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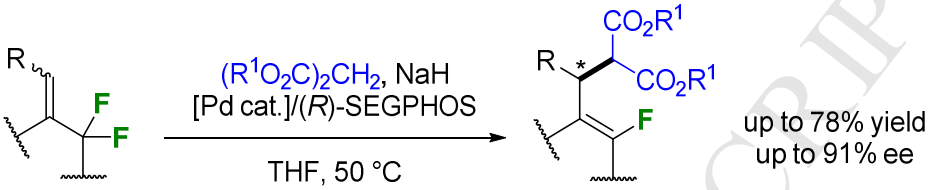

enantioselective reaction involving the activation of a C–F bond

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Enantioselective palladium-catalyzed addition of malonates to 3,3-difluoropropenes

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ABSTRACT

Monofluoroalkenes bearing a malonate unit at the β position can be synthesized by the enantioselective addition of diesters to 3,3-difluoropropenes. The difference in reactivity regarding the geometry and the substituents of the alkene of the 3,3-difluoropropenes, as well as the alkyl groups of the malonates, was studied and limitations were identified. The reaction was also performed with different 3,3-difluoropropenes. Further synthetic transformations of a newly functionalized monofluoroalkene were also accomplished.

1. Introduction

The fluorine atom presents unique and interesting properties,[1] which explains the importance of its incorporation in organic molecules for applications in medicinal chemistry, agrochemistry and material sciences.[2,3,4] Of all the fluorinated motifs, monofluoroalkenes are useful as non-hydrolyzable amide bonds or enol ethers isosteres.[5,6] Numerous synthetic strategies towards monofluoroalkenes have been developed over the years.[7] Our group has been particularly interested in using 3,3-difluoropropenes as starting materials to access monofluoroalkenes using catalyzed or metal-free process (Figure 1a).[8,9,10] In this context, we recently reported the palladium-catalyzed addition of dimethylmalonate and its derivatives to different 3,3-difluoropropenes (Figure 1b).[11] Many monofluoroalkenes bearing a malonate at the β position were obtained in up to 78% yield. As a preliminary result, we also disclosed that the reaction of trisubstituted alkene (*E*)-**1** provided the chiral monofluoroalkene **2** in 56% yield and 55% ee using (*R*)-BINAP as the chiral ligand (Figure 1c), a rare example of enantioselective reaction involving the activation of a C–F bond.[12] Herein, we report our progress based on this initial result (Figure 1d). Specifically, optimization of the chiral ligand and a study of the reactivity depending on the geometry of the alkene, on its substituents and on the alkyl groups of the malonate was performed, as well as the extension of the reaction on different 3,3-difluoropropenes. This study allowed the identification of some limitations. Synthetic transformations were also accomplished on a monofluoroalkene.

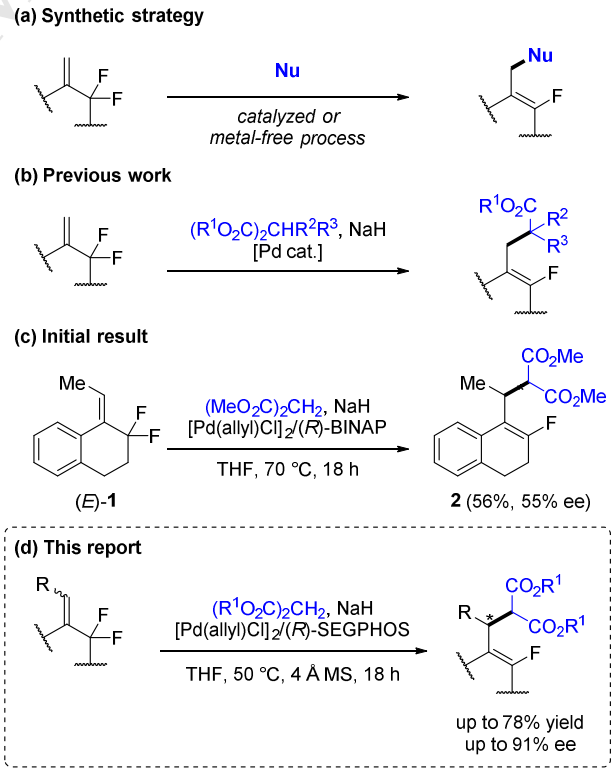

Fig. 1. Previous work, initial result and current work.

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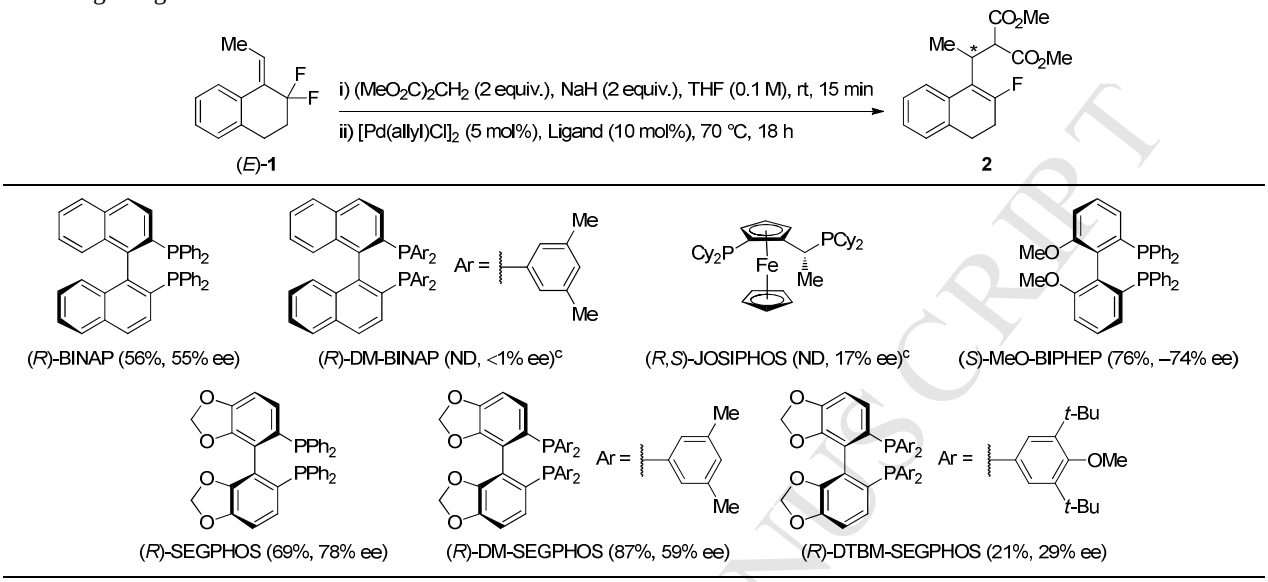
2. Results and Discussion

The enantioselective palladium-catalyzed addition of dimethylmalonate was first studied on 3,3-difluoropropene (*E*)-**1** and the initial screening of chiral ligands is summarized in Table 1. As reported previously,[11] (*R*)-BINAP provided the higher ee at this point (55% ee),[13] compared to (*R*)-DM-BINAP (<1% ee) and (*R,S*)-JOSIPHOS (17% ee). Further screening revealed that (*R*)-SEGPHOS (78% ee) was superior that its more hindered analogs: (*R*)-DM-SEGPHOS (59% ee) and (*R*)-DTBM-SEGPHOS (29% ee). While (*S*)-MeO-BIPHEP also gave interesting results (−74% ee), it was decided to pursue the study with (*R*)-SEGPHOS.

