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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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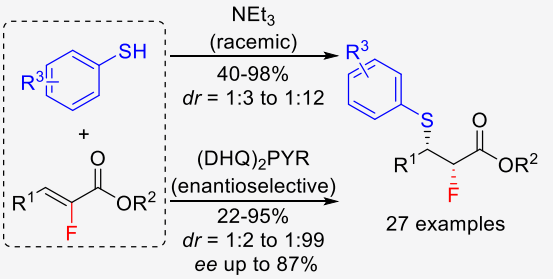
ABSTRACT: In this manuscript, a simple and efficient sulfa-Michael addition reaction of aryl thiols to trisubstituted α-fluoro-α,β-unsaturated esters both in racemic and, for the first time, in enantioselective version is reported. The commercially available dimer of cinchona derivatives $(DHQ)_2PYR$ was used as a 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, because of 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 sp^2 substrates. In this context, organocatalysis emerged as a powerful tool in asymmetric synthesis[3] 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 a Michael acceptor. Surprisingly, although 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-carbonyl[7] or -sulfonyl derivatives[8] have also been submitted to Michael addition in the presence of various nucleophiles but, to our knowledge, no asymmetric reaction and no conjugate addition on trisubstituted fluoroalkene 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 the 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. Although 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 the 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 2-fluoro-3-methoxyacrylate, a specially designed Michael acceptor, using a catalytic amount of *t*-BuOK or 1 equiv 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]

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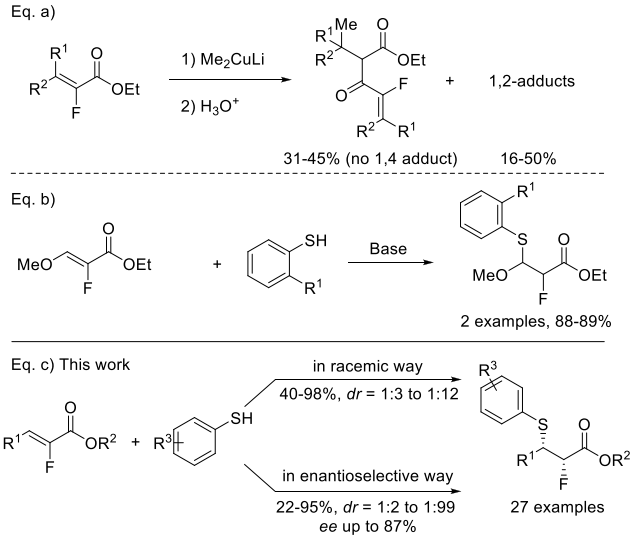
Scheme 1. Conjugate Addition on β-Substituted-α-fluoroacrylates: State of the Art and This Work



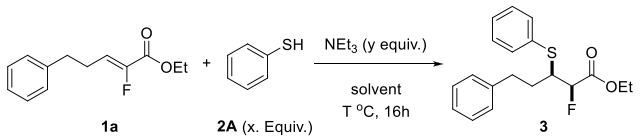
Considering the dearth of examples for the racemic and asymmetric conjugate addition of nucleophiles with fluoroacrylates, herein, we report the sulfa-Michael addition (SMA)[4c,12] of thiophenol derivatives with α-fluoroacrylates both in racemic and enantioselective ways (Scheme 1, eq c).

Two more general points highlighted the relevance of our study: (i) sulfur-containing compounds[13] 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 toward biorelevant molecules; (ii) although the asymmetric SMA reaction is known from a long time and has been studied with a large variety of Michael acceptors,[4c,12a] only few organocatalytic studies have been reported with α,β-unsaturated esters substituted in the α[14] or 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 (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (**1a**) as a model Michael acceptor and the thiophenol as a nucleophile to begin our study on the 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 pK_a of thiophenol and use the weak base NEt_3 as a catalyst. Worthy of note is that 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 byproducts, all the tests were performed in degassed solvents under argon. Traces of 1,4-adducts were identified by ^{19}F NMR (characteristic doublet of doublet corresponding to two diastereoisomers at −195.0 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 because of difficulties to separate product **3** from the remaining starting material and disulfide byproducts (Table 1, entry 4). The structure of 1,4-adduct was approved by ^1H, ^{13}C, and ^{19}F NMR experiments and also by mass spectrometry. Diastereoisomers were obtained in a 73/27 ratio according to ^{19}F NMR of the crude. The SMA reaction did not proceed in the absence of triethylamine (Table 1, entry 5). It is noteworthy that the use of sodium thiophenolate instead of the couple thiophenol/triethylamine was totally inefficient.[17] Increasing the amount of thiophenol to 2 equiv led to an improved 84% yield in 16 h (Table 1, entry 6). With 2 equiv of thiophenol, the amount of NEt_3 could be reduced to 0.1 equiv giving almost the same isolated yield and dr (Table 1, entry 7). We finally found that this reaction could be performed in neat thiophenol (Table 1, entries 8−10). Comparing different equivalents of thiophenol, 5 equiv 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 equiv of thiophenol (Table 1, entry 10). The use of other tertiary amines such as *N*,*N*-diisopropylethylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene led to lower isolated yields of the reaction, while slightly improving the dr.[17]

Table 1. Optimization of SMA Reactions in the Racemic Version



entry	*x*	*y*	solvent	*T* °C	conv. (%)[a]; (yield (%))[b]	dr[a]
1	1.1	0.14	CH_2Cl_2	22	Traces	
2[d]	1.1	0.14	CH_2Cl_2	reflux	Traces	
3	1.1	0.14	CH_3CN	22	50	
4[d]	1.1	0.14	CH_3CN	80	75 (37)	73:27
5	1.1		CH_3CN	80	0	
6	2	0.14	CH_3CN	80	98 (84)	77:23
7	2	0.1	CH_3CN	80	94 (81)	76:24
8	3	0.1		80	91 (77)	74:26
9	5	0.1		80	100 (89)	76:24
10	10	0.1		80	100 (91)	77:23

[a]Determined by ^{19}F NMR. [b]Isolated yield of the mixture of diastereoisomers. [c]dr determined by ^{19}F NMR of the crude mixture. [d]24 h reaction.

