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Indium Promoted Reformatsky Reaction: A Straightforward Access to β-amino and β-hydroxy α,α-difluoro Carbonyl Compounds.

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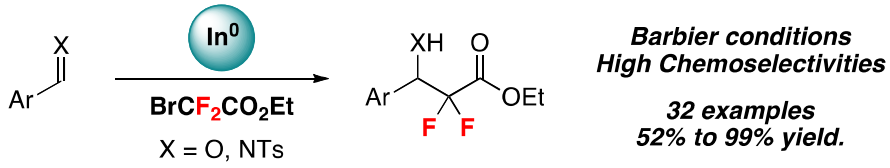


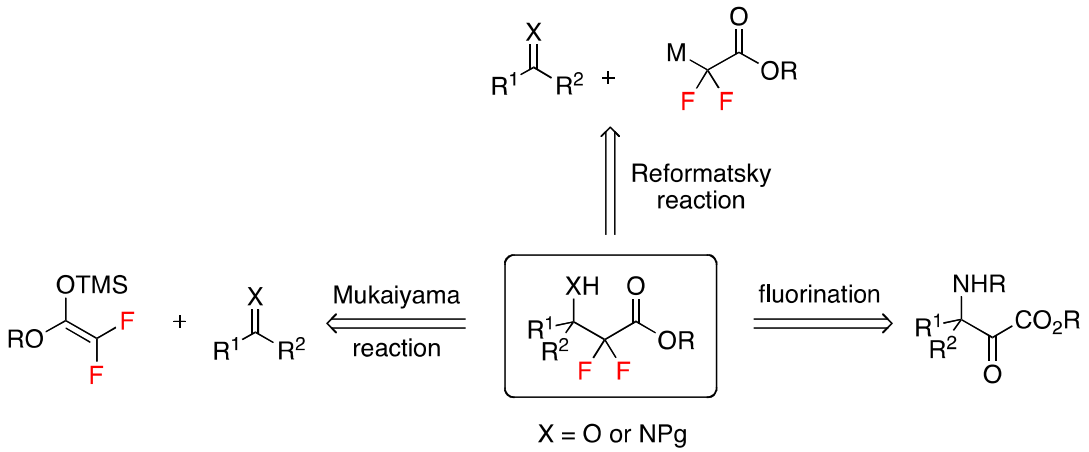
Abstract: A versatile and practical methodology to access to β-amino- and β-hydroxy α,α-difluoro carbonyl compounds using indium metal is described. This methodology has been successfully applied to a broad range of substrates including aldehydes, ketones and imines affording the corresponding and highly valuable gem-difluoro esters. The high substrate scope highlight the chemoselectivity of the process.

Introduction

Fluorinated molecules are of utmost interest in medicinal [1] and agrochemical chemistry.[2] The unique properties of the fluorine atom, such as its electronegativity and its small ionic radius, strongly affect several molecular properties.[3] For instance the lipophilicity, the bioavailability and the metabolic stability of a drug might be enhanced with the introduction of fluorine atoms onto its backbone. This remarkable ability to modify those properties is demonstrated by the presence of at least one fluorine atom in almost 20% of the entire pharmaceuticals and 30% of the entire agrochemicals.[1] Therefore it is not surprising that the introduction of fluorine atoms into molecules is becoming a remarkable challenge and several efforts were recently devoted to develop straightforward access to fluorinated molecules.[4] Among all of these fluorinated molecules, β-amino and β-hydroxy gem-difluorocarbonyl compounds are important compounds and relevant building blocks for the synthesis of more complex fluorinated molecules and biomolecules. For example α,α-difluorinated β-amino acid are often used for the conformational analysis of peptides or as enzymes inhibitors or to perform ,[5] while β-hydroxy α,α-difluorinated ester are important building blocks for the synthesis of fluorinated peptides [6] and other bioactive compounds.[7]

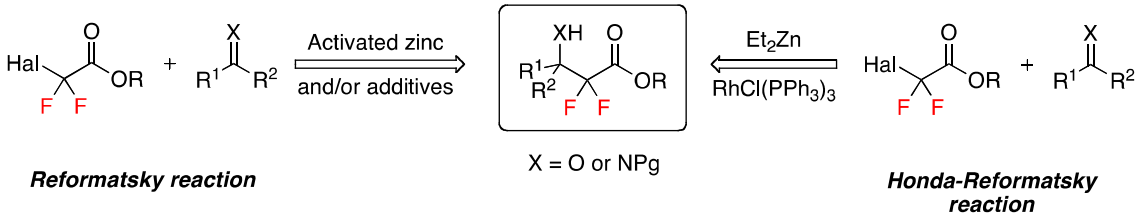
The introduction of highly relevant gem-difluoromethylene units is usually achieved by fluorination of the corresponding ketones using DAST or Deoxofluor,[8] by addition of fluorinated building blocks to an aldehyde or an imine through a Mukaiyama addition reaction of an unstable fluorinated silicon enolates, [9] or fluorinated Reformatsky-type reagents (scheme 1).

Scheme 1. Classical methods for the synthesis of β-amino- and β-hydroxy α,α-difluoro carbonyl compounds



The latter strategy mainly uses zinc metal to perform the Reformatsky process and it is still hampered by several major drawbacks.[10,11]

Scheme 2. Reformatsky and Honda-Reformatsky reaction with $BrCF_2CO_2Et$



Reformatsky reaction ***Honda-Reformatsky reaction***

Firstly, the preparation of unstable organozinc reagents usually requires specific and sometimes difficult-to-control protocols in order to enahance the reactivity of the zinc metal .[12] Secondly, the use of large excesses of the organometallic reagent in combination with several additives such as AgOAc or Et_2AlCl,[10c] Cp_2TiCl_2[11b] and CuCl,[11e] poses a significant problem in terms of atom economy. To ensure good conversions of desired fluorinated Reformatsky adducts is the use of exotic activation protocols or unusual reaction conditions. Sonication has been found helpful to enhance the reactivity of the electrophile and to extend the half-life of the unstable Reformatsky reagent.[13] An electrochemical process involving a sacrificial Zn anode and a nickel catalyst has been reported by Périchon and coworkers.[14]

The other preferred pathway to have access to the Reformatsky adduct is the Honda-Reformatsky reaction.[15] This methodology uses an excess of expensive and pyrophoric Et_2Zn along with a catalytic amount of $RhCl(PPh_3)_3$ (Wilkinson's catalyst). Although this catalytic process does not require the use of activated zinc metal, it can be severely affected by a lack of selectivity due to radical side reactions. In fact, depending on the reaction solvent, α,β-unsaturated ketones might afford either 1,2 or 1,3 adducts.

In order to tackle these major drawbacks, we speculated that indium metal might be a convenient and practical alternative to zinc. Indium metal gives numerous advantages compared to others metals. First, indium (0) is stable and easy to handle and in contrast to zinc it does not require any prior-to-use activation. Moreover, indium-mediated addition reactions can be performed under Barbier conditions, thus providing a practical procedure that does not require an initial generation of an organometallic species.[16] Additionally, the low toxicity of indium metal and its associated reagents,[17] combined with the broad functional group tolerance and the impressive level of chemoselectivity, make it very appealing from a synthetic point of view.

Extensive use of indium in allylation, crotylation, propargylation and allenylation reactions of aldehydes, ketones and imines have been reported.[18] For example, Yus and coworkers recently described an elegant In(0)-promoted diastereoselective allylation reaction of imines.[19] It should be noted that In(0) has been previously used in Reformatsky reactions with aldehydes and ketones.[20] Interestingly, when the reaction was carried out with an imine as the electrophile, lower yields were obtained with In(0) comparatively to Zn.[20i] Pioneer results on the In-promoted Reformatsky reactions were reported by Rieke using In(0) generated from potassium and $InCl_3$.[20a]

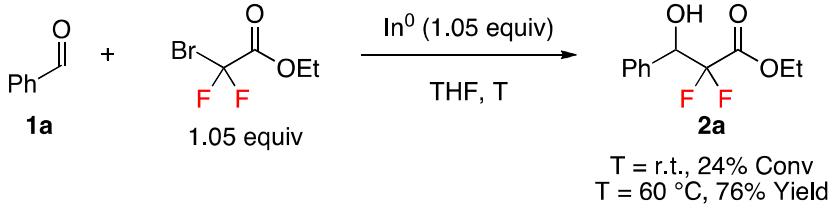
Later, Araki[20b-d] showed that commercially available indium metal was suitable and extended the scope of those reactions. During the last decade, Baba[20e-g] reported the use of mixtures of In (0) and In(I) and enhanced remarkably the diastereoselectivity of the reaction. This elegant work showed that both In(I) and In(III) enolates were formed in the reaction media and the authors proposed the In(I) enolate to be the most reactive organometallic species. [20f,21]

To the best of our knowledge the In(0)-mediated Reformatsky reaction with halo-gem-difluoroacetate has not been investigated to date. Thus, taking into account the appealing properties of In(0), we decided to explore this new pathway to access to β-amino- and β-hydroxy α,α-difluoro carbonyl compounds. Herein we report a straightforward and practical access to the Reformatsky adduct using indium metal.