Table 1
Initial screening of ligands[a,b]

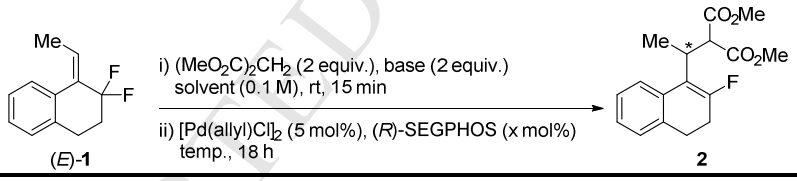


[a]Isolated yield of **2**.

[b]The ee's were determined by chiral HPLC.

[c]The yield could not be determined. Numerous side products were present in the crude mixture and purification only provided a small pure sample for HPLC analysis.

Table 2
Screening of solvents, bases and temperature.



Entry	Base	Solvent	x (mol%)	Temperature (°C)	Yield (%)[a]	ee (%)[b]
1	NaH	Toluene	10	110	33	67
2	NaH	CH_3CN	10	85	71	69
3	NaH	Et_2O	10	40	20	75
4	NaH	DCE	10	85	55	75
5	NaH	Dioxane	10	70	67	71
6	NaH	2-Me-THF	10	70	61	76
7	NaH	CH_2Cl_2	10	40	23	84
8	NaH	THF/CH_2Cl_2 (1:1)	10	70	66	77
9	NaH	THF/CH_2Cl_2 (1:3)	10	70	58	77
10	NaH	THF	10	60	54	80
11	NaH	THF	10	50	72	82
12	NaH	THF	20	50	51	86
13	Et_2Zn	THF	20	50	0	-
14	KH	THF	20	50	0	-
15	BSA (3 equiv.)	THF	20	50	0	-
16	NaOMe	THF	20	50	0	-
17	BSA (3 equiv.), KOAc (0.3 equiv.)	THF	20	50	0	-
18	NaH	THF	15	50	67	82
19[c]	NaH	THF	15	50	75	80

[a]Isolated yield of **2**.

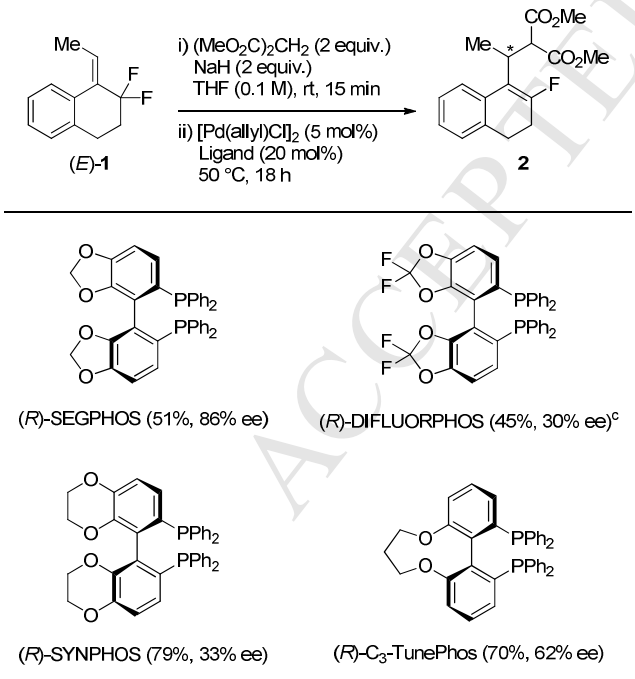
[b]The ee's were determined by chiral HPLC.

[c]Molecular sieves (4Å) were added to the reaction mixture.

Further optimization of the reaction conditions was then undertaken (Table 2). A screening of solvents (Table 2, entries 1-9) showed that when the reaction was run in toluene, Et_2O or CH_2Cl_2, low yields and similar enantiomeric excess were observed compared to THF. Using of CH_3CN, dioxane or 2-methyl(tetrahydrofuran) provided similar results to THF. Interestingly, performing the transformation in CH_2Cl_2 afforded **2** with a higher enantiomeric excess (Table 2, entry 7), however, in low yield due to an incomplete conversion. A mixture of CH_2Cl_2 and THF was explored, but no improvement was observed (Table 2, entries 8-9). To counter the formation of unidentified side products, lower temperatures (Table 2, entries 10-11) were tested, and 50 °C was found to be the most efficient. It was noted that using 20 mol% of (*R*)-SEGPHOS (Table 2, entry 12) provided a small increase of the enantiomeric excess, but at the expense of the yield due to purification issues. Other bases were screened (Table 2, entries 13-17), but no formation of the final product was observed. Finally, using 15 mol% of (*R*)-SEGPHOS and adding 4Å molecular sieves in the reaction mixture provided a good compromise between yield and enantioselectivity as **2** was isolated in 75% yield with 80% ee (Table 2, entry 19).

In parallel, a few additional ligands structurally-related to SEGPHOS were screened (Table 3) using the conditions reported in entry 12 of Table 2. No reaction was observed at 50 °C when using (*R*)-DIFLUORPHOS. However, at 70 °C, the product was obtained in 45% yield and 30% ee. In the case of (*R*)-SYNPHOS, a good yield was obtained (79%), but with lower enantioselectivity (33% ee) compared to (*R*)-SEGPHOS. Finally, (*R*)-C_3-TunePhos gave the monofluoroalkene with a better yield, but with a lower enantiomeric excess than with (*R*)-SEGPHOS (70%, 62% ee). In the end, (*R*)-SEGPHOS provided the highest enantioselectivity and the conditions used in entry 19 of Table 2 were used for the rest of the study.

Table 3
Additional ligand screening.[a,b]



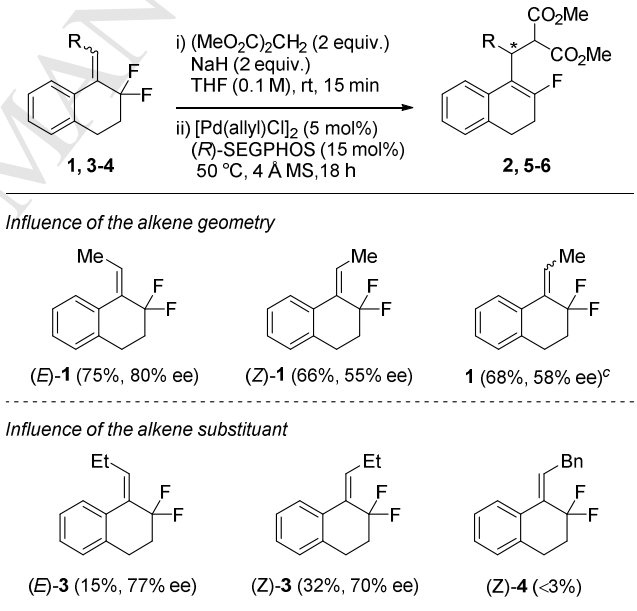
[a]Isolated yield of **2**.

[b]The ee's were determined by chiral HPLC.

[c]Reaction was conducted at 70 °C.

As the synthesis of the 3,3-difluoropropenes allowed, in some cases (vide infra), the separation of the (*E*) and (*Z*) isomers, the effect of the alkene geometry on the reaction was studied (Table 4). Higher yield and enantiomeric excess were observed starting from (*E*)-**1** (75%, 80% ee) compared to (*Z*)-**1** (66%, 55% ee).[14] Furthermore, when a 29:71 *E*/*Z* mixture of **1** was used, the reactivity was found to be closer to that of (*Z*)-**1** (68%, 58% ee). The difference may be due to the nature of the diastereomeric π-allyl complex formed.[15] Indeed, in the case of the (*E*) isomer, the most stable syn π-allyl complex is initially produced while with the (Z) isomer, the less stable anti π-allyl complex would be generated. The latter could isomerize via a σ-π-σ mechanism producing a mixture of diastereomeric π-allyl complexes, with different (and lower) enantioselectivity. Afterwards, the influence of the alkene substituent was evaluated. The replacement of the methyl group by an ethyl moiety resulted in a considerable decrease in the yields for both (*E*)-**3** (15%) and (*Z*)-**3** (32%), probably due to an increase in the steric hindrance. Interestingly, the reaction showed a similar enantioselectivity with (*E*)-**3** (77% ee) compared to (*E*)-**1**, while it was superior for (*Z*)-**3** (70% ee) compared to (*Z*)-**1**. Finally, when a benzyl was present on the alkene, less than 3% of the desired monofluoroalkene was observed. Overall, this transformation seems, under the current reaction conditions, limited to the use of methyl trisubstituted alkenes.