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 a catalyst allowed us to obtain an enantioselectivity but with a 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 alkaloids[19] $(DHQ)_2PYR$ gave full conversion, good diastereoisomeric

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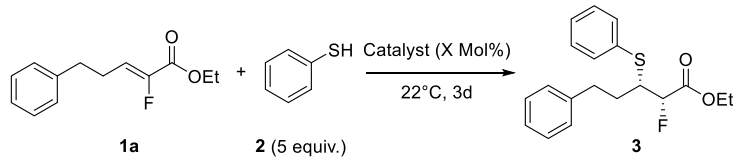
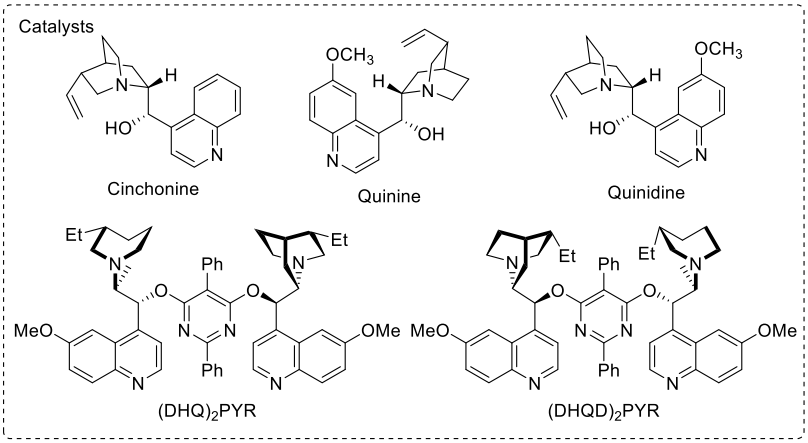
Table 2. Optimization of the Asymmetric SMA Reaction





entry	catalyst	x	conv. (%)[a]; (yield (%))[b]	dr[c]	ee[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	$(DHQ)_2PYR$	10	100	89:11	66
6	$(DHQD)_2PYR$	10	63	88:12	−72
7	$(DHQ)_2PYR$	5	98	87:13	60
8[e]	$(DHQ)_2PYR$	10	100	85:15	37
9[f]	$(DHQ)_2PYR$	10	89 (73)	85:15	70
10[g]	$(DHQ)_2PYR$	10	42	81:19	73
11[f,h]	$(DHQ)_2PYR$	10	100 (82)	84:16	71

[a]Determined by ^{19}F NMR. [b]Isolated yield of the mixture of diastereoisomers. [c]dr determined by ^{19}F NMR of the crude mixture. [d]Determined for major diastereoisomer by HPLC. [e]Reaction carried out at 80 °C, 16 h of reaction. [f]Reaction carried out at 0 °C. [g]Reaction carried out at −20 °C. [h]5 days of reaction.

ratio, and allowed us to significantly enhance the ee value to 66% (Table 2, entry 5).

The use of $(DHQD)_2PYR$ gave 72% ee but incomplete conversion (Table 2, entry 6). Lowering 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 16 h but gave a low 37% ee value (Table 2, entry 8). Decreasing the temperature allowed us to increase the ee value to 70 and 73%, at 0 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. It is noteworthy that we tested more than 15 catalysts, including 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 the 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 ee values. It is important to note that, in order to increase the enantiomeric excess, we studied the influence of about 15 solvents on the reaction. None of them was more efficient that 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 ee values.[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 a reagent and solvent. With the optimized conditions in hand, the scope of the 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 detail 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 1a).[21a]

