JOC The Journal of Organic Chemistry

Article

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Direct and Diastereoselective Alkylation and Aldol Reactions of α-Bromo-α-fluoro-β-lactams

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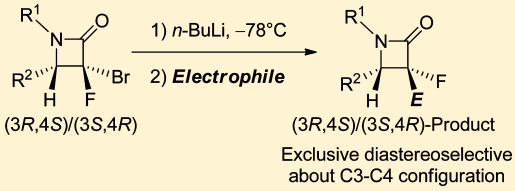
Supporting Information

ABSTRACT: Herein, we describe the development of a method for the direct alkylation and aldol reaction of α-bromo-α-fluoro-β-lactams. This method provides facile access to a wide range of 3-alkyl- and 3-hydroxyalkyl-fluoro-β-lactams in good yields under mild conditions. The products were obtained with complete diastereoselectivity with regard to the relative configuration of the β-lactam ring at C3 and C4 positions. The reaction conditions were tolerant of a broad range of electrophiles, which highlights the overall scope and utility of this procedure.



INTRODUCTION

Fluorinated compounds have recently been highlighted as important chemical scaffolds in both medicinal chemistry and agrochemical research.[1] The incorporation of a fluorine atom at a suitable position within a target molecule can lead to unique changes in the overall properties of the target molecule, such as increased lipophilicity, modified bioavailability, and improved metabolic stability. These changes are effectively facilitated by the chemical properties of the fluorine atom,[2] and the significance of design strategies using fluorine in this way is exemplified by the fact that almost 20% of all pharmaceuticals[3] and 30% of all agrochemicals[4] contain fluorine(s). The development of synthetic methods allowing for the incorporation of fluorine atoms into target molecules is, therefore, of particular importance, and extensive research efforts have already been deployed in this area.[5]

β-Lactams are a particularly well-known structural class of bioactive compounds, with activities reported not only in antibiotics but also in the inhibition of a diverse range of enzymes.[6] For example, thienamycin (**1**) has been used as a carbapenem-type antibiotic, whereas ezetimibe (**2**) has been used as a cholesterol absorption inhibitor (Figure 1). Ezetimibe (**2**), in particular, has been used clinically for the treatment of hypercholesteremia, and theoretical structure activity relationships have also been developed in this context for a related series of azetidin-2-ones.[7] Interestingly, β-lactams of this type typically possess a characteristic 3-alkylated substructure on the

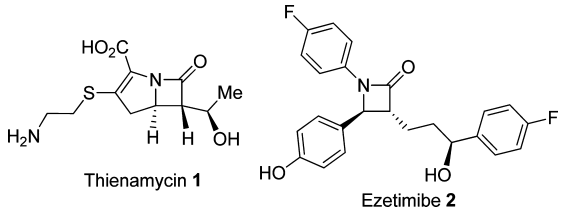


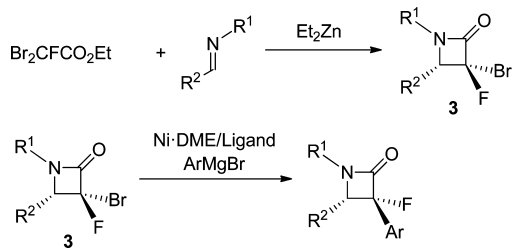
Figure 1. Bioactive 3-alkylated or 3-hydroxyalkylated β-lactams.

β-lactam ring. The design of synthetic strategies allowing for the functionalization of the fluoro-β-lactam scaffold is, therefore, of special importance. With this in mind, our recent research efforts have been focused on the development of methods for the synthesis of 3-alkyl-3-fluoroazetidin-2-ones. To date, there have been a significant number of reports in the literature describing the development of methods for the construction of 3-alkyl β-lactams, including the direct alkylation of β-lactams via the condensation of the corresponding β-lactam enolates with electrophiles,[8] as well as the direct Lewis acid mediated arylation and allylation of β-lactams with different nucleophiles.[9] Furthermore, a variety of substituted β-lactam compounds have been prepared using a Staudinger ketene−imine [2 + 2] cycloaddition reaction.[10] Among them, the enolate−alkyl halide condensation is the simplest and most powerful method in this particular reaction class. Although a variety of different methods have been reported for the construction of β-lactam and α-monofluoro-β-lactam compounds,[11] to the best of our knowledge, there have only been two reports in the literature concerning the direct alkylation of fluoro-β-lactam.[12] The first of these reports described the synthesis of diastereomerically pure 3-alkylated β-lactams via the deprotonation of 3-fluoroazetidin-2-one with LDA, followed by the trapping of the resulting enolate with an electrophile, such as an alkyl halide or carbonyl compound.[12a] Unfortunately, the practical application of this approach was severely limited by the requirement for particularly low temperature conditions (i.e., −100 to −90 °C) during the lithiation of 3-fluoroazetidin-2-one. Furthermore, with the exception of the methylated product, the yields were invariably low and only a limited number of electrophiles were used. In the second of these two reports, the radical chain reaction of 3-fluoro-3-iodo-β-lactam with olefins was used for the construction of 3-alkylated β-lactams. In this particular case, the

Received: May 22, 2013
Published: July 18, 2013

substrate scope was limited. Furthermore, the alkylated products contained an alkyl iodide moiety, and an additional step involving the use of toxic Bu_3SnH was required to furnish the desired products, further limiting the practical application of this method.[12b] Although an electrophilic fluorination of azetidinone through the β-lactam enolate has been also reported, the reaction example was with only one substrate and there was no information of the scope and limitation.[13] We recently reported the synthesis of α-bromo-α-fluoro-β-lactam (**3**) via a Reformatsky-type reaction and the subsequent functionalization of **3** under Kumada coupling reaction conditions using a variety of aryl Grignard reagents (Scheme 1).[14,15] Although this method allowed for the successful

Scheme 1. Synthesis of α-Bromo-α-fluoro-β-lactam 3 and Cross-Coupling of 3 with Grignard Reagent

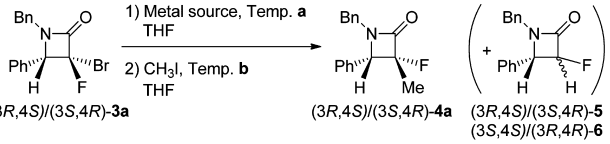


arylation of **3**, it remained difficult to alkylate **3** using this method. During the course of our ongoing work toward the synthesis of functionalized β-lactam systems, we recently observed that the lithium enolate of **3** could be readily generated using a halogen−lithium exchange reaction. Herein, we wish to report the alkylation of **3** according to a condensation reaction between its corresponding enolate and a range of alkyl halides.