Table 4
Influence of the alkene geometry and the alkene substituant.[a,b]



[a]Isolated yield of **2, 5-6**.

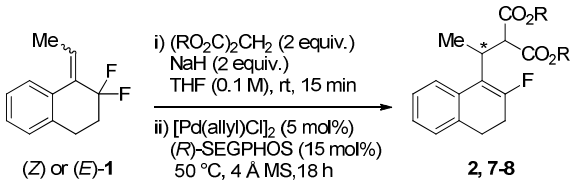
[b]The ee's were determined by chiral HPLC.

[c]Compound **1** was a 29:71 *E*/*Z* mixture.

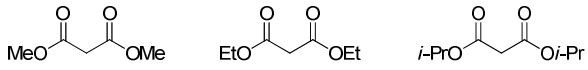
The influence of the ester groups on the malonate was studied and as such, dimethylmalonate, diethylmalonate and diisopropylmalonate were subjected to the palladium-catalyzed reaction on (*E*)-**1** and (*Z*)-**1** (Table 5). For the reaction on (*E*)-**1**, the yields decreased from methyl (75%, 80% ee) to ethyl (66%, 81% ee) to isopropyl (52%, 83% ee), while the enantiomeric excess stayed similar. A slightly different behavior was observed with (*Z*)-**1**. The best results were obtained using dimethylmalonate (66%, 55% ee), but diethylmalonate gave a lower yield with a similar enantiomeric excess (41%, 55% ee) and diisopropylmalonate gave a similar yield, but with a lower enantiomeric excess (62%, 46% ee). Overall, the best result was obtained when using dimethylmalonate on (*E*)-**1**. Unfortunately,

di-*tert*-butylmalonate, dibenzylmalonate and α-substituted malonates were unsuitable substrates for the transformation.

Table 5
Influence of the malonate alkyl groups.[a,b]

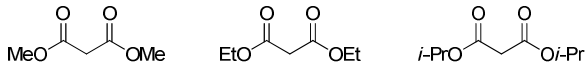


From (*E*)-**1**



2 (75%, 80% ee) **7** (66%, 81% ee) **8** (52%, 83% ee)

From (*Z*)-**1**

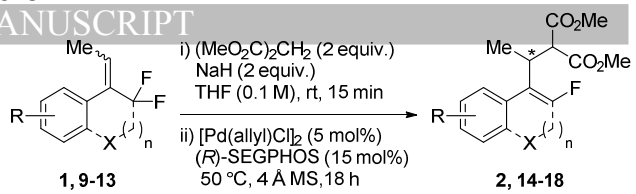


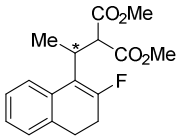
2 (66%, 55% ee) **7** (41%, 54% ee) **8** (62%, 46% ee)

[a]Isolated yield of **2, 7-8**.

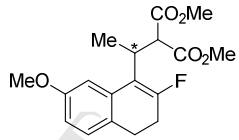
[b]The ee's were determined by chiral HPLC.

We next explored the extension of this reaction to different 3,3-difluoropropene derivatives (Table 6). It should be noted that in some cases, the separation of the (*E*) and (*Z*) alkenes was not possible and thus, the catalytic reactions were performed on the mixture. The presence of a methoxy group on the starting material (i.e. **9**) was well tolerated. Reaction on the *E*/*Z* mixture gave **14** (69%, 58% ee), with similar yields and enantiomeric excesses than the ones observed with the *E*/*Z* mixture of **1** (68%, 58% ee). The reaction also tolerated heteroatoms in the 6-membered cyclic structure. In the case of the thiochromanone derivative **10**, the monofluoroalkene **15** was obtained with moderate yield and high enantiomeric excess starting from (*Z*) (46%, 91% ee), and good yield and enantiomeric excess starting from (*E*) (78%, 87% ee). For the chromanone derivative **11**, **16** was observed in 76% yield and 80% ee, although the reaction was performed on a *E*/*Z* mixture of the 3,3-difluoropropene. Unfortunately, starting from the indanone **12**, the five-membered cycle equivalent, almost racemic monofluoroalkene **17** was obtained in moderate yields from either isomer. Finally, this methodology can also be applied to the acyclic 3,3-difluoropropene **13** to give the terminal monofluoroalkene **18**, but with low yield and enantiomeric excess (18%, 24% ee).

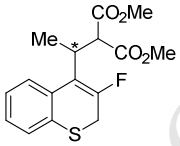




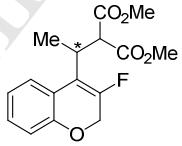
2 from (Z)-**1** (75%, 80% ee)
2 from (*E*)-**1** (66%, 55% ee)
2 from **1** (68%, 58% ee)[c]



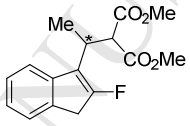
14 from **9** (69%, 58% ee)[d]



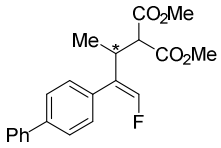
15 from (*Z*)-**10** (46%, 91% ee)
15 from (*E*)-**10** (78%, 87% ee)



16 from **11** (76%, 80% ee)[e]



17 from (*Z*)-**12** (47%, 3% ee)[f]
17 from (*E*)-**12** (60%, 2% ee)[f]



18 from **13** (18%, 24% ee)[g]

[a]Isolated yield of **2, 14-18**.

[b]The ee's were determined by chiral HPLC.

[c]Compound **1** was a 29:71 *E*/*Z* mixture.

[d]Compound **9** was a 24:76 mixture.

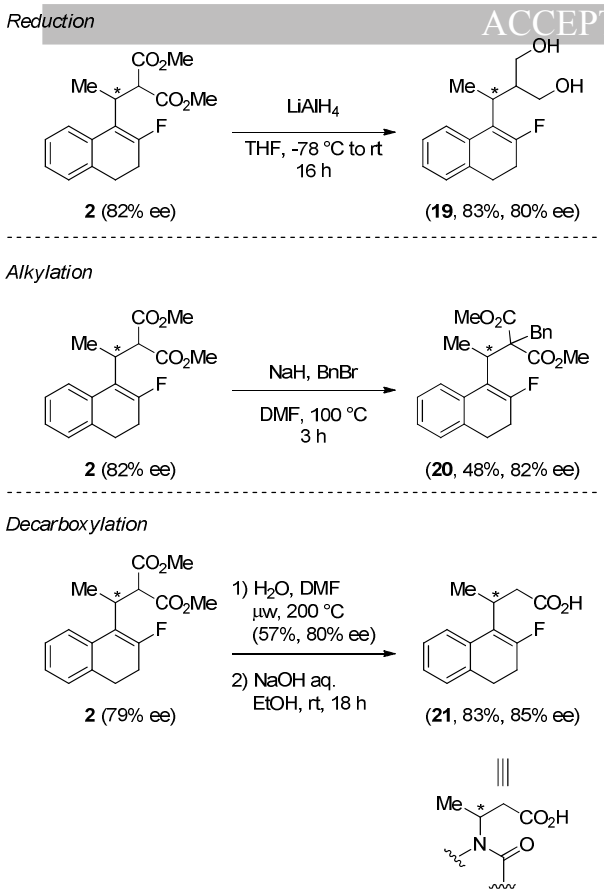
[e]Compound **11** was a 43:57 mixture.