For the 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**

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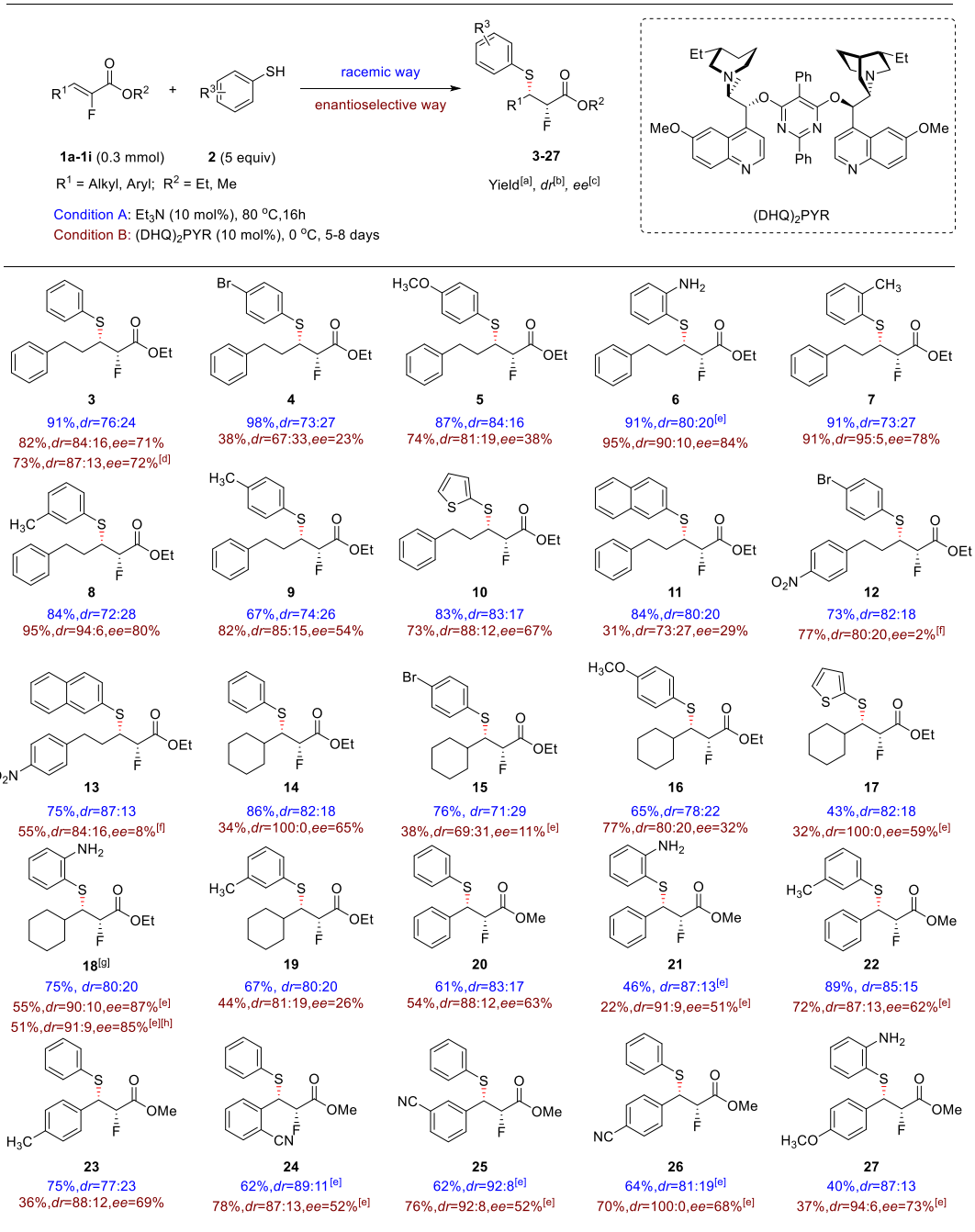
Scheme 2. Scope of the SMA Reaction on α-Fluoroacrylates



[a]Isolated yield of diastereoisomers. [b]Determined by ^{19}F NMR of the crude mixture. [c]Determined for the major diastereoisomer by HPLC. [d]Reaction performed on the 1.5 mmol scale of α-fluoroacrylate **1a**. [e]Reaction carried out at 22 °C (room temperature). [f]Toluene as a solvent. [g]Absolute configuration of **18** was determined using a single-crystal X-ray diffractometer; the two stereogenic centers are both in the *S* absolute configuration. [h]Reaction performed on the 1 mmol scale of α-fluoroacrylate **1c**.

and ortho- or meta-substituted thioaryl **6**–**8**, good ee values were obtained (71 to 84%). However, thioaryl bearing a substituent in para-position **4** (*p*-Br), **5** (*p*-OMe), and **9** (*p*-Me) was obtained in low-to-fair ee values: 23, 38, and 54%, respectively. Unfortunately, 2-thionaphthol, which proved to be the best aryl thiol 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 also occurred in good yields and diastereoselectivities but without enantioselectivities for products **12** and **13**. Usually, diastereomeric ratios were better in the enantioselective version of the reaction than in the 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%) and good-to-complete diastereoselectivities, from 69:31 for **15**, bearing a bromine atom in the para-position, to 100:0 leading to the formation of a single diastereoisomer for

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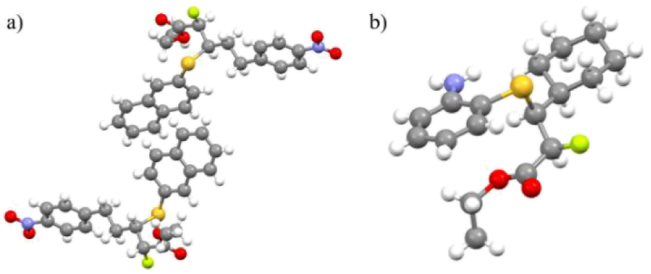
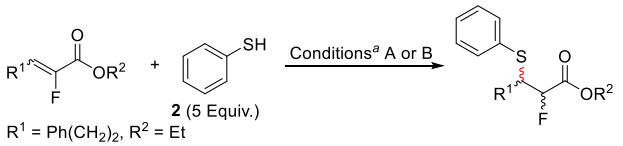


Figure 1. (a) X-ray of major diastereoisomers of **13** obtained in the racemic way (mixture of syn-enantiomers). (b) X-ray of major enantiomer of **18**.

the products **14** and **17**, obtained from thiophenol and thiophene thiol, respectively. As for substrate **1a**, substitution in the para-position was detrimental for ee giving a low value for products **15** and **16**. Substitution in the meta-position also led, 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 1b).[21b]

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 values 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 the phenyl moiety gave the desired products **24**−**26** in similar results showing no significant substituent effects. Although the electronic feature of fluoroacrylates or aryl thiol does not seem to have an impact on the reaction, having a substituent in para-position 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 the *E* configuration and submitted them to the SMA reaction. Interestingly, although 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 on the double-bond configuration with the SMA reaction between thiophenol and α,β-trisubstituted acrylates in the presence of a catalytic amount of the base and proposed a concerted process to explain their results.[22] In our case, we probably also have a concerted mechanism with the thiol addition 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 carried out with success starting from **1a** (1.5 mmol) and **1c** (1 mmol),

