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Tetrahedron
Tetrahedron 63 (2007) 12352–12366

Chemoselective and stereoselective synthesis of *gem*-difluoro-β-aminoesters or *gem*-difluoro-β-lactams from ethylbromodifluoroacetate and imines during Reformatsky reaction

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Received 28 August 2007; revised 24 September 2007; accepted 25 September 2007
Available online 29 September 2007

Abstract—The chemoselective and stereoselective synthesis of *gem*-difluoro-β-aminoesters or *gem*-difluoro-β-lactams was investigated from ethylbromodifluoroacetate and imines during Reformatsky reaction. Influence of various reaction parameters, such as nature of the amine part, nature of the chiral auxiliary, was evaluated. High levels of stereoselectivity (up to 98%) were obtained for *gem*-difluoro-β-aminoesters and *gem*-difluoro-β-lactams using either (*R*)-phenylglycinol or (*R*)-methoxyphenylglycinol.

1. Introduction

In recent years, fluoro compounds have received a great deal of interest. The presence of a fluorine atom introduces modifications to the physiological activity of bioactive compounds.[1] Indeed, fluorine's small van der Waals radius and its high electronegativity have important effects on the physical and chemical properties of the molecule. This led to the discovery of potent medicinal agents and the development of original methods of preparation, especially in the asymmetric series.[2] Among them, *gem*-difluoro amino acids and derivatives have been the subject of an important area of research since the CF_2/CH_2 transposition has been recognized as a valuable tool in the blockage of metabolic processes. Replacement of various functional groups by a *gem*-difluoromethylene moiety has generated potent transition-state-type inhibitors.[3] Additionally, β-amino acids are now recognized as valuable tools for the generation of new derivatives such as β-peptides[4] as well as building blocks for β-lactam antibiotics.[5] In this context, the development of a new synthetic methodology for preparing pure fluorine-containing β-amino acids is of particular interest. Numerous methods have been described for the synthesis of such compounds (Scheme 1). Several strategies have been investigated for the selective and efficient introduction of fluorine atoms into organic compounds in solution. Direct introduction of fluorine can be achieved with fluorinating agents (DAST, SF_4, CF_3OF, HF, and others). However, their use is clearly limited to specific compounds because of their high reactivity. In addition, many of these reagents are expensive, toxic, and hazardous. This strategy, consisting in the nucleophilic fluorination of ketoester[6] (method a) or ketone[7] (method b), has been, respectively, used by Takei and Fokina. In general, fairly good yields are obtained during the fluorinating step (20–31%). Consequently, with the increasing accessibility of fluorinated building blocks, the CF_2-synthon approach has efficiently emerged. An effective strategy involves the 1,2 addition of *gem*-difluoromethylene organometallic reagents to imines or imine derivatives by Reformatsky reaction.[8] Methods c (Fokina[9]), d (Soga[10]), and e (Ohta[11]) used this strategy by generating a unique common intermediate, namely a α,α-difluoro-β-hydroxy ester (obtained via a Reformatsky reaction between ethyl bromodifluoroacetate and an aldehyde), which was further functionalized leading to the expected α,α-difluoro-β-amino acid. Lastly, methods f (Katritzky,[12] Houghten[13]), g (Staas,[14] Soloshonok[15]), h (Kobayashi[16]), and i (Quirion[17]) used the same Reformatsky reagent, which was condensed with an imine or imine derivative (iminium, sulfinimine, and oxazolidine). All these methods allowed to get the expected α, α-difluorinated β-amino acid in good isolated yields and

Keywords: Reformatsky reaction; Difluoro-β-aminoesters; Difluoro-β-lactams; (*R*)-Methoxyphenylglycinol.
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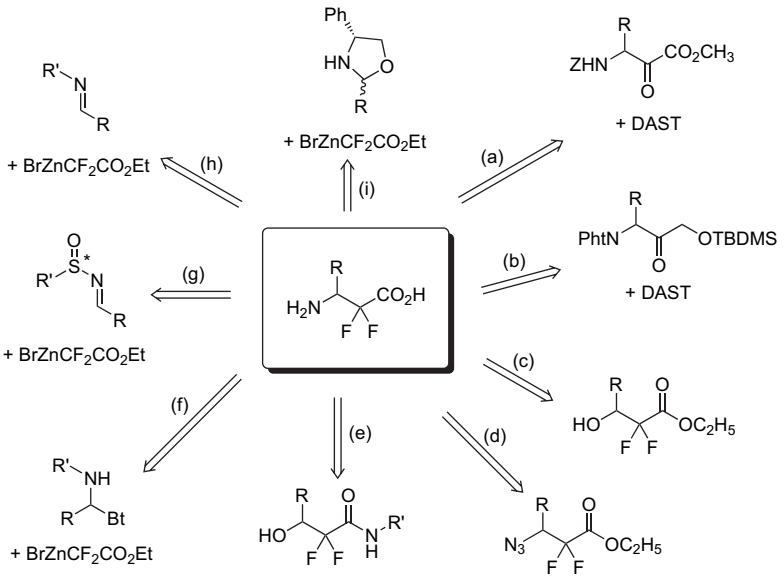
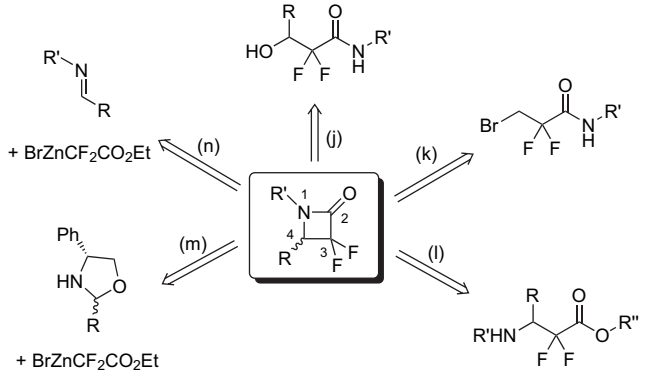
doi:10.1016/j.tet.2007.09.058



Scheme 1.

for the three last ones in good to very good diastereomeric excesses.

3,3-Difluoroazetidin-2-one derivatives (Scheme 2) have been prepared either as enzyme inhibitors or as synthetic intermediates for modified peptides.[18] Very recently, these difluoro-β-lactams have been efficiently used as 3,3-difluoroazetidines' precursors.[19] Only few examples of efficient syntheses of 3,3-difluoroazetidin-2-one derivatives have been reported. This first strategy is based on the obtention of a β-hydroxy ester[10,11,16c,20] (method j), which undergoes a transamidation reaction and finally a N1–C4 cyclization under Mitsunobu conditions. Wakselman[21] (method k) reported the same type of cyclization of *N*-aryl-3-bromo-2,2-difluoropropioamides under strongly basic conditions. N1–C2 cyclization[22] (method l) has been also described (R=H). More efficiently, these types of compounds can be obtained from the cycloaddition of difluoroenolate with oxazolidines[17] (method m) or imines[16b,17,23] (method n). These two last methods, by analogy with methods h and i, can lead, depending on the reaction conditions and/or the substitution of the substrate, either to the β-aminoester or to the 3,3-difluoroazetidin-2-one derivative or to the mixture of these two products (which are difficult to separate in most cases).



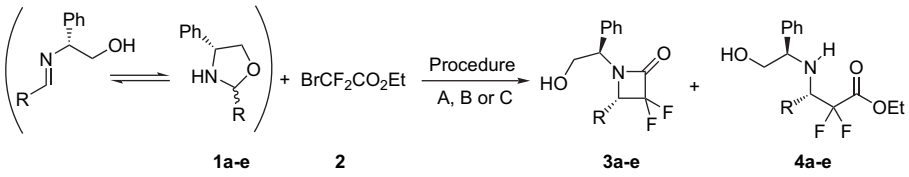
Scheme 2.

2. Results and discussion

In the course of a medicinal chemistry program aimed at the discovery of new protease inhibitors, we need an easy and secure access toward *N*-protected 3,3-difluoroazetidin-2-ones or α,α-difluoro-β-amino acids selectively. In this paper, we report our study related to the parameters, which influence the selective formation of difluoro-β-lactams during Reformatsky reaction between ethyl bromodifluoroacetate and oxazolidines or imine derivatives. To our knowledge, this type of study has only been partially reported in the methylene series by Dardoize,[24] Adrian,[25] Bartsch,[26] and Honda.[27]

Several parameters have been investigated namely the influence of the imine, the chiral auxiliary, the organozinc reagent, and the presence of additives.

As recently described by our group[17] and others,[28] (*R*)-phenylglycinol was selected as an efficient chiral auxiliary. Oxazolidines **1a–e** were easily prepared in quantitative yields by condensation of this aminoalcohol and aldehydes and were then used after isolation without purification (Scheme 3). Although these 1,3-oxazolidines (obtained as a mixture of diastereoisomers) were in equilibrium with the corresponding imino alcohols, reaction with ethyl bromodifluoroacetate **2** occurred in all cases. It was sometimes necessary to adapt the procedure to the substrate in order to improve the yields. Three different methods have been used: method A used activated zinc as previously described,[17] method B used the same protocol with the addition of a catalytic amount of Cp_2TiCl_2, which enables to carry out the reaction at room temperature in THF.[29] The last one (method C) is the method developed by Honda,[27,30] Kumadaki,[31] and Fujii[20b] who carried out Reformatsky reaction using diethylzinc and Wilkinson catalyst. More recently, asymmetric nickel-catalyzed Reformatsky type three component reactions were developed with success.[32] All the results are collected in Table 1. In all cases, we were pleased to observe a high diastereoisomeric excess (85–98%). As previously described, this high asymmetric induction can



Scheme 3.

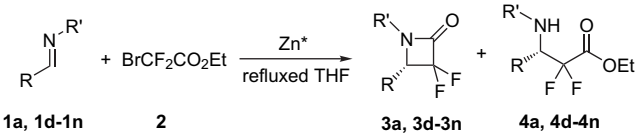
Table 1. Diastereoselective formation of β-lactams **3** or β-aminoesters **4**

Entry	Substrate	R	Procedure[a]	**3** (%)	de[b] (%)	**4** (%)	de[b] (%)	Yield[c] (%)
1[d]	**1a**	Ph	A	100	>98	0	—	56
2	**1a**	Ph	C	100	>98	0	—	62
3	**1b**	3-Thienyl	A	100	>98	0	—	71
4[d]	**1c**	2-Furyl	A	100	85	0	—	62
5	**1d**	4-Pyridyl	A	0	—	100	>98	67
6	**1d**	4-Pyridyl	C	Deg.[e]	—	Deg.[e]	—	—
7	**1d**	4-Pyridyl	B	0	—	100	>98	47
8	**1e**	3-Pyridyl	A	0	—	100	—	15
9	**1e**	3-Pyridyl	C	Deg.[e]	—	Deg.[e]	—	—
10	**1e**	3-Pyridyl	B	0	—	100	>98	50

[a] A: Zn*, refluxed THF, 2 h. B: Zn*, Cp_2TiCl_2 (5 mol %), THF, rt, 1 h. C: [$RhCl(PPh_3)_3$] (2 mol %), Et_2Zn, CH_3CN, rt, 5 h.
[b] Determined by ^{19}F NMR.
[c] Isolated yields.
[d] See Ref. 17 for full characterization of this compound.
[e] Degradation.

be explained by the strongly chelated intermediate proposed by Pridgen.[33] In this model, the zinc of the alcoholate is chelated by the nitrogen atom, and the nucleophilic attack occurs on the less hindered side opposite to the phenyl group of the chiral auxiliary. Nevertheless, when imines of pyridine-4-carboxaldehyde or pyridine-3-carboxaldehyde were used, we observed a complete inversion of the β-lactam **3**/β-aminoester **4** ratio (entries 5, 7, 8 and 10), but with a high diastereoselectivity (>98%). It also appeared that this modification did not modify the chelated transition state but inhibited the intramolecular cyclization.

In order to clarify this phenomenon, we investigated the influence of the chiral auxiliary on the β-lactam **3**/β-aminoester **4** ratio when benzaldehyde, pyridine-4-carboxaldehyde, and pyridine-3-carboxaldehyde were used as imine precursor (Scheme 4). Two other chiral auxiliaries: (*R*)-methoxyphenylglycinol, α-(*R*)-methylbenzylamine and one achiral: *p*-methoxybenzylamine were tested. All the results are collected in Table 2.



Scheme 4.

In the case of benzaldehyde (Table 2, entries 1–4) as the imine precursor, the best results were obtained when (*R*)-phenylglycinol was used as the chiral inductor. Less chelating chiral auxiliaries led to a decrease of diastereoselectivity and the concomitant production of 7–17% of β-aminoester **4** (Table 2, entries 2 and 3). However, only racemic β-lactam **3** was isolated with 4-methoxybenzylamine.