[f]Reaction conditions of Table 1 were used ((*R*)-BINAP (10 mol%), THF, 70 °C).

[g]Compound **13** was a 18/82 mixture.

Finally, some transformations of **2** were explored to demonstrate the versatility of the monofluoroalkenes obtained. The diester can be reduced in the corresponding diol **19** in good yield (85%, 80% ee) using $LiAlH_4$. Also, the use of benzyl bromide in presence of sodium hydride allowed the alkylation in alpha of the diester to give **20** in moderated yield (48%, 82% ee). This transformation represents an alternative to the addition of a α-substituted malonate, an unsuccessful reaction under the current conditions (vide supra). Finally, as shown previously,[10,11] **2** can be transformed into the corresponding monofluoroalkene **21** in a 2-step sequence (monodecarboalkoxylation/hydrolysis; 57%, 80% ee/83%, 85% ee). The monofluoroalkene containing a carboxylic acid obtained here can be seen as a "beta-alanine" isostere.

Table 6
Extension to other derivatives.[a,b]



Scheme 1. Synthetic transformation of **2**.

3. Conclusion

The enantioselective palladium-catalyzed addition of malonates to 3,3-difluoropropenes was developed as a novel approach to enantioenriched functionalized monofluoroalkenes. A study of the impact on the structure of the alkenes and the malonates was performed and some limitations were found. Further derivatization of the products was also possible. Overall, the transformation reported herein represents a rare example of enantioselective reactions involving the activation of a C–F bond.

4. Experimental section

Materials and Methods

The following includes general experimental procedures, specific details for representative reactions and isolation, and spectroscopic information for the new compounds prepared. All reactions were carried out under an argon atmosphere with dry solvents. Et_2O, THF, CH_3CN, CH_2Cl_2 and toluene were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All other commercially available compounds were used as received. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Silicycle silica gel 60 Å F254 TLC plates, and visualized under UV (λ = 254 nm) or by staining with potassium permanganate. Flash column chromatography was carried out on Silicycle silica gel 60 Å, 230–400 mesh. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at ambient temperature using Agilent DD2 500 and Varian Inova 400 spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane (^{1}H NMR) or residual $CHCl_3$ (^{1}H and ^{13}C NMR) as the internal standard. For ^{19}F NMR, $CFCl_3$ is used as the external standard. Coupling constants (*J*) are measured in hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, hept = heptuplet, m = multiplet, bs = broad signal. High-resolution mass spectra were obtained on a LC/MS–TOF Agilent 6210 using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI). Infrared spectra were recorded using a ABB MB 3000 FT-IR spectrometer. Melting points were recorded on a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-360 Polarimeter with a sodium lamp at ambient temperature. Enantiomeric excesses were determined by HPLC analysis using a Hewlett Packard 1200 Series and Daicel Corporation columns (OJ-H, AD-H or IB)

4.1. General procedure

To a solution of NaH (2 equiv.) in THF (0.1 M, 1/3 of the total amount) containing 4 Å MS (approx. 10 mg) was added dropwise dimethylmalonate (2 equiv.) at rt and the resulting reaction mixture was stirred for 15 min. The 3,3-difluoropropene (1 equiv.) was dissolved in THF (0.1 M, 1/3 of the total amount) and added dropwise, followed by a solution of $[Pd(allyl)Cl]_2$ (5 mol%) and (*R*)-SEGPHOS (15 mol%) in THF (0.1 M, 1/3 of the total amount). The reaction mixture was then warmed to 50 °C and stirred for 18 h. The reaction mixture was cool to room temperature, quenched with H_2O and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated.

*Dimethyl 2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl) malonate (**2**)*

For the racemic synthesis of **2**, see ref. 11. <1% *ee* (determined by chiral HPLC, OJ-H, hexanes/2-propanol = 98:2, flow rate 1.1 mL min^{-1}, $t_{r,1}$ = 26.6 min, $t_{r,2}$ = 29.9 min, wavelength = 254 nm; or IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 6.9 min, $t_{r,2}$ = 7.4 min, wavelength = 220 nm). For the enantioselective synthesis starting from (*Z*)-**1**, the general procedure was performed on a 0.155 mmol scale to give **2** (31 mg, 66%) as a yellow oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +11.2 (*c* 0.048, MeOH); 55% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 7.0 min, $t_{r,major}$ = 7.6 min, wavelength = 220 nm). For the enantioselective synthesis starting from (*E*)-**1**, the general procedure was performed on a 0.155 mmol scale to give **2** (35 mg, 75%) as a yellow oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +15.7 (*c* 0.48, MeOH); 80% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 6.9 min, $t_{r,major}$ = 7.4 min, wavelength = 220 nm). For the enantioselective synthesis starting from a mixture (*E*)/(*Z*) = 29:71 of **1**, the general procedure was performed on a 0.155 mmol scale to give **2** (32 mg, 68%) as a colourless oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +11.1 (*c* 0.48, MeOH); 58% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 7.0 min, $t_{r,major}$ = 7.5 min, wavelength = 220 nm).

*Dimethyl 2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)propyl) malonate (**5**)*

For the racemic synthesis of **5**, the general procedure was followed on a 0.24 mmol scale of (*Z*)-**3** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **5** (14 mg, 18%) was isolated as a yellow oil by flash chromatography (10% EtOAc/hexanes). IR (ATR, diamond) ν = 2955, 2839, 1755, 1738, 1670, 1435, 1225, 1148, 1097, 764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 7.9 Hz), 7.21 (1H, m), 7.09 (2H, d, *J* = 4.4 Hz), 4.03 (1H, d, *J* = 11.3 Hz), 3.78 (3H,

s), 3.45 (3H, s), 2.94-2.82 (2H, m), 2.49 (2H, q, J = 7.6 Hz), 1.78 (1H, m), 1.67 (1H, m), 0.88 (3H, t, J = 7.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −96.0 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 168.5, 160.9 (d, J_{C-F} = 270.0 Hz), 133.0, 127.3, 127.2, 126.7, 126.0 (d, J_{C-F} = 2.0 Hz), 123.7 (d, J_{C-F} = 6.2 Hz), 119.3, 55.8 (d, J_{C-F} = 5.0 Hz), 52.6, 52.2, 38.8, 29.2 (d, J_{C-F} = 6.4 Hz), 25.4 (d, J_{C-F} = 25.0 Hz), 25.1, 12.2; HRMS-ESI calcd for $C_{18}H_{22}FO_4$ $[M+H]^+$ 321.1497, found 321.1470; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 98:2, flow rate 0.8 mL min^{-1}, $t_{r,1}$ = 6.7 min, $t_{r,2}$ = 7.1 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*Z*)-**3**, the general procedure was performed on a 0.144 mmol scale to give **5** (16 mg, 32%) as a yellow oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +13.5 (*c* 0.72, MeOH); 70% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 98:2, flow rate 0.8 mL min^{-1}, $t_{r,minor}$ = 6.7 min, $t_{r,major}$ = 7.1 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*E*)-**3**, the general procedure was performed on a 0.144 mmol scale to give **5** (7 mg, 15%) as a yellow oil by flash chromatography (3% Et_2O/toluene) followed by a second flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +10.7 (*c* 0.38, MeOH); 77% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 98:2, flow rate 0.8 mL min^{-1}, $t_{r,minor}$ = 6.3 min, $t_{r,major}$ = 6.8 min, wavelength = 254 nm).