Table 3. Influence of the Double-Bond Geometry



1a: R^1 = Ph$(CH_2)_2$, R^2 = Et
1d: R^1 = Ph, R^2 = Me

entry	substrate	cond.	yield (%)[b]	dr[c]	ee[d] (%)
1	(*Z*)-**1a**	A	91	76:24	
2	(*E*)-**1a**	A	93	26:74	
3	(*Z*)-**1d**	A	61	87:13	
4	(*E*)-**1d**[e]	A	74	33:67	
5	(*Z*)-**1a**	B	82	84:16	71
6	(*E*)-**1a**	B	86	14:86	74
7	(*Z*)-**1d**	B	54	88:12	63
8	(*E*)-**1d**[e]	B	56	24:76	51

[a]Conditions A = NEt_3 (10 mol %), 80 °C, overnight: conditions B = $(DHQ)_2PYR$ (10 mol %), 0 °C, 5 or 8 days. [b]Isolated yield of the mixture of diastereoisomers. [c]dr determined by ^{19}F NMR of the crude mixture. [d]Determined for the major diastereoisomer by HPLC. [e]Contaminated with 10% of (*Z*)-**1d**.

furnishing the desired products **3** and **18** in 73% of isolated yield, 87:13 of dr, and 72% of ee and 51% of isolated yield, 91:9 of dr, and 85% of ee, respectively.

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 cyclization under acid catalysis followed by an alkylation reaction, allowed us to obtain, without variation of ee values, 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]

CONCLUSIONS

In summary, we developed a simple and efficient SMA 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 a racemic way (40−98%, dr = 3:1 to 12:1).

In an enantioselective way, good levels of reactivity, fair-to-excellent diastereoselectivities, and moderate-to-good enantioselectivities were achieved using commercially available $(DHQ)_2PYR$ as a 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 reactions 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 sources and used without further purification. All reactions were carried out in an 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), CH_2Cl_2 (CaH_2), and toluene (Na, benzophenone). Anhydrous DMF, CH_3CN, 1,4-dioxane, Et_2O, and DME were purchased from Acros Organics (Solvents Extra Dry over Molecular Sieve, Acroseal). Flash chromatography was carried out using Silicaflash P60 silica gel (40−60 mm); solvents used were PE = petroleum ether and EA =

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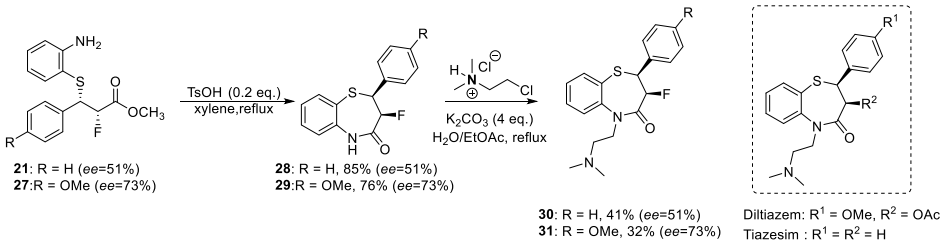
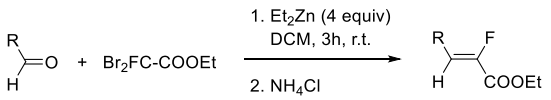
Scheme 3. Synthesis of Fluorinated Analogues of Biomolecules



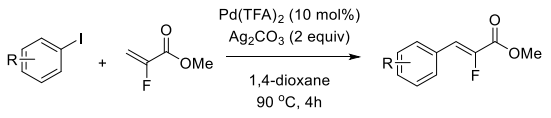
ethyl acetate. Melting points (mp) were determined on a Fisher Scientific hot-stage melting-point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using a Bruker AVANCE-300 spectrometer operating at 300 MHz (^{1}H), 75 MHz (^{13}C), and 282 MHz (^{19}F), using $CDCl_3$ as an NMR solvent. The chemical shifts (δ) were calibrated on residual proton and carbon resonances of $CDCl_3$ (^{1}H, δ = 7.26 ppm and ^{13}C, δ = 77.2 ppm) or relative to external $CFCl_3$ (^{19}F, 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 a PerkinElmer 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 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 CH_2Cl_2



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 antialcohol was not detected by ^{19}F NMR). The resulting solution was then poured into saturated NH_4Cl, CH_2Cl_2 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 Et_2O (2 × 20 mL/mmol of aldehyde), dried over $MgSO_4$, and concentrated under reduced pressure and then purified by flash silica gel column chromatography.

Synthesis of Aromatic Fluoroacrylates.[5b] In a vial were added iodoarene (1.0 equiv), fluoroacrylate (1.5 equiv), Ag_2CO_3 (2.0 equiv),



and $Pd(TFA)_2$ (10 mol %). The vial was then filled with 1,4-dioxane (5 mL/mmol of iodoarene) and then was heated to 90 °C (oil bath) for 4 h. The crude was filtered over celite and washed with EA (3 × 30 mL/mmol of iodoarene) and then the solvent was evaporated. The crude was then purified by flash silica gel column chromatography.