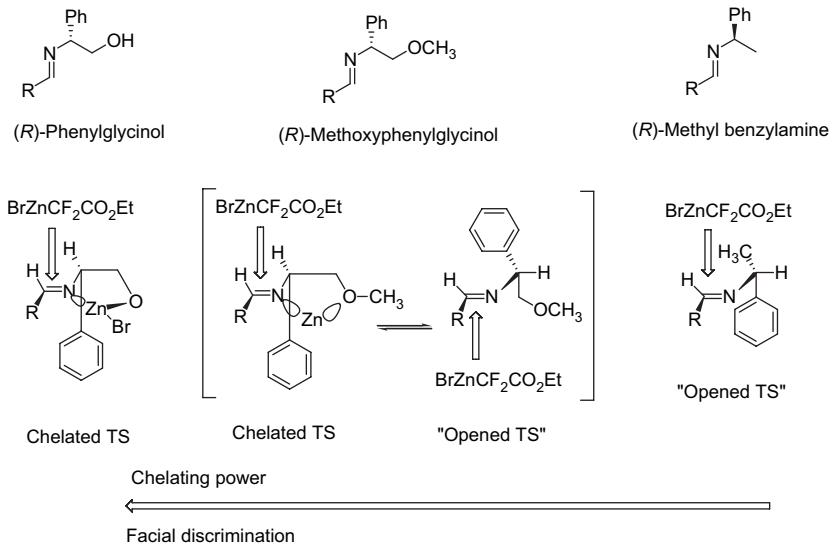
Pyridine imine derivatives gave totally different results. The less chelating the chiral auxiliary was, the higher the ratio β-lactam/β-aminoester was (entries 5/6/7 and 9/10/11); however, this phenomenon was followed by a strong decrease of the diastereoselectivity. As previously observed in the benzaldehyde series, 4-methoxybenzylamine derivatives led nearly exclusively to the formation of racemic β-lactams (entries 8 and 12) with excellent isolated yields.

The diastereoselectivity observed in this series of experiments can be explained by the proposed mechanism depicted in Scheme 5. (*R*)-Phenylglycinol leads to a single chelated intermediate in which a five-membered ring is created by chelation between nitrogen and zinc alcoholate. (*R*)-Alkoxyphenylglycinol derivatives have been used for the diastereoselective addition of Reformatsky-type reagents on various imines with high diastereoselectivity.[20b,34] In our case, with (*R*)-methoxyphenylglycinol, the diastereoselectivity

Table 2. Diastereoselective formation of β-lactams **3** or β-aminoesters **4** using activated zinc

Entry	Substrate	R	R′	**3**[b] (%)	de[b] (%)	**4**[b] (%)	de[b] (%)	Yield[c] (%)
1[d]	**1a**	Ph	(*R*)-Phenylglycinol	100	>98	0	—	56
2	**1f**	Ph	(*R*)-Methoxy phenylglycinol	93	97	7	94	53
3	**1g**	Ph	α-(*R*)-Methyl benzylamine	83	23	17	30	61
4[d]	**1h**	Ph	*p*-Methoxy benzylamine	100	—	0	—	74
5	**1d**	4-Pyridyl	(*R*)-Phenylglycinol	0	—	100	>98	67
6	**1i**	4-Pyridyl	(*R*)-Methoxy phenylglycinol	72	77	28	75	65
7	**1j**	4-Pyridyl	α-(*R*)-Methyl benzylamine	94	30	6	32	93
8	**1k**	4-Pyridyl	*p*-Methoxy benzylamine	89	—	11	—	85
9[a]	**1e**	3-Pyridyl	(*R*)-Phenylglycinol	0	—	100	>98	50
10	**1l**	3-Pyridyl	(*R*)-Methoxy phenylglycinol	96	87	4	87	98
11	**1m**	3-Pyridyl	α-(*R*)-Methyl benzylamine	91	46	9	55	67
12	**1n**	3-Pyridyl	*p*-Methoxy benzylamine	90	—	10	—	86

[a] Zn*, Cp_2TiCl_2 (5 mol %), THF, rt, 1 h.
[b] Determined by ^{19}F NMR.
[c] Isolated yields.
[d] See Ref. 17 for full characterization of this compound.



Scheme 5.

of the zinc enolate addition is lower. The transition state model can be used to rationalize the reaction outcome. Less stable chelated transition state could be in equilibrium with an opened form, which could react without selectivity with the organozinc reagent. Finally, α-(*R*)-methylbenzylamine can lead only to the opened transition state, which can be alkylated with a very low selectivity (32–55%).

It is more difficult to explain the differences observed between the three series concerning the ratio β-lactam/β-aminoester. Indeed, with benzylidenamine, β-lactam is the only product isolated when (*R*)-phenylglycinol was used (entry 1) and a slight increase of formation of β-aminoester was observed with less chelating auxiliaries (entries 2 and 3) while an opposite result was obtained in the pyridine series (entries 5/6/7 and 9/10/11). The π-deficient character of pyridine and/or its ability to complex Lewis acid could explain the origin of a specific interaction with the transition zinc amide, thus preventing cyclization.

Moreover, in order to determine the influence of the *gem*-difluoro moiety on the β-lactam/β-aminoester ratio, we engaged the imine **1k** with ethyl bromodifluoroacetate **2** and ethyl bromoacetate **5**. Previous studies in the methylene series showed that β-lactams and β-aminoesters were formed in ratio that were temperature and reaction time dependent.[24,26] The results obtained are collected in Scheme 6.

The difluoromethylene moiety had clearly a negative influence on the cyclization step. This group has a dual effect: it increases the electrophilicity of the carbonyl group, which is in favor of the cyclization, but on the other side, it also decreases the nucleophilicity of the zinc amide. Moreover, as the β-lactam is concerned, the presence of two fluorine atoms activates the carbonyl group toward a potential re-opening reaction.

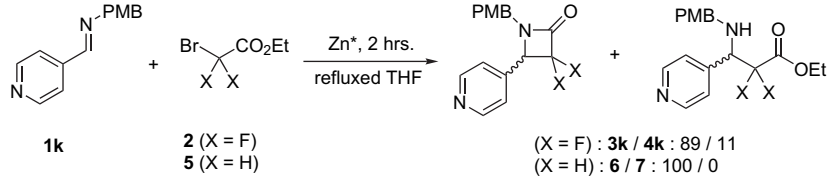
We next examined the influence of the nature of the imine and in particular the amine part, especially its electronic feature. Indeed, few reports have been published in the methylene[25,26,32] and difluoromethylene[19,35] series related to this parameter. The main conclusion of these studies was that the decisive element is the inductive or resonance effect of the substituents connected to the phenyl ring on the electronic density of the amide. As a result, we engaged imines **1k**, **8a–d** with ethyl bromodifluoroacetate **2** (Scheme 7) under classical conditions (activated zinc, refluxed THF, 2 h).

From *p*-methoxybenzylamine (Table 3, entry 1) and *p*-methoxyaniline (entry 2) containing imine precursors, similar β-lactams/β-aminoesters' ratios were obtained, showing that conjugation with the lone pair of nitrogen atom has only little influence. When the same substituent (OCH_3) is

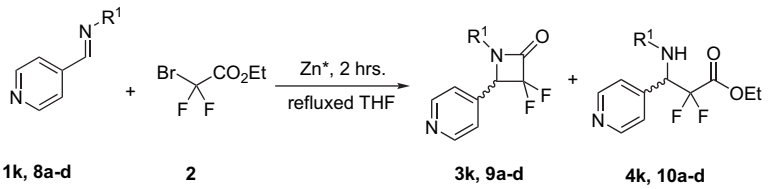
Table 3. Influence of the amine substitution R^1 on the β-lactams/β-aminoesters' ratio

Entry	Imine	R^1	β-Lactam[a] (%)	β-Aminoester[a] (%)
1	**1k**	4-CH_3O–C_6H_4–CH_2–	89 (**3k**)	11 (**4k**)
2	**8a**	4-CH_3O–C_6H_4–	84 (**9a**)	16 (**10a**)
3	**8b**	2-CH_3O–C_6H_4–	0 (**9b**)	100 (**10b**)
4	**8c**	4-F–C_6H_4–	81 (**9c**)	19 (**10c**)
5	**8d**	4-CF_3–C_6H_4–	45 (**9d**)	55 (**10d**)

[a] Determined by ^{19}F NMR.



Scheme 6.

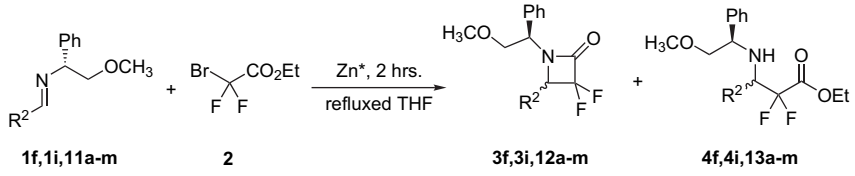


Scheme 7.

connected to two different positions (entries 2 and 3), opposite results are obtained. As previously described,[36] the inductive effects dominated over the resonance effects for *ortho* substituents while it was opposite for several *para* substituents. As previously reported in the methylene series,[25,27] we ascribe that the restraining effects of the *ortho*-methoxyphenyl substituent on nitrogen to an inductive effect arising from the close proximity of the electronegative oxygen of the methoxy group to the nitrogen–zinc bond lead to the reduction of the nucleophilic character of nitrogen, thereby decreasing the proportion of β-lactam **9b** in the mixture (entry 3). As for *para*-methoxyaniline, when *para*-fluoroaniline (entry 4) was used, in which the resonance effect dominates, a high proportion of β-lactam **9c** was obtained. In contrast, when *para*-CF_3 (entry 5) substitution was tested, for which only inductive effects can be considered, the nucleophilic character of the amide was decreased and as a consequence the proportion of β-lactam **9d** was lower.

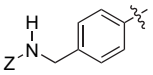
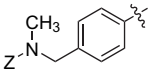
We then examined the influence of the aldehyde moiety of the imine. Indeed, in the methylene series, previous reports had shown a slight influence of the nature of the aldehyde (or its substituents) on the β-lactam/β-aminoester ratio.[24,25] In order to determine the importance of such modifications of the aldehydic part in the difluoromethylene series, we synthesized a series of imines **1f**, **1i**, **11a**–**m** from various aldehydes and (*R*)-methoxyphenylglycinol to evaluate the influence of such modifications on the diastereoisomeric excess and on the β-lactam/β-aminoester ratio (Scheme 8).

In all cases (Table 4), β-lactams are the major or exclusive products obtained (except entry 11). The observed diastereoisomeric excesses for the β-lactams and for β-aminoesters were generally similar. Nevertheless, the aldehydic function has a real impact on the measured diastereoisomeric level. Indeed, when aromatic aldehydes are substituted either by an electron-withdrawing and/or withdrawal by conjugation group (–I and –M: NO_2: entries 3 and 4; CN: entry 5; –I: CF_3: entry 6) or by a π-deficient heterocycle (pyridine: entry 2), diastereoisomeric excesses were lower (77–90%) compared to unsubstituted benzaldehyde (entry 1). This influence is much more significant when the substituent is



Scheme 8.

Table 4. Influence of the aldehyde substitution R^2 on the diastereoisomeric excesses and on the β-lactams/β-aminoesters' ratio

Entry	Imine	R^2	β-Lactam[a] (%)	de[a] (%)	β-Aminoester[a] (%)	de[a] (%)	Yield[c] (%)
1	**1f**	Ph	91 (**3f**)	97	9 (**4f**)	94	53
2	**1i**	4-Pyridyl	72 (**3i**)	77	28 (**4i**)	75	55
3	**11a**	4-NO_2–C_6H_4–	93 (**12a**)	86	7 (**13a**)	n.d.[b]	45
4	**11b**	2-NO_2–C_6H_4–	77 (**12b**)	84	23 (**13b**)	n.d.	58
5	**11c**	4-CN–C_6H_4–	92 (**12c**)	90	8 (**13c**)	n.d.[b]	63
6	**11d**	4-CF_3–C_6H_4–	100 (**12d**)	89	0	—	48
7	**11e**	4-F–C_6H_4–	100 (**12e**)	94	0	—	63
8	**11f**	2-CH_3O–C_6H_4–	100 (**12f**)	>98	0	—	60
9	**11g**	4-CH_3O–C_6H_4–	95 (**12g**)	96	5 (**13g**)	n.d.	42
10	**11h**	2,4,6-$(CH_3O)_3$–C_6H_2–	100 (**12h**)	>98	0	—	79
11	**11i**		46 (**12i**)	>98	54 (**13i**)	>98	77
12	**11j**		100 (**12j**)	>98	0	—	67
13	**11k**	CH_3–$(CH_2)_4$–	100 (**12k**)	>98	0	—	52
14	**11l**	$(CH_3)_3$–C–	78 (**12l**)	>98	22 (**13l**)	>98	33
15	**11m**		100 (**12m**)	90	0	—	53

[a] Determined by ^{19}F NMR.
[b] Not determined.
[c] Isolated yield.

closer to imino group (entries 3 and 4). In contrast, no modification of the diastereoisomeric excesses was observed in the case of a donating group by conjugation (though electron-withdrawing one, entries 8–10). It also seems that the resonance effects overcome inductive ones. Increasing reactivity of the imino group, and decreasing the electronic density of nitrogen atom of aldimine, induced a clear lowering of facial discrimination. This observation is in favor of a less efficient chelated model, in which zinc is simultaneously chelated by the oxygen atom (of the chiral auxiliary) and the nitrogen lone pair. Accordingly, if the chelation between zinc and oxygen is less efficient, it might induce an equilibrium between a chelated transition state and an opened (or less chelated) form, thus explaining the reduction of stereoselectivity.