*Dimethyl 2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)-2-phenylethyl)malonate (**6**)*

For the racemic synthesis of **6**, the general procedure was followed on a 0.18 mmol scale of (*Z*)-**4** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **6** (4 mg, 5%, *not pure*) was isolated as a yellow oil by flash chromatography (3% Et_2O/toluene). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.46 (2H, m), 7.40-7.36 (2H, m), 7.32-7.28 (2H, m), 7.19-7.16 (3H, m), 6.88 (1H, dt, J = 16.5, 1.6 Hz), 6.68 (1H, d, J = 16.4 Hz), 5.07 (1H, bs), 3.77 (6H, s), 3,42 (1H, bs), 2.88-2.81 (2H, m), 2.52-2.47 (2H, m); ^{19}F NMR (470 MHz, $CDCl_3$) δ −95.5 (1F, s). As the substrate was not suitable, the reaction using (*R*)-SEGPHOS was not performed. Furthermore, a full characterization was not performed as the final product was not pure.

*Diethyl 2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl)malonate (**7**)*

For the racemic synthesis of **7**, the general procedure was followed on a 0.183 mmol scale of (*Z*)-**1** using *rac*-BINAP (10 mol%) as the ligand, diethylmalonate (2 equiv.) as the nucleophile and stirring at 70 °C. The desired product **7** (48 mg, 78%) was isolated as a colorless oil by flash chromatography (10% EtOAc/hexanes). IR (ATR, diamond) ν = 2980, 2897, 1751, 1726, 1452, 1367, 1225, 1148, 1028, 762 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, d, J = 8.5 Hz), 7.21 (1H, dt, J = 8.2, 4.2 Hz), 7.09 (2H, d, J = 4.0 Hz), 4.25 (2H, q, J = 7.2 Hz), 4.01 (1H, d, J = 11.4 Hz), 3.95 (2H, q, J = 7.21 Hz), 3.62 (1H, dq, J = 13.5, 7.1 Hz), 2.94-2.81 (2H, m), 2.43-2.40 (2H, m), 1.36-1.27 (6H, m), 0.96 (3H, t, J = 7.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −97.8 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 168.2, 160.7 (d, J_{C-F} = 269.4 Hz), 134.2 (d, J_{C-F} = 8.5 Hz), 133.0, 127.3, 126.7, 126.1 (d, J_{C-F} = 1.9 Hz), 123.1 (d, J_{C-F} = 6.3 Hz), 116.3 (d, J_{C-F} = 10.6 Hz), 61.5, 61.1, 56.7 (d, J_{C-F} = 5.6 Hz), 31.9, 29.0 (d, J_{C-F} = 6.8 Hz), 25.4 (d, J_{C-F} = 24.9 Hz), 15.6 (d, J_{C-F} = 2.6 Hz), 14.1, 13.7; HRMS-ESI calcd for $C_{19}H_{27}FNO_4$ $[M+NH_4]^+$ 352.19487, found 352.19186; <1% *ee* (determined by chiral HPLC, OJ-H, hexanes/2-propanol = 93:7, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 8.3 min, $t_{r,2}$ = 10.1 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*Z*)-**1**, the general procedure was performed on a 0.155 mmol scale using diethylmalonate (2 equiv.) instead of dimethylmalonate to give **7** (21 mg, 41%) as a pink oil by flash chromatography (5% Et_2O/toluene). $[\alpha]^{21}_D$ = +20.2 (*c* 0.20, MeOH); 54% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 97:3, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 6.6 min, $t_{r,major}$ = 7.3 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*E*)-**1**, the general procedure was performed on a 0.155 mmol scale diethylmalonate (2 equiv.) instead of dimethylmalonate to give **7** (33 mg, 66%) as a yellow oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +11.3 (*c* 0.20, MeOH); 81% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 97:3, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 6.5 min, $t_{r,major}$ = 7.0 min, wavelength = 254 nm).

*Diisopropyl 2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl) malonate (**8**)*

For the racemic synthesis of **8**, the general procedure was followed on a 0.18 mmol scale of (*Z*)-**1** using *rac*-BINAP (10 mol%) as the ligand, diisopropylmalonate (2 equiv.) as the nucleophile and stirring at 70 °C. The desired product **8** (41 mg, 63%) was isolated as a colorless oil by flash chromatography (5/35/60 EtOAc/toluene/hexanes). IR (ATR, diamond) ν = 2980, 2837, 1747, 1728, 1672, 1452, 1225, 1182, 1099, 762 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, d, J = 7.8 Hz), 7.21 (1H, m), 7.12-7.05 (2H, m), 5.11 (1H, hept, J = 6.4 Hz), 4.81 (1H, hept, J = 6.2 Hz), 3.94 (1H, d, J = 11.3 Hz), 3.59 (1H, dt, J = 17.2, 6.6 Hz), 2.86 (2H, td, J = 8.1, 2.6 Hz), 2.55-2.37 (2H, m), 1.38-1.21 (12H, m), 1.04 (3H, d, J = 6.2 Hz), 0.86 (3H, d, J = 6.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −97.8 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 167.7, 160.6 (d, J_{C-F} = 269.3 Hz), 134.4 (d, J_{C-F} = 8.6 Hz), 133.0, 127.3, 126.7, 126.0 (d, J_{C-F} = 1.9 Hz), 123.2 (d, J_{C-F} = 6.3 Hz), 116.5 (d, J_{C-F} = 10.9 Hz), 68.9, 68.5, 57.1 (d, J_{C-F} = 5.6 Hz), 31.6, 29.0 (d, J_{C-F} = 6.7 Hz), 25.4 (d, J_{C-F} = 24.9 Hz), 21.7, 21.6, 21.5, 21.0, 17.6 (d, J_{C-F} = 2.7 Hz); HRMS-ESI calcd for $C_{21}H_{28}FO_4$ $[M+H]^+$ 363.1966, found 363.1954; <1% *ee* (determined by chiral HPLC, OJ-H, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 5.8 min, $t_{r,2}$ = 6.5 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*Z*)-**1**, the general procedure was performed on a 0.155 mmol scale using diisopropylmalonate (2 equiv.) instead of dimethylmalonate to give **8** (35 mg, 62%) as a yellow oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +5.3 (*c* 0.52, MeOH); 46% *ee* (determined by chiral HPLC, AD-H, hexanes/2-propanol = 97:3, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 10.6 min, $t_{r,major}$ = 9.0 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*E*)-**1**, the general procedure was performed on a 0.155 mmol scale using diisopropylmalonate (2 equiv.) instead of dimethylmalonate to give **8** (29 mg, 52%) as a yellow oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +12.0 (*c* 0.52, MeOH); 83% *ee* (determined by chiral HPLC, AD-H, hexanes/2-propanol = 97:3, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 10.6 min, $t_{r,major}$ = 9.1 min, wavelength = 254 nm).