RESULT AND DISCUSSION

The halogen−metal exchange reaction is a useful method for the generation of carbon nucleophiles under mild conditions.[8c,d,16] The lithiation of (3*R*,4*S*)/(3*S*,4*R*)-1-benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one (**3a**) was initially conducted using 1.5 equiv of *n*-BuLi at −78 °C, followed by treatment with 2 equiv of methyl iodide. Following the addition of the electrophile, the reaction temperature was slowly raised to 0 °C, affording the desired product (**4a**) diastereoselectively in quantitative yield (Scheme 2).[17] The insertion of other metals, such as samarium and zinc, into **3a** was also examined.

Scheme 2. Halogen−Metal Exchange Reaction of 3a Using Several Metal Reagents



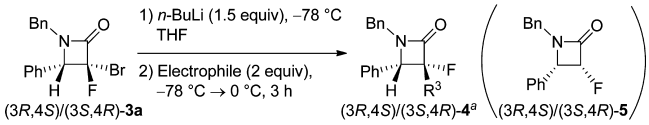
Metal source	Temp. a	b	Yield (%)[a]
n-BuLi (1.5 equiv)	−78 °C	0 °C	quant. (77[b])
SmI_2 (1.0 equiv)	−78 °C	0 °C	–[c]
Zn (1.2 equiv)	Reflux	Reflux	–[d]

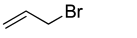
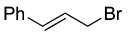
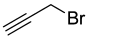
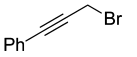
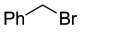
a: ^{19}F NMR yields.
b: Isolated yield.
c: β-Lactam **3a** was recovered in 82%
d: Diastereomixture of **5** and **6** was obtained in 83% (*RS*/*SR* : *SS*/*RR* = 68 : 15).

Unfortunately, however, the use of SmI_2 failed to promote the metal insertion, and the starting material **3a** was recovered in 82% yield.

Although zinc was successfully inserted into **3a**, only a diastereomeric mixture of the hydrogen substituted products **5** and **6** was obtained in a combined yield of 83%, with none of the desired product **4a** detected. Further screening of the conditions revealed that the reaction could be performed with several different alkyl lithium reagents without any reduction in the product yield.[18] Thus, with the optimal reaction conditions in hand, we proceeded to explore the scope and limitations of this reaction using several different alkyl halides (Table 1).

Table 1. Direct Alkylation of 3a with Various Alkyl Halides[a,b,c]



Entry	Electrophile	Products	Yield (%)[b]
1	CH_3I	**4a**	quant. (77[c])
2		**4b**	78
3		**4c**	96
4		**4d**	61
5		**4e**	91
6		**4f**	43
7		**4g**	89
8	TMS—OTf	**4h**	60 (60[c])
9	MeOH	**5**	76

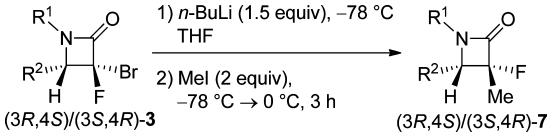
[a]Compound **4h** is (3*S*,4*S*)/(3*R*,4*R*). [b]^{19}F NMR yields. [c]Isolated yield.

Allyl, cinnamyl, propargyl, TMS-protected propargyl, and benzyl groups were well tolerated under the optimized reaction conditions, providing the desired products in good yields (Table 1, entries 2−5 and 7). In contrast, the yield of the 3-phenylpropargylated product **4f** was relatively low (Table 1, entry 6). Interestingly, the reaction also worked well when TMSOTf was used as the electrophile to give the desired product in moderate yield (Table 1, entry 8). It is noteworthy that the *C*-silylated product was observed in this particular case with none of the *O*-silylated product detected. The treatment of lithiated **3a** with methanol afforded the corresponding protonated product **5** (Table 1, entry 9). In all of these reactions, excellent levels of diastereoselectivity were achieved to form the (3*R*,4*S*)/(3*S*,4*R*)-isomers exclusively.

The condensation reaction between the enolate of **3** and methyl iodide was evaluated with a series of different α-bromo-α-fluoro-β-lactams (**3**) (Table 2). The results revealed that substrates bearing bulky substituents on the nitrogen atom of **3** proceeded smoothly through the reaction (Table 2, entries 1−4). In contrast, the substrate bearing a methyl group on the nitrogen atom **3e** did not give the desired product **7e** when the reaction was conducted under the optimized conditions (Table 2, entry 5) and only gave the desired product in moderate yield when the lithiation reaction of **3e** was performed at −100 °C (Table 2, entry 6). On the basis of these results, it was assumed that the lithium enolate of **3e** could potentially be thermally unstable. Interestingly, the introduction of a methoxy or a

dx.doi.org/10.1021/jo401072h | J. Org. Chem. 2013, 78, 7903−7911

Table 2. Direct Methylation of Several α-Bromo-α-fluoro-β-lactams (3)



entry	R^1	R^2		products	yield (%)[a]
1	Bn	Ph	**3a**	**4a**	quant. (77[b])
2	PMB	Ph	**3b**	**7b**	quant. (93[b])
3	benzhydryl	Ph	**3c**	**7c**	92
4	*tert*-Bu	Ph	**3d**	**7d**	87 (72[b])
5	Me	Ph	**3e**	**7e**	0
6[c]	Me	Ph	**3e**	**7e**	68
7	Bn	4-MeO-C_6H_4	**3f**	**7f**	82
8	Bn	4-F-C_6H_4	**3g**	**7g**	81

[a]^{19}F NMR yields. [b]Isolated yields. [c]The lithiation of **3e** was carried out at −100 °C.

fluorine substituent at the *para* position of the R^2 phenyl ring did not affect the yield of products, suggesting that the scope of this reaction could be readily expanded into a series of β-lactams containing differentially substituted phenyl groups at the R^2 positions. It is important to note that the reactions occurred with complete diastereoselectivity in all cases to give a mixture of the (3*R*,4*S*)/(3*S*,4*R*)-isomers.

The relative configuration of products was determined on the basis of the coupling constant between the C4 hydrogen and C3 fluorine atoms of **4** using ^{19}F NMR spectroscopy. The (3*R*,4*S*)/(3*S*,4*R*)-isomer **5** had a hydrogen−fluorine coupling constant of 4.3 Hz, whereas the (3*S*,4*S*)/(3*R*,4*R*)-isomer **6** provided a larger hydrogen−fluorine coupling constant of 10.7 Hz. Furthermore, the NOESY spectra of the two isomers provided conclusive conformation of the relative configuration, with strong NOE correlations observed between the protons at the C3 and C4 positions in the (3*R*,4*S*)/(3*S*,4*R*)-isomer **5**. All of the (3*R*,4*S*)/(3*S*,4*R*)-isomer products possessed a small hydrogen−fluorine coupling constant of approximately 4 Hz. The relative configurations of the other substituted products were tentatively assumed by analogy. The facial selectivity associated with the introduction of the alkyl group has been attributed to the desire of the system to avoid the phenyl ring lying on the same convex face of the β-lactam substrate (Figure 2).