Influence of the substituents connected to the aldehydic part of the imine on the intramolecular cyclization process is less characterized. Generally speaking, if the substituent has –I and –M characters (entries 3–6), the formation of the β-lactam is slightly disfavored. On the other hand, cyclization was greatly favored in the cases of substituents having electron-withdrawing and electron-donating by conjugation character (entries 8–10). This influence is much more significant when the substituent is closer to imino group (entries 3 and 4). A particular case was observed when Reformatsky reaction was carried out with imine **11i**. Referring to the electronic point of view, this substituent (entry 11, R^2=$C_6H_4CH_2NHZ$) is similar to phenyl, so that we expected to obtain the same results as for imine **1f**. A 1:1 β-lactam **12i**/β-aminoester **13i** ratio was obtained with excellent stereoselectivity for each product. In order to understand this specific reactivity, without modifying electronic effects, the *N*-methylated analog **11j** was synthesized, which removed the second acidic site. Again, homogeneous results were obtained: β-lactam **12j** was the exclusive product with excellent diastereoselectivity. The presence of a second amide position, from the amide ester intermediate, greatly disfavored the cyclization step. When aliphatic aldehydes are used, diastereoisomeric excesses are good to excellent (entries 13–15) and β-lactam **12** is the major or the exclusive product. On the contrary, the addition of ethyl bromodifluoroacetate to aliphatic imines using Honda procedure in the presence of (*R*)-methoxyphenylglycinol[34] led to the exclusive formation of the corresponding β-aminoester with complete diastereoselection. In this protocol, imine was used without isolation and the presence of 1 equiv of water (as proposed by Kumadaki and Ando[31]) could inhibit the cyclization by quenching the zinc amide intermediate.

Finally, we studied the influence of reaction conditions (especially concentration, solvent, additives) on the outcome of Reformatsky reaction between imine **1k** and ethyl bromodifluoroacetate **2** as depicted in Scheme 9. All the results are collected in Table 5.

Table 5. Influence of the reaction conditions on the β-lactams **3k**/β-aminoesters **4k** ratio

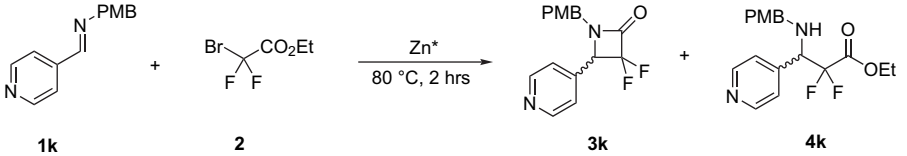
Entry	Solvent	Additive	β-Lactam **3k**[a] (%)	β-Aminoester **4k**[a] (%)
1	THF	—	89	11
2	THF[b]	—	86	14
3	CH_2Cl_2[c]	—	93	7
4	DMF	—	34	66
5	DMSO	—	11	89
6	THF	Pyridine (5 equiv)	84	16
7	THF	2,2′-Bipyridine (3 equiv)	5	95
8	THF	$ZnCl_2$ (5 equiv)	86	14
9	THF	LiBr (1 equiv)	79	21
10	THF	$MgCl_2$ (1 equiv)	38	62
11	THF	EtONa (1 equiv)	0	100

[a] Determined by ^{19}F NMR.
[b] Reaction mixture was 15 times diluted.
[c] Temperature: 40 °C.

Dilution of the reaction mixture had no influence on the β-lactam **3k**/β-aminoester **4k** ratio. In contrast, nature of the solvent proved to be crucial. In a less polar solvent such as THF, CH_2Cl_2 (entries 1 and 3), β-lactam **3k** was obtained as the major product, whereas in more polar solvents (DMF, DMSO) a reverse ratio (major product: β-aminoester **4k**) was observed. Reformatsky reactions have been carried out in various solvents but etheral and aromatic hydrocarbon solvents are mostly used. It has been shown that the nature of the solvent has a great influence on the aggregation state of the organozinc reagent (dimeric in THF and CH_2Cl_2, monomeric in DMSO).[37] The more solvating and polar the solvent is, the more stabilized the amide is and the less favored the cyclization is. It is likewise that in polar solvents, the intermediate can exist as a stabilized zinc amide intermediate, in which the nucleophilicity of the nitrogen would be very low. Addition of Lewis base such as pyridine (entry 6) has no effect, but addition of 2,2′-bipyridine (entry 7) totally inhibited the intramolecular cyclization due to efficient stabilization of the amide ester intermediate. Addition of Lewis acids slightly disfavored (entries 8 and 9) or strongly disfavored (entry 10) the cyclization. For example, $MgCl_2$, the hardest Lewis acid of the series, either chelates the intermediate efficiently, inducing its stabilization, or activates the carbonyl function of β-lactam **3k**, which is therefore much sensitive to a potential re-opening reaction. The same hypothesis can be put forward in the case of the addition of sodium ethoxide (entry 11).

3. Conclusion

We have developed a complete study of the parameters, which can influence the selective synthesis of β-lactam or β-aminoester during Reformatsky reaction between ethyl bromodifluoroacetate and various imines. It clearly appeared that the diastereoselectivity of the reaction is highly



1k 2 3k 4k

PMB: *para*-methoxybenzyl

Scheme 9.

dependent on the nature of the chiral auxiliary i.e. (*R*)-phenylglycinol. It also appeared that the ratio between β-aminoester and β-lactam was depending on the nature of the imine and the reactions conditions. The study conducted in the pyridine series demonstrated that several factors can influence the cyclization of the intermediate. We showed that by modifying the nature of the amine or the reactions conditions, it was always possible to inverse the β-aminoester/β-lactam ratio.

Functionalization of these β-aminoesters or β-lactams is currently under investigation in our laboratory. The results of these investigations will be reported in due course.

4. Experimental section

4.1. General methods

Unless otherwise mentioned, all the reagents were purchased from commercial source and used as received. All glasswares were dried in an oven at 100 °C prior to use. THF was distilled under nitrogen from sodium benzophenone ketyl prior to use. CH_2Cl_2 was distilled under nitrogen from P_2O_5 prior to use. DMSO was distilled under nitrogen from CaH_2 prior to use. DMF was distilled under nitrogen from BaO prior to use. NMR were recorded on a Bruker DXP 300. Chemical shifts of ^1H NMR (300.13 MHz) were expressed in parts per million downfield from tetramethylsilane (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR (75.47 MHz) were expressed in parts per million downfield from $CDCl_3$ as internal standard (δ=77.16). Chemical shifts of ^{19}F NMR (282.40 MHz) were expressed in parts per million downfield from $CFCl_3$ as internal standard (δ=0). Coupling constants are reported in Hertz. Abbreviations used for peak multiplicity are s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet. *J* was used to indicate coupling constant in Hertz. TLC was performed on Merck 60F-250 silica gel plates. Flash column chromatography purifications were carried out using silica gel 60A (40–63 mesh). Silica TLC plates were visualized under UV light, by a 10% solution of phosphomolybdic acid in ethanol followed by heating or by a 1 N solution of aqueous alkali potassium permanganate by heating. Optical rotations were measured on a Perkin–Elmer 341 (λ=589 nm, 25 °C, concentrations used in $cg \cdot mL^{-1}$). Infrared spectra (IR) were recorded on a Perkin–Elmer 1420. Absorption bands are reported in cm^{-1}. Elementary analysis was performed on a Carlo Erba 1106. Melting points are uncorrected. Mass spectrums were performed on ThermoFinnigan Navigator 2.1 for Electrospray or on JEOL AX500 (Isobutane, 200 eV) for IC. HRMS were performed on JEOL AX500 spectrometer.

(*R*)-2-Methoxy-1-phenylethanamine was prepared according to a modification of a literature procedure.[38] A solution of (*R*)-(−)-2-phenylglycinol (25.0 g, 182.2 mmol) in anhydrous tetrahydrofuran (THF) (370 mL) is added dropwise via an oven-dried, 500-mL, pressure-equalizing addition funnel to an oven-dried, 2-L, round-bottomed flask containing a stirred suspension of sodium hydride (95%) (4.93 g, 195 mmol) in anhydrous THF (150 mL) at 25 °C under an argon atmosphere. The resultant pale yellow mixture is stirred overnight and then treated dropwise with a solution of methyl iodide (25.2 g, 177.6 mmol) in THF (220 mL) over 2 h at room temperature. The resultant mixture is stirred for an additional 3 h, poured into cold (5 °C) saturated aqueous sodium chloride solution (1.5 L), and extracted with anhydrous diethyl ether (4×250 mL). The combined organic extracts are dried over $MgSO_4$. Filtration and evaporation give a yellow oil that is purified by vacuum distillation (bp 47–50 °C, 0.2 mm) to yield 21 g (78%) of (*R*)-2-methoxy-1-phenylethanamine as a colorless oil.

All substrate oxazolidines were readily synthesized by condensation of the appropriate aldehyde with the prerequisite chiral amino alcohol according to the following procedure. To a solution of (*R*)-phenylglycinol (1 g) in CH_2Cl_2 (10 mL), at ambient temperature, were added anhydrous $MgSO_4$ (2 g) and 1 equiv of the appropriate aldehyde. The mixture was stirred at ambient temperature for 12 h. Filtration of the solids by suction followed by concentration under reduced pressure afforded the corresponding 1,3-oxazolidine, which was in equilibrium with the corresponding imino alcohol, in a quantitative way. It was used without purification.

All substrate imines were readily synthesized by condensation of the appropriate aldehyde with the prerequisite amine according to the following procedure. To a solution of the corresponding amine (10 mmol) in CH_2Cl_2 (10 mL), at ambient temperature, were added anhydrous $MgSO_4$ (2 g) and 1 equiv of the appropriate aldehyde. The mixture was stirred at ambient temperature for 12 h. Filtration of the solids by suction followed by concentration under reduced pressure afforded the corresponding imine in a quantitative way. It was used without purification.

4.2. Typical procedures for Reformatsky reactions

Procedure A: To a suspension of freshly acid washed zinc dust[39] (1.34 g, 20.5 mmol) in dry THF (4 mL) were added chlorotrimethylsilane (130 μL, 5 mol %) and 1,2-dibromoethane (90 μL, 5 mol %). The mixture was stirred at room temperature for 10 min. Controlled addition of a solution of ethyl bromodifluoroacetate (3.05 g, 15 mmol) was performed with a syringe. A temperature of ca. 50 °C was maintained during the addition (self-heating). The reaction mixture was allowed to stir at room temperature for 10 min after the end of the addition. The corresponding imine (4.3 mmol) in THF (4 mL) was added. The reaction mixture was then heated to reflux for 2 h. The reaction mixture was allowed to cool to 25 °C and quenched by the addition of saturated NH_4Cl solution (10 mL). After filtration, the aqueous layer was extracted with EtOAc (2×25 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum. The residue was then purified by flash chromatography.

Procedure B: This typical procedure is a modification of a literature procedure[29] as followed: To a suspension of freshly activated zinc dust (1.73 g, 26.5 mmol) in dry THF (6 mL) was added bis(cyclopentadienyl)titanium dichloride (110 mg, 5 mol %). The mixture was stirred at room temperature for 10 min. Controlled addition of a solution of ethyl bromodifluoroacetate (3.75 g, 18.5 mmol) and the

corresponding imine (8.8 mmol) in THF (6 mL) was performed with a syringe. A temperature of ca. 50 °C was maintained during the addition (self-heating). The reaction mixture was allowed to stir at room temperature for 1 h after the addition was complete. The reaction mixture was quenched by the addition of saturated NH_4Cl solution (10 mL). After filtration, the aqueous layer was extracted with EtOAc (2×25 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum. The residue was then purified by flash chromatography.

Procedure C: This typical procedure is a modification of a literature procedure[27] as followed: under an argon atmosphere, to a solution of ethyl bromodifluoroacetate (2.4 g, 11.8 mmol) and $RhCl(PPh_3)_3$ (54 mg, 2 mol %) in acetonitrile (24 mL) was added a solution of diethylzinc in hexane (1 M, 12 mL, 12 mmol) at 0 °C in 1 h. After 30 min, the solution of the corresponding imine (3 mmol) in acetonitrile (4 mL) was added at room temperature and the reaction mixture was then stirred at the same temperature for 5 h. The reaction mixture was worked-up as usual. The residue was then purified by flash chromatography.