General Procedure for SMA of Fluoroacrylates. *Racemic Pathway.* In an over-dried sealed tube, α-fluoroacrylate 1 (0.3 mmol, 1 equiv) and thiol 2 (1.5 mmol, 5 equiv), followed by NEt_3 (0.03 mmol, 10 mol %) were introduced, and the tube was sealed and then freezed by liquid nitrogen, the air was removed under high vacuum, and argon was introduced. The reaction mixture was stirred at 80 °C (oil bath) for 16 h and then was cooled to room temperature. The reaction mixture was purified by silica gel column chromatography (eluent: PE/EtOAc or PE/CH_2Cl_2).

Enantioselective Pathway. In an over-dried sealed tube, α-fluoroacrylate (0.3 mmol, 1 equiv) and 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, the air was removed under high vacuum, and argon was introduced. The reaction mixture was stirred at 0 °C or at 22 °C (room temperature) for 5 to 8 days. Then, the reaction mixture was purified by silica gel column chromatography (eluent: PE/EtOAc or PE/CH_2Cl_2).

Characterization Data for Products. *(2S,3S)-Ethyl 2-Fluoro-5-phenyl-3-(phenylthio)pentanoate (**3**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 84:16. The crude was purified by silica gel column chromatography (PE/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 (*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.

$[\alpha]_D^{20}$ −18.0 (*c* 1.23, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.34 (m, 2H), 7.22−7.05 (m, 8H), 4.97 (dd, 1H, $^{2}J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.0 (dd, $^{2}J_{F-H}$ = 48.0 Hz, $^{3}J_{F-H}$ = 28.2 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.9 (d, $^{2}J_{C-F}$ = 22.5 Hz), 140.7, 133.8, 132.9, 129.0, 128.5, 128.5, 127.6, 126.2, 90.5 (d, $^{1}J_{C-F}$ = 195.0 Hz), 61.7, 50.5 (d, $^{2}J_{C-F}$ = 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 $C_{19}H_{22}FO_2S$, 333.1325; found, 333.1319.

*(2S,3R)-Ethyl 2-Fluoro-5-phenyl-3(phenylthio)pentanoate (**anti-3**).* (*E*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 14:86. The crude was purified by silica gel column chromatography (PE/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). About 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.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.37 (m, 2H), 7.25−7.09 (m, 8H), 4.80 (dd, 1H, $^{2}J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −195.7 (dd, $^{2}J_{F-H}$ = 48.0 Hz, $^{3}J_{F-H}$ = 22.6 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 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.

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*(2S,3S)-Ethyl 3-((4-Bromophenyl)thio)-2-fluoro-5-phenylpentanoate (**4**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 67:33. The crude was purified by silica gel column chromatography (PE/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). About 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, $CDCl_3$); mp 54−56 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34−7.31 (m, 2H), 7.22−7.06 (m, 7H), 4.97 (dd, 1H, $^2J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.2 (dd, $^2J_{F-H}$ = 51.0 Hz, $^3J_{F-H}$ = 31.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.8 (d, $^2J_{C-F}$ = 22.5 Hz), 140.4, 134.5, 132.8, 132.0, 128.6, 128.5, 126.3, 122.0, 90.6 (d, $^1J_{C-F}$ = 187.5 Hz), 61.8, 50.4 (d, $^2J_{C-F}$ = 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 $C_{19}H_{21}BrFO_2S$, 411.0430; found, 411.0429.

*(2S,3S)-Ethyl 2-Fluoro-3-((4-methoxyphenyl)thio)-5-phenylpentanoate (**5**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 81:19. The crude was purified by silica gel column chromatography (PE/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). About 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, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.33 (m, 2H), 7.19−7.06 (m, 5H), 6.75−6.73 (m, 2H), 4.92 (d, 1H, $^2J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.1 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.2 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1 (d, $^2J_{C-F}$ = 30.0 Hz), 159.9, 140.9, 136.2, 128.6, 128.5, 126.2, 123.4, 114.5, 90.8 (d, $^1J_{C-F}$ = 187.5 Hz), 61.7, 55.4, 51.1 (d, $^1J_{C-F}$ = 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 $C_{20}H_{24}FO_3S$, 363.1430; found, 363.1426.

*(2S,3S)-Ethyl 3-((2-Aminophenyl)thio)-2-fluoro-5-phenylpentanoate (**6**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 90:10. The crude was purified by silica gel column chromatography (PE/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). About 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.

$[\alpha]_D^{20}$ +13.4 (*c* 1.08, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30−7.02 (m, 7H), 6.63−6.56 (m, 2H), 4.92 (d, 1H, $^2J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −196.0 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 25.4 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 187.5 Hz), 61.8, 49.6 (d, $^2J_{C-F}$ = 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 $C_{19}H_{23}FNO_2S$, 348.1434; found, 348.1426.

*(2S,3S)-Ethyl 2-Fluoro-5-phenyl-3-(o-tolylthio)pentanoate (**7**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 95:5. The crude was purified by silica gel column chromatography (PE/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). About 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.

$[\alpha]_D^{20}$ +29.4 (*c* 0.68, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24−7.06 (m, 9H), 4.98 (d, 1H, $^2J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −196.5 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.2 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.8 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 187.5 Hz), 61.7, 49.7 (d, $^2J_{C-F}$ = 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 $C_{20}H_{24}FO_2S$, 347.1481; found, 347.1480.

*(2S,3S)-Ethyl 2-Fluoro-5-phenyl-3-(m-tolylthio)pentanoate (**8**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 94:6. The crude was purified by silica gel column chromatography (PE/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). About 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.

$[\alpha]_D^{20}$ −18.8 (*c* 0.89, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.23−6.97 (m, 9H), 4.97 (d, 1H, $^2J_{H-F}$ = 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −196.8 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.2 Hz). $^{13}C\{^1H\}$ 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*: [M + H]$^+$ calcd for $C_{20}H_{24}FO_2S$, 347.1481; found, 347.1479.