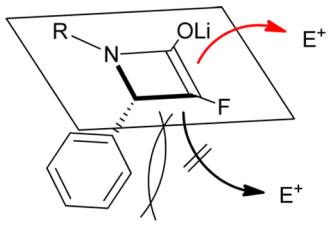


Figure 2. The plausible stereoinduction model of the alkylation reaction.

An aldol reaction is one of the most common strategies for the introduction of hydroxylalkyl groups to the α-position of carbonyl compounds.[19] In a further expansion of the scope of our current methodology, we investigated the introduction of a 3-hydroxyalkyl side chain to the β-lactam with the aim of generating structural motifs similar to those found in the important antibiotic thienamycin. When benzaldehyde was used as an electrophile under the optimized reaction conditions, its aldol reaction with lithiated **3a** gave the desired product as a mixture of diastereoisomers (**8a** and **9a**) in good yield (Table 3, entry 1). Interestingly, as well as in the case of the alkylation of **3**, the stereocenter at the C3 position of the β-lactam was constructed with complete diastereoselectivity with respect to the relative configurations of the C3 and C4 positions. The scope of this aldol reaction was explored using a variety of different carbonyl compounds, and the results are listed in Table 3. The results revealed that a wide range of aromatic aldehydes and ketone proceeded smoothly through the aldol reaction to afford the corresponding products in good yields (Table 3, entries 1−6). In contrast to the results reported by Welch et al.,[12a] good levels of stereoselectivity were observed at the C1′ position of the side chain. Furthermore, aliphatic aldehydes and ketones were well tolerated under the current reaction conditions and afforded the corresponding products in good yield (Table 3, entries 7−12). Unfortunately, however, these substrates did not experience the same level of stereocontrol at the newly formed C1′ position, with the diastereoselective outcomes in these cases being similar to those reported by Welch et al.[12a]

CONCLUSIONS

We have developed a mild and efficient method for the direct alkylation and aldol reaction of α-bromo-α-fluoro-β-lactams **3**, with both reactions occurring with complete diastereoselectivity with respect to the relative configurations at the C3 and C4 positions. The current alkylation reaction has been shown to be particularly versatile and tolerant of a range of different electrophiles, providing the desired alkylated fluoro-β-lactam products in good yields. When aromatic aldehydes and ketone were used as the electrophiles in the aldol reaction, high levels of diastereoselectivity were observed at the C1′ position of the side chain of the fluoro-β-lactam products. In contrast, however, the use of aliphatic aldehydes and ketones as the electrophiles resulted in low levels of diastereoselectivity at the same position. This method has provided effective access to 3-alkylated and 3-hydroxyalkylated α-fluoro-β-lactams, with potential applications in a number of different areas of research.

EXPERIMENTAL SECTION

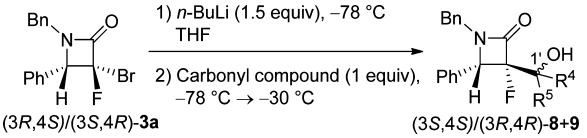
NMR spectra were obtained from a solution in $CDCl_3$ using 600 and 400 MHz for ^{1}H, 150 and 100 MHz for ^{13}C, and 564 and 90 MHz for ^{19}F. Chemical shifts of ^{1}H NMR and ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard. Chemical shifts of ^{19}F NMR are reported in ppm from benzotrifluoride as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet doublet, br = broad, brs = broad-singlet, m = multiplet), coupling constants (Hz). High-resolution mass spectroscopy (HRMS) experiments were measured on a double-focusing mass spectrometer with an ionization mode of EI or positive FAB as indicated for each compound. Infrared (IR) spectra were recorded in KBr tablets or thin films on either KBr disks. Melting points were measured uncorrected.

Anhydrous THF and diethyl ether (Et_2O) were distilled over benzophenone ketyl sodium just before use. All commercially available materials were used as received without further purification. All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

Synthesis of α-Bromo-α-fluoro-β-lactam (3) by the Reformatsky-type Reaction. Ethyl dibromofluoroacetate (1.5 mmol) was

dx.doi.org/10.1021/jo401072h | J. Org. Chem. 2013, 78, 7903−7911

Table 3. Aldol Reaction of 3a with Various Carbonyl Compounds



(3*R*,4*S*)/(3*S*,4*R*)-**3a** (3*S*,4*S*)/(3*R*,4*R*)-**8+9**

entry	R^4	R^5	time (h)	products	diastereo ratio[a] of **8**:**9**	yield (%)[b]
1	Ph	H	18	**8a** + **9a**	82:18	85 (79[c])
2	4-MeO-C_6H_4	H	22	**8b** + **9b**	78:22	77
3	4−Cl-C_6H_4	H	18	**8c** + **9c**	80:20	72
4	1-naphthyl	H	20	**8d** + **9d**	79:21	83
5	2-naphthyl	H	23	**8e** + **9e**	80:20	78
6	Ph	Me	17	**8f** + **9f**	81:19	92
7[d]	Me	H	17	**8g** + **9g**	56:44	65
8	*iso*-Pro	H	20	**8h** + **9h**	51:49	76
9	cyclohexyl	H	18	**8i** + **9i**	52:48	89
10	*tert*-Bu	H	23	**8j** + **9j**	67:33	74
11	Me	Et	18	**8k** + **9k**	57:43	73
12	Me	Me	22	**8l**		76

[a]From ^{19}F NMR spectra of crude mixture. [b]^{19}F NMR yields. [c]Isolated yield. [d]Exess of acetaldehyde was used (ca. 3 equiv).

added to a solution of the corresponding imine (1 mmol) in Et_2O (4 mL) at 0 °C. Et_2Zn (1.0 M) in hexane (1.5 mL, 1.5 mmol) was then slowly added to the mixture at 0 °C, and the resulting mixture was stirred at the same temperature for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and was filtered through a Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane) to afford the corresponding α-bromo-α-fluoro-β-lactams **3a**−**3g**.

*(3R,4S)/(3S,4R)-1-Benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one **3a**.* Compound **3a** was obtained as a colorless solid in 70% yield (7.052 g), after column chromatography (AcOEt/hexane = 1:9). This reaction was conducted in 30 mmol scale. mp 81.5−82.0 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.93 (1H, d, J = 14.9 Hz), 4.77 (1H, d, J = 10.3 Hz), 4.97 (1H, d, J = 14.9 Hz), 7.12−7.15 (2H, m), 7.19−7.22 (2H, m), 7.31−7.34 (3H, m), 7.44−7.46 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.9, 69.4 (d, J = 25 Hz), 106.2 (d, J = 299 Hz), 127.8, 128.3, 128.5, 128.7, 129.0, 129.7, 132.2, 133.3, 161.0 (d, J = 26 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ −54.9 (1F, d, J = 10.3 Hz); MS m/z = 333 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{16}H_{14}BrFNO$, 334.0243 ([M + H]$^+$); found, 334.0237 ([M + H]$^+$, 100%), 336.0227 (96); IR (KBr) cm^{-1} 1787, 1204.