4.2.1. (*S*)-3,3-Difluoro-1-((*R*)-2-hydroxy-1-phenylethyl)-4-(thiophen-3-yl)azetidin-2-one (3b). This compound was prepared by the above General Procedure A, using 3-thiophenecarboxaldehyde (0.48 g, 4.3 mmol), (*R*)-phenylglycinol (0.59 g, 4.3 mmol), zinc (1.34 g, 20.5 mmol), ethyl bromodifluoroacetate (3.05 g, 15 mmol), and THF (8 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (10:0–7:3) to give the product as a yellow oil, yield 71% (0.95 g); $[\alpha]_D^{25}$ +21.1 (*c* 0.70, MeOH); TLC: silica gel, 1:1 cyclohexane/CH_2Cl_2, R_f 0.26; IR (KBr) 3434, 1778, 1329, 1301, 1202, 1103, 1065, 757, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.30–7.05 (m, 7H), 6.84 (dd, 1H, *J*=1 and 5 Hz), 4.89 (dd, 1H, *J*=2.5 and 7.5 Hz), 4.63 (dd, 1H, *J*=5 and 9 Hz), 4.04 (dd, 1H, *J*=9 and 12 Hz), 3.75 (dd, 1H, *J*=5 and 12 Hz), 2.66 (br d, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 161.8 (t, *J*=31 Hz), 134.7, 132.2, 128.9, 128.7, 127.8, 126.9, 126.6, 119.6 (t, *J*=290 Hz), 65.8 (t, *J*=25 Hz), 63.3, 61.8; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −115.5 (dd, *J*=8 and 226 Hz), −121.5 (dd, *J*=2 and 226 Hz); HRMS (CI^+) calcd for $C_{15}H_{13}F_2NO_2S$: 310.0714. Found: 310.0736. Anal. Calcd for $C_{15}H_{13}F_2NO_2S$: C, 58.24; H, 4.24; N, 4.53; S, 10.37. Found: C, 58.31; H, 4.31; N, 4.58; S, 10.52.

4.2.2. (*S*)-Ethyl 3-((*R*)-2-hydroxy-1-phenylethylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (4d). This compound was prepared by the above General Procedure A, using 4-pyridinecarboxaldehyde (0.945 g, 8.8 mmol), (*R*)-phenylglycinol (1.21 g, 8.8 mmol), zinc (2.3 g, 35.2 mmol), ethyl bromodifluoroacetate (5.36 g, 26.4 mmol), and THF (25 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–97:3:0.3) to give the product as a pale yellow solid, yield 67% (2.07 g); mp=109 °C; $[\alpha]_D^{25}$ −6.2 (*c* 1.08, $CHCl_3$); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.26; IR (KBr) 3349, 1770, 1619, 1604, 1493, 1454, 1419, 1374, 1323, 1283, 1203, 1127, 1065, 762, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.49 (d, 2H, *J*=6 Hz), 7.2–7.1 (m, 5H), 7.1–7.0 (m, 2H), 4.43 (dd, 1H, *J*=7.5 and 19 Hz), 4.32 (q, 2H, *J*=7 Hz), 3.77 (dd, 1H, *J*=4.5 and 7.5 Hz), 3.67 (dd, 1H, *J*=4.5 and 11 Hz), 3.60 (dd, 1H, *J*=7.5 and 11 Hz), 3.0–2.3 (2 br s, 2H), 1.31 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 163.6 (dd, *J*=31 and 32.5 Hz), 149.4, 145.5, 139.7, 128.7, 128.2, 127.3, 124.2, 114.8 (dd, *J*=256 and 258.5 Hz), 66.6, 63.5, 63.4, 62.0 (dd, *J*=22 and 26 Hz), 14.0; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −108.2 (dd, *J*=6 and 261 Hz), −119.2 (dd, *J*=19 and 261 Hz); MS (CI^+) 351 ($[M+H]^+$); MS (ESI^+) 351.21 ($[M+H]^+$); HRMS (CI^+) calcd for $C_{18}H_{21}F_2N_2O_3$: 351.1520. Found: 351.1518. Anal. Calcd for $C_{18}H_{20}F_2N_2O_3$: C, 61.71; H, 5.75; N, 8.00. Found: C, 61.02; H, 5.85; N, 7.82.

4.2.3. (*S*)-Ethyl 3-((*R*)-2-hydroxy-1-phenylethylamino)-2,2-difluoro-3-(pyridin-3-yl)propanoate (4e). This compound was prepared by the above General Procedure B, using 3-pyridinecarboxaldehyde (0.945 g, 8.8 mmol), (*R*)-phenylglycinol (1.21 g, 8.8 mmol), zinc (2.3 g, 35.2 mmol), ethyl bromodifluoroacetate (5.36 g, 26.4 mmol), bis(cyclopentadienyl)titanium dichloride (110 mg), and THF (17 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–96:4:0.4) to give the product as an orange oil, yield 49% (1.51 g); $[\alpha]_D^{25}$ −16.7 (*c* 0.86, $CHCl_3$); TLC: silica gel, 90:10:1 CH_2Cl_2/MeOH/NH_4OH, R_f 0.42; IR (KBr) 3339, 3255, 1770, 1586, 1581, 1455, 1430, 1374, 1292, 1204, 1125, 1066, 1030, 762, 735, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.43 (dd, 1H, *J*=1 and 5 Hz), 8.34 (br d, 1H), 7.49 (d, 1H, *J*=8 Hz), 7.5–7.1 (m, 4H), 7.05–7.00 (m, 2H), 4.39 (dd, 1H, *J*=8 and 19 Hz), 4.29 (q, 2H, *J*=7 Hz), 3.75 (dd, 1H, *J*=4.5 and 7 Hz), 3.65 (dd, 1H, *J*=4.5 and 11 Hz), 3.56 (dd, 1H, *J*=7.5 and 11 Hz), 2.61 (br d, 1H), 2.28 (br d, 1H), 1.28 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 163.7 (dd, *J*=31 and 33 Hz), 149.9, 149.7, 139.8, 136.0, 130.8, 128.7, 128.0, 127.1, 123.4, 115.0 (t, *J*=259 Hz), 66.3, 63.3, 63.2, 60.8 (dd, *J*=22 and 27 Hz), 13.9; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −108.5 (dd, *J*=7.5 and 260 Hz), −119.2 (dd, *J*=19.5 and 260 Hz); MS (CI^+) 351 ($[M+H]^+$); MS (ESI^+) 351.20 ($[M+H]^+$); HRMS (CI^+) calcd for $C_{18}H_{21}F_2N_2O_3$: 351.1521. Found: 351.1518.

4.2.4. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-phenylazetidin-2-one (3f) and (*S*)-ethyl 3-((*R*)-2-methoxy-1-phenylethylamino)-2,2-difluoro-3-phenylpropanoate (4f). These compounds were prepared by the above General Procedure A, using benzaldehyde (0.50 g, 4.7 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.71 g, 4.7 mmol), zinc (0.92 g, 14.1 mmol), ethyl bromodifluoroacetate (1.9 g, 9.35 mmol), and THF (9 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (100:0–80:20) to give the product as a colorless oil, yield 53% (0.80 g); $[\alpha]_D^{25}$ +48.4 (*c* 1.44, $CHCl_3$); TLC: silica gel, 8:2 cyclohexane/EtOAc, R_f 0.61; IR (KBr) 1788, 1498, 1457, 1301, 1202, 1121, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) (β-lactam) 7.45–7.35 (m, 6H), 7.35–7.15 (m, 4H), 4.91 (dd, 1H, *J*=4.5 and 9.5 Hz), 4.82 (dd, 1H, *J*=2 and 8 Hz), 3.81 (t, 1H, 10 Hz), 3.49 (dd, 1H, *J*=4.5 and 10 Hz), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) (β-lactam) 161.6 (t, *J*=30.5 Hz), 134.9, 131.5, 129.7, 129.0, 128.7, 128.6, 128.3, 127.9, 119.9 (dd, *J*=288 and 292.5 Hz), 72.1, 69.8 (dd, *J*=24 and 26.5 Hz), 58.7, 58.1; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −115.4 (dd, *J*=7.5 and

229.5 Hz), −121.8 (d, *J*=229.5 Hz); (minor diastereomer of β-lactam) −115.1 (dd, *J*=7.5 and 229 Hz), −122.8 (d, *J*=229 Hz); MS (CI^+) 318 ($[M+H]^+$). Anal. Calcd for $C_{18}H_{17}F_2NO_2$: C, 68.13; H, 5.40; N, 4.41. Found: C, 68.09; H, 5.39; N, 4.37; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-aminoester) −111.4 (dd, *J*=10 and 259 Hz), −116.3 (dd, *J*=18.5 and 260 Hz); (minor diastereomer of β-aminoester) −110.8 (dd, *J*=10 and 261 Hz), −117.0 (dd, *J*=17.5 and 261 Hz).

4.2.5. (*R*)-3,3-Difluoro-4-phenyl-1-((*R*)-1-phenylethyl)-azetidin-2-one (3g) and (*R*)-ethyl 3-((*R*)-1-phenylethylamino)-2,2-difluoro-3-phenylpropanoate (4g). These compounds were prepared by the above General Procedure A, using benzaldehyde (0.64 g, 6 mmol), (*R*)-α-methylbenzylamine (0.73 g, 6 mmol), zinc (1.18 g, 18 mmol), ethyl bromodifluoroacetate (2.44 g, 12 mmol), and THF (15 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (95:5–85:15) to give the mixture of products as a colorless oil, yield 61% (1.08 g); $[\alpha]_D^{25}$ +29.6 (*c* 1.62, $CHCl_3$); TLC: silica gel, 8:2 cyclohexane/EtOAc, R_f 0.43; IR (KBr) 1784, 1634, 1496, 1456, 1380, 1300, 1200, 1109, 1071, 1026, 766, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) (major diastereomer of β-lactam) 7.4–7.1 (m, 10H), 5.11 (q, 1H, *J*=7 Hz), 4.58 (dd, 1H, *J*=2 and 8.5 Hz), 1.40 (d, 3H, *J*=7 Hz) and (minor diastereomer of β-lactam) 7.4–7.1 (m, 10H), 4.65 (dd, 1H, *J*=2 and 7.5 Hz), 4.38 (dq, 1H, *J*=1 and 7 Hz), 1.87 (d, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) (mixture of diastereomers of β-lactams) 161.3 (t, *J*=30.5 Hz), 161.1 (t, *J*=30.5 Hz), 139.6, 138.1, 131.9, 130.5, 129.9, 129.8, 129.1, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 127.5, 126.9, 120.0 (dd, *J*=288.5 and 292 Hz), 68.4 (dd, *J*=23 and 26 Hz), 68.3 (dd, *J*=24 and 26 Hz), 54.9, 52.8, 20.0, 19.2; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −115.5 (dd, *J*=8.5 and 224.5 Hz), −122.8 (d, *J*=224.5 Hz); (minor diastereomer of β-lactam) −115.8 (dd, *J*=7.5 and 224.5 Hz), −121.5 (d, *J*=224.5 Hz); (major diastereomer of β-aminoester) −108.2 (dd, *J*=6.5 and 257 Hz), −121.8 (dd, *J*=22.5 and 257 Hz); (minor diastereomer of β-aminoester) −108.4 (dd, *J*=7.5 and 255.5 Hz), −121.1 (dd, *J*=20.5 and 255.5 Hz); MS (CI^+) 334 ($[M'+H]^+$), 288 ($[M+H]^+$).