Results and Discussion

At the very beginning, the aldol-type Reformatsky reaction was carried out with benzaldehyde using 1.05 equivalent of indium metal and 1.05 equivalent of ethyl bromodifluoroacetate in THF at room temperature and after 18 hours the desired product **2a** was formed in a modest 24% conversion . To our delight, increasing the reaction temperature to 60 °C led to a complete conversion and **2a** was isolated in 76% yield (scheme 3).

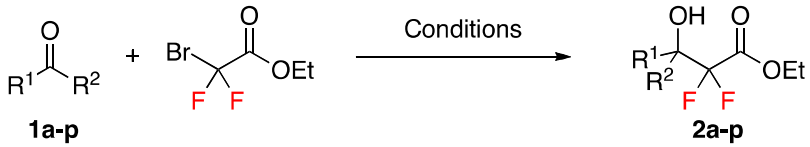
Scheme 3. Initial experiments.



Remarkably, a further screening revealed that the reaction could be performed in several organic solvents without erosion of the reaction yield.[22]

With this optimized reaction conditions, we extended the reaction scope using several aldehydes and ketones (Table 1).

Table 1. Indium mediated Reformatsky reaction with aldehyde and ketones.[a]



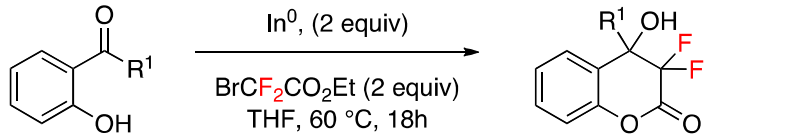
1a-p **2a-p**

Entry	R^1	R^2	Product	Yield (%)[b]
1	C_6H_5	H	**2a**	76
2	2-Me-C_6H_5	H	**2b**	60
3	1-naphthyl	H	**2c**	61
4	4-Br-C_6H_4	H	**2d**	72
5	3,4-Cl_2-C_6H_4	H	**2e**	69
6	4-CF_3-C_6H_4	H	**2f**	91
7	4-CN-C_6H_4	H	**2g**	66
8	4-CO_2Me-C_6H_4	H	**2h**	52
9	3-OH-C_6H_4	H	**2i**	63
10	3,4-(OCH_2O)-C_6H_4	H	**2j**	61
11[c]	(*E*)- C_6H_5-CH_2=CH_2	C_6H_5	**2k**	68
12[c]	C_6H_5	Me	**2l**	66
13[c]	C_6H_5	Et	**2m**	99
14[c]	α-tetralone		**2n**	84
15[c]	3-thienyl	Me	**2o**	69
16[c]	C_6H_5	CH_2CH_2Cl	**2p**	91

[a] Conditions: **1** (0.5 mmol), $BrCF_2CO_2Et$ (1.05 equiv), In^0 (1.05 equiv), THF (1 mL), 60 °C, 6h. [b] Isolated yield. [c] 1.5 equiv of In^0 and $BrCF_2CO_2Et$ were used and the reaction time was extended to 12h.

We were pleased to find that our practical process could be applied to a broad range of aromatic aldehydes.[23] Halogens substituents (**2d**, **2e**, entries 4 and 5) as well the CF_3 group (entry 6) were tolerated. Nitrile and ester groups are also compatible with the reaction conditions (entries 7 and 8). These last results further highlight the high level of chemoselectivity of this reaction. Impressively, a phenolic hydrogen did not affect the reaction and the corresponding adduct **2i** was obtained in good yield (entry 9). Ketones reacted smoothly but a slight excess of indium metal (1.5 equiv) and ethyl bromodifluoroacetate (1.5 equiv) was used in order to ensure complete conversions after 18 hours. Under these modified reaction conditions the corresponding tertiary alcohols **2l-p** were isolated in good to excellent yields. In contrast with the Honda-Reformatsky, α,β-unsaturated ketones such as chalcone gave exclusively the 1,2- adduct **2k** in good yield (entry 11), while the Rh catalyzed Honda-Reformatsky reaction affords a mixture of 1,2- and 1,3- adduct.[15] Remarkably, an aliphatic chlorinated substituent was compatible and the corresponding 1,2-addition product **2p** was obtained in excellent yield (entry 16). Having evaluated the scope of the In-promoted Refomatsky process, we speculated that 2'-hydroxy ketones could undergo a subsequent cyclization, allowing the formation of the corresponding fluorinated lactones. Thus, using 2'-hydroxy ketones **3a** and **3b** we were pleased to observe the one-pot formation of the gem-difluorinated lactones **4a** and **4-b** in 41% and 48% yields respectively (scheme 4).

Scheme 4. Synthesis of fluorinated lactones.

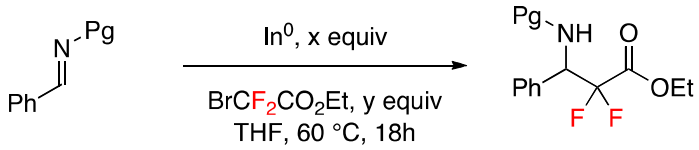


3a-b

R_1 = Et, **4a**, 41% yield
R_1 = $(CH_2)_2$Ph, **4b**, 48% yield

A further extension of our methodology would be represented by the Mannich-type Reformatsky reaction. The success of this strategy would give easy access to highly valuable gem-difluorinated β-amino ester.

Table 2. Optimization of the Mannich type Reformatsky reaction.[a]



Entry	Pg	x	y	Conv[b] (%)[c]
1	Ph	1.05	1	13
2[d]	4-OMePh	1.05	1	16
3	SO_2Ph	1.05	1	58
4	SO_2Ph	2.0	2.0	100 (70)
5	SO_2Ph	1.5	2.0	92
6	SO_2Ph	1.05	2.0	58
7	SO_2Ph	1.05	1.5	59
8	SO_2Ph	1.5	1.5	93

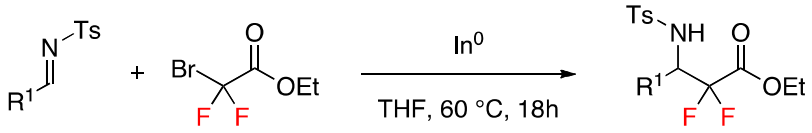
9[e]	SO_2Ph	1.5	1.5	100 (71)

[a]Conditions: imine (0.5 mmol), In^0 (x equiv), $BrCF_2CO_2Et$ (y equiv), THF (1 mL), 60 °C, 18h. [b]Determined by ^1H and ^{19}F NMR using an internal standard. [c] Isolated yield. [d] Imine was formed in situ. [e] Reaction time: 24 h.

First, using the reaction conditions previously established, a survey of *N*-protecting groups revealed the sulfonamide protecting group to be ideal and the corresponding adduct was obtained in 58% conversion after 18h (table 2, entry 3). Interestingly, no traces of the corresponding gem-difluoro-β-lactam were detected. This is in contrast to the Zn- mediated Reformatsky addition [24] and the previous indium based reactions.[20i] A further increase of the of indium and ethyl bromodifluoroacetate, from 1 to 2 equivalents, led to a full conversion and the desired adduct was isolated as the sole product in 70% yield (entry 4). It should be noted that the amount of indium and bromodifluoro ester could be reduced to 1.5 equivalents by extension of the reaction time from 18h to 24h (entry 9).

With these optimized conditions in hand, the reaction scope was successfully extended to several *N*-Ts aldimine. Substrates bearing an halogen substituent were suitable and the corresponding products were isolated in excellent yield (entries 6-8). Nitrile and ester functionalities were also compatible and the corresponding products were obtained in good yield (entries 9 and 10). Heteroaromatic aldimines proved to be suitable substrates yielding the corresponding β-amino gem-difluoro esters (entries 11 to 13). α,β-Unsaturated imine derived from cinnamaldehyde was also a suitable substrate affording exclusively the 1,2- adduct in 73% yield (entry 14). Unfortunately our methodology could not be extended to N-Tos ketimines.[25]

Table 3. Indium mediated Reformatsky reaction with *N*-Tos imine.[a]



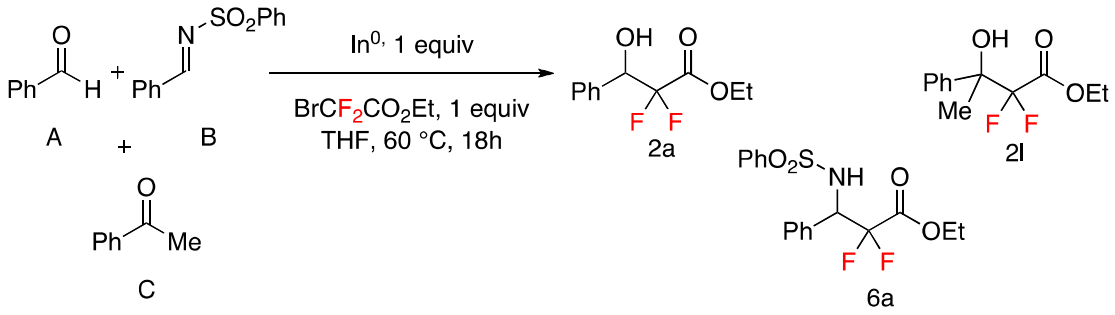
5a-n **6a-n**

Entry	R^1	Product	Yield (%)[b]
1[c]	Ph	**6a**	70
2	4-OMe-C_6H_4	**6b**	68
3	1-naphthyl	**6c**	80
4	3,4-OCH_2O-C_6H_4	**6d**	71
5	4-CF_3-C_6H_4	**6e**	75
6	4-Br-C_6H_4	**6f**	81
7	4-Cl-C_6H_4	**6g**	85
8	3,4-Cl C_6H_3	**6h**	81
9	4-CN-C_6H_4	**6i**	73
10	4-CO_2Me-C_6H_4	**6j**	65
11	3-furyl	**6k**	72
12	2-thienyl	**6l**	69
13	3-pyridyl	**6m**	76
14	Cinnamyl	**6n**	73

[a] Conditions: imine (0.5 mmol), In^0 (2 equiv), $BrCF_2CO_2Et$ (2 equiv), THF (1 mL), 60 °C, 18h. [b] Isolated yield. [c] *N*-benzensulfonylimine was used instead of *N*-Ts imine.