*(2S,3S)-Ethyl 2-Fluoro-5-phenyl-3-(p-tolylthio)pentanoate (**9**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 85:15. The crude was purified by silica gel column chromatography (PE/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). About 54% 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) = 7.347 min, *t* (major) = 8.143 min]. The racemic product has been obtained

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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.

$[\alpha]_D^{20}$ −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). $^{13}C\{^1H\}$ 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*: $[M + H]^+$ calcd for $C_{20}H_{24}FO_2S$, 347.1481; found, 347.1481.

*(2S,3S)-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) and $(DHQ)_2PYR$ (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 the crude product showed dr = 88:12. The crude was purified by silica gel column chromatography (PE/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). About 67% 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) = 6.183 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.

$[\alpha]_D^{20}$ −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). $^{13}C\{^1H\}$ 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*: $[M + H]^+$ calcd for $C_{17}H_{20}FO_2S_2$, 339.0889; found, 339.0899.

*(2S,3S)-Ethyl 2-Fluoro-3-(naphthalen-2-ylthio)-5-phenylpentanoate (**11**).* (*Z*)-Ethyl 2-fluoro-5-phenylpent-2-enoate (0.3 mmol, 66.6 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 73:27. The crude was purified by silica gel column chromatography (PE/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). About 29% 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) = 7.777 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, $CDCl_3$); ^1H 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, $^2J_{H-F}$ = 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_{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). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.9 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 187.5 Hz), 61.7, 50.3 (d, $^2J_{C-F}$ = 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*: $[M + H]^+$ calcd for $C_{23}H_{24}FO_2S$, 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), and $(DHQ)_2PYR$ (0.03 mmol, 26.4 mg) were stirred in toluene at 0 °C for 8 days according to the general procedure **b**. ^{19}F NMR of the crude product showed dr = 80:20. The crude was purified by silica gel column chromatography (PE/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). About 2% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 99/1, flow = 1 mL/min, λ = 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, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, 2H, J_{H-H} = 9.0 Hz), 7.37−7.34 (m, 2H), 7.27−7.19 (m, 4H), 4.98 (dd, 1H, $^2J_{H-F}$ = 48.0 Hz, J_{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_{H-H} = 6.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −196.4 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.2 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.6 (d, $^2J_{C-F}$ = 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, $^2J_{C-F}$ = 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*: $[M]^+$ calcd for $C_{19}H_{19}BrFNO_4S$, 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), and $(DHQ)_2PYR$ (0.03 mmol, 26.4 mg) were stirred in toluene at 0 °C for 8 days according to the general procedure **b**. ^{19}F NMR of the crude product showed dr = 84:16. The crude was purified by silica gel column chromatography (PE/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). About 8% 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) = 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; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 2H, J_{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, $^2J_{H-F}$ = 48.0 Hz, J_{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_{H-H} = 6.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −196.0 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.2 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.7 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 187.5 Hz), 61.9, 50.4 (d, $^2J_{C-F}$ = 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*: $[M]^+$ calcd for $C_{23}H_{22}FNO_4S$, 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) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 100:0. The crude was purified by silica gel column chromatography (PE/EtOAc, from 15/1 to 10/1, v/v) affording only one diastereoisomer in 34% yield (32 mg as a colorless oil). About 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.

$[\alpha]_D^{20}$ −5.6 (*c* 0.32, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.9 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 36.7 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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,

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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 $C_{17}H_{24}FO_2S$, 311.1481; found, 311.1491.

*(2S,3S)-Ethyl 3-((4-Bromophenyl)thio)-3-cyclohexyl-2-fluoropropanoate (**15**).* (*Z*)-Ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 69:31. The crude was purified by silica gel column chromatography (PE/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). About 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.

$[\alpha]_D^{20}$ +2.5 (*c* 1.02, $CDCl_3$); mp 31−33 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.7 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 33.8 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{17}H_{23}BrFO_2S$, 389.0586; found, 389.0596.

*(2S,3S)-Ethyl 3-Cyclohexyl-2-fluoro-3-((4-methoxyphenyl)thio)-propanoate (**16**).* (*Z*)-Ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 80:20. The crude was purified by silica gel column chromatography (PE/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). About 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.

$[\alpha]_D^{20}$ −5.4 (*c* 0.61, $CDCl_3$); mp 57−58 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.9 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 36.7 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{18}H_{26}FO_3S$, 341.1587; found, 341.1581.

*(2S,3S)-Ethyl 3-Cyclohexyl-2-fluoro-3-(thiophen-2-ylthio)-propanoate (**17**).* (*Z*)-Ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 100:0. The crude was purified by silica gel column chromatography (PE/EtOAc, from 15/1 to 10/1, v/v) affording only one diastereoisomer in 32% yield (30 mg as a yellow oil). About 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.

$[\alpha]_D^{20}$ −8.3 (*c* 0.06, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −198.3 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 33.8 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{22}FO_2S_2$, 317.1045; found, 317.1051.

*(2S,3S)-Ethyl 3-((2-Aminophenyl)thio)-3-cyclohexyl-2-fluoropropanoate (**18**).* (*Z*)-Ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 90:10. The crude was purified by silica gel column chromatography (PE/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). About 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.

$[\alpha]_D^{20}$ +24.1 (*c* 0.22, $CDCl_3$); mp 112−113 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −196.1 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 33.8 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{17}H_{25}FNO_2S$, 326.1590; found, 326.1594.