4.2.6. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(pyridin-4-yl)azetidin-2-one (3i) and (*S*)-ethyl 3-((*R*)-2-methoxy-1-phenylethylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (4i). These compounds were prepared by the above General Procedure A, using 4-pyridinecarboxaldehyde (0.50 g, 4.7 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.71 g, 4.7 mmol), zinc (0.92 g, 14.1 mmol), ethyl bromodifluoroacetate (1.9 g, 9.35 mmol), and THF (9 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/EtOAc (9:1–8:2) to give the mixture of products as a pale yellow oil, yield 65% (0.86 g); mp=160 °C (dec); $[\alpha]_D^{25}$ +52.9 (*c* 0.85, $CHCl_3$); TLC: silica gel, 9:1 CH_2Cl_2/EtOAc, R_f 0.35; IR (KBr) 1790, 1622, 1432, 1299, 1201, 1111, 1070, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) (major diastereomer of β-lactam) 8.83 (d, 2H, *J*=6 Hz), 7.43 (d, 2H, *J*=6 Hz), 7.4–7.1 (m, 5H), 4.96 (dd, 1H, *J*=2 and 7.5 Hz), 4.84 (dd, 1H, *J*=4.5 and 10 Hz), 3.91 (t, 1H, *J*=10 Hz), 3.55 (dd, 1H, *J*=4.5 and 10 Hz), 3.29 (s, 3H); (major diastereomer of β-aminoester) 8.74 (d, 2H, *J*=6 Hz), 7.46 (d, 2H, *J*=6 Hz), 7.4–7.1 (m, 5H), 4.95–4.90 (m, 1H), 4.37 (q, 2H, *J*=7 Hz), 4.0–3.9 (m, 1H), 3.50–3.35 (m, 2H), 3.35 (s, 3H), 2.7 (br d, 1H), 1.36 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) (major diastereomer of β-lactam) 160.8 (t, *J*=30 Hz), 149.1, 145.2, 134.4, 129.2, 129.1, 127.6, 124.3, 119.4 (dd, *J*=292 and 294 Hz), 71.8, 68.4 (dd, *J*=23 and 26.5 Hz), 59.2, 58.7; (major diastereomer of β-aminoester) 162.8 (dd, *J*=30.5 and 32 Hz), 148.2, 145.2, 139.0, 128.6, 128.1, 127.4, 125.9, 114.5 (dd, *J*=257 and 260 Hz), 77.6, 66.4 (dd, *J*=25.5 and 27 Hz), 63.3, 61.0, 58.7, 13.8; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −114.1 (dd, *J*=7.5 and 223.5 Hz), −119.8 (d, *J*=223.5 Hz); (minor diastereomer of β-lactam) −113.6 (dd, *J*=6.5 and 223.5 Hz), −120.7 (d, *J*=223.5 Hz); (major diastereomer of β-aminoester) −107.4 (dd, *J*=7.5 and 261 Hz), −117.8 (dd, *J*=18.5 and 261 Hz); (minor diastereomer of β-aminoester) −105.5 (dd, *J*=4.5 and 261 Hz), −122.5 (dd, *J*=22.5 and 261 Hz); MS (CI^+) 319 ($[M+H]^+$).

4.2.7. (*R*)-3,3-Difluoro-1-((*R*)-1-phenylethyl)-4-(pyridin-4-yl)azetidin-2-one (3j) and (*R*)-ethyl 3-((*R*)-1-phenylethylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (4j). These compounds were prepared by the above General Procedure A, using 4-pyridinecarboxaldehyde (1 g, 9.3 mmol), (*R*)-α-methylbenzylamine (1.13 g, 9.3 mmol), zinc (1.82 g, 27.8 mmol), ethyl bromodifluoroacetate (3.78 g, 18.6 mmol), and THF (36 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–98:2:0.2) to give the mixture of products as a yellow oil, yield 93% (2.51 g); $[\alpha]_D^{25}$ +35.3 (*c* 1.82, $CHCl_3$); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.51; IR (KBr) 1790, 1622, 1433, 1380, 1297, 1200, 1110, 1070, 1029, 703, 546 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) (major diastereomer of β-lactam) 8.64 (d, 2H, *J*=6 Hz), 7.1–7.0 (m, 3H), 7.0–6.9 (m, 4H), 4.70 (dd, 1H, *J*=1.5 and 7.5 Hz), 4.55 (q, 1H, *J*=7 Hz), 1.84 (d, 3H, *J*=7 Hz) and (minor diastereomer of β-lactam) 8.68 (d, 2H, *J*=6 Hz), 7.15–7.10 (m, 3H), 7.1–7.0 (m, 2H), 7.0–6.9 (m, 2H), 4.60 (dd, 1H, *J*=1.5 and 8 Hz), 4.37 (q, 1H, *J*=7 Hz), 1.49 (d, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) (mixture of diastereomers of β-lactams) 160.3 (t, *J*=30.5 Hz), 149.7, 143.2, 142.0, 138.5, 137.6, 129.2, 128.9, 127.3, 126.9, 123.9, 123.6, 119.6 (dd, *J*=291.5 and 294.5 Hz), 119.5 (dd, *J*=291.5 and 294.5 Hz), 67.0 (dd, *J*=23.5 and 27 Hz), 66.6 (dd, *J*=23.5 and 27 Hz), 54.9, 53.8, 19.3, 19.2; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −114.5 (dd, *J*=8 and 224 Hz), −121.1 (d, *J*=224 Hz); (minor diastereomer of β-lactam) −114.8 (dd, *J*=8 and 224 Hz), −120.2 (d, *J*=224 Hz); (major diastereomer of β-aminoester) −106.6 (dd, *J*=4.5 and 260.5 Hz), −121.5 (dd, *J*=22 and 260.5 Hz); (minor diastereomer of β-aminoester) −106.8 (dd, *J*=5.5 and 260.5 Hz); MS (CI^+) 335 ($[M'+H]^+$), 289 ($[M+H]^+$); MS (ESI^+) 335.13 ($[M'+H]^+$), 289.20 ($[M+H]^+$); HRMS (CI^+) calcd for $C_{16}H_{15}F_2N_2O$: 289.1152. Found: 289.1169.

4.2.8. 1-(4-Methoxybenzyl)-3,3-difluoro-4-(pyridin-4-yl)azetidin-2-one (3k) and ethyl 3-(4-methoxybenzylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (4k). These compounds were prepared by the above General Procedure A, using 4-pyridinecarboxaldehyde (0.50 g, 4.65 mmol), *p*-methoxylbenzylamine (0.64 g, 4.65 mmol),

zinc (0.9 g, 14 mmol), ethyl bromodifluoroacetate (1.85 g, 9.1 mmol), and THF (9 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–98:2:0.2) to give the mixture of products as a yellow oil, yield 85% (1.21 g); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.32; IR (KBr) 1794, 1693, 1673, 1613, 1514, 1432, 1300, 1251, 1200, 1114, 1052, 1032, 822, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.66 (d, 2H, J=4.5 Hz), 7.14 (d, 2H, J=4.5 Hz), 7.00 (d, 2H, J=8.5 Hz), 6.81 (d, 2H, J=8.5 Hz), 4.87 (d, 1H, J=14.5 Hz), 4.64 (dd, 1H, J=2 and 7 Hz), 3.93 (dd, 1H, J=2 and 14.5 Hz), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 160.3 (t, J=31 Hz), 159.8, 150.3, 139.8, 130.0, 124.6, 122.7, 120.1 (t, J=292 Hz), 114.5, 66.5 (dd, J=23.5 and 26.5 Hz), 55.3, 44.3; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (β-lactam) −114.0 (dd, J=7.5 and 223.5 Hz), −120.6 (d, J=223.5 Hz); (β-aminoester) −106.7 (dd, J=4.5 Hz and J=261 Hz), −120.4 (dd, J=21 and 261 Hz); MS (CI^+) 305 ($[M+H]^+$); MS (ESI^+) 351 ($[M'+H]^+$), 305 ($[M+H]^+$).

4.2.9. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(pyridin-3-yl)azetidin-2-one (3l) and (*S*)-ethyl 3-((*R*)-2-methoxy-1-phenylethylamino)-2,2-difluoro-3-(pyridin-3-yl)propanoate (4l). These compounds were prepared by the above General Procedure A, using 3-pyridinecarboxaldehyde (0.54 g, 5 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.76 g, 5 mmol), zinc (0.98 g, 15 mmol), ethyl bromodifluoroacetate (2.03 g, 10 mmol), and THF (15 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–96:4:0.4) to give the mixture of products as a pale yellow oil, quantitative yield (1.76 g); $[\alpha]_D^{25}$ +23.0 (*c* 1.51, $CHCl_3$); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.64; IR (KBr) 1789, 1660, 1455, 1301, 1202, 1119, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) (β-lactam) 8.70 (dd, 1H, J=1 and 5 Hz), 8.55 (s, 1H), 7.68 (dd, 1H, J=2 and 8 Hz), 7.35 (dd, 1H, J=5 and 8 Hz), 7.35–7.30 (m, 3H), 7.20–7.15 (m, 2H), 4.9–4.8 (m, 2H), 3.76 (t, 1H, J=10 Hz), 3.48 (dd, 1H, J=4.5 and 10 Hz), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) (β-lactam) 161.2 (t, J=30.5 Hz), 150.8, 149.5, 137.4, 134.7, 129.4, 129.2, 128.8, 127.9, 124.2, 119.8 (dd, J=291 and 292.5 Hz), 71.9, 67.3 (dd, J=23.5 and 27 Hz), 58.9, 58.6; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −115.1 (dd, J=7.5 and 225.5 Hz), −121.1 (d, J=225.5 Hz); (minor diastereomer of β-lactam) −114.7 (dd, J=6.5 and 225 Hz), −122.0 (d, J=225 Hz); (major diastereomer of β-aminoester) −109.0 (dd, J=8.5 and 259 Hz), −117.5 (dd, J=17 and 259 Hz); (minor diastereomer of β-aminoester) −105.9 (dd, J=8 and 260 Hz); MS (ESI^+) 365.33 ($[M'+H]^+$), 319.47 ($[M+H]^+$); MS (CI^+) 365 ($[M'+H]^+$), 319 ($[M+H]^+$); HRMS (CI^+) calcd for $C_{17}H_{17}F_2N_2O_2$: 319.1258. Found: 319.1278.

4.2.10. (*R*)-3,3-Difluoro-1-((*R*)-1-phenylethyl)-4-(pyridin-3-yl)azetidin-2-one (3m) and (*R*)-ethyl 3-((*R*)-1-phenylethylamino)-2,2-difluoro-3-(pyridin-3-yl)propanoate (4m). These compounds were prepared by the above General Procedure A, using 3-pyridinecarboxaldehyde (0.64 g, 6 mmol), (*R*)-α-methylbenzylamine (0.73 g, 6 mmol), zinc (1.18 g, 18 mmol), ethyl bromodifluoroacetate (2.44 g, 12 mmol), and THF (15 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–97:3:0.3) to give the mixture of products as an orange oil, yield 67% (1.18 g); $[\alpha]_D^{25}$ +39.0 (*c* 2.60, $CHCl_3$); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.48; IR (KBr) 1788, 1682, 1598, 1580, 1495, 1455, 1435, 1380, 1299, 1201, 1111, 1025, 868, 763, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) (major diastereomer of β-lactam) 8.62 (dd, 1H, J=1.5 and 5 Hz), 8.41 (d, 1H, J=2 Hz), 7.45 (m, 1H), 7.35–7.20 (m, 4H), 7.15–7.05 (m, 2H), 4.73 (dd, 1H, J=2 and 7 Hz), 4.53 (dq, 1H, J=1 and 7 Hz), 1.82 (d, 3H, J=7 Hz); (major diastereomer of β-lactam) 8.66 (dd, 1H, J=1.5 and 5 Hz), 8.43 (d, 1H, J=2 Hz), 7.59 (m, 1H), 7.35–7.20 (m, 4H), 7.15–7.05 (m, 2H), 5.06 (q, 1H, J=7 Hz), 4.60 (dd, 1H, J=2 and 8 Hz), 1.45 (d, 3H, J=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) (major diastereomer of β-lactam) 160.5 (t, J=30.5 Hz), 150.7, 149.4, 138.6, 136.6, 129.2, 128.7, 127.4, 126.9, 124.1, 119.8 (t, J=291 Hz), 65.8 (dd, J=23.5 and 27 Hz), 54.5, 19.3; (minor diastereomer of β-lactam) 161.2 (t, J=31 Hz), 150.9, 149.6, 137.6, 136.9, 129.2, 128.9, 127.4, 127.3, 124.0, 119.8 (t, J=291 Hz), 65.9 (dd, J=23 and 27 Hz), 53.4, 19.1; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −115.1 (dd, J=7.5 and 231 Hz), −121.9 (d, J=231 Hz); (minor diastereomer of β-lactam) −115.4 (dd, J=9 and 230 Hz), −120.1 (d, J=230.5 Hz); (major diastereomer of β-aminoester) −107.1 (dd, J=5.5 and 264.5 Hz), −121.4 (dd, J=23 and 265.5 Hz); (minor diastereomer of β-aminoester) −107.5 (dd, J=6.5 and 264.5 Hz); MS (ESI^+) 335.20 ($[M'+H]^+$), 289.33 ($[M+H]^+$); MS (CI^+) 335 ($[M'+H]^+$), 289 ($[M+H]^+$).