*(3R,4S)/(3S,4R)-3-Bromo-3-fluoro-1-(4-methoxybenzyl)-4-phenylazetidin-2-one **3b**.* Compound **3b** was obtained as a colorless solid in 75% yield (2.715 g), after column chromatography (AcOEt/hexane = 1:4). This reaction was conducted in 10 mmol scale. mp 102.0−103.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.80 (3H, s), 3.88 (1H, d, J = 14.8 Hz), 4.75 (1H, d, J = 10.5 Hz), 4.91 (1H, d, J = 14.8 Hz), 6.84 (2H, d, J = 8.6 Hz), 7.05 (2H, d, J = 8.6 Hz), 7.19−7.22 (2H, m), 7.44−7.46 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.3 (d, J = 2 Hz), 55.3, 69.2 (d, J = 26 Hz), 106.2 (d, J = 300 Hz), 114.3, 125.3, 127.8, 128.7, 129.6, 129.9, 132.3, 159.5, 161.0 (d, J = 26 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −55.0 (1F, d, J = 10.5 Hz); MS m/z = 363 (M^+); HRMS (*pos*-FAB, NBA) Calcd for $C_{17}H_{16}BrFNO_2$, 364.0348 ([M + H]$^+$); found, 364.0346 ([M + H]$^+$, 100%), 366.0321 (90); IR (KBr) cm^{-1} 1793, 1248.

*(3R,4S)/(3S,4R)-1-Benzhydryl-3-bromo-3-fluoro-4-phenylazetidin-2-one **3c**.* Compound **3c** was obtained as a colorless solid in 35% yield (287 mg), after recrystallization from hexane. This reaction was conducted in 2 mmol scale. mp 113.5−114.0 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.97 (1H, d, J = 11.3 Hz), 5.53 (1H, s), 7.18−7.20 (2H, m), 7.23−7.25 (2H, m), 7.28−7.40 (11H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 62.9 (d, J = 2 Hz), 71.0 (d, J = 25 Hz), 105.6 (d, J = 297 Hz), 128.1, 128.2, 128.2, 128.5, 128.6, 128.7, 128.9, 129.6, 132.7, 132.7, 136.9, 137.6, 161.3 (d, J = 26 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −54.9 (1F, d, J = 11.3 Hz); MS m/z = 409 (M^+); HRMS (*pos*-FAB, NBA) Calcd for $C_{22}H_{18}BrFNO$, 410.0556 ([M + H]$^+$); found, 410.0556 ([M + H]$^+$, 99.6%), 412.0660 (100); IR (KBr) cm^{-1} 1784.

*(3R,4S)/(3S,4R)-3-Bromo-1-tert-butyl-3-fluoro-4-phenylazetidin-2-one **3d**.* Compound **3d** was obtained as a colorless solid in 51% yield (459 mg), after recrystallization from Et_2O/hexane. This reaction was conducted in 3 mmol scale. mp 120.0−121.0 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (9H, s), 4.98 (1H, d, J = 11.9 Hz), 7.33−7.36 (2H, m), 7.42−7.45 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.0, 55.7 (d, J = 1 Hz), 69.8 (d, J = 25 Hz), 105.4 (d, J = 294 Hz), 127.8, 128.3, 128.4, 135.1 (d, J = 1 Hz), 161.0 (d, J = 25 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −56.0 (1F, d, J = 11.9 Hz); MS m/z = 299 (M^+); HRMS (*pos*-FAB, NBA) Calcd for $C_{13}H_{16}BrFNO$, 300.0399 ([M + H]$^+$); found, 300.0404 ([M + H]$^+$, 100%), 302.0387 (99.6); IR (KBr) cm^{-1} 1778.

*(3R,4S)/(3S,4R)-3-Bromo-3-fluoro-1-methyl-4-phenylazetidin-2-one **3e**.* Compound **3e** was obtained as a colorless solid in 47% yield (362 mg), after recrystallization from hexane. This reaction was conducted in 3 mmol scale. mp 79.0−81.0 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.94 (3H, s), 4.96 (1H, d, J = 10.0 Hz), 7.23−7.26 (2H, m), 7.45−7.50 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.5 (d, J = 2 Hz), 71.8 (d, J = 25 Hz), 106.7 (d, J = 300 Hz), 127.7, 128.9, 129.8, 132.4, 161.4 (d, J = 26 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −54.9 (1F, d, J = 10.0 Hz); MS m/z = 257 (M^+); HRMS (EI) Calcd for $C_{10}H_9BrFNO$, 256.9852 (M^+); found, 256.9858 (M^+, 99.1%), 258.9836 (100); IR (KBr) cm^{-1} 1790.

*(3R,4S)/(3S,4R)-1-Benzyl-3-bromo-3-fluoro-4-(4-methoxyphenyl)-azetidin-2-one **3f**.* Compound **3f** was obtained as a colorless solid in 56% yield (821 mg), after recrystallization from Et_2O−hexane. This reaction was conducted in 4 mmol scale. mp 78.0−79.0 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.85 (3H, s), 3.89 (1H, d, J = 14.8 Hz), 4.72 (1H, d, J = 10.2 Hz), 4.93 (1H, d, J = 14.8 Hz), 6.94−6.95 (2H, d, J = 8.6 Hz), 7.12−7.14 (4H, m), 7.31−7.33 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 44.7 (d, J = 2 Hz), 55.3, 69.2 (d, J = 25 Hz), 106.9 (d, J = 299 Hz), 114.2, 124.0, 128.4, 128.6, 129.0, 129.4, 133.5, 160.7, 161.2 (d, J = 26 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −55.0 (1F, d, J = 10.2 Hz); MS m/z = 363 (M^+); HRMS (*pos*-FAB, NBA) Calcd for $C_{17}H_{16}BrFNO_2$, 364.0348 ([M + H]$^+$); found, 364.0346 ([M + H]$^+$, 38.0%), 366.0326 (37.8); IR (KBr) cm^{-1} 1783.

*(3R,4S)/(3S,4R)-1-Benzyl-3-bromo-3-fluoro-4-(4-fluorophenyl)-azetidin-2-one **3g**.* Compound **3g** was obtained as a colorless solid in 66% yield (929 mg), after column chromatography (AcOEt/hexane = 1:9). mp 42.0−43.0 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.92 (1H, d, J = 14.9 Hz), 4.75 (1H, d, J = 10.3 Hz), 4.94 (1H, d, J = 14.9 Hz), 7.11−7.14 (4H, m), 7.17−7.19 (2H, m), 7.32−7.34 (3H, m); ^{13}C NMR

dx.doi.org/10.1021/jo401072h | J. Org. Chem. 2013, 78, 7903−7911

($CDCl_3$, 150 MHz) δ 44.9, 68.9 (d, J = 25 Hz), 106.3 (d, J = 299 Hz), 116.0 (d, J = 22 Hz), 128.1 (d, J = 3 Hz), 128.5, 128.6, 129.1, 129.8 (d, J = 9 Hz), 133.3, 161.0 (d, J = 26 Hz), 163.5 (d, J = 251 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −48.3 (1F, m), −55.1 (1F, d, J = 10.3 Hz); MS m/z = 351 (M^+); HRMS (*pos*-FAB, NBA) Calcd for $C_{16}H_{13}BrF_2NO$, 352.0149 ($[M + H]^+$); found, 352.0140 ($[M + H]^+$, 48.8%), 354.0135 (43.6); IR (KBr) cm^{-1} 1792.