*Dimethyl 2-(1-(2-fluoro-7-methoxy-3,4-dihydronaphthalen-1-yl) ethyl)malonate (**14**)*

For the racemic synthesis of **14**, the general procedure was followed on a 0.223 mmol scale of a mixture (*E*)/(*Z*) = 24:76 of **9** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **14** (62 mg, 77%) was isolated as a colourless oil by flash chromatography (10% EtOAc/hexanes). IR (ATR, diamond) ν = 2953, 2837, 1755, 1736, 1670, 1433, 1227, 1144, 1043, 818 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03-6.97 (2H, m), 6.63 (1H, dd, J = 8.2, 2.5 Hz), 4.05 (1H, d, J = 11.3 Hz), 3.81 (3H, s), 3.78 (3H, s), 3,56 (1H, m), 3.51 (3H, s), 2.83-2.76 (2H,

m), 2.51-2.38 (2H, m), 1.31 (3H, d, J = 7.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −97.1 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 168.5, 161.4 (d, J_{C-F} = 269.8 Hz), 158.7, 135.4 (d, J_{C-F} = 9.0 Hz), 127.9, 125.2, 116.2 (d, J_{C-F} = 11.0 Hz), 110.2 (d, J_{C-F} = 6.6 Hz), 110.1 (d, J_{C-F} = 2.0 Hz), 56.2, 55.4, 52.6, 52.2, 32.2, 28.1 (d, J_{C-F} = 6.7 Hz), 25.8 (d, J_{C-F} = 24.6 Hz), 17.5 (d, J_{C-F} = 2.8 Hz); HRMS-ESI calcd for $C_{18}H_{22}F_5$ $[M+H]^+$ 338.1480, found 338.1506; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 97:3, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 9.1 min, $t_{r,2}$ = 9.7 min, wavelength = 254 nm). For the enantioselective synthesis starting from a mixture (*E*)/(*Z*) = 24:76 of **9**, the general procedure was performed on a 0.132 mmol scale to give **14** (31 mg, 69%) as a colourless oil by flash chromatography (10% EtOAc/hexanes). $[\alpha]^{21}_D$ = +6.3 (*c* 0.33, MeOH); 58% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 97:2, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 9.1 min, $t_{r,major}$ = 9.8 min, wavelength = 254 nm).

*Dimethyl 2-(1-(3-fluoro-2H-thiochromen-4-yl)ethyl)malonate (**15**)*

For the racemic synthesis of **15**, the general procedure was followed on a 0.236 mmol scale of (*Z*)-**10** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **15** (45 mg, 58%) was isolated as a yellow oil by flash chromatography (3% Et_2O/toluene). IR (ATR, diamond) ν = 2955, 2847, 1751, 1738, 1664, 1435, 1263, 1198, 1148, 935 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 7.9 Hz), 7.30 (1H, dd, J = 7.7, 1.4 Hz), 7.20 (1H, m), 7.09 (1H, td, J = 7.5, 1.3 Hz), 4.05 (1H, d, J = 11.4 Hz), 3.78 (3H, s), 3.56 (1H, m), 3.54 (3H, s), 3.50-3.31 (2H, m), 1.33 (3H, d, J = 6.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −94.3 (1F, t, J = 10.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 168.4, 154.5 (d, J_{C-F} = 275.7 Hz), 133.9 (d, J_{C-F} = 6.8 Hz), 129.7, 127.3, 126.8 (d, J_{C-F} = 1.8 Hz), 126.3, 125.3 (d, J_{C-F} = 5.6 Hz), 118.1 (d, J_{C-F} = 12.8 Hz), 56.2 (d, J_{C-F} = 5.8 Hz), 52.6, 52.4, 34.2, 26.1 (d, J_{C-F} = 31.4 Hz), 17.6 (d, J_{C-F} = 3.2 Hz); HRMS-ESI calcd for $C_{16}H_{18}FO_4S$ $[M+H]^+$ 325.0904, found 325.0903; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 8.3 min, $t_{r,2}$ = 8.8 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*Z*)-**10**, the general procedure was performed on a 0.141 mmol scale to give **15** (21 mg, 46%) as a pinky oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +26.2 (*c* 0.33, MeOH); 91% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 8.3 min, $t_{r,major}$ = 9.0 min, wavelength = 254 nm). For the enantioselective synthesis starting from (*E*)-**1**, the general procedure was performed on a 0.141 mmol scale to give **15** (38 mg, 78%) as a colourless oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = +20.5 (*c* 0.33, MeOH); 87% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 8.3 min, $t_{r,major}$ = 8.9 min, wavelength = 254 nm).

*Dimethyl 2-(1-(3-fluoro-2H-chromen-4-yl)ethyl)malonate (**16**)*

For the racemic synthesis of **16**, the general procedure was followed on a 0.204 mmol scale of a mixture (*E*)/(*Z*) = 43:57 of **11** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **16** (51 mg, 84%) was isolated as a colorless oil by flash chromatography (10% EtOAc/hexanes). IR (ATR, diamond) ν = 2955, 2845, 1755, 1736, 1690, 1487, 1252, 1189, 1144, 928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, dd, J = 7.9, 1.6 Hz), 7.11 (1H, td, J = 7.7, 1.6 Hz), 6.99 (1H, t, J = 7.6 Hz), 6.85 (1H, dd, J = 8.0, 1.3 Hz), 4.66 (4.66 (2H, d, J = 3.9 Hz), 3.99 (1H, d, J = 11.3 Hz), 3.79 (3H, s), 3.60 (1H, m), 3.55 (3H, s), 1.31 (3H, d, J = 6.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −113.7 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 168.3, 151.5 (d, J_{C-F} = 271.5 Hz), 151.8, 128.1 (d, J_{C-F} = 2.2 Hz), 123.9 (d, J_{C-F} = 6.3 Hz), 122.2, 121.8 (d, J_{C-F} = 6.1 Hz), 116.0, 114.0 (d, J_{C-F} = 7.9 Hz), 63.7, 63.4, 56.0 (d, J_{C-F} = 4.6 Hz), 52.6 (d, J_{C-F} = 30.1 Hz), 31.1, 17.3 (d, J_{C-F} = 2.9 Hz); HRMS-ESI calcd for $C_{16}H_{18}FO_5$ $[M+H]^+$ 309.1133, found 309.1163; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 7.8 min, $t_{r,2}$ = 8.5 min, wavelength = 220 nm). For the enantioselective synthesis starting from a mixture (*E*)/(*Z*) = 43:57 of **11**, the general procedure was performed on a 0.155 mmol scale to give **16** (26 mg, 76%) as a colourless oil by flash chromatography (10% EtOAc/hexanes). $[\alpha]^{21}_D$ = +5.5 (*c* 0.24, MeOH); 80% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 7.9 min, $t_{r,major}$ = 8.6 min, wavelength = 220 nm).

*Dimethyl 2-(1-(2-fluoro-1H-inden-3-yl)ethyl)malonate (**17**)*

For the racemic synthesis of **17**, the general procedure was followed on a 0.278 mmol scale of (*Z*)-**12** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **17** (45 mg, 57%) was isolated as a yellow oil by flash chromatography (10% EtOAc/hexanes). IR (ATR, diamond) ν = 2955, 2843, 1790, 1736, 1437, 1271, 1155, 1009, 912, 764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (1H, dt, J = 7.4, 1.1 Hz), 7.29 (2H, d, J = 7.3 Hz), 7.15 (1H, td, J = 7.5, 1.2 Hz), 3.93 (1H, d, J = 11.0 Hz), 3.79 (3H, s), 3.64 (1H, m), 2.88 (3H, m), 3.42 (2H, m), 1.34 (3H d, J = 7.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −122.0 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 168.3, 163.2 (d, J_{C-F} = 281.4 Hz), 141.9 (d, J_{C-F} = 7.0 Hz), 134.8 (d, J_{C-F} = 8.1 Hz), 126.8, 124.4 (d, J_{C-F} = 4.3 Hz), 123.7 (d, J_{C-F} = 1.4 Hz), 119.6 (d, J_{C-F} = 8.1 Hz), 119.4 (d, J_{C-F} = 6.7 Hz), 55.9 (d, J_{C-F} = 2.8 Hz), 52.6, 52.4, 35.1 (d, J_{C-F} = 21.1 Hz), 29.8 (d, J_{C-F} = 1.9 Hz), 16.9 (d, J_{C-F} = 2.2 Hz); HRMS-ESI calcd for $C_{16}H_{18}FO_4$ $[M+H]^+$ 293.11836, found 293.12063; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 99:1, flow rate 0.8 mL min^{-1}, $t_{r,1}$ = 8.6 min, $t_{r,2}$ = 9.2 min, wavelength = 220 nm). For the enantioselective synthesis starting from (*Z*)-**12**, the general procedure was performed on a 0.278 mmol scale using (*R*)-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **17** (38 mg, 47%) was isolated as a yellow oil by flash chromatography (10% EtOAc/hexanes). $[\alpha]^{21}_D$ = +4.0 (*c* 0.28, MeOH); 3% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 99:1, flow rate 0.8 mL min^{-1}, $t_{r,minor}$ = 8.5 min, $t_{r,major}$ = 9.1 min, wavelength = 220 nm). For the enantioselective synthesis starting from (*E*)-**12**, the general procedure was performed on a 0.278 mmol scale using (*R*)-BINAP (10 mol%) as the ligand and stirring at 70 °C. The desired product **17** (49 mg, 60%) was isolated as a yellow oil by flash chromatography (10% EtOAc/hexanes). $[\alpha]^{21}_D$ = +2.8 (*c* 0.28, MeOH); 2% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 99:1, flow rate 0.8 mL min^{-1}, $t_{r,minor}$ = 8.4 min, $t_{r,major}$ = 9.1 min, wavelength = 220 nm).