4.2.11. 1-(4-Methoxybenzyl)-3,3-difluoro-4-(pyridin-3-yl)azetidin-2-one (3n) and ethyl 3-(4-methoxybenzylamino)-2,2-difluoro-3-(pyridin-3-yl)propanoate (4n). These compounds were prepared by the above General Procedure A, using 3-pyridinecarboxaldehyde (0.50 g, 4.65 mmol), *p*-methoxylbenzylamine (0.64 g, 4.65 mmol), zinc (0.92 g, 14 mmol), ethyl bromodifluoroacetate (1.89 g, 9.3 mmol), and THF (9 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–98:2:0.2) to give the mixture of products as a yellow oil, yield 86% (1.2 g); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.49; IR (KBr) 1788, 1498, 1458, 1389, 1301, 1202, 1121, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.70 (d, 1H, J=4.5 Hz), 8.5 (br d, 1H), 7.60 (d, 1H, J=8 Hz), 7.40 (dd, 1H, J=5 and 7.5 Hz), 6.99 (d, 2H, J=8.5 Hz), 6.80 (d, 2H, J=8.5 Hz), 4.80 (d, 1H, J=14.5 Hz), 4.73 (dd, 1H, J=2 and 7 Hz), 3.95 (dd, 1H, J=2 and 14.5 Hz), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 160.3 (t, J=30.5 Hz), 159.8, 150.65, 149.15, 136.7, 130.1, 127.4, 124.6, 124.3, 120.3 (t, J=292.5 Hz), 114.6, 65.4 (dd, J=23.5 and 27 Hz), 55.3, 44.3; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (β-lactam) −114.4 (dd, J=7.5 and 224.5 Hz), −121.1 (d, J=224.5 Hz); (β-aminoester) −107.8 (dd, J=6.5 and 264.5 Hz), −120.2 (dd, J=20.5 and 260 Hz); MS (CI^+) 305 ($[M+H]^+$); HRMS (CI^+) calcd for $C_{16}H_{15}F_2N_2O_2$: 305.1130. Found: 305.1122.

4.2.12. 1-(4-Methoxybenzyl)-4-(pyridin-4-yl)azetidin-2-one (6). This compound was prepared by the above General Procedure A, using 4-pyridinecarboxaldehyde (0.235 g, 2.2 mmol), *p*-methoxylbenzylamine (0.30 g, 2.2 mmol), zinc (0.39 g, 4 mmol), ethyl bromoacetate (0.67 g, 4 mmol), and THF (4.5 mL). The crude product was purified

by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–95:5:0.5) to give the product as a yellow oil, yield 46% (0.27 g); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.33; IR (KBr) 1748, 1614, 1514, 1434, 1392, 1304, 1248, 1177, 1031, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.58 (d, 2H, J=6 Hz), 7.19 (d, 2H, J=6 Hz), 6.95 (d, 2H, J=8.5 Hz), 6.72 (d, 2H, J=8.5 Hz), 4.63 (d, 1H, J=14.5 Hz), 4.33 (dd, 1H, J=2.5 and 5.5 Hz), 3.78 (d, 1H, J=14.5 Hz), 3.69 (s, 3H), 3.32 (dd, 1H, J=5.5 and 14.5 Hz), 2.74 (dd, 1H, J=2.5 and 14.5 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 165.7, 158.7, 149.3, 149.0, 129.3, 126.1, 113.6, 54.7, 51.5, 46.1, 44.2; MS (CI^+) 269 ([M+H]$^+$).

4.2.13. 3,3-Difluoro-1-(4-methoxyphenyl)-4-(pyridin-4-yl)azetidin-2-one (9a) and ethyl 3-(4-methoxyphenylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (10a). These compounds were prepared by the above General Procedure A, using pyridine-4-carboxaldehyde (0.50 g, 4.7 mmol), *p*-anisidine (0.58 g, 4.7 mmol), zinc (0.83 g, 12.7 mmol), ethyl bromodifluoroacetate (1.69 g, 8.35 mmol), and THF (9 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–97:3:0.3) to give the product as an orange oil, yield 82% (1.15 g); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.34.

Mixture of products: ^{19}F NMR ($CDCl_3$, 288.3 MHz) −106.6 (d, J=267.5 Hz), −112.2 (dd, J=6.5 and 229.5 Hz), −118.0 (d, J=229.5 Hz), −120.0 (dd, J=21 and 267.5 Hz); MS (ESI^+) 337.33 ([M′+H]$^+$), 291.27 ([M+H]$^+$).

Azetidin-2-one: IR (KBr) 1781, 1621, 1514, 1394, 1308, 1299, 1252, 1158, 1031, 831, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.71 (d, 2H, J=6 Hz), 7.33 (d, 2H, J=6 Hz), 7.20 (d, 2H, J=9 Hz), 6.82 (d, 2H, J=9 Hz), 5.39 (dd, 1H, J=1 and 7 Hz), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 157.8, 156.5 (t, J=31.5 Hz), 150.2, 141.0, 128.4, 122.9, 119.5, 115.6, 114.8 (t, J=264.5 Hz), 67.5 (dd, J=24.5 and 27 Hz), 55.6; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −113.0 (dd, J=7.5 and 225.5 Hz), −118.7 (d, J=224.5 Hz); MS (CI^+) 291 ([M+H]$^+$); HRMS (CI^+) calcd for $C_{15}H_{13}F_2N_2O_2$: 291.0945. Found: 291.0950.

4.2.14. Ethyl 3-(2-methoxyphenylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (10b). This compound was prepared by the above General Procedure A, using pyridine-4-carboxaldehyde (0.64 g, 6 mmol), *o*-anisidine (0.74 g, 6 mmol), zinc (1.18 g, 18 mmol), ethyl bromodifluoroacetate (2.44 g, 12 mmol), and THF (15 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–98:2:0.2) to give the product as an orange oil, yield 42% (0.69 g); TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.55; IR (KBr) 3386, 1770, 1715, 1682, 1615, 1603, 1514, 1505, 1463, 1434, 1373, 1284, 1253, 1221, 1179, 1138, 1026, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.78 (d, 2H, J=6 Hz), 7.57 (d, 2H, J=6 Hz), 6.80–6.65 (m, 3H), 6.45–6.35 (m, 1H), 5.3–5.1 (m, 1H), 5.03 (d, 1H, J=10.5 Hz), 4.30 (q, 2H, J=7 Hz), 3.86 (s, 3H), 1.26 (t, 3 H, J=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 162.5 (dd, J=30 and 33 Hz), 149.0, 148.2, 147.5, 133.8, 125.2, 121.2, 119.8, 113.8 (dd, J=257 and 260.5 Hz), 111.8, 110.4, 63.9, 59.2 (dd, J=23 and 28 Hz), 55.7, 13.9; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −106.5 (dd, J=5.5 and 261 Hz), −121.0 (dd, J=20.5 and 262 Hz); MS (ESI^+) 337.33 ([M+H]$^+$).

4.2.15. 3,3-Difluoro-1-(4-fluorophenyl)-4-(pyridin-4-yl)-azetidin-2-one (9c) and ethyl 3-(4-fluorophenylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (10c). These compounds were prepared by the above General Procedure A, using pyridine-4-carboxaldehyde (0.535 g, 5 mmol), 4-fluoroaniline (0.555 g, 5 mmol), zinc (0.88 g, 13.4 mmol), ethyl bromodifluoroacetate (1.8 g, 8.85 mmol), and THF (10 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–97:3:0.3) to give the product as an orange oil, yield 57% (0.82 g); mp=125 °C; TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.3.

Mixture of compounds: ^{19}F NMR ($CDCl_3$, 288.3 MHz) −106.4 (dd, J=5.5 and 267 Hz), −112.8 (dd, J=6.5 and 230 Hz), −114.35 (m), −118.7 (d, J=230 Hz), −121.3 (dd, J=21 and 267 Hz).

Azetidin-2-one: IR (KBr) 1790, 1602, 1513, 1420, 1392, 1316, 1231, 1158, 1109, 1010, 834, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.64 (d, 2H, J=6 Hz), 7.25–7.15 (m, 4H), 6.97 (dd, 2H, J=8 and 9 Hz), 5.32 (dd, 1H, J=1.5 and 7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 160.4 (d, J=247 Hz), 157.0 (t, J=31.5 Hz), 150.7, 139.1, 131.5 (d, J=3.5 Hz), 122.3, 119.7 (d, J=8 Hz), 119.6 (dd, J=289 and 291.5 Hz), 116.8 (d, J=23 Hz), 67.9 (dd, J=24.5 and 27 Hz); ^{19}F NMR ($CDCl_3$, 288.3 MHz) −113.1 (dd, J=7.5 and 225 Hz), −114. 5 (m), −118.7 (d, J=225 Hz); MS (CI^+) 279 ([M+H]$^+$); MS (ESI^+) 279.24 ([M+H]$^+$). Anal. Calcd for $C_{14}H_9F_3N_2O$: C, 60.44; H, 3.26; N, 10.07. Found: C, 60.22; H, 3.25; N, 9.98.

4.2.16. 3,3-Difluoro-1-(4-(trifluoromethyl)phenyl)-4-(pyridin-4-yl)azetidin-2-one (9d) and ethyl 3-(4-(trifluoromethyl)phenylamino)-2,2-difluoro-3-(pyridin-4-yl)propanoate (10d). These compounds were prepared by the above General Procedure A, using pyridine-4-carboxaldehyde (0.536 g, 5 mmol), 4-aminobenzotrifluoride (0.810 g, 5 mmol), zinc (0.98 g, 15 mmol), ethyl bromodifluoroacetate (2.03 g, 10 mmol), and THF (15 mL). The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH/NH_4OH (99:1:0.1–97:3:0.3) to give the product as an orange oil, yield 51% (0.91 g). TLC: silica gel, 95:5:0.5 CH_2Cl_2/MeOH/NH_4OH, R_f 0.45. Because of their instability, these compounds cannot be purified properly. β-aminoester: IR (KBr) 3296, 1771, 1682, 1615, 1327, 1283, 1114, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 8.55 (d, 2H, J=6 Hz), 7.35–7.20 (m, 4H), 6.60 (d, 2H, J=8.5 Hz), 5.38 (d, 1H, J=9.5 Hz), 5.14 (ddd, 1H, J=2.5, 9.5 and 19.5), 4.20 (q, 2H, J=7 Hz), 1.14 (t, 3H, J=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 162.6 (t, J=30 Hz), 149.8, 147.6, 142.8, 127.1 (q, J=3.5), 124.9 (q, J=271), 123.3, 121.0 (q, J=32.5), 113.5 (t, J=271 Hz), 113.1, 63.6, 58.6 (dd, J=23 and 27.5 Hz), 13.6; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −61.9, −108.5 (dd, J=6.5 and 266.5 Hz), −119.4 (dd, J=20 and 266.5 Hz).

Azetidin-2-one: IR (KBr) 1791, 1614, 1523, 1418, 1388, 1326, 1284, 1157, 1116, 1069, 1010, 838 cm^{-1}; ^1H NMR

(MeOD-d_4, 300.3 MHz) 8.64 (d, 2H, J=6 Hz), 7.68 (d, 2H, J=8.5 Hz), 7.60–7.45 (m, 4H), 5.98 (dd, 1H, J=2 and 7.5 Hz); ^{13}C NMR (MeOD-d_4, 75.4 MHz) 158.5 (t, J=32 Hz), 150.7, 141.4, 139.6, 128.7 (q, J=33), 127.6 (q, J=3.5), 125.2 (q, J=271.5), 123.9, 120.9 (t, J=288 Hz), 119.4, 68.2 (dd, J=24.5 and 27.5 Hz); ^{19}F NMR (MeOD-d_4, 288.3 MHz) −64.3, −115.5 (dd, J=8 and 227 Hz), −121.3 (d, J=227 Hz). MS (CI$^+$) 375 ([M′+H]$^+$), 329 ([M+H]$^+$); MS (ESI$^+$) 375.20 ([M′+H]$^+$), 329.07 ([M+H]$^+$).

4.2.17. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(4-nitrophenyl)azetidin-2-one (12a). This compound was prepared by the above General Procedure A, using 4-nitrobenzaldehyde (0.27 g, 1.8 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.27 g, 1.8 mmol), zinc (0.31 g, 4.7 mmol), ethyl bromodifluoroacetate (0.64 g, 3.1 mmol), and THF (4.5 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (95:5–80:20) to give the product as an orange oil, yield 45% (290 mg); $[\alpha]_D^{25}$ +78.2 (*c* 1.36, $CHCl_3$); TLC: silica gel, 8:2 cyclohexane/EtOAc, R_f 0.27; IR (KBr) 3568, 1790, 1526, 1351, 1303, 1202, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.3 MHz) 8.12 (d, 2H, J=8.5 Hz), 7.37 (d, 2H, J=8.5 Hz), 7.35–7.25 (m, 3H), 7.2–7.1 (m, 2H), 4.88 (dd, 1H, J=2 and 8 Hz), 4.77 (dd, 1H, J=4.5 and 9.5 Hz), 3.79 (t, 1H, J=10), 3.44 (dd, 1H, J=4.5 and 10 Hz), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 160.6 (t, J=30.5 Hz), 148.15, 138.3, 134.2, 128.8, 128.7, 128.5, 126.8, 123.4, 119.2 (dd, J=290.5 and 293.5 Hz), 71.5, 68.6 (dd, J=23.5 and 27 Hz), 58.4, 58.2; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −114.4 (dd, J=7.5 and 228 Hz), −115.0 (dd, J=7.5 and 229 Hz), −120.0 (d, J=228 Hz), −121.8 (d, J=229 Hz); MS (CI$^+$) 363 ([M+H]$^+$). Anal. Calcd for $C_{18}H_{16}F_2N_2O_4$: C, 59.67; H, 4.45; N, 7.73. Found: C, 59.76; H, 4.20; N, 7.48.