Then, in order to highlight the high chemoselectivity of our methodology we performed competition reactions between, aldehyde, ketone and imine (scheme 5).

Scheme 5. Competition reactions[a]



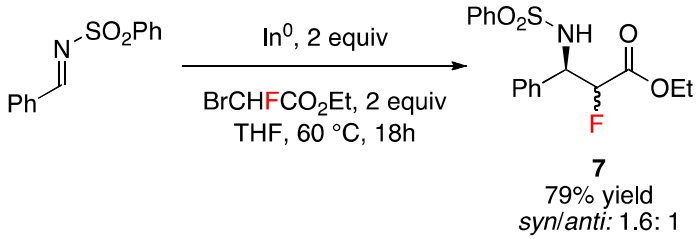
A	B	C	2a	6a	2l
1 equiv	1 equiv	0 equiv	87	13	-
1 equiv	0 equiv	1 equiv	85	-	15
0 equiv	1 equiv	1 equiv	-	20	80

[a] Ratios were determined by ^{19}F NMR using $C_6H_5CF_3$ as an internal standard.

In order to evaluate the reactivity of the different starting materials used in our study several competition experiments were performed. As shown in Scheme 5, the reaction in the presence of benzaldehyde and *N*-benzenesulfonylimine revealed that the aldehyde reacts faster than the imine. When benzaldehyde was reacted in the presence of acetophenone, a similar trend was observed with ketones reacting faster than imines. These initial experiments clearly highlight the high chemoselectivity of the organoindium reagents.

We next sought to extend our methodology employing the highly valuable ethyl bromofluoroacetate. The resulting α-fluoro β-amino esters are of great interest for the development of fluorinated analogue of β-amino α-hydroxy esters and for conformational studies of β-amino acids.[26] Using our optimized conditions, the reaction proceeded smoothly and the Mannich adduct **7** was isolated in 78% yield as an inseparable 1.6: 1 mixture of diastereoisomers (scheme 6). Further attempts to improve the diastereoselectivity were unsuccessful.[27]

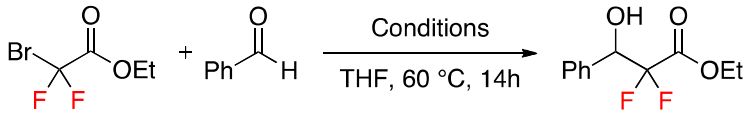
Scheme 6: Addition of ethyl bromofluoroacetate to *N*-sulfonylimine.



7
79% yield
syn/*anti:* 1.6: 1

Presumably, the observed low diastereoselectivity arises from the presence of a mixture of E and Z In-enolate.[28] Unfortunately, all our attempts to characterize the indium reagents or to quantify the E/Z ratio by use of ^{1}H or ^{19}F NMR spectroscopy were unsuccessful. Nevertheless, in order to get information about the reaction pathway and to demonstrate the practicability of our methodology, reactions were carried out with commercially available InCl and unactivated Zn in place of In(0) (scheme 7).

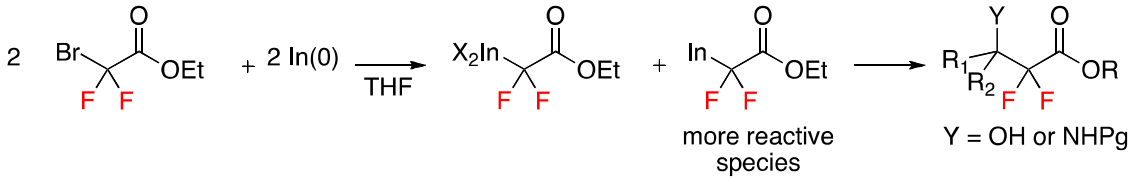
Scheme 7. Test experiments.



Conditions: In(0) : 76%
unactivated Zn: 43%
InCl: 79%

Interestingly, when unactivated Zn was used instead of In(0) a significant drop of reactivity was observed. After 14h only 43% of the corresponding product was detected by ^{19}F NMR. This result clearly point out the advantage to use indium metal instead of Zn. When InCl was used, the reaction proceeded smoothly affording the Reformatsky adduct in 79% NMR yield (*vs* 76% isolated yield with In(0)). According to Baba's observations,[20f] this result might be explained invoking the formation of an In(I) enolate, which might then react with the electrophile. Therefore, by analogy with Baba's proposal, the following tentative mechanism was envisaged (figure 1).

Figure 1. Proposed mechanism.



As depicted in figure 1, the reaction of indium metal with ethyl bromodifluoroacetate in THF affords a mixture of In(III) and In(I) enolate. The latter reacts faster with the electrophile affording the Reformatsky adduct. Although radical process cannot be ruled out, we assume the radical derived from ethyl bromodifluoroacetate would not be nucleophilic enough to react with aldehydes, ketones or imines.[29]

Conclusion

In summary a straightforward and practical access to α-hydroxy and α-amino gem-difluoroesters has been reported using indium (0) as metal. The remarkable functional groups tolerance associated with the unique properties of indium allowed the extension of this methodology to a broad selection of substrates in good to excellent yields. This method allows a straightforward access to highly valuable β-amino and β-hydroxy gem-difluorinated carbonyl compounds.

Experimental section

Residual $CHCl_3$ served as internal standards (δ = 7.26) for ^1H NMR, $CFCl_3$ served as internal standard (δ = 0.0) for ^{19}F NMR and $CDCl_3$ served as internal standard (δ = 77.16) for ^{13}C NMR. Flash chromatographies were performed with silica gel (0.063 – 0.200 mm). Analytical thin layer chromatographies (TLC) were performed on silica gel aluminum plates with F-254 indicator and visualized by UV fluorescence and/or staining with $KMnO_4$ or PMA. THF was distilled over Na/benzophenone prior to use.

HRMS analyses were performed under (ESI) conditions with a micro TOF detector. All experiments were conducted under nitrogen atmosphere in oven-dried glassware with magnetic stirring using standard Schlenk techniques. All aldehydes were recrystallized, distilled or filtered through basic alumina prior to use. All ketones were used as received. *N*-Tos-aldimines were prepared according to literature methods[30] and recrystallized from a boiling mixture of petroleum ether and ethyl acetate prior to use.

Reformatsky reaction with aldehyde: To a solution of In^0 (powder, 0.55 mmol, 60 mg) and the corresponding aldehyde (0.5 mmol) in THF (1 mL) was added $BrCF_2CO_2Et$ (0.55 mmol, 64 µL). The resulting mixture was stirred at 60°C for 6h and then cooled to room temperature. The solution was quenched with aqueous HCl (0.5 M, 5 mL) and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc) to afford the corresponding β-hydroxy gem-difluoroester **2a-j**.

Ethyl 2,2-difluoro-3-hydroxy-3-phenyl-propionate **2a**:

Compound **2a** was obtained as a colorless oil in 76% yield (87 mg), after flash chromatography (SiO_2, cyclohexane/EtOAc, 4: 1, Rf = 0.30 cyclohexane/EtOAc 4:1). ^1H NMR (300 MHz, $CDCl_3$): 7.47-7.39 (m, 5H), 5.24-5.14 (m, 1H), 4.32 (q, 2H, *J* = 7.1 Hz), 2.62 (dd, 1H, *J* = 5.3 Hz, *J* = 0.4 Hz), 1.30 (t, 3H, *J* = 7.1 Hz) ^{13}C NMR (75 MHz, $CDCl_3$): 163.7 (dd, *J* = 32.4 Hz, *J* = 30.8 Hz), 134.6 (d, *J* = 2.0 Hz), 129.3, 128.5, 127.8, 113.9 (dd, *J* = 259.2 Hz, *J* = 254.1 Hz), 73.8 (dd, *J* = 27.8 Hz, *J* = 24.4 Hz), 63.3, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -113.9 (dd, 1F, *J* = 262.4 Hz *J* = 8.0 Hz), -120.4 (dd, 1F, *J* = 262.4 Hz *J* = 15.3 Hz). IR (cm^{-1}): 2989, 1755, 1456, 1376, 1192,

1092, 856, 718, 698. HRMS (ESI-): calcd for [M-H] $C_{11}H_{11}F_2O_3$: 229.0676, found: 229.0671 (-2.1 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(2-methyl-phenyl)propionate **2b**:

Compound **2b** was obtained as a colorless oil in 60% yield (73 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc, 19: 1 to 9:1, Rf = 0.54 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.54-7.51 (m, 1H), 7.26-7.24 (m, 2H), 7.19-7.16 (m, 1H), 5.46 (dt, 1H, *J* = 16.8 Hz, *J* = 5.1 Hz), 4.31 (q, 2H, *J* = 7.1 Hz), 2.53 (d, 1H, *J* = 5.4 Hz), 2.38 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.9 (t, *J* = 31.8 Hz), 137.0, 133.1,130.7, 129.2, 127.6 (d, *J* = 1.5 Hz), 126.3, 114.3 (t, *J* = 256.9 Hz), 69.8 (dd, *J* = 28.9 Hz, *J* = 24.0 Hz), 63.3, 19.6, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): -112.8 (d, 1F, *J* = 263.6 Hz), -121.4 (d, 1F, *J* = 263.6 Hz). IR (cm^{-1}): 3216, 1759, 1294, 1121, 1058, 1002, 831, 731. HRMS (ESI-): calcd for [M-H] $C_{12}H_{13}F_2O_3$: 243.0833, found: 243.0829 (+1.6 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(1-naphtyl)propionate **2c**:

Compound **2c** was obtained as a yellow oil in 61% yield (86 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1, Rf = 0.50 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 8.12-8.09 (m, 1H), 7.89 (d, 2H, *J* = 8.0 Hz), 7.79 (d, 1H, *J* = 7.2 Hz), 7.59-7.49 (m, 3H), 6.11-6.02 (m, 1H), 4.27 (q, 2H, *J* = 7.1 Hz), 2.87 (d, 1H, *J* = 5.1 Hz), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.8 (t, *J* = 31.8 Hz), 133.7, 131.5, 130.8 (d, *J* = 1.6 Hz), 130.0, 129.0, 126.7, 126.3, 125.9, 125.3, 123.3 (t, *J* = 1.3 Hz), 114.4 (t, *J* = 257.3 Hz), 69.9 (dd, *J* = 28.3 Hz, *J* = 24.4 Hz), 63.3, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -112.9 (d, *J* = 261.03 Hz), -120.1 (d, *J* = 260.85 Hz). IR (cm^{-1}): 3493, 1755, 1305, 1081, 1065, 788. HRMS (ESI^-): calcd for [M-H] $C_{15}H_{13}F_2O_3$: 279.0833, found: 279.0835 (+ 0.7 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(4-bromo-phenyl)propionate **2d**:

Compound **2d** was obtained as a pale yellow oil in 72% yield (111 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1, Rf = 0.50 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.51 (d, 2H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 8.3 Hz), 5.13 (ddd, 1H, *J* = 15.3 Hz, *J* = 7.4 Hz, *J* = 5.3 Hz), 4.30 (q, 2H, *J* = 7.1 Hz), 2.94 (d, 1H, *J* = 5.2 Hz), 1.30 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.5 (t, *J* = 31.6 Hz), 133.6 (d, *J* = 1.7 Hz), 131.7, 129.5, 123.6, 113.5 (t, *J* = 257.2 Hz), 73.3 (dd, *J* = 28.0 Hz, *J* = 24.4 Hz), 63.4, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): -113.7 (d, *J* = 264.0 Hz), -121.1 (*J* = 264.3 Hz). IR (cm^{-1}): 3218, 1768, 1289, 1118, 1066, 1009, 833, 734. HRMS (ESI^-) : calcd for [M-H] $C_{11}H_{10}F_2O_3Br$: 306.9781, found : 306.9778 (-1.0 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(3,4-dichloro-phenyl)propionate **2e**:

Compound **2e** was obtained as a white solid in 69% yield (103 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1, Rf = 0.61 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.55 (d, 1H, *J* = 1.5 Hz), 7.45 (d, 1H, *J* = 8.3 Hz), 7.29-7.26 (m, 1H), 5.14 (ddd, 1H, *J* = 15.2 Hz, *J* = 7.0 Hz, *J* = 5.3 Hz), 4.32 (q, 2H, *J* = 7.1 Hz), 3.05 (d, 1H, *J* = 5.2 Hz), 1.31 (t, 3H, *J* = 7.15 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.4 (t, *J* = 31.5 Hz), 134.7 (d, *J* = 1.4 Hz), 133.6, 132.8, 130.5, 129.8 (d, *J* = 1.3 Hz), 127.1, 113.4 (t, *J* = 257.6 Hz), 72.7 (dd, *J* = 28.4 Hz *J* = 24.6 Hz), 63.6, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): -113.1 (dd, *J* = 265.9 Hz, *J* = 7.21 Hz), -121.1 (dd, *J* = 265.8 Hz *J* = 15.26 Hz). IR (cm^{-1}): 3431, 1764, 1466, 1302, 1181, 1120, 1000, 850, 757, 679. HRMS (ESI-): calcd for [M-H] $C_{11}H_9Cl_2F_2O_3$: 296.9897, found: 296.9904 (+ 2.3 ppm). Mp: 74-75 °C.

Ethyl 2,2-difluoro-3-hydroxy-3-(4-trifluoromethyl-phenyl)propionate **2f**:

Compound **2f** was obtained as a white solid in 91% yield (135 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1 to 4:1 to 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): 7.65 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.3 Hz), 5.29-5.20 (m, 1H), 4.31 (q, 2H, *J* = 7.1 Hz), 3.03 (d, 1H, *J* = 5.2 Hz), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.4 (dd, *J* = 32.2 Hz, *J* = 30.8 Hz), 138.5, 131.5 (q, *J* = 32.63 Hz), 128.3 (d, *J* = 1.0 Hz), 125.5 (q, *J* = 3.8 Hz), 124.1 (d, *J* = 272.3 Hz), 113.5 (dd, *J* = 260.7 Hz, *J* = 254.7 Hz), 73.31 (dd, , *J* = 28.1 Hz, *J* = 24.5 Hz), 63.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -63.3, -113.2 (dd, *J* = 266.3 Hz, *J* =7.2 Hz), -121.1 (dd, *J* = 266.3 Hz, *J* = 15.4 Hz). IR (cm^{-1}): 3217, 1767, 1320, 1161, 1065, 1016, 836, 709, 543. HRMS (ESI^-): calcd for [M-H] $C_{12}H_{10}F_5O_3$: 297.0550, found: 297.0545 (-1.7 ppm). Mp: 99-100 °C.

Ethyl 2,2-difluoro-3-hydroxy-3-(4-cyano-phenyl)propionate **2g**:

Compound **2g** was obtained as a colorless oil in 66% yield (84 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1 to 4: 1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.65 (d, 2H, *J* = 8.3 Hz), 7.57 (d, 1H, *J* = 8.1 Hz), 5.23 (dt, *J* = 15.7 Hz, *J* = 6.1 Hz), 4.31 (q, 2H, *J* = 7.1 Hz), 3.52 (d, 1H, *J* = 5.4 Hz), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.3 (t, *J* = 31.5 Hz), 140.1 (*J* = 1.0 Hz), 132.1, 128.6, 118.5, 113.4 (t, *J* = 254.5 Hz), 112.8, 72.9 (dd, *J* = 28.4 Hz, *J* = 24.5 Hz), 63.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -112.2 (dd, *J* = 265.5 Hz, *J* = 6.9 Hz), -121.2 (dd, *J* = 265.5 Hz, *J* = 15.9 Hz). IR (cm^{-1}): 3434, 2232, 1756, 1315, 1190, 1102, 1071, 565. HRMS (ESI-): calcd for [M-H] $C_{12}H_{10}F_2NO_3$: 254.0629, found: 254.0624 (-2.0 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(4-methyl-benzoate)propionate **2h**:

Compound **2h** was obtained as a pale yellow oil in 52% yield (75 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1 to 4: 1, Rf = 0.34 Petroleum

ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 8.01 (d, *J* = 8.2 Hz), 7.51 (d, *J* = 8.2 Hz), 5.27-5.18 (m, 1H), 4.30 (q, 2H, *J* = 7.1 Hz), 3.90 (s, 3H), 3.26 (d, 1H, *J* = 5.2 Hz), 1.28 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 166.9, 163.4 (t, *J* = 31.5 Hz), 139.6 (d, *J* = 1.6 Hz), 130.9, 129.7, 127.9, 113.7 (t, *J* = 257.4 Hz), 73.4 (dd, *J* = 28.0 Hz, *J* = 24.4 Hz), 63.4, 52.4, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): -113.4 (d, *J* = 264.2 Hz), -120.9 (d, *J* = 265.5 Hz). IR (cm^{-1}): 3461, 1758, 1721, 1438, 1278, 1104, 1071, 1019, 731. HRMS (ESI+): calcd for [M+NH_4] $C_{13}H_{18}F_2NO_5$: 306.1153 found: 306.1154 (+0.3 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(3-hydroxy-phenyl)propionate **2i**:

Compound **2i** was obtained as a colorless oil in 63% yield (78 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 17: 1 to 4: 1, Rf = 0.23 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.27-7.20 (m, 1H), 6.95 (d, 2H, *J* = 7.4 Hz), 6.85 (dd, 1H, *J* = 7.4 Hz, *J* = 1.7 Hz), 6.00 (brs, 1H), 5.14-5.07 (m, 1H), 4.30 (q, 2H, *J* = 7.1 Hz), 3.38 (brs, 1H), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.9 (t, *J* = 31.6 Hz), 155.9, 136.2 (d, *J* = 2.0 Hz), 129.6, 120.3, 116.6, 114.7, 113.9 (t, *J* = 259.3 Hz), 73.7 (dd, *J* = 27.7 Hz, *J* = 24.5 Hz), 63.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -114.4 (d, *J* = 260.6 Hz), -120.6 (d, *J* = 260.6 Hz). IR (cm^{-1}): 3401, 1750, 1593, 1458, 1095, 1071, 771. HRMS (ESI-): calcd for [M-H] $C_{11}H_{11}F_2O_4$: 245.0625, found: 245.0632 (+2.9 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(3,4-methylenedioxyphenyl)propionate **2j**:

Compound **2j** was obtained as a yellow oil in 61% yield (83 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1 to 4: 1). ^{1}H NMR (300 MHz, $CDCl_3$): 6.94 (s, 1H), 6.87 (d, 1H, *J* = 8.1 Hz), 6.79 (d, 1H, *J* = 8.0 Hz), 5.96 (d, 2H), 5.11-5.02 (m, 1H), 4.31 (q, 2H, *J* = 7.1 Hz), 2.81 (d, 1H, *J* = 4.9 Hz), 1.31 (t, 3H, *J* =

7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.7 (t, *J* = 31.7 Hz), 148.5, 148.0, 128.3 (d, *J* = 2.1 Hz), 121.8 (d, *J* = 0.9 Hz), 113.8 (t, *J* = 258.7 Hz), 108.2, 108.2 (t, *J* = 1.5 Hz), 101.4, 73.7 (dd, *J* = 27.9 Hz, *J* = 24.2 Hz), 63.2, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): -114.6 (dd, *J* = 261.3 Hz, *J* = 8.1 Hz), -121.0 (dd, *J* = 261.3 Hz, *J* = 15.1 Hz). IR (cm^{-1}): 3503, 1755, 1505, 1489, 1489, 1306, 1244, 1096, 1067, 1036, 926, 853, 791, 712, 547. HRMS (ESI-): calcd for [M-H] $C_{12}H_{11}F_2O_5$: 273.0575, found: 273.0569 (-2.2 ppm).

Reformatsky reaction with ketone: To a solution of In^0 (powder, 0.75 mmol, 90 mg) and the corresponding ketones (0.5 mmol) in THF (1 mL) was added $BrCF_2CO_2Et$ (0.75 mmol, 96 µL). The resulting mixture was stirred at 60°C for 12h and then cooled to room temperature. The solution was quenched with aqueous HCl (0.5 M, 5 mL) and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, Petroleum ether/EtOAc) to afford the corresponding β-hydroxy gem-difluoroester **2k-p** and **4a-b**.

Ethyl 2,2-difluoro-3-hydroxy-3,5-diphenylpent-4-enoate **2k**:

Compound **2k** was obtained as a viscous pale yellow oil in 68% yield (113 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc, 9: 1 to 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.59 (d, 2H, *J* = 7.3 Hz), 7.39-7.21 (m, 8H), 6.80 (m, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 3.47 (brs, 1H), 1.10 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 136.6 (t, *J* = 32.0 Hz), 138.1, 136.1, 132.7 (d, *J* = 1.2 Hz), 128.7, 128.6, 128.4, 128.3, 127.0, 126.9 (t, *J* = 1.9 Hz), 126.8 (d, *J* = 2.5 Hz), 114.4 (t, *J* = 262.8 Hz), 77.9 (t, *J* = 24.0 Hz), 63.3, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): -114.8 (d, *J* = 16.9 Hz). IR (cm^{-1}): 3496,

1756, 1603, 1454, 1373, 1095, 1004, 975, 745, 687. HRMS (ESI-): calcd for [M-H] $C_{19}H_{17}F_2O_3$: 331.1146, found: 331.1148 (+0.6 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-phenyl-butanoate **2l**:

Compound **2l** was obtained as a yellow oil in 66% yield (80 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.52 (d, 2H, *J* = 7.2 Hz), 7.40-7.32 (m, 3H), 4.15 (q, 2H, *J* = 7.1 Hz), 3.11 (s, 1H), 1.75 (s, 3H), 1.12 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.7 (t, *J* = 32.2 Hz), 139.7 (d, *J* = 1.3 Hz), 128.4, 128.3, 126.1 (t, *J* = 1.7 Hz), 114.9 (t, *J* = 261.4), 76.1 (t, *J* = 24.5 Hz), 63.1, 23.4 (d, *J* = 2.6Hz), 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): -116.0 (d, *J* = 15.1 Hz). IR (cm^{-1}): 1753, 1307, 1126, 1106, 1036, 761, 699. HRMS (ESI^-): calcd for [M-H] $C_{12}H_{13}F_2O_3$: 243.0833, found: 243.0841 (+3.3 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-phenyl-pentanoate **2m**:

Compound **2m** was obtained as a white solid in 99% yield (128 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1, Rf = 0.35 Petroleum ether/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.49 (d, 2H, *J* = 7.5 Hz), 7.38-7.29 (m, 3H), 4.11 (q, 2H, *J* = 7.1 Hz), 3.09 (s, 1H), 2.28-2.04 (m, 2H), 1.07 (t, 3H, *J* = 7.1 Hz), 0.76 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.7 (t, *J* = 31.8 Hz), 137.4, 128.2, 128.1, 126.6 (t, *J* = 1.8 Hz), 115.3 (t, *J* = 260.1 Hz), 78.6 (t, *J* = 23.4 Hz), 62.9, 27.2 (t, *J* = 2.2 Hz), 13.6, 6.7. ^{19}F NMR (282 MHz, $CDCl_3$): -116.3. IR (cm^{-1}): 3501, 2979, 1756, 1454, 1310, 1157, 1128, 1109, 989, 831, 759. HRMS (ESI-): calcd for [M-H] $C_{13}H_{15}F_2O_3$: 257.0989, found: 257.0998 (+3.5 ppm). Mp: 44-45 °C.

Ethyl 1-(Hydroxy-1,2,3,4-tetrahydronaphtalen-1-yl)-1,1-difluoroacetate **2n**:

Compound **2n** was obtained as a colourless oil in 84% yield (114 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.66 (d, 1H, *J* = 7.2 Hz), 7.29-7.20 (m, 2H), 7.15-7.12 (m, 1H), 4.27 (qd, 2H, *J* = 7.1 Hz, *J* = 1.9 Hz), 2.85-2.69 (m, 3H), 2.35-2.23 (m, 1H), 2.04-1.95 (m, 2H), 1.89-1.77 (m, 1H), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.8 (t, *J* = 32.4 Hz), 138.9, 133.7 (d, *J* = 1.4 Hz), 129.1, 128.7, 127.8 (t, *J* = 3.4 Hz), 126.2, 116.0 (t, *J* = 261.0 Hz), 73.6 (t, *J* = 22.6 Hz), 33.2 (t, *J* = 1.6 Hz), 29.5, 18.7 (t, *J* = 1.8 Hz), 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): -112.3 (d, *J* = 257.3 Hz), -113.9 (d, *J* = 257.3 Hz). IR (cm^{-1}): 3500, 1754, 1451, 1372, 1305, 1123, 1017, 760, 729. HRMS (ESI+): calcd for $[M+NH_4]$ $C_{14}H_{20}F_2NO_3$: 288.1411, found: 288.1407 (-1.4 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-(3-thienyl)-butyrate **2o**:

Compound **2o** was obtained as a yellow oil in 69% yield (86 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 4: 1, Rf = 0.34 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.33-7.28 (m, 2H), 7.12 (dd, 1H, *J* = 5.0 Hz, *J* = 0.8 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 3.25 (s, 1H), 1.17 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.7 (t, *J* = 32.1 Hz), 141.6 (d, *J* = 2.1 Hz), 126.2 (t, *J* = 2.1 Hz), 126.à, 122.7 (t, *J* = 1.6 Hz), 114.6 (t, *J* = 261.3 Hz), 75.3 (t, *J* = 25.3 Hz), 63.1, 23.3, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): -115.8 (d, *J* = 257.9 Hz), -116.5 (d, *J* = 257.9 Hz). IR (cm^{-1}): 3510, 1753, 1308, 1106, 1035, 792, 657. HRMS (ESI-): calcd for [M-H] $C_{10}H_{11}F_2SO_3$: 249.0397, found: 249.0390 (-2.8 ppm).