*(Z)-dimethyl 2-(3-([1,1'-biphenyl]-4-yl)-4-fluorobut-3-en-2-yl)malonate (**18**)*

For the racemic synthesis of **18**, the general procedure was followed on a 0.205 mmol scale of a mixture (*E*)/(*Z*) = 18:82 of **13** using *rac*-BINAP (10 mol%) as the ligand and stirring at 70 °C. The major *Z*-isomer **18** (19 mg, 26%) was isolated as a colorless oil by flash chromatography (3% Et_2O/toluene). IR (ATR, diamond) ν = 3030, 2953, 1755, 1736, 1666, 1489, 1435, 1273, 1196, 1009 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.58 (4H, m), 7.45 (2H, t, J = 7.7 Hz), 7.38-7.31 (3H, m), 3.73 (3H, s), 3.72 (3H, s), 3.49 (1H, d, J = 9.6 Hz), 3.33 (1H, m), 1.20 (3H, d, J = 6.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −130.9 (1F, d, J = 83.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 168.3, 146.2 (d,

J_{C-F} = 260.4 Hz), 140.6 (d, J_{C-F} = 1.3 Hz), 132.5 (d, J_{C-F} = 1.9 Hz), 129.54, 129.52, 128.8, 127.4, 127.1, 127.0, 124.9 (d, J_{C-F} = 4.8 Hz), 56.0 (d, J_{C-F} = 2.9 Hz), 52.6, 52.5, 36.3 (d, J_{C-F} = 5.6 Hz), 17.3 (d, J_{C-F} = 2.3 Hz); HRMS-ESI calcd for $C_{21}H_{22}FO_4$ $[M+H]^+$ 357.1497, found 357.1495; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,1}$ = 8.5 min, $t_{r,2}$ = 9.0 min, wavelength = 254 nm). The stereochemistry of the alkene was proven by 1D ^{1}H-^{1}H-NOESY and NOE experiments. For the enantioselective synthesis starting from a mixture (*E*)/(*Z*) = 18:82 of **13**, the general procedure was performed on a 0.123 mmol scale to give the major isomer (*Z*)-**18** (8 mg, 18%) as a colourless oil by flash chromatography (3% Et_2O/toluene). $[\alpha]^{21}_D$ = −1.3 (*c* 0.40, MeOH); 24% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 9.1 min, $t_{r,major}$ = 8.6 min, wavelength = 254 nm).

4.2. Synthetic transformation of 2

4.2.1. Reduction[Error! Bookmark not defined.]

*2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl)propane-1,3-diol2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl)propane-1,3-diol (**19**)*

$LiAlH_4$ (22 mg, 0.59 mmol, 6 equiv.) was added to THF (3.3 mL, 0.03 M) at −78 °C. Then, the racemic monofluoroalkene **2** (30 mg, 0.098 mmol, 1 equiv.) was added dropwise. The mixture was stirred at −78 °C for 1 h, then allowed to warm to room temperature overnight. The reaction was cooled to 0 °C, sat. aq. Na_2CO_3 was added and the reaction was filtered using Et_2O. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (5% MeOH/CH_2Cl_2) afforded the final product **19** as a white solid (20 mg, 81%). mp = 79.6-83.8 °C; ; IR (ATR, diamond) ν = 3350, 2941, 2887, 1666, 1485, 1178, 1148, 1065, 762 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 7.8 Hz), 7.19 (1H, td, *J* = 7.4, 1.9 Hz), 7.16-7.08 (2H, m), 4.06 (1H, dd, *J* = 10.9, 2.8 Hz), 3.90 (1H, dd, *J* = 10.9, 6.1 Hz), 3.83 (10.8, 3.3 Hz), 3.70 (1H, dd, *J* = 10.7, 5.9 Hz), 3.09 (1H, dq, *J* = 13.1, 6.4 Hz), 2.97-2.85 (2H, m), 2.54-2.45 (2H, m), 2.19 (1H, m), 1.34 (3H, d, *J* = 7.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −98.5 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (d, J_{C-F} = 267.4 Hz), 133.5, 127.6, 126.73, 126.70, 126.1 (d, J_{C-F} = 1.8 Hz), 123.3 (d, J_{C-F} = 6.3 Hz), 117.6 (d, J_{C-F} = 11.3 Hz), 65.8, 64.6, 44.7 (d, J_{C-F} = 3.4 Hz), 29.2 (d, J_{C-F} = 6.8 Hz), 28.4, 25.4 (d, J_{C-F} = 25.7 Hz), 17.2 (d, J_{C-F} = 3.3 Hz); HRMS-ESI calcd for $C_{15}H_{20}FO_2$ $[M+H]^+$ 251.1442, found 251.1427; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 90:10, flow rate 0.7 mL min^{-1}, t_{min} = 10.6 min, t_{maj} = 11.9 min, wavelength = 220 nm). The reaction was also performed using the same protocol on a 0.096 mmol scale of the enantioenriched monofluoroalkene **2** (30 mg, 82% *ee*). The final product **19** (20 mg, 83%) was isolated as a white solid by flash chromatography (5% MeOH/CH_2Cl_2). $[\alpha]^{21}_D$ = +21.3 (*c* 0.78, MeOH); 80% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 90:10, flow rate 0.7 mL min^{-1}, t_{min} = 10.6 min, t_{maj} = 11.9 min, wavelength = 220 nm).