4.2.18. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(2-nitrophenyl)azetidin-2-one (12b) and (*S*)-ethyl 3-((*R*)-2-methoxy-1-phenylethylamino)-2,2-difluoro-3-(2-nitrophenyl)propanoate (13b). These compounds were prepared by the above General Procedure A, using 2-nitrobenzaldehyde (0.17 g, 1.1 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.17 g, 1.1 mmol), zinc (0.22 g, 3.3 mmol), ethyl bromodifluoroacetate (0.45 g, 2.2 mmol), and THF (6 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–8:2) to give the product as a pale yellow solid, yield 58% (240 mg); mp=87 °C; $[\alpha]_D^{25}$ −47.7 (*c* 0.88, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.43; IR (KBr) 1790, 1532, 1349, 1303, 1201, 1118, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.3 MHz) 8.2–8.1 (m, 1H), 7.6–7.5 (m, 2H), 7.45–7.30 (m, 6H), 5.60 (dd, 1H, J=1.5 and 7 Hz), 4.56 (dd, 1H, J=4.5 and 10 Hz), 4.09 (t, 1H, J=10 Hz), 3.55 (dd, 1H, J=4.5 and 10 Hz), 3.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 162.5 (dd, J=30 and 31.5 Hz), 148.6, 135.5, 133.9, 130.2, 129.4, 129.3, 129.0, 128.3, 128.1, 119.7 (t, J=291.5 Hz), 72.7, 68.6 (t, J=24.5 Hz), 61.3, 59.0; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −114.7 (dd, J=7.5 and 226.5 Hz), −121.2 (dd, J=2 and 226.5 Hz); (minor diastereomer of β-lactam) −114.8 (dd, J=8.5 and 223.5 Hz), −121.3 (d, J=223.5 Hz); MS (CI$^+$) 363 ([M+H]$^+$). Anal. Calcd for $C_{18}H_{16}F_2N_2O_4$: C, 59.67; H, 4.45; N, 7.73. Found: C, 59.61; H, 4.43; N, 7.69. ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-aminoester) −109.0 (dd, J=7.5 and 258 Hz), −118.8 (dd, J=19.5 and 258 Hz).

4.2.19. 4-((*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-oxoazetidin-2-yl)benzonitrile (12c) and (*S*)-ethyl 3-((*R*)-2-methoxy-1-phenylethylamino)-3-(4-cyanophenyl)-2,2-difluoro propanoate (13c). These compounds were prepared by the above General Procedure A, using 4-cyanobenzaldehyde (0.145 g, 1.1 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.17 g, 1.1 mmol), zinc (0.22 g, 3.3 mmol), ethyl bromodifluoroacetate (0.45 g, 2.2 mmol), and THF (6 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–8:2) to give the product as a colorless oil, yield 63% (240 mg); $[\alpha]_D^{25}$ +86.4 (*c* 1.31, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.41; IR (KBr) 1789, 1612, 1456, 1300, 1202, 1113, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.3 MHz) 7.64 (d, 2H, J=8.5 Hz), 7.4–7.3 (m, 5H), 7.25–7.15 (m, 2H), 4.86 (dd, 1H, J=2 and 8 Hz), 4.80 (dd, 1H, J=4.5 and 9.5 Hz), 3.84 (t, 1H, J=10 Hz), 3.48 (dd, 1H, J=4.5 and 10 Hz), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 161.4 (t, J=30.5 Hz), 137.1, 134.9, 132.5, 129.35, 129.2, 127.9, 119.8 (dd, J=290 and 293 Hz), 118.2, 113.8, 72.1, 69.5 (dd, J=23.5 and 26.5 Hz), 59.0, 58.9; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −111.2 (dd, J=7.5 and 229 Hz), −117.3 (d, J=229 Hz); (minor diastereomer of β-lactam) −110.8 (dd, J=7.5 and 229.5 Hz), −118.2 (d, J=229 Hz); MS (CI$^+$) 343 ([M+H]$^+$). Anal. Calcd for $C_{19}H_{16}F_2N_2O_2$: C, 66,66; H, 4.71; N, 8.18. Found: C, 66.46; H, 4.70; N, 7.76. ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-aminoester) −105.8 (dd, J=8.5 and 262 Hz), −113.5 (dd, J=19.5 and 263.5 Hz); (minor diastereomer of β-aminoester) −102.5 (dd, J=4.5 and 264.5 Hz), −118.9 (dd, J=23 and 265.5 Hz).

4.2.20. (*S*)-3,3-Difluoro-4-(4-(trifluoromethyl)phenyl)-1-((*R*)-2-methoxy-1-phenylethyl)azetidin-2-one (12d). This compound was prepared by the above General Procedure A, using 4-(trifluoromethyl)benzaldehyde (0.19 g, 1.1 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.17 g, 1.1 mmol), zinc (0.22 g, 3.3 mmol), ethyl bromodifluoroacetate (0.45 g, 2.2 mmol), and THF (6 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (95:5–90:10) to give the product as a colorless oil, yield 48% (200 mg); $[\alpha]_D^{25}$ +54.4 (*c* 0.57, $CHCl_3$); TLC: silica gel, 8:2 cyclohexane/EtOAc, R_f 0.40; IR (KBr) 1790, 1622, 1497, 1456, 1427, 1327, 1304, 1203, 1170, 1125, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.3 MHz) 7.54 (d, 2H, J=8 Hz), 7.27 (d, 2H, J=8 Hz), 7.25–7.20 (m, 3H), 7.15–7.05 (m, 2H), 4.76 (dd, 1H, J=2 and 6 Hz), 4.73 (dd, 1H, J=4.5 and 10 Hz), 3.71 (t, 1H, J=10 Hz), 3.37 (dd, 1H, J=4.5 and 10 Hz), 3.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 161.5 (t, J=30.5 Hz), 135.8, 134.9, 131.9 (q, J=33 Hz), 129.3, 129.1, 128.9, 127.9, 125.7 (q, J=3.5 Hz), 123.8 (q, J=272 Hz), 119.9 (dd, J=289 and 292.5 Hz), 72.1, 69.5 (dd, J=23.5 and 26.5 Hz), 58.8, 58.7; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −63.2, −115.1 (dd, J=8.5 and 224.5 Hz), −121.4 (d, J=224.5 Hz); (minor diastereomer of β-lactam) −63.2, −114.7 (dd, J=7.5 and 228 Hz), −122.3 (d, J=229 Hz); MS (CI$^+$) 386 ([M+H]$^+$). Anal. Calcd for $C_{19}H_{16}F_5NO_2$: C, 59.22; H, 4.19; N, 3.64. Found: C, 59.27; H, 4.21; N, 3.59.

4.2.21. (*S*)-3,3-Difluoro-4-(4-fluorophenyl)-1-((*R*)-2-methoxy-1-phenylethyl)azetidin-2-one (12e). This compound was prepared by the above General Procedure A, using 4-fluorobenzaldehyde (0.30 g, 2.4 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.36 g, 2.4 mmol), zinc (0.47 g, 7.2 mmol), ethyl bromodifluoroacetate (0.97 g, 4.8 mmol), and THF (9 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (95:5–90:10) to give the product as a pale yellow oil, yield 63% (510 mg); $[\alpha]_D^{25}$ +44.4 (*c* 1.58, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.54; IR (KBr) 1785, 1608, 1513, 1455, 1303, 1232, 1201, 1120, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.40–7.35 (m, 2H), 7.3–7.2 (m, 4H), 7.05 (t, 2H, *J*=8.5 Hz), 4.88 (dd, 1H, *J*=4.5 and 9.5 Hz), 4.82 (dd, 1H, *J*=2 and 8 Hz), 3.81 (t, 1H, *J*=9.5 Hz), 3.49 (dd, 1H, *J*=4.5 and 10 Hz), 3.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 163.5 (d, *J*=248.5 Hz), 161.5 (t, *J*=30.5 Hz), 134.9, 130.3 (d, *J*=8.5 Hz), 129.1, 128.8, 127.8, 127.3 (d, *J*=3 Hz), 119.9 (dd, *J*=288.5 and 292 Hz), 115.8 (d, *J*=22 Hz), 71.9, 69.1 (dd, *J*=23.5 and 26.5 Hz), 58.7, 58.3; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −111.6, −115.6 (dd, *J*=8.5 and 225 Hz), −122.0 (d, *J*=225 Hz); (minor diastereomer of β-lactam) −111.6, −115.3 (dd, *J*=7.5 and 229.5 Hz), −123.0 (d, *J*=229.5 Hz); MS (CI^+) 336 ($[M+H]^+$). Anal. Calcd for $C_{18}H_{16}F_3NO_2$: C, 64.47; H, 4.81; N, 4.18. Found: C, 64.41; H, 4.67; N, 4.06.

4.2.22. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(2-methoxyphenyl)azetidin-2-one (12f). This compound was prepared by the above General Procedure A, using 2-methoxybenzaldehyde (0.18 g, 1.3 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.20 g, 1.3 mmol), zinc (0.26 g, 4 mmol), ethyl bromodifluoroacetate (0.53 g, 2.6 mmol), and THF (4.5 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–8:2) to give the product as a white solid, yield 60% (270 mg); mp=116 °C; $[\alpha]_D^{25}$ +85.3 (*c* 0.80, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.55; IR (KBr) 1783, 1607, 1498, 1472, 1297, 1251, 1206, 1113, 1022, 762, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.40–7.25 (m, 6H), 7.10 (d, 1H, *J*=7.5 Hz), 6.88 (d, 1H, *J*=8.5 Hz), 6.86 (t, 1H, *J*=7.5 Hz), 5.38 (dd, 1H, *J*=2 and 8.5 Hz), 4.72 (dd, 1H, *J*=4.5 and 9.5 Hz), 3.93 (t, 1H, *J*=10 Hz), 3.79 (s, 3H), 3.50 (dd, 1H, *J*=4.5 and 10 Hz), 3.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 162.4 (t, *J*=30.5 Hz), 157.9, 135.8, 130.5, 129.1, 128.7, 128.2, 120.6, 120.2 (dd, *J*=287.5 and 292 Hz), 110.7, 72.6, 65.2 (dd, *J*=24 and 27 Hz), 59.6, 58.9, 55.7; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −115.9 (dd, *J*=8.5 and 223.5 Hz), −122.2 (d, *J*=223.5 Hz); MS (CI^+) 348 ($[M+H]^+$); MS (ESI^+) 348.02 ($[M+H]^+$). Anal. Calcd for $C_{19}H_{19}F_2NO_3$: C, 65.70; H, 5.51; N, 3.95. Found: C, 65.71; H, 5.48; N, 3.95.

4.2.23. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(4-methoxyphenyl)azetidin-2-one (12g). This compound was prepared by the above General Procedure A, using 4-methoxybenzaldehyde (0.25 g, 1.85 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.28 g, 1.85 mmol), zinc (0.33 g, 5 mmol), ethyl bromodifluoroacetate (0.67 g, 3.3 mmol), and THF (4.5 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–8:2) to give the product as a colorless oil, yield 42% (275 mg); $[\alpha]_D^{25}$ +59.0 (*c* 1.34, $CHCl_3$); TLC: silica gel, 8:2 cyclohexane/EtOAc, R_f 0.34; IR (KBr) 1785, 1614, 1517, 1455, 1305, 1254, 1202, 1123, 1032, 840, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.35–7.30 (m, 3H), 7.25–7.15 (m, 4H), 6.87 (d, 2H, *J*=9 Hz), 4.87 (dd, 1H, *J*=5 and 9.5 Hz), 4.72 (dd, 1H, *J*=2.5 and 8 Hz), 3.80 (s, 3H), 3.75 (t, 1H, *J*=10 Hz), 3.44 (dd, 1H, *J*=5 and 10 Hz), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 161.8 (t, *J*=30.5 Hz), 160.8, 135.0, 1129.9, 129.1, 128.8, 128.1, 123.4, 120.1 (dd, *J*=288.5 and 291.5 Hz), 114.2, 72.2, 69.5 (dd, *J*=24 and 26.5 Hz), 58.9, 58.0, 55.4; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −115.7 (dd, *J*=8.5 and 224.5 Hz), −122.2 (d, *J*=224.5 Hz); MS (CI^+) 348 ($[M+H]^+$).