Ethyl 2,2-difluoro-3-hydroxy-3-phenyl-5-chloro-pentanoate **2p**:

Compound **2p** was obtained as a white solid in 91% yield (133 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc, 9: 1, Rf = 0.45 Petroleum ether/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.48 (d, 2H, *J* = 7.4 Hz), 7.42-7.32 (m,

3H), 4.11 (q, 2H, *J* = 7.1 Hz), 3.56 (td, 1H, *J* = 10.2 Hz, *J* = 6.8 Hz), 3.49 (s, 1H), 3.21 (td, 1H, *J* = 10.2 Hz, *J* = 6.2 Hz), 2.70-2.55 (m, 2H), 1.06 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 163.3 (t, *J* = 31.6 Hz), 136.5 (d, *J* = 2.5 Hz), 128.7, 128.6, 126.3 (t, *J* = 2.1 Hz), 114.4 (t, *J* = 262.9 Hz), 77.8 (t, *J* = 23.5 Hz), 63.2, 39.0, 37.8, 13.6. ^{19}F NMR (282 MHz, $CDCl_3$): -115.6 (d, *J* = 258.6 Hz), -116.8 (d, *J* = 258.6 Hz). IR (cm^{-1}): 3440, 1746, 1449, 1321, 1180, 947, 767, 701, 610. HRMS (ESI^-): calcd for [M-H] $C_{13}H_{14}F_2O_3Cl$: 291.0600, found: 291.0608 (+2.7 ppm). Mp: 73-74 °C.

4-hydroxy-4-ethyl-3,3-difluoro-3,4-dihydrocoumarin **4a**:

Compound **4a** was obtained as a white solid in 41% yield (47 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (d, 1H, *J* = 8.1 Hz), 7.55-7.49 (m, 1H), 7.38-7.33 (m, 2H), 2.89 (qd, 2H, *J* = 7.6 Hz, *J* = 2.3 Hz), 1.31 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 155.4 (d, *J* = 30.3 Hz), 150.9 (d, *J* = 2.7 Hz), 145.2, 141.9, 136.4 (d, *J* = 12.7 Hz), 130.7, 125.1, 124.6, 117.4, 17.8 (d, *J* = 2.8 Hz), 13.1 (d, *J* = 1.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): -136.80. IR (cm^{-1}): 2983, 1727, 1649, 1448, 1150, 1093, 775, 754, 459. HRMS (ESI^-): calcd for $[M+OH]^-$ $C_{11}H_{11}F_2O_4$: 245.0625, found: 245.0631 (+2.4 ppm). Mp: 69-70 °C.

4-hydroxy-4-phenethyl-3,3-difluoro-3,4-dihydrocoumarin **4b**:

Compound **4b** was obtained as a white solid in 48% yield (73 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (d, 1H, *J* = 8.1 Hz), 7.51-7.46 (m, 1H), 7.34-7.25 (m, 4H), 7.21-7.17 (m, 3H), 3.14-3.08 (m, 2H), 2.95-2.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 155.2 (d, *J* = 30.2 Hz), 150.8 (d, *J* = 2.72 Hz), 142.9 (d, *J* = 253.0 Hz), 139.9, 134.0 (d, *J* = 12.7 Hz), 130.7 (d, *J* = 2.7 Hz), 128.8, 128.4, 126.9, 125.1, 124.6 (d, *J* = 6.1 Hz), 118.8 (d, *J* = 3.1 Hz), 117.4 (d, *J* = 1.4 Hz), 34.6 (d, *J* = 1.8 Hz), 18.4 (d, *J* = 1.6 Hz). ^{19}F NMR

(282 MHz, $CDCl_3$): -135.19. IR (cm^{-1}): 1731, 1601, 1448, 1146, 1098, 902, 748, 716, 698, 454. HRMS (ESI^-): calcd for $[M+OH]^-$ $C_{17}H_{15}F_2O_4$: 321.0938, found: 321.0944 (+1.9 ppm). Mp: 101-102 °C.

Reformatsky reaction with aldimine: To a solution of In^0 (powder, 1.0 mmol, 120 mg), aldimine (0.5 mmol) in THF (1 mL) was added $BrCF_2CO_2Et$ (1.0 mmol, 0.128 mL). The resulting mixture was stirred at 60°C for 18h and then cooled to room temperature. The solution was quenched with HCl (0.5 M, 5 mL) and extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (SiO_2, Petroleum ether/ EtOAc) to afford the Mannich adduct **6a-n**.

Ethyl 2,2-Difluoro-3-(benzenesulfonylamino)-3-phenylpropionate **6a**:

Compound **6a** was obtained as a white solid in 70% yield (129 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15, Rf = 0.36 Petroleum ether/EtOAc 4:1). ^1H NMR (300 MHz, $CDCl_3$): 7.67 (d, 2H, *J* = 7.7 Hz), 7.41 (t, 1H, *J* = 7.4 Hz), 7.28 (t, 2H, *J* = 7.6 Hz), 7.22-7.11 (m, 5H), 5.91 (d, 1H, *J* = 10.2 Hz), 5.05 (dt, 1H, *J* = 16.5 Hz, *J* = 9.8 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.7 (t, *J* = 31.5 Hz), 140.1, 132.7, 131.7 (d, *J* = 2.0 Hz), 129.1, 128.8, 128.6, 128.3, 127.0, 113.7 (t, *J* = 257.8 Hz), 63.5, 59.8 (dd, *J* = 27.4 Hz, *J* = 23.6 Hz), 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): -111.6 (dd, *J* = 258.4 Hz, *J* = 9.5 Hz), -115.6 (dd, *J* = 258.4 Hz, *J* = 16.5 Hz). IR (cm^{-1}): 3242, 1758, 1337, 1165, 1063, 717, 685, 543. HRMS (ESI+): calcd for $[M+H]$ $C_{17}H_{18}F_2SNO_4$: 370.0925, found: 370.0916 (-2.4 ppm). Mp: 109-110 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(4-methoxy-phenyl)-propionate **6b**:

Compound **6b** was obtained as a viscous colourless oil in 68% yield (140 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 4: 1 to 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): 7.54 (d, 2H, *J* = 8.3 Hz), 7.10 (d, 2H, *J* = 8.1 Hz), 7.04 (d, 2H, *J* = 8.7 Hz), 6.70 (d, 2H, *J* = 8.7 Hz), 5.63 (d, 1H, *J* = 9.9 Hz), 4.96 (dt, 1H, *J* = 16.1 Hz, *J* = 10.0 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 3.74 (s, 3H), 2.33 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.8 (t, *J* = 31.6 Hz), 160.1, 143.6, 137.3, 129.6, 129.5, 127.2, 124.0 (d, *J* = 2.2 Hz), 114.0, 113.8 (t, *J* = 254.9 Hz), 63.5, 59.3 (dd, *J* = 26.9 Hz, *J* = 23.8 Hz), 55.4, 21.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -112.1 (dd, *J* = 257.6 Hz, *J* = 10.1 Hz), 115.3 (dd, *J* = 257.6 Hz, *J* = 16.1 Hz). IR (cm^{-1}): 3255, 1774, 1613, 1518, 1441, 1330, 1258, 1160, 912, 808, 666, 544. HRMS (ESI+): calcd for [M+H] $C_{19}H_{22}F_2NSO_5$: 414.1187, found: 414.1182 (-1.2 ppm).

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(1-naphtyl)-propionate **6c:**

Compound **6c** was obtained as a viscous yellow oil in 80% yield (173 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 4: 1, Rf = 0.24 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.93 (d, 2H, *J* = 8.5 Hz), 7.68 (d, 1H, *J* = 7.6 Hz), 7.62 (d, 1H, *J* = 8.1 Hz), 7.50-7.37 (m, 2H), 7.29-7.26 (m, 3H), 7.17 (dd, 1H, *J* = 8.5 Hz, *J* = 6.9 Hz), 6.66 (d, 2H, *J* = 8.1 Hz), 5.98-5.85 (m, 2H), 4.18-4.07 (m, 2H), 2.05 (s, 3H), 1.10 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.7 (t, *J* = 31.7 Hz), 143.3, 136.6, 133.5, 131.6, 129.6, 129.0, 128.7, 128.4 (d, *J* = 1.7 Hz), 127.0, 126.9, 126.1, 125.1, 122.7, 114.1 (t, *J* = 257.7 Hz), 63.6, 54.2 (dd, *J* = 28.0 Hz, *J* = 23.5 Hz), 21.3, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$): -110.7 (d br, *J* = 262.0 Hz), -114.4 (d br, *J* = 257.0 Hz). IR (cm^{-1}): 1774, 1331, 1199, 1051, 773, 555, 407. HRMS (ESI+): calcd for [M+H] $C_{22}H_{22}F_2NSO_4$: 434.1238, found: 434.1227 (-2.5 ppm).