Alkylation of α-Bromo-α-fluoro-β-lactam. To a solution of the corresponding α-bromo-α-fluoro-β-lactam **3a**−**3g** (0.5 mmol) in 5 mL of THF at −78 °C was slowly added a solution of 1.65 M *n*-BuLi (0.45 mL, 0.75 mmol). After 10 min, 1.0 mmol of the appropriate alkylating agent was added at the same temperature, and then the reaction mixture was allowed to warm gradually to 0 °C. The resulting mixture was stirred for 3 h and was quenched with 10% aqueous HCl, followed by extraction with ethyl acetate. The extraction was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane) to afford the corresponding 3-alkylated-3-fluoroazetidin-2-one. The product yields were determined by ^{19}F NMR spectroscopy from the crude mixture, because it was difficult to separate the alkylated product. The spectra data were obtained from the pure fraction of chromatography.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-3-methyl-4-phenylazetidin-2-one ***4a***. Compound **4a** was obtained as a colorless liquid in 77% yield (103 mg), after column chromatography (AcOEt/hexane = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (3H, d, J = 22.3 Hz), 3.87 (1H, dd, J = 14.9, 2.4 Hz), 4.33 (1H, d, J = 3.6 Hz), 4.90 (1H, d, J = 14.9 Hz), 7.11−7.14 (2H, m), 7.24−7.40 (8H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2 (d, J = 25 Hz), 43.9 (d, J = 2 Hz), 66.9 (d, J = 23 Hz), 100.5 (d, J = 223 Hz), 127.9, 127.9, 128.4, 128.6, 128.8, 128.9, 132.5, 134.4, 166.1 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −101.0 (1F, q, J = 22.3 Hz); MS m/z = 269 (M^+); HRMS (EI) Calcd for $C_{17}H_{16}FNO$, 269.1216 (M^+); found, 269.1213 (M^+); IR (neat) cm^{-1} 1764.

(3R,4S)/(3S,4R)-3-Allyl-1-benzyl-3-fluoro-4-phenylazetidin-2-one ***4b***. Compound **4b** was obtained as a colorless liquid in 78% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.61−2.69 (1H, m), 2.75−2.81 (1H, m), 3.87 (1H, dd, J = 14.8, 2.4 Hz), 4.43 (1H, d, J = 3.8 Hz), 4.89 (1H, d, J = 14.8 Hz), 5.15 (1H, d, J = 10.3 Hz), 5.20 (1H, d, J = 17.1 Hz), 5.72−5.79 (1H, m), 7.12−7.14 (2H, m), 7.23−7.24 (2H, m), 7.29−7.31 (3H, m), 7.37−7.39 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 36.6 (d, J = 24 Hz), 44.1, 64.6 (d, J = 23 Hz), 101.7 (d, J = 229 Hz), 120.5, 128.0, 128.1, 128.6, 128.7, 128.9, 128.9, 129.7 (d, J = 7 Hz), 132.6, 134.5, 165.5 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ −106.0 (1F, dd, J = 24.6, 14.2 Hz); MS m/z = 295 (M^+); HRMS (EI) Calcd for $C_{19}H_{18}FNO$, 295.1372 (M^+); found, 295.1375 (M^+); IR (neat) cm^{-1} 1768.

(3R,4S)/(3S,4R)-1-Benzyl-3-cinnamyl-3-fluoro-4-phenylazetidin-2-one ***4c***. Compound **4c** was obtained as a colorless solid in 96% yield. mp 102.0−103.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80−2.95 (2H, m), 3.85 (1H, dd, J = 14.6, 2.4 Hz), 4.50 (1H, d, J = 3.9 Hz), 4.92 (1H, d, J = 14.6 Hz), 6.12 (1H, dt, J = 15.8, 7.3 Hz), 6.56 (1H, d, J = 15.8 Hz), 7.04−7.39 (15H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 35.5 (d, J = 25 Hz), 43.9 (d, J = 2 Hz), 64.1 (d, J = 23 Hz), 102.1 (d, J = 226 Hz), 120.4 (d, J = 9 Hz), 126.2, 127.6, 127.7, 127.9 (d, J = 1 Hz), 128.2, 128.4, 128.5, 128.6, 128.8, 132.2, 134.0, 135.3, 136.3, 165.2 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −104.5 (1F, t, J = 17.0 Hz); MS m/z = 371 (M^+); HRMS (EI) Calcd for $C_{25}H_{22}FNO$, 371.1685 (M^+); found, 371.1685 (M^+); IR (neat) cm^{-1} 1758.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-4-phenyl-3-(prop-2-yn-1-yl)-azetidin-2-one ***4d***. Compound **4d** was obtained as a colorless liquid in 61% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.92 (1H, m), 2.82−2.93 (2H, m), 3.91 (1H, dd, J = 14.9, 2.4 Hz), 4.71 (1H, d, J = 3.9 Hz), 4.92 (1H, d, J = 14.9 Hz), 7.17−7.18 (2H, m), 7.28−7.30 (5H, m), 7.40−7.41 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.4 (d, J = 31 Hz), 44.3 (d, J = 1 Hz), 64.5 (d, J = 23 Hz), 72.1 (d, J = 2 Hz), 75.9 (d, J = 14 Hz), 100.4 (d, J = 229 Hz), 128.1, 128.2, 128.7, 128.8, 128.9, 129.1, 132.1, 134.3, 164.3 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ −105.0 (1F, m); MS m/z = 293 (M^+); HRMS (EI) Calcd for $C_{19}H_{16}FNO$, 293.1216 (M^+); found, 293.1223 (M^+); IR (neat) cm^{-1} 3294, 1769.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-4-phenyl-3-{3-(trimethylsilyl)-prop-2-yn-1-yl}azetidin-2-one ***4e***. Compound **4e** was obtained as a colorless solid in 91% yield. mp 85.0−86.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.13 (9H, s), 2.78−3.01 (2H, m), 4.01 (1H, dd, J = 14.7, 2.2 Hz), 4.71 (1H, d, J = 4.0 Hz), 4.85 (1H, d, J = 14.7 Hz), 7.13−7.15 (2H, m), 7.26−7.31 (5H, m), 7.37−7.39 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.07, 24.1 (d, J = 28 Hz), 44.5 (d, J = 2 Hz), 65.3 (d, J = 23 Hz), 88.9 (d, J = 1 Hz), 98.2 (d, J = 8 Hz), 100.3 (d, J = 229 Hz), 128.1, 128.2 (d, J = 1 Hz), 128.6, 128.7, 128.9, 129.0, 132.2, 134.4, 164.5 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −105.8 (1F, m); MS m/z = 365 (M^+); HRMS (EI) Calcd for $C_{22}H_{24}FNOSi$, 365.1611 (M^+); found, 365.1620 (M^+); IR (KBr) cm^{-1} 1774.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-4-phenyl-3-(3-phenylprop-2-yn-1-yl)azetidin-2-one ***4f***. Compound **4f** was obtained as a colorless liquid in 43% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.06−3.17 (2H, m), 3.93 (1H, dd, J = 14.9, 2.5 Hz), 4.80 (1H, d, J = 4.0 Hz), 4.93 (1H, d, J = 14.9 Hz), 7.05−7.17 (5H, m), 7.28−7.34 (7H, m), 7.38−7.41 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.2 (d, J = 31 Hz), 44.1 (d, J = 1 Hz), 64.6 (d, J = 23 Hz), 81.3 (d, J = 15 Hz), 83.8 (d, J = 2 Hz), 100.9 (d, J = 227 Hz), 128.2 (d, J = 1 Hz), 128.3, 128.4, 128.5, 128.7, 128.8, 129.1, 131.9, 132.1, 134.1, 164.4 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −104.5 (1F, m); MS m/z = 369 (M^+); HRMS (EI) Calcd for $C_{25}H_{20}FNO$, 369.1529 (M^+); found, 369.1527 (M^+); IR (neat) cm^{-1} 1771.