4.2.24. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-(2,4,6-trimethoxyphenyl) azetidin-2-one (12h). This compound was prepared by the above General Procedure A, using 2,4,6-trimethoxybenzaldehyde (0.26 g, 1.3 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.20 g, 1.3 mmol), zinc (0.26 g, 4 mmol), ethyl bromodifluoroacetate (0.53 g, 2.6 mmol), and THF (4.5 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (8:2–6:4) to give the product as a pale yellow oil, yield 79% (415 mg); $[\alpha]_D^{25}$ −79.7 (*c* 1.13, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.42; IR (KBr) 1778, 1610, 1592, 1457, 1307, 1230, 1207, 1157, 1140, 1071, 817, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.30–7.25 (m, 3H), 7.25–7.15 (m, 2H), 6.03 (s, 2H), 5.45 (dd, 1H, *J*=2 and 9.5 Hz), 4.67 (t, 1H, *J*=7 Hz), 3.84 (dd, 1H, *J*=7.5 and 9.5 Hz), 3.79 (s, 3H), 3.61 (s, 6H), 3.50 (dd, 1H, *J*=6.5 and 9.5 Hz), 3.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 162.6, 161.6 (t, *J*=30.5 Hz), 160.8, 136.2, 128.6, 128.2, 128.1, 121.1 (dd, *J*=281 and 297 Hz), 99.3, 90.4, 72.1, 61.7 (dd, *J*=24 and 28.5 Hz), 58.9, 57.8, 55.5, 55.4; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −115.1 (dd, *J*=9.5 and 219 Hz), −119.5 (dd, *J*=2 and 219 Hz); MS (CI^+) 408 ($[M+H]^+$); MS (ESI^+) 408.00 ($[M+H]^+$). Anal. Calcd for $C_{21}H_{23}F_2NO_5$: C, 61.91; H, 5.69; N, 3.44. Found: C, 61.55; H, 5.71; N, 3.21.

4.2.25. Benzyl 4-((*S*)-3,3-difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-oxoazetidin-2-yl) benzyl carbamate (12i) and benzyl 4-((*S*)-1-((*R*)-2-methoxy-1-phenylethylamino)-2-(ethoxy carbonyl)-2,2-difluoroethyl)benzylcarbamate (13i). These compounds were prepared by the above General Procedure A, using benzyl 4-formylbenzylcarbamate (0.27 g, 1 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.15 g, 1 mmol), zinc (0.32 g, 5 mmol), ethyl bromodifluoroacetate (0.61 g, 3 mmol), and THF (4.5 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–6:4) to give the product as a colorless oil, yield 77% (390 mg); TLC: silica gel, 6:4 cyclohexane/EtOAc, R_f 0.51.

Mixture of two products: IR (KBr) 3341, 1774, 1702, 1519, 1455, 1410, 1306, 1259, 1203, 1115, 756, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.4–7.1 (m, 28H), 5.15–5.00 (br d, 6H), 4.80 (dd, 1H, *J*=4.5 and 9.5 Hz), 4.71 (dd, 1H, *J*=2 and 8 Hz), 4.40 (dd, 1H, *J*=10 and 19.5 Hz), 4.35–4.25 (m, 6H), 3.94 (dd, 1H, *J*=4.5 and 7.5 Hz), 3.71 (t, 1H, *J*=10 Hz), 3.5–3.3 (m, 3H), 3.25 (s, 3H), 3.22 (m, 3H), 1.30 (t, 3H, *J*=7 Hz); ^{19}F NMR ($CDCl_3$, 288.3 MHz) −110.7 (dd, *J*=8.5 and 255 Hz), −115.4 (dd, *J*=8.5 and 224 Hz), −116.9 (dd, *J*=17 and 255 Hz), −121.8 (d, *J*=224 Hz).

Azetidin-2-one: $[\alpha]_D^{25}$ +38.3 (*c* 1.31, $CHCl_3$); IR (KBr) 3337, 1784, 1703, 1519, 1455, 1428, 1303, 1256, 1203, 1112, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.4–7.1 (m, 14H), 5.15 (br d, 1H), 5.12 (s, 2H), 4.86 (dd, 1H, *J*= 4.5 and 10 Hz), 4.77 (dd, 1H, *J*=2 and 8 Hz), 4.41 (d, 1H, *J*=7 Hz), 4.36 (d, 1H, *J*=7 Hz), 3.77 (t, 1H, *J*=10 Hz), 3.44 (dd, 1H, *J*=4.5 and 10 Hz), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 161.8 (t, *J*=30.5 Hz), 156.6, 140.3, 136.4, 134.9, 130.8, 129.2, 128.9, 128.8, 128.7, 128.4, 128.3, 128.0, 127.8, 119.9 (dd, *J*=288.5 and 292.5 Hz), 72.2, 69.6 (dd, *J*=23.5 and 26.5 Hz), 67.1, 58.8, 58.3, 44.7; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −115.4 (dd, *J*=8.5 and 224.5 Hz), −121.8 (d, *J*=224.5 Hz); MS (CI^+) 481 ($[M+H]^+$); MS (ESI^+) 481.00 ($[M+H]^+$); HRMS (CI^+) calcd for $C_{27}H_{27}F_2N_2O_4$: 481.1939. Found: 481.1924.

4.2.26. Benzyl 4-((*S*)-3,3-difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-oxoazetidin-2-yl)benzyl methylcarbamate (12j). This compound was prepared by the above General Procedure A, using benzyl 4-formylbenzylmethylcarbamate (0.28 g, 1 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.15 g, 1 mmol), zinc (0.32 g, 5 mmol), ethyl bromodifluoroacetate (0.61 g, 3 mmol), and THF (4.5 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–7:3) to give the product as a pale yellow oil, yield 67% (330 mg); $[\alpha]_D^{25}$ +32.2 (*c* 2.15, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.40; IR (KBr) 3257, 1784, 1682, 1455, 1405, 1367, 1305, 1203, 1142, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.4–7.1 (m, 14H), 5.17 (s, 2H), 4.9–4.8 (m, 1H), 4.78 (dd, 1H, *J*=2 and 8 Hz), 4.50 (s, 2H), 3.77 (t, 1H, *J*=10 Hz), 3.45 (dd, 1H, *J*=5 and 10 Hz), 3.27 (s, 3H), 2.88 (d, 3H, *J*=10.5 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 161.8 (t, *J*=30.5 Hz), 156.9 and 156.4, 139.3, 135.0, 130.8, 129.2, 128.9, 128.8, 128.7, 128.2, 128.0, 127.6, 120.0 (t, *J*=293 Hz), 72.2, 69.7 (t, *J*=23.5 Hz), 67.6, 58.9, 58.4, 52.4 and 52.2, 34.8 and 34.0; ^{19}F NMR ($CDCl_3$, 288.3 MHz) −115.4 (dd, *J*=8.5 and 224.5 Hz), −121.7 (d, *J*=224.5 Hz); MS (CI^+) 495 ($[M+H]^+$); MS (ESI^+) 495.13 ($[M+H]^+$). Anal. Calcd for $C_{28}H_{28}F_2N_2O_4$: C, 68.00; H, 5.71; N, 5.66. Found: C, 67.83; H, 5.75; N, 5.66.

4.2.27. (*S*)-3,3-Difluoro-1-((*R*)-2-methoxy-1-phenylethyl)-4-pentylazetidin-2-one (12k). This compound was prepared by the above General Procedure A, using hexanal (0.50 g, 5 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.76 g, 5 mmol), zinc (0.98 g, 15 mmol), ethyl bromodifluoroacetate (2.03 g, 10 mmol), and THF (12 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (9:1–7:3) to give the product as a pale yellow oil, yield 52% (470 mg); $[\alpha]_D^{25}$ +50.7 (*c* 1.22, $CHCl_3$); TLC: silica gel, 7:3 cyclohexane/EtOAc, R_f 0.68; IR (KBr) 1782, 1682, 1456, 1380, 1353, 1314, 1202, 1166, 1125, 1068, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.35–7.25 (m, 5H), 4.63 (dd, 1H, *J*=5.5 and 9.5 Hz), 4.09 (t, 1H, *J*=9.5 Hz), 3.85–3.75 (m, 1H), 3.65 (dd, 1H, *J*=5 and 9.5 Hz), 3.39 (s, 3H), 1.6–1.4 (m, 2H), 1.35–1.00 (m, 6H), 0.82 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 160.9 (t, *J*=30.5 Hz), 136.2, 129.1, 128.6, 127.5, 120.5 (dd, *J*=284.5 and 288.5 Hz), 72.8, 67.3 (dd, *J*=23 and 24.5 Hz), 59.1, 31.5, 28.5, 25.0, 22.4, 13.9; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −116.0 (dd, *J*=8.5 and 229 Hz), −127.5 (d, *J*=230 Hz); (minor diastereomer of β-lactam) −115.6 (dd, *J*=8.5 and 230 Hz), −127.6 (d, *J*=230 Hz); MS (CI^+) 312 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{23}F_2NO_2$: C, 65.58; H, 7.45; N, 4.50. Found: C, 65.71; H, 7.37; N, 4.32.

4.2.28. (*S*)-4-*tert*-Butyl-3,3-difluoro-1-((*R*)-2-methoxy-1-phenylethyl)azetidin-2-one (12l) and (*S*)-ethyl 3-((*R*)-2-methoxy-1-phenylethylamino)-2,2-difluoro-4,4-dimethyl pentanoate (13l). These compounds were prepared by the above General Procedure A, using trimethylacetaldehyde (0.34 g, 4 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.61 g, 4 mmol), zinc (0.78 g, 12 mmol), ethyl bromodifluoroacetate (1.62 g, 8 mmol), and THF (12 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (95:5–90:10) to give the mixture of products as a pale yellow solid, yield 33% (460 mg); mp=86 °C; $[\alpha]_D^{25}$ +107.3 (*c* 1.82, $CHCl_3$); IR (KBr) 1783, 1456, 1403, 1350, 1304, 1212, 1122, 1081, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.45–7.25 (m, 5H), 4.37 (dd, 1H, *J*=4 and 11 Hz), 4.26 (t, 1H, *J*=10 Hz), 3.76 (dd, 1H, *J*=2.5 and 11.5 Hz), 3.52 (ddd, 1H, *J*=1.5, 4 and 9.5 Hz), 3.37 (s, 3H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 162.5 (t, *J*=30 Hz), 137.0, 129.1, 128.4, 127.9, 120.6 (dd, *J*=280 and 292.5 Hz), 77.9 (dd, *J*=21.5 and 24 Hz), 77.4, 73.1, 63.7, 59.1, 26.1; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (β-lactam) −112.5 (dd, *J*=12 and 235.5 Hz), −122.3 (d, *J*=236.5 Hz); (β-aminoester) −103.7 (dd, *J*=11 and 263.5 Hz), −107.6 (dd, *J*=16 and 263.5 Hz); MS (CI^+) 344 ($[M'+H]^+$) and 298 ($[M+H]^+$).

4.2.29. (*S*)-4-Cyclopropyl-3,3-difluoro-1-((*R*)-2-methoxy-1-phenylethyl)azetidin-2-one (12m). This compound was prepared by the above General Procedure A, using cyclopropane carboxaldehyde (0.30 g, 4 mmol), (*R*)-2-methoxy-1-phenylethanamine (0.61 g, 4 mmol), zinc (0.78 g, 12 mmol), ethyl bromodifluoroacetate (1.62 g, 8 mmol), and THF (12 mL). The crude product was purified by silica gel column chromatography with cyclohexane/EtOAc (95:5–90:10) to give the product as a yellow oil, yield 53% (590 mg); $[\alpha]_D^{25}$ −10.9 (*c* 1.0, $CHCl_3$); TLC: silica gel, 8:2 cyclohexane/EtOAc, R_f 0.29; IR (KBr) 1782, 1496, 1456, 1405, 1354, 1317, 1289, 1202, 1151, 1125, 1078, 970, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300.3 MHz) 7.4–7.3 (m, 5H), 4.82 (dd, 1H, *J*=5.5 and 9.5 Hz), 4.15 (t, 1H, *J*=9.5 Hz), 3.75 (dd, 1H, *J*=5.5 and 10 Hz), 3.40 (s, 3H), 3.041 (ddd, 1H, *J*=2.5, 7.5 and 9.5 Hz), 0.82–0.67 (m, 1H), 0.67–0.58 (m, 1H), 0.57–0.46 (m, 1H), 0.29–0.19 (m, 1H), 0.19–0.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 160.9 (t, *J*=31 Hz), 136.2, 129.1, 128.6, 127.6, 120.3 (t, *J*=287.5 Hz), 72.5, 72.1 (dd, *J*=23 and 25.5 Hz), 59.1, 57.9, 8.5, 3.7, 2.2; ^{19}F NMR ($CDCl_3$, 288.3 MHz) (major diastereomer of β-lactam) −117.1 (dd, *J*=7.5 and 230 Hz), −124.95 (d, *J*=230 Hz); (minor diastereomer of β-lactam) −117.05 (dd, *J*=7.5 and 231 Hz), −125.3 (d, *J*=231 Hz); MS (CI^+) 282 ($[M+H]^+$). Anal. Calcd for $C_{15}H_{17}F_2NO_2$: C, 64.05; H, 6.09; N, 4.98. Found: C, 64.13; H, 5.97; N, 4.91.

Acknowledgements

We gratefully acknowledge financial support (grant to N.B.) from the 'Institut de Recherches SERVIER'. We also

warmly thank Louise Chervel, Maryse Thiverny, and Elisabeth Roger for their initial contribution to this work.

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