4.2.2. Alkylation[Error! Bookmark not defined.]

*Dimethyl 2-benzyl-2-(1-(2-fluoro-3,4-dihydronaphthalen-1-yl)ethyl)malonate (**20**)*

NaH (60% in mineral oil, 4 mg, 0.108 mmol, 1.1 equiv.) was added to DMF (0.98 mL, 0.1 M) at 0 °C, followed by the racemic monofluoroalkene **2** (29 mg, 0.098 mmol, 1 equiv.) and the mixture was stirred for 15 min. Benzyl bromide (14 µL, 0.118 mmol, 1.2 equiv.) was added and the reaction was heated at 100 °C for 3 h. EtOAc was added, and the organic layer was washed with brine (3×) to remove the DMF, and then dried over $MgSO_4$ and concentrated. Purification by flash chromatography (10% EtOAc/hexanes) afforded the final product **20** (22 mg, 57%) as a colourless oil. IR (ATR, diamond) ν = 3030, 2949, 2839, 1724, 1668, 1433, 1259, 1178, 1090, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (1H, m), 7.20 (1H, m), 7.15-7.09 (5H, m), 7.07-7.01 (2H, m), 3.83 (1H, q, *J* = 6.8 Hz), 3.73 (3H, s), 3.44 (1H, d, *J* = 13.7 Hz), 3.40 (3H, s), 3.07 (1H, td, *J* = 15.0, 6.7 Hz), 2.90-2.73 (2H, m), 2.57 (1H, td, *J* = 15.7, 6.5 Hz), 2.42 (1H, s), 1.49 (3H, d, *J* = 7.2 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −92.1 (1F, d, *J* = 13.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 170.6, 161.9 (d, *J* = 270.8 Hz), 137.0, 135.5 (d, J_{C-F} = 9.2 Hz), 133.3, 130.2, 127.7, 127.5, 126.8, 126.6, 126.0 (d, J_{C-F} = 1.8 Hz), 123.0 (d, J_{C-F} = 6.2 Hz), 114.4 (d, J_{C-F} = 11.7 Hz), 63.9, 51.9, 51.8, 41.0, 37.9, 29.1 (d, J_{C-F} = 6.7 Hz), 25.8 (d, J_{C-F} = 25.4 Hz), 16.1 (d, J_{C-F} = 5.5 Hz); HRMS-ESI calcd for $C_{24}H_{26}FO_4$ $[M+H]^+$ 397.1810, found 397.1810; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, t_{min} = 6.1 min, t_{maj} = 6.5 min, wavelength = 254 nm). The reaction was also performed using the same protocol on a 0.096 mmol scale of the enantioenriched monofluoroalkene **2** (29 mg, 82% *ee*). The final product **20** (18 mg, 48%) was isolated as a colourless oil by flash chromatography (10% EtOAc/hexanes). $[\alpha]^{21}_D$ = −6.4 (*c* 0.98, MeOH); 83% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 96:4, flow rate 0.7 mL min^{-1}, t_{min} = 6.1 min, t_{maj} = 6.5 min, wavelength = 254 nm).

4.2.3. Decarboxylation[Error! Bookmark not defined.]

*Methyl 3-(2-fluoro-3,4-dihydronaphthalen-1-yl)butanoate (**21a**)*

H_2O (18 mg, 1.00 mmol, 2.4 equiv.) was weighted in a microwave vial, and a solution of the racemic monofluoroalkene **2** (128 mg, 0.418 mmol, 1 equiv.) in DMF (4.2 mL, 0.1 M) was next added. The mixture was stirred at 200 °C for 75 minutes under microwave irradiation, and then brought back to ambient temperature. Et_2O and water were added, and the layers were separated. The ethereal layer was washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired product (70 mg, 68%) was isolated as a colorless oil by flash chromatography using 100% toluene. IR (ATR, diamond) ν = 2949, 2839, 1736, 1672, 1435, 1223, 1148, 1082, 926 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (1H, d, *J* = 7.8 Hz), 7.22 (1H, m), 7.15-7.02 (2H, m), 3.66 (3H, s), 3.36 (1H, app. br. hex. *J* = 7.1 Hz), 2.91 (2H, td, *J* = 8.1, 2.7 Hz), 2.82-2.70 (2H, m), 2.49 (2H, td, *J* = 8.1, 6.4 Hz), 1.34 (3H, d, *J* = 6.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −99.6 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 160.3 (d, J_{C-F} = 268.4 Hz), 134.5 (d, J_{C-F} = 8.5 Hz), 133.3, 127.5, 126.7, 125.9 (d, J_{C-F} = 1.9 Hz), 122.8 (d, J_{C-F} = 6.6 Hz), 117.8 (d, J_{C-F} = 10.7 Hz), 51.5, 39.9 (d, J_{C-F} = 5.2 Hz), 29.1 (d, J_{C-F} = 7.1 Hz), 28.6, 25.5 (d, J_{C-F} = 25.3 Hz), 19.2 (d, J_{C-F} = 3.7 Hz); HRMS-ESI calcd for $C_{15}H_{18}FO_2$ $[M+H]^+$ 249.1285, found 249.1268; <1% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 6.0 min, $t_{r,major}$ = 7.5 min, wavelength = 254 nm).The reaction was also performed using the same protocol on a 0.234 mmol scale of the enantioenriched monofluoroalkene **2** (72 mg, 79% *ee*). The final product **21a** (33 mg, 57%) was isolated as a colourless oil by flash chromatography using 100% toluene. $[\alpha]^{21}_D$ = +12.9 (*c* 0.49, MeOH); 80% *ee* (determined by chiral HPLC, IB, hexanes/2-propanol = 95:5, flow rate 0.7 mL min^{-1}, $t_{r,minor}$ = 6.1 min, $t_{r,major}$ = 7.3 min, wavelength = 254 nm).

*3-(2-fluoro-3,4-dihydronaphthalen-1-yl)butanoic acid (**21**)*

To a solution of the racemic ester **21a** (70 mg, 0.28 mmol) in EtOH (1.2 mL, 0.24 M) was added aqueous NaOH (0.5 M, 1.1 mL, 0.57 mmol, 2 equiv.). The resulting mixture was stirred at

ambient temperature for 18 hours. HCl (3 M) was added, and the aqueous mixture was extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired product **21** (63 mg, 95%) was isolated as a colorless oil by flash chromatography using 3% MeOH/CH_2Cl_2. IR (ATR, diamond) ν = 3061, 2932, 2625, 1701, 1663, 1414, 1294, 905, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 7.8 Hz), 7.20 (1H, m), 3.33 (1H, app. br. hex., *J* = 7.3 Hz), 2.89 (2H, td, *J* = 8.1, 2.6 Hz), 2.85-2.72 (2H, m), 2.47 (2H, dt, *J* = 9.2, 6.9 Hz), 1.35 (3H, d, *J* = 7.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −99.5 (1F, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 160.4 (d, J_{C-F} = 268.5 Hz), 134.4 (d, J_{C-F} = 8.6 Hz), 133.3, 127.5, 126.7, 126.0 (d, J_{C-F} = 1.9 Hz), 122.7 (d, J_{C-F} = 6.3 Hz), 117.6 (d, J_{C-F} = 10.9 Hz), 39.8 (d, J_{C-F} = 5.4 Hz), 29.0 (d, J_{C-F} = 6.8 Hz), 28.3, 25.5 (d, J_{C-F} = 25.2 Hz), 19.2 (d, J_{C-F} = 3.3 Hz); HRMS-ESI calcd for $C_{14}H_{16}FO_2$ $[M+H]^+$ 235.1129, found 235.1106; <1% *ee* (determined by chiral HPLC, AD-H, hexanes/2-propanol = 98:2, flow rate 1.1 mL min^{-1}, $t_{r,minor}$ = 14.3 min, $t_{r,major}$ = 16.6 min, wavelength = 254 nm). The reaction was also performed using the same protocol on a 0.133 mmol scale of the enantioenriched ester **21a** (33 mg, 80% *ee*). The final product **21** (26 mg, 83%) was isolated as a colourless oil by flash chromatography (3% MeOH/CH_2Cl_2). $[\alpha]^{21}_D$ = +6.9 (*c* 0.44, MeOH); 85% *ee* (determined by chiral HPLC, AD-H, hexanes/2-propanol = 98:2, flow rate 1.1 mL min^{-1}, $t_{r,minor}$ = 17.2 min, $t_{r,major}$ = 14.8 min, wavelength = 254 nm).

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Supplementary Material

Electronic supplementary information (ESI) available: Full experimental details for the synthesis of the 3,3-difluoropropenes and ^1H, ^{13}C, and ^{19}F NMR spectra for all the new compounds.

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13. It has not been possible, so far, to determine the absolute stereochemistry of any of the chiral products generated in this study.
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