(3R,4S)/(3S,4R)-1,3-Dibenzyl-3-fluoro-4-phenylazetidin-2-one ***4g***. Compound **4g** was obtained as a colorless solid in 89% yield. mp 112.5−113.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.19−3.35 (2H, m), 3.77 (1H, dd, J = 15.0, 2.5 Hz), 4.43 (1H, d, J = 4.4 Hz), 4.83 (1H, d, J = 15.0 Hz), 6.68−6.70 (2H, m), 7.06−7.08 (2H, m), 7.13−7.21 (3H, m), 7.26−7.34 (8H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.9 (d, J = 25 Hz), 43.7 (d, J = 2 Hz), 63.4 (d, J = 23 Hz), 102.7 (d, J = 226 Hz), 127.4, 127.6, 127.9, 128.5, 128.6, 128.7, 128.7, 130.3, 132.2, 133.0, 133.1, 133.8, 165.5 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −102.3 (1F, m); MS m/z = 345 (M^+); HRMS (EI) Calcd for $C_{23}H_{20}FNO$, 345.1529 (M^+); found, 345.1528 (M^+); IR (KBr) cm^{-1} 1769.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-4-phenyl-3-(trimethylsilyl)-azetidin-2-one ***4h***. Compound **4h** was obtained as a colorless solid in 60% yield (98 mg), after column chromatography (AcOEt/hexane = 1:9). mp 114.0−116.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (9H, s), 3.85 (1H, dd, J = 14.4, 2.8 Hz), 4.43 (1H, d, J = 5.3 Hz), 4.87 (1H, d, J = 14.4 Hz), 7.14−7.16 (2H, m), 7.24−7.31 (5H, m), 7.36−7.42 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.4 (d, J = 3 Hz), 44.4 (d, J = 1 Hz), 61.5 (d, J = 22 Hz), 100.5 (d, J = 230 Hz), 127.9 (d, J = 1 Hz), 128.0, 128.5, 128.6, 128.7, 128.9, 133.2 (d, J = 2 Hz), 134.6, 166.0 (d, J = 19 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −135.7 (1F, d, J = 5.3 Hz); MS m/z = 327 (M^+); HRMS (*pos*-FAB, NBA) Calcd for $C_{19}H_{23}FNOSi$, 328.1533 ($[M + H]^+$); Found, 328.1537 ($[M + H]^+$); IR (KBr) cm^{-1} 1741.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-4-phenylazetidin-2-one ***5***. Compound **5** was obtained as a colorless liquid in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (1H, dd, J = 14.8, 2.5 Hz), 4.64 (1H, dd, J = 4.6, 4.3 Hz), 4.86 (1H, d, J = 14.8 Hz), 5.54 (1H, dd, J = 55.0, 4.6 Hz), 7.12−7.14 (2H, m), 7.25−7.32 (5H, m), 7.38−7.41 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2 (d, J = 2 Hz), 60.6 (d, J = 23 Hz), 92.4 (d, J = 227 Hz), 127.9, 128.1 (d, J = 1 Hz), 128.4, 128.5, 128.7, 128.9, 131.8 (d, J = 1 Hz), 134.1, 163.6 (d, J = 22 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ −136.8 (1F, d, J = 55.0 Hz); MS m/z = 255 (M^+); HRMS (EI) Calcd for $C_{16}H_{14}FNO$, 255.1059 (M^+); found, 255.1053 (M^+); IR (neat) cm^{-1} 1768.

(3R,4S)/(3S,4R)-3-Fluoro-1-(4-methoxybenzyl)-3-methyl-4-phenylazetidin-2-one ***7b***. Compound **7b** was obtained as a colorless liquid in 93% yield (140 mg), after column chromatography (AcOEt/hexane = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63 (3H, d, J = 22.2 Hz), 3.79−3.84 (4H, m), 4.31 (1H, d, J = 3.8 Hz), 4.84 (1H, d, J = 14.7 Hz), 6.83 (2H, d, J = 8.5 Hz), 7.04 (2H, d, J = 8.5 Hz),7.24−7.26 (2H, m), 7.38−7.40 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2 (d, J = 25 Hz), 43.4 (d, J = 2 Hz), 55.1, 66.7 (d, J = 23 Hz), 100.3 (d, J =

dx.doi.org/10.1021/jo401072h | J. Org. Chem. 2013, 78, 7903−7911

222 Hz), 114.1, 126.3, 127.8 (d, J = 1 Hz), 128.5, 128.7, 129.6, 132.5, 159.1, 165.9 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −101.1 (1F, q, J = 22.2 Hz); MS m/z = 299 (M^+); HRMS (EI) Calcd for $C_{18}H_{18}FNO_2$, 299.1322 (M^+); found, 299.1323 (M^+); IR (neat) cm^{-1} 1768.