*(2S,3S)-Ethyl 3-Cyclohexyl-2-fluoro-3-(m-tolylthio)propanoate (**19**).* (*Z*)-Ethyl 3-cyclohexyl-2-fluoroacrylate (0.3 mmol, 60.0 mg) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the crude product showed dr = 81:19. The crude was purified by silica gel column chromatography (PE/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). About 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, $CDCl_3$); ^1H 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, $^2J_{H-F}$ = 51.0 Hz, J_{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_{H-H} = 12.0 Hz), 1.71−1.60 (m, 5H), 1.20−1.01 (m, 8H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.7 (dd, $^2J_{F-H}$ = 51.0 Hz, $^3J_{F-H}$ = 33.8 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.6 (d, $^2J_{C-F}$ = 22.5 Hz), 138.6, 135.5, 132.4, 128.9, 128.7, 127.9, 89.3 (d, $^1J_{C-F}$ = 187.5 Hz), 61.6, 57.8 (d, $^2J_{C-F}$ = 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: $[M + H]^+$ calcd for $C_{18}H_{26}FO_2S$, 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) and $(DHQ)_2PYR$ (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

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the general procedure **b**. ^{19}F NMR of the crude product showed dr = 88:12. The crude was purified by silica gel column chromatography (PE/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). About 63% 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) = 6.530 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; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31−7.22 (m, 7H), 7.18−7.14 (m, 3H), 5.16 (dd, 1H, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.60 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 3.0 Hz), 3.61 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −194.2 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.9 (d, $^2J_{C-F}$ = 30.0 Hz), 137.8, 133.6, 132.9, 128.9, 128.7, 128.4, 128.4, 126.2, 127.7, 91.3 (d, $^1J_{C-F}$ = 187.5 Hz), 55.8 (d, $^2J_{C-F}$ = 22.5 Hz), 52.6. IR: 2947, 1755, 1438, 1225, 1087, 1001, 736, 701, 688, 540, 467 cm^{-1}. HRMS (API$^+$) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{16}FO_2S$, 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) and $(DHQ)_2PYR$ (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}F NMR of the crude product showed dr = 24:76. The crude was purified by silica gel column chromatography (PE/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). About 51% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 95/5, flow = 1 mL/min, λ = 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.

^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.34 (m, 2H), 7.25−7.19 (m, 8H), 5.09 (dd, 1H, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.56 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 6.0 Hz), 3.54 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −195.0 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 26.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.0 (d, $^2J_{C-F}$ = 22.5 Hz), 135.5, 133.5, 132.9, 129.2, 128.9, 128.8, 128.6, 128.4, 128.4, 89.2 (d, $^1J_{C-F}$ = 195.0 Hz), 54.6 (d, $^2J_{C-F}$ = 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) and $(DHQ)_2PYR$ (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}F NMR of the 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). About 51% 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) = 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, $^2J_{H-F}$ = 48.0, J_{H-H} = 3.0 Hz), 4.48 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 3.0 Hz), 4.23 (s, 2H), 3.56 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −194.2 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 195.0 Hz), 54.0 (d, $^2J_{C-F}$ = 22.5 Hz), 52.5. IR: 3432, 3327, 2951, 1755, 1609, 1217, 1101, 751, 698, 530, 457 cm^{-1}. HRMS (API$^+$) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{17}FNO_2S$, 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) and $(DHQ)_2PYR$ (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 the crude product showed dr = 87:13. The crude was purified by silica gel column chromatography (PE/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). About 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, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.59 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 3.0 Hz), 3.60 (s, 3H), 2.18 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −194.1 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.0 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 187.5 Hz), 55.7 (d, $^2J_{C-F}$ = 22.5 Hz), 52.5, 21.2. IR: 2960, 1765, 1741, 1437, 1219, 1101, 774, 692, 544, 436 cm^{-1}. HRMS (API$^+$) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{18}FO_2S$, 305.1012; found, 305.1024.

*(2S,3S)-Methyl 2-Fluoro-3-(phenylthio)-3-(p-tolyl)propanoate (**23**).* (*Z*)-Methyl 2-fluoro-3-(*p*-tolyl)acrylate (0.3 mmol, 58.3 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 88:12. The crude was purified by silica gel column chromatography (PE/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). About 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, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 6.0 Hz), 4.57 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 6.0 Hz), 3.60 (s, 3H), 2.24 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −194.0 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.0 (d, $^2J_{C-F}$ = 22.5 Hz), 138.0, 134.8, 133.8, 132.8, 129.4, 128.9, 128.3, 128.2, 127.8, 91.5 (d, $^1J_{C-F}$ = 195.0 Hz), 55.5 (d, $^2J_{C-F}$ = 22.5 Hz), 52.6, 21.2. IR: 2927, 1739, 1434, 1269, 1085, 1008, 741, 570, 413 cm^{-1}. HRMS (API$^+$) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{18}FO_2S$, 305.1012; found, 305.1009.

*(2S,3S)-Methyl 3-(2-Cyanophenyl)-2-fluoro-3-(phenylthio)-propanoate (**24**).* (*Z*)-Methyl 3-(2-cyanophenyl)-2-fluoroacrylate (0.3 mmol, 61.6 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 87:13. The crude was purified by silica gel column chromatography (PE/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). About 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, $CDCl_3$); mp 71−72 °C; ^1H NMR (300 MHz, $CDCl_3$): 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, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 3.0 Hz), 5.12 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 3.0 Hz), 3.64 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −195.8 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.0 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 195.0 Hz), 53.0 (d, $^2J_{C-F}$ = 15.0 Hz), 52.8. IR: 2947, 2224, 1732, 1438, 1283, 1106, 1016, 743, 692,

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555, 491 cm^{-1}. HRMS (API^+) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}FNO_2S$, 316.0808; found, 316.0814.