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(3,4-methylenedioxyphenyl)-propionate **6d**:

Compound **6d** was obtained as a yellow solid in 71% yield (152 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 4: 1 to 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): 7.52 (d, 2H, *J* = 8.3 Hz), 7.11 (d, 2H, *J* = 8.0 Hz), 6.59 (m, 3H), 5.98 (d, 1H, *J* = 10.1 Hz), 5.87 (dd, 1H, *J* = 3.8 Hz, *J* = 1.3 Hz), 4.96-4.87 (m, 1H), 4.23 (q, 2H, *J* = 7.1 Hz), 2.33 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.7 (t, *J* = 31.6 Hz), 148.2, 147.8, 143.6, 137.2, 129.4, 127.2, 125.5 (d, *J* = 2.1 Hz), 122.7, 113.6 (t, *J* = 257.5 Hz), 108.4, 108.2, 101.4, 63.6, 59.5 (dd, *J* = 27.4 Hz, *J* = 23.5 Hz), 21.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -111.8 (dd, *J* = 257.3 Hz, *J* = 9.6 Hz), -115.7 (dd, *J* = 257.3 Hz, *J* = 16.6 Hz). IR (cm^{-1}): 1774, 1443, 1324, 1246, 1161, 1040, 917, 808, 670, 542. HRMS (ESI+): calcd for [M+H] $C_{19}H_{20}F_2NSO_6$: 428.0979, found: 428.0988 (+2.1 ppm). Mp: 107-108 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(4-trifluoromethyl-phenyl)-propionate **6e**:

Compound **6e** was obtained as a white solid in 75% yield (170 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 9: 1, Rf = 0.36 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.49 (d, 2H, *J* = 8.3 Hz), 7.41 (d, 2H, *J* = 8.2 Hz), 7.25 (d, 2H, *J* = 7.8 Hz), 7.05 (d, 2H, *J* = 8.1 Hz), 5.95 (d, 1H, *J* = 10.2 Hz), 5.16-5.04 (m, 1H), 4.27 (q, 2H, *J* = 7.1 Hz), 2.30 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.4 (t, *J* = 31.5 Hz), 144.1, 136.8, 135.8, 131.1 (q, *J* = 32.7 Hz), 129.5, 129.1, 127.1, 125.4 (q, *J* = 3.7 Hz), 123.9 (d, *J* = 272.3 Hz), 113.4 (t, *J* = 258.2 Hz), 63.9, 59.4 (dd, *J* = 28.7 Hz, *J* = 23.4 Hz), 21.3, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -63.4, (dd, *J* = 260.8 Hz, *J* = 7.9 Hz), (dd, *J* = 260.8 Hz, *J* = 17.9 Hz). IR (cm^{-}

^{1}): 3228, 1761, 1449, 1325, 1162, 1061, 807, 668, 553. HRMS (ESI+): calcd for [M+H] $C_{19}H_{19}F_5NSO_4$: 452.0955, found: 452.0954 (-0.2 ppm). Mp: 134-135 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(4-bromo-phenyl)-propionate **6f**:

Compound **6f** was obtained as a white solid in 81% yield (187 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15, Rf = 0.36 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.52 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 2H, *J* = 8.2 Hz), 7.00 (d, 2H, *J* = 8.4 Hz), 5.92 (d, 1H, *J* = 10.1 Hz), 5.05-4.93 (m, 1H), 4.24 (q, 2H, *J* = 7.1 Hz), 2.35 (s, 3H), 1.28 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.5 (t, *J* = 31.6 Hz), 144.0, 136.9, 131.8, 130.9 (d, *J* = 1.7 Hz), 130.1, 129.6, 127.1, 123.4, 113.4 (t, *J* = 257.9 Hz), 63.8, 59.3 (dd, *J* = 28.0 Hz, *J* = 23.6 Hz), 21.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -111.0 (dd, *J* = 259.8 Hz, *J* = 8.9 Hz), -116.2 (dd, *J* = 259.8 Hz, *J* = 17.1 Hz). IR (cm^{-1}): 3228, 1764, 1447, 1338, 1163, 1067, 794, 668, 552. HRMS (ESI+): calcd for [M+H] $C_{18}H_{19}BrF_2NSO_4$: 462.0186, found: 462.0183 (-0.6 ppm). Mp: 131-132 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(4-chloro-phenyl)-propionate **6g**:

Compound **6g** was obtained as a white solid in 85% yield (177 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15, Rf = 0.33 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.53 (d, 2H, *J* = 8.3 Hz), 7.17-7.05 (m, 6H), 5.90 (d, 1H, *J* = 10.0 Hz), 5.00 (dt, 1H, *J* = 17.0 Hz, *J* = 9.4 Hz), 4.24 (q, 2H, *J* = 7.1 Hz), 2.35 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.5 (t, *J* = 31.6 Hz), 144.0, 137.0, 135.2, 130.4 (d, *J* = 1.7 Hz), 129.8, 129.6, 128.8, 127.1, 113.4 (t, *J* = 256.0 Hz), 63.7, 59.2 (dd, *J* = 27.9 Hz, *J* = 23.7 Hz), 21.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -110.5 (dd, *J* = 259.7 Hz, *J* = 8.8 Hz), -115.7 (dd, *J* = 259.7 Hz, *J* = 16.9 Hz). IR (cm^{-1}): 3228, 1767, 1446, 1318, 1162, 1118, 1066, 911, 806, 551.

HRMS (ESI+): calcd for [M+H] $C_{18}H_{19}F_2ClNSO_4$: 418.0691, found: 418.0676 (-3.6 ppm). Mp: 121-122 °C.

Ethyl 2,2-difluoro-3-(para-tolylsulfonylamino)-3-(3,4-dichloro-phenyl)-propionate **6h**:

Compound **6h** was obtained as a white solid in 81% yield (183 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15, Rf = 0.29 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.51 (d, 2H, *J* = 8.3 Hz), 7.25 (d, 1H, *J* = 8.3 Hz), 7.12-7.10 (m, 3H), 7.05-7.02 (m, 1H), 7.11 (d, 1H, *J* = 10.2 Hz), 4.97 (ddd, 1H, *J* = 17.9 Hz, *J* = 10.0 Hz, *J* = 7.9 Hz), 4.29 (q, 2H, *J* = 7.1 Hz), 2.35 (s, 3H), 1.31 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.4 (t, *J* = 31.5 Hz), 144.3, 136.7, 133.5, 132.8, 131.9 (d, *J* = 1.2 Hz), 130.6, 130.6, 129.6, 127.8, 113.2 (t, *J* = 258.1 Hz), 63.9, 58.9 (dd, *J* = 28.8 Hz, *J* = 23.6 Hz), 21.5, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -110.2 (dd, *J* = 260.8 Hz, *J* = 7.9 Hz), -116.9 (dd, *J* = 260.8 Hz, *J* = 17.8 Hz). IR (cm^{-1}): 3237, 1756, 1469, 1459, 1344, 1215, 1167, 1071, 807, 682, 534. HRMS (ESI+): calcd for [M+H] $C_{18}H_{18}Cl_2F_2NSO_4$: 452.0302, found: 452.0304 (+0.4 ppm). Mp: 117-118 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(4-cyano-phenyl)-propionate **6i**:

Compound **6i** was obtained as a white solid in 73% yield (149 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 7: 3). ^{1}H NMR (300 MHz, $CDCl_3$): 7.51 (m, 2H), 7.31-7.26 (m, 2H), 7.12 (d, 2H, *J* = 8.1 Hz), 6.11 (dd, 1H, *J* = 10.2 Hz, *J* = 0.1 Hz), 5.15-5.03 (m, 1H), 4.25 (q, 2H, *J* = 7.1 Hz), 2.35 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.2 (t, *J* = 31.2 Hz), 144.3, 137.2 (d, *J* = 1.1 Hz), 136.8, 132.3, 129.7, 129.3, 127.1, 118.1, 113.2 (t, *J* = 258.3 Hz), 113.0, 64.0, 59.3 (dd, *J* = 28.5 Hz, *J* = 23.7 Hz), 21.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -109.8 (dd, *J* = 261.6 Hz, *J* = 7.6 Hz), -116.7 (dd, *J* = 261.6 Hz, *J* = 17.6 Hz). IR (cm^{-1}):

3256, 2245, 1174, 1448, 1332, 1283, 1163, 1088, 917, 836 , 666, 549. HRMS (ESI+): calcd for [M+H] $C_{19}H_{19}F_2N_2SO_4$: 409.1034, found: 409.1020 (-3.4 ppm). Mp: 171-172 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(4-methyl-carboxylate-phenyl)-propionate **6j**:

Compound **6j** was obtained as a white solid in 65% yield (143 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15 to 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): 7.83 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 2H, *J* = 8.2 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 6.23 (d, 1H, *J* = 10.3 Hz), 5.09 (dt, 1H, *J* = 17.7 Hz, *J* = 9.0 Hz), 4.24 (q, 2H, *J* = 7.1 Hz), 3.89 (s, 3H), 2.28 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz).. ^{13}C NMR (75 MHz, $CDCl_3$): 166.5, 162.4 (t, *J* = 31.5 Hz), 143.9, 137.0, 136.8, 130.7, 129.7, 129.5, 128.8, 127.1, 113.5 (t, *J* = 258.2 Hz), 63.7, 59.5 (dd, *J* = 28.0 Hz, *J* = 23.6 Hz), 52.4, 21.4, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -110.1 (dd, *J* = 259.5 Hz, *J* = 8.5 Hz), -115.7 (ddd, *J* = 259.5 Hz, *J* = 17.3 Hz, *J* = 2.6 Hz). IR (cm^{-1}): 1768, 1703, 1446, 1346, 1285, 1190, 1115, 1071, 1013, 906, 817, 701, 671. HRMS (ESI+): calcd for [M+H] $C_{20}H_{22}F_2NSO_6$: 442.1136, found: 442.1143 (+1.6 ppm). Mp: 156-157 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(3-furyl)-propionate **6k**:

Compound **6k** was obtained as a white solid in 72% yield (134 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15). ^{1}H NMR (300 MHz, $CDCl_3$): 7.65 (d, 2H, *J* = 8.3 Hz), 7.25-7.20 (m, 4H), 6.22 (s, 1H), 5.54 (d, 1H, *J* = 10.0 Hz), 5.02 (dt, 2H, *J* = 15.5 Hz, *J* = 9.8 Hz), 4.24 (qd, 2H, *J* = 7.1 Hz, *J* = 1.9 Hz), 2.38 (s, 3H), 1.28 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.6 (t, *J* = 31.6 Hz), 143.9, 143.8, 141.7, 137.3, 129.7, 127.2, 117.6 (d, *J* = 2.6 Hz), 113.5 (t, *J* = 257.5 Hz), 109.2, 63.6, 52.5 (dd, *J* = 28.0 Hz, *J* = 25.2 Hz), 21.6, 13.9. ^{19}F NMR (282 MHz,

$CDCl_3$): -111.9 (dd, *J* = 259.7 Hz, *J* = 9.7 Hz), -115.5 (dd, *J* = 259.7 Hz, *J* = 15.6 Hz). IR (cm^{-1}): 1773, 1448, 1321, 1247, 1161, 1040, 918, 808, 669, 551. HRMS (ESI+): calcd for [M+H] $C_{16}H_{18}F_2NSO_5$: 374.0874, found: 374.0881 (+1.9 ppm). Mp: 79-80 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(2-thienyl)-propionate **6l**:

Compound **6l** was obtained as a white solid in 69% yield (134 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15). ^1H NMR (300 MHz, $CDCl_3$): 7.60 (d, 2H, *J* = 8.3 Hz), 7.20 (dd, 1H, *J* = 5.0 Hz, *J* = 1.2 Hz), 7.18-7.15 (m, 2H), 6.89-6.88 (m, 1H), 6.83 (dd, 1H, *J* = 5.0 Hz, *J* = 3.6 Hz), 5.48 (d, 1H, *J* = 10.0 Hz), 5.33 (dt, 1H, *J* = 15.1 Hz, *J* = 9.6 Hz), 4.25 (q, 2H, *J* = 7.1 Hz), 2.36 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.4 (t, *J* = 31.7 Hz), 143.8, 137.2, 134.1 (d, *J* = 2.1 Hz), 129.6, 128.4, 127.2 (2C), 127.0, 113.1 (t, *J* = 258.3 Hz), 63.7, 55.7 (dd, *J* = 27.9 Hz, *J* = 25.3 Hz), 21.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -111.6 (dd, *J* = 258.8 Hz, *J* = 9.2 Hz), -115.2 (dd, *J* = 258.8 Hz, *J* = 15.1 Hz). IR (cm^{-1}): 3240, 1775, 1444, 1328, 1289, 1160, 1066, 912, 809, 725, 685, 539. HRMS (ESI+): calcd for [M+H] $C_{16}H_{18}F_2NS_2O_4$: 390.0645, found: 390.0650 (+1.3 ppm). Mp: 123-124 °C.

Ethyl 2,2-Difluoro-3-(para-tolylsulfonylamino)-3-(3-pyridyl)-propionate **6m**:

Compound **6m** was obtained as a yellow solid in 76% yield (146 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 1: 1 to 2: 3, Rf = 0.22 Petroleum ether/EtOAc 1:1). ^1H NMR (300 MHz, $CDCl_3$): 8.50 (dd, 1H, *J* = 4.7 Hz, *J* = 1.3 Hz), 8.41 (d, 1H, *J* = 1.8 Hz), 7.56-7.50 (m, 3H), 7.17-7.11 (m, 3H), 6.08 (d, 1H, *J* = 9.9 Hz), 5.14-5.02 (m, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 2.33 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.3 (t, *J* = 31.4 Hz), 150.2, 149.7, 144.1, 136.9, 135.8,

129.7, 128.3, 127.1, 123.6, 113.4 (t, *J* = 258.2 Hz), 63.9, 57.8 (dd, *J* = 28.7 Hz, *J* = 23.9 Hz), 21.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -110.1 (dd, *J* = 261.3 Hz, *J* = 8.2 Hz), -116.6 (dd, *J* = 261.3 Hz, *J* = 17.7 Hz). IR (cm^{-1}): 2926, 1756 1597, 1482, 1437, 1330, 1292, 1154, 1064, 806, 739, 669, 542. HRMS (ESI+): calcd for [M+H] $C_{17}H_{19}F_2N_2SO_4$: 385.1034, found: 385.1031 (-0.8 ppm). Mp: 172-173 °C.

Ethyl 2,2-difluoro-3-(para-tolylsulfonylamino)-5-phenyl-pent-4-enoate **6n**:

Compound **6n** was obtained as a yellow solid in 73% yield (149 mg), after flash chromatography (SiO_2, Petroleum ether/EtOAc 85: 15, Rf = 0.30 Petroleum ether/EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): 7.73 (d, 2H, *J* = 8.3 Hz), 7.30-7.25 (m, 3H), 7.20 (d, 2H, *J* = 8.1 Hz), 7.16-7.13 (m, 2H), 6.37 (d, 1H, *J* = 15.9 Hz), 5.80 (dd, 1H, *J* = 15.9 Hz, *J* = 7.6 Hz), 5.08 (d, 1H, *J* = 9.9 Hz), 4.70-4.56 (m, 1H), 4.33-4.23 (m, 2H), 2.28 (s, 3H), 1.32 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.6 (t, *J* = 31.6 Hz), 144.1, 137.6, 137.1, 135.3, 129.8, 128.7, 128.7, 127.4,126.8, 118.7 (dd, *J* = 3.1 Hz, *J* = 1.7 Hz), 113.6 (t, *J* = 257.4 Hz), 63.6, 58.6 (dd, *J* = 27.9 Hz, *J* = 24.6 Hz), 21.5, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$): -111.6 (dd, *J* = 260.7 Hz, *J* = 8.6 Hz), -116.9 (dd, *J* = 260.7 Hz, *J* = 15.3 Hz). IR (cm^{-1}): 3228, 1773, 1444, 1337, 1159, 1074, 967, 815, 745, 667, 541. HRMS (ESI+): calcd for [M+H] $C_{20}H_{22}F_2NSO_4$: 410.1238, found: 410.1237 (-0.2 ppm). Mp: 124-125 °C.

Ethyl 2-fluoro-3-(benzenesulfonylamino))-3-(phenyl)-propionate **7**:

Compound **7** was obtained as a yellow oil in 79% yield (138 mg, dr = 1.6: 1), after flash chromatography (SiO_2, Petroleum ether/EtOAc 7: 3). ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.56 (m, 5H), 7.38-7.30 (m, 3H), 7.27-7.18 (m, 6H), 7.11-7.03 (m, 10H), 6.99-6.97 (m, 2H), 5.85 (d, 1.6H, *J* = 9.5 Hz), 5.80 (d, 1H, *J* = 9.1 Hz), 5.14 (dd, 1H, $J_{H\text{-}F}$ = 48.7 Hz, *J* = 3.7 Hz), 5.02-4.77 (m, 4.5H), 4.13-3.94 (m, 5.2H), 1.16 (t, 4.8H),

0.99 (t, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): 167.0 (d, *J* = 24.6 Hz), 166.5 (d, *J* = 23.0 Hz), 140.4, 140.2, 135.6, 134.0, 132.7, 132.5, 129.0, 128.8, 128.7, 128.7, 128.6, 128.4, 127.8, 127.8, 127.1, 127.0, 90.96 (d, *J* = 193.7 Hz), 90.66 (d, *J* = 194.1 Hz), 62.4, 61.9, 58.8 (d, *J* = 3.9 Hz), 58.5 (d, *J* = 3.6 Hz), 14.1, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$): -201.5 (dd, *J* = 47.5 Hz, *J* = 25.3 Hz), -202.3 (dd, *J* = 48.7 Hz, *J* = 26.2 Hz). IR (cm^{-1}): 1771, 1438, 1341, 1154, 971, 812, 741, 540. HRMS (ESI+): calcd for [M+H] $C_{18}H_{21}FNSO_4$: 366.1175, found: 366.1168 (-1.9 ppm).

Competition reaction (scheme 5): To a solution of In^0 (powder, 0.5 mmol, 58 mg), benzaldehyde (0.5 mmol) and the corresponding aldimine (0.5 mmol) in THF (1 mL) was added $BrCF_2CO_2Et$ (0.5 mmol, 64 μL). The resulting mixture was stirred at 60°C for 18h and then cooled to room temperature. After a usual work-up, ratios were determined by ^{19}F NMR using $C_6H_5CF_3$ as an internal standard.

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Supporting Information

^{1}H and ^{13}C NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] CH_2Cl_2, toluene, CH_3CN might be use as solvent without erosion of the efficiency of the reaction.

[23] So far, we have not been able to extend this methodology to aliphatic aldehydes and ketones with decent yield. Indeed, with hydrocinnamaldehyde the corresponding adduct has been obtained in less than 30% yield.

[24] For discussion on the formation of the β–lactam species in the course of the Zn mediated Reformatsky addition reaction see refs.11a-b and references therein.

[25] Mannich adduct derived from ketimines were obtained in very low yield (<20%). For the sole example of the addition of ethyl bromodifluoroacetate to a ketimine using zinc metal see: ref. 11e.

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