(3R,4S)/(3S,4R)-1-Benzhydryl-3-fluoro-3-methyl-4-phenylazetidin-2-one ***7c***. Compound **7c** was obtained as a colorless solid in 92% yield. mp 138.0−140.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.70 (3H, d, J = 22.3 Hz), 4.48 (1H, d, J = 3.8 Hz), 5.69 (1H, s), 7.16−7.35 (15H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 18.4 (d, J = 26 Hz), 62.0 (d, J = 2 Hz), 68.8 (d, J = 22 Hz), 99.5 (d, J = 223 Hz), 127.8, 127.9, 128.2, 128.3, 128.4, 128.5 (d, J = 2 Hz), 128.5, 128.6, 128.8, 133.1, 137.7, 138.2, 166.6 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −100.7 (1F, q, J = 22 Hz); MS m/z = 345 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{23}H_{21}FNO$, 346.1607 ([M + H]$^+$); found, 346.1606 ([M + H]$^+$); IR (KBr) cm^{-1} 1752.

(3R,4S)/(3S,4R)-1-tert-Butyl-3-fluoro-3-methyl-4-phenylazetidin-2-one ***7d***. Compound **7d** was obtained as a colorless solid in 72% yield (84 mg), after column chromatography (AcOEt/hexane = 1:4). mp 70.0−71.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.28 (9H, s), 1.66 (3H, d, J = 22.0 Hz), 4.55 (1H, d, J = 3.0 Hz), 7.34−7.40 (5H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 18.3 (d, J = 26 Hz), 28.2, 54.6 (d, J = 1 Hz), 67.5 (d, J = 22 Hz), 97.9 (d, J = 224 Hz), 128.1 (d, J = 2 Hz), 128.4, 128.8, 135.3, 166.4 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −101.8 (1F, qd, J = 22.0, 3.0 Hz); MS m/z = 235 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{14}H_{19}FNO$, 236.1451 ([M + H]$^+$); found, 236.1453 ([M + H]$^+$); IR (KBr) cm^{-1} 2937, 1748.

(3R,4S)/(3S,4R)-3-Fluoro-1,3-dimethyl-4-phenylazetidin-2-one ***7e***. Compound **7e** was obtained as a colorless liquid in 68% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (3H, d, J = 22.5 Hz), 2.85 (3H, d, J = 1.6 Hz), 4.50 (1H, d, J = 3.6 Hz), 7.27−7.30 (2H, m), 7.40−7.43 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (d, J = 26 Hz), 26.5 (d, J = 2 Hz), 69.4 (d, J = 23 Hz), 100.8 (d, J = 222 Hz), 127.6 (d, J = 1 Hz), 128.6, 128.9, 132.5 (d, J = 1 Hz), 134.6, 166.3 (d, J = 25 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −100.6 (1F, q, J = 22.5 Hz); MS m/z = 193 (M^+); HRMS (EI) Calcd for $C_{11}H_{12}FNO$, 193.0903 (M^+); found, 193.0895 (M^+); IR (neat) cm^{-1} 1769.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-4-(4-methoxyphenyl)-3-methylazetidin-2-one ***7f***. Compound **7f** was obtained as a colorless liquid in 82% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63 (3H, d, J = 22.3 Hz), 3.82−3.86 (4H, m), 4.29 (1H, d, J = 3.7 Hz), 4.87 (1H, d, J = 14.8 Hz), 6.92 (2H, d, J = 8.5 Hz), 7.11−7.13 (2H, m), 7.17 (2H, d, J = 8.5 Hz), 7.30−7.31 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1 (d, J = 26 Hz), 43.7 (d, J = 2 Hz), 55.2, 66.5 (d, J = 23 Hz), 100.4 (d, J = 222 Hz), 113.9, 124.2 (m), 127.8, 128.3, 128.7, 129.2 (d, J = 1 Hz), 134.4, 159.9, 166.0 (d, J = 25 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −101.2 (1F, q, J = 22.3 Hz); MS m/z = 299 (M^+); HRMS (EI) Calcd for $C_{18}H_{18}FNO_2$, 299.1322 (M^+); found, 299.1312 (M^+); IR (neat) cm^{-1} 1768.

(3R,4S)/(3S,4R)-1-Benzyl-3-fluoro-4-(4-fluorophenyl)-3-methylazetidin-2-one ***7g***. Compound **7g** was obtained as a colorless liquid in 84% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (3H, d, J = 22.4 Hz), 3.87 (1H, dd, J = 14.8, 2.4 Hz), 4.31 (1H, d, J = 3.8 Hz), 4.86 (1H, d, J = 14.8 Hz), 7.05−7.13 (4H, m), 7.19−7.23 (2H, m), 7.30−7.32 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0 (d, J = 26 Hz), 44.0 (d, J = 2 Hz), 66.3 (d, J = 23 Hz), 100.4 (d, J = 223 Hz), 115.6 (d, J = 22 Hz), 127.9, 128.3, 128.8, 129.6 (d, J = 1 Hz), 129.7 (d, J = 1 Hz), 134.2, 162.9 (d, J = 245 Hz), 165.8 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −50.0 (1F, m), −100.9 (1F, q, J = 22.4 Hz); MS m/z = 287 (M^+); HRMS (EI) Calcd for $C_{17}H_{15}F_2NO$, 287.1122 (M^+); found, 287.1124 (M^+); IR (neat) cm^{-1} 1769.

Insertion of Zinc Metal into α-Bromo-α-fluoro-β-lactam. To the suspension of zinc metal (0.6 mmol) in 5 mL of THF was added TMSCl (0.1 mmol), and then the resulting mixture was heated at 50 °C. After 30 min, the mixture was cooled to room temperature and the α-bromo-α-fluoro-β-lactam **3a** (0.5 mmol) was added. The reaction mixture was refluxed for 1 h, and the heating was stopped before methyl iodide (1 mmol) was added. The whole mixture was refluxed for 3 h and was quenched with 10% aqueous HCl, followed by extraction with ethyl acetate. The extraction was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane) to afford the hydrogen substituted products (**5** and **6**) without the formation of the methylated product **4a**.

*1-Benzyl-3-fluoro-4-phenylazetidin-2-one (****5*** *and* ***6****)*. Compounds (3*R*,4*S*/(3*S*,4*R*)-**5** and (3*S*,4*S*)/(3*R*,4*R*)-**6** were obtained as a colorless liquid in 83% yield (*RS*/*SR*:*SS*/*RR* = 68:15). (3*S*,4*S*)/(3*R*,4*R*)-Isomer **6**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.89 (1H, d, J = 15.0 Hz), 4.48 (1H, dd, J = 10.7, 1.3 Hz), 4.88 (1H, d, J = 15.0 Hz), 5.24 (1H, ddd, J = 54.4, 1.3, 0.6 Hz), 7.12−7.14 (2H, m), 7.19−7.26 (2H, m), 7.29−7.33 (3H, m), 7.39−7.42 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 44.5, 62.5 (d, J = 24 Hz), 97.9 (d, J = 226 Hz), 126.8, 128.1, 128.6, 128.9, 129.2, 129.3, 134.2, 134.3, 163.6 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −127.2 (1F, dd, J = 54.4, 10.7 Hz); MS m/z = 255 (M^+); HRMS (EI) Calcd for $C_{16}H_{14}FNO$, 255.1059 (M^+); found, 255.1060 (M^+); IR (neat) cm^{-1} 1770.

Aldol Reaction of α-Bromo-α-fluoro-β-lactam. To a solution of the α-bromo-α-fluoro-β-lactam **3a** (0.5 mmol) in 5 mL of THF at −78 °C was slowly added a solution of 1.65 M *n*-BuLi (0.45 mL, 0.75 mmol). After 10 min, 0.5 mmol of the appropriate carbonyl compound was added at the same temperature, and then the reaction mixture was allowed to warm gradually to −30 °C. The resulting mixture was stirred for the appropriate time and was quenched with 10% aqueous HCl, followed by extraction with ethyl acetate. The extraction was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane) to afford the corresponding 3-hydroxyalkylated-3-fluoroazetidin-2-one (**8** and **9**). The product yields were determined by ^{19}F NMR spectroscopy from the crude mixture, because it was difficult to separate the aldol products. The spectra data were obtained from the pure fraction of chromatography. Furthermore, separable diastereomixtures showed the data of each isomer, whereas inseparable diastereomixtures showed the data of both isomers.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(phenyl)methyl}-4-phenylazetidin-2-one ***8a*** *and* ***9a***. Compounds **8a** and **9a** were obtained as a colorless solid in 79% yield (143 mg, **8a**/**9a** = 82/18). Major isomer **8a**: mp 152.0−153.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (1H, d, J = 4.6 Hz), 3.92 (1H, dd, J = 15.2, 2.4 Hz), 4.76 (1H, d, J = 4.5 Hz), 4.92 (1H, d, J = 15.2 Hz), 5.22 (1H, dd, J = 9.0, 4.6 Hz), 6.89−6.91 (2H, m), 7.06−7.09 (2H, m), 7.23−7.27 (6H, m), 7.32−7.35 (3H, m), 7.43−7.45 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2 (d, J = 1 Hz), 61.5 (d, J = 23 Hz), 71.1 (d, J = 28 Hz), 103.4 (d, J = 226 Hz), 126.7 (d, J = 2 Hz), 127.7, 127.7 (d, J = 1 Hz), 128.1, 128.3, 128.3, 128.5, 128.6, 131.9, 133.9, 137.1, 165.1 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ −111.5 (1F, m); MS m/z = 361 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{23}H_{21}FNO_2$, 362.1556 ([M + H]$^+$); found, 362.1557 ([M + H]$^+$); IR (KBr) cm^{-1} 3373, 1749. Minor isomer **9a**: mp 156.0−156.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53 (1H, dd, J = 2.8, 1.3 Hz), 3.72 (1H, dd, J = 15.0, 2.7 Hz), 4.63 (1H, d, J = 4.4 Hz), 4.75 (1H, d, J = 15.0 Hz), 5.32 (1H, dd, J = 11.5, 2.8 Hz), 6.44−6.46 (2H, m), 7.06−7.09 (2H, m), 7.14−7.23 (3H, m), 7.35−7.40 (6H, m), 7.55−7.58 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.6 (d, J = 2 Hz), 60.6 (d, J = 23 Hz), 72.7 (d, J = 26 Hz), 104.4 (d, J = 227 Hz), 127.1 (d, J = 1 Hz), 127.4, 127.7, 128.0 (d, J = 1 Hz), 128.5, 128.6 (d, J = 1 Hz), 128.6, 128.7, 132.2 (d, J = 1 Hz), 133.2, 135.4, 135.5, 164.0 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.3 (1F, m); MS m/z = 361 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{23}H_{21}FNO_2$, 362.1556 ([M + H]$^+$); found, 362.1553 ([M + H]$^+$); IR (KBr) cm^{-1} 3488, 1752.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(4-methoxyphenyl)-methyl}-4-phenylazeti-din-2-one ***8b*** *and* ***9b***. Compounds **8b** and **9b** were obtained as a colorless solid in 77% yield (**8b**/**9b** = 78/22). Major isomer **8b**: mp 156.0−157.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (1H, d, J = 4.5 Hz), 3.80 (3H, s), 3.89 (1H, dd, J = 15.2, 2.5 Hz), 4.73 (1H, d, J = 4.4 Hz), 4.91 (1H, d, J = 15.2 Hz), 5.15 (1H, dd, J = 9.2, 4.5 Hz), 6.85−6.87 (2H, d, J = 8.5 Hz), 6.96−6.98 (2H, m), 7.02−7.05 (2H, m), 7.24−7.28 (6H, m), 7.34−7.36 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.1 (d, J = 2 Hz), 55.2, 61.5 (d, J = 22 Hz), 71.0 (d, J = 28 Hz), 103.5 (d, J = 227 Hz), 113.7, 127.7, 127.8 (d, J = 1 Hz), 128.1 (d, J = 2 Hz), 128.1, 128.4, 128.6, 128.6,

dx.doi.org/10.1021/jo401072h | J. Org. Chem. 2013, 78, 7903−7911

129.1 (d, J = 1 Hz), 132.0 (d, J = 1 Hz), 133.8, 159.7, 165.1 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −111.5 (1F, m); MS m/z = 391 (M^+); HRMS (EI) Calcd for $C_{24}H_{22}FNO_3$, 391.1584 (M^+); found, 391.1584 (M^+); IR (KBr) cm^{-1} 3399, 1752. Minor isomer **9b**: mp 156.0−157.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (1H, bs), 3.70 (1H, dd, J = 15.2, 2.6 Hz), 3.86 (3H,s), 4.64 (1H, d, J = 4.2 Hz), 4.76 (1H, d, J = 15.2 Hz), 5.27 (1H, d, J = 11.0 Hz), 6.49−6.51 (2H, m), 6.88−6.91 (2H, d, J = 8.7 Hz), 7.07−7.11 (2H, m), 7.16−7.19 (1H, m), 7.23−7.26 (3H, m), 7.37−7.39 (3H, m), 7.46−7.48 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.6 (d, J = 2 Hz), 55.2, 60.5 (d, J = 23 Hz), 72.2 (d, J = 25 Hz), 104.5 (d, J = 227 Hz), 113.9, 127.4, 127.5, 127.7, 128.0 (d, J = 1 Hz), 128.3 (d, J = 1 Hz), 128.4, 128.6, 128.7, 132.3 (d, J = 1 Hz), 133.3, 159.7, 164.0 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.0 (1F, m); MS m/z = 391 (M^+); HRMS (EI) Calcd for $C_{24}H_{22}FNO_3$, 391.1584 (M^+); found, 391.1590 (M^+); IR (KBr) cm^{-1} 3483, 1753.

(3S,4S)/(3R,4R)-1-Benzyl-3-{(4-chlorophenyl)hydroxymethyl}-3-fluoro-4-phenylazetidin-2-one ***8c*** *and* ***9c***. Compounds **8c** and **9c** were obtained as a colorless solid in 72% yield (**8c**/**9c** = 80/20). Major isomer **8c