*(2S,3S)-Methyl 3-(3-Cyanophenyl)-2-fluoro-3-(phenylthio)-propanoate (**25**).* (*Z*)-Methyl 3-(3-cyanophenyl)-2-fluoroacrylate (0.3 mmol, 61.6 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 92:8. The crude was purified by silica gel column chromatography (PE/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). About 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, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56−7.48 (m, 3H), 7.37−7.32 (m, 1H), 7.23−7.16 (m, 5H), 5.16 (dd, 1H, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.60 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 3.0 Hz), 3.69 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −195.4 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.5 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 195.0 Hz), 55.2 (d, $^2J_{C-F}$ = 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 $C_{17}H_{15}FNO_2S$, 316.0808; found, 316.0808.

*(2S,3S)-Methyl 3-(4-Cyanophenyl)-2-fluoro-3-(phenylthio)-propanoate (**26**).* (*Z*)-Methyl 3-(4-cyanophenyl)-2-fluoroacrylate (0.3 mmol, 61.6 mg) and $(DHQ)_2PYR$ (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 the crude product showed dr = 100:0. The crude was purified by silica gel column chromatography (PE/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 70% yield (66 mg as a white solid). About 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, $CDCl_3$); mp 79−80 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54−7.38 (m, 4H), 7.23−7.16 (m, 5H), 5.17 (dd, 1H, $^2J_{H-F}$ = 48.0 Hz, J_{H-H} = 3.0 Hz), 4.61 (dd, 1H, $^3J_{H-F}$ = 28.0 Hz, J_{H-H} = 3.0 Hz), 3.70 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −195.3 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.5 (d, $^2J_{C-F}$ = 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, $^1J_{C-F}$ = 195.0 Hz), 55.6 (d, $^2J_{C-F}$ = 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 $C_{17}H_{15}FNO_2S$, 316.0808; found, 316.0790.

*(2S,3S)-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) and $(DHQ)_2PYR$ (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**. ^{19}F NMR of the 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). About 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.

$[\alpha]_D^{20}$ +183.2 (*c* 2.20, $CDCl_3$); mp 80−82 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −193.9 (dd, $^2J_{F-H}$ = 48.0 Hz, $^3J_{F-H}$ = 28.0 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{17}H_{19}FNO_3S$, 336.1070; found, 336.1062.

*(2S,3S)-3-Fluoro-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**28**).* Compound **21** (0.35 mmol, 106.8 mg) and *p*-TsOH (0.07 mmol, 6.9 mg) were added into 2 mL of 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 (PE/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].

$[\alpha]_D^{23}$ +126.1 (*c* 0.80, $CDCl_3$); mp 161−163 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −190.5 (dd, $^2J_{F-H}$ = 47.9 Hz, $^3J_{F-H}$ = 8.5 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{13}FNOS$, 274.0702; found, 274.0707.

*(2S,3S)-3-Fluoro-2-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]-thiazepin-4(5H)-one (**29**).* Compound **27** (0.2 mmol, 67.0 mg) and *p*-TsOH (0.04 mmol, 3.9 mg) were added into 1.2 mL of 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 (PE/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].

$[\alpha]_D^{23}$ +122.2 (*c* 0.54, $CDCl_3$); mp 165−166 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −190.4 (ddd, $^2J_{F-H}$ = 47.9 Hz, $^3J_{F-H}$ = 8.5 Hz, $^4J_{F-H}$ = 2.8 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{16}H_{15}FNO_2S$, 304.0808; found, 304.0812.

*(2S,3S)-5-(2-(Dimethylamino)ethyl)-3-fluoro-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**30**).* To a solution of compound **28** (0.25 mmol, 68.5 mg) in EA (1.5 mL) were added 2-dimethylaminoethyl chloride hydrochloride (72.0 mg, 0.50 mmol), followed by potassium carbonate (138.0 mg, 1.0 mmol) and H_2O (15 μL). After the mixture was stirred for 24 h under reflux, it was cooled to room temperature. The mixture was dried over Na_2SO_4 and 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, $CDCl_3$); mp 165−166 °C; ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −189.3 (d, $^2J_{F-H}$ = 47.9 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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,

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766, 602, 591, 428 cm^{-1}. HRMS (ESI^+) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}FN_2OS$, 345.1437; found, 345.1449.

*(2S,3S)-5-(2-(Dimethylamino)ethyl)-3-fluoro-2-(4-Methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (**31**).* To a solution of compound **29** (0.15 mmol, 45.0 mg) in EA (1.0 mL) were added 2-dimethylaminoethyl chloride hydrochloride (43.2 mg, 0.30 mmol), followed by potassium carbonate (82.8 mg, 0.6 mmol) and H_2O (10 μL). After the mixture was stirred for 24 h under reflux, it was cooled to room temperature. The mixture was dried over Na_2SO_4 and 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, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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). ^{19}F NMR (282 MHz, $CDCl_3$): δ −189.2 (d, $^2J_{F-H}$ = 47.9 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{24}FN_2O_2S$, 375.1543; found, 375.1532.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02081.

Optimization tables; kinetic studies; crystallographic data for products **13** and **18**; copies of NMR (^1H, ^{19}F, and $^{13}C\{^1H\}$) spectra for all new compounds; and HPLC chromatograms (PDF)

Crystallographic data for product **13** (CIF)

Crystallographic data for product **18** (CIF)

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Notes

The authors declare no competing financial interest.

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