ²J_{C-F} = 22.5 Hz), 47.7, 45.5. IR: 3058, 2938, 2770, 1676, 1609, 1511, 1251, 1178, 1092, 1029, 732, 602, 407 cm⁻¹. HRMS (ESI⁺) m/z: [M+H]⁺ calcd for C₂₀H₂₄FN₂O₂S: 375.1543, found: 375.1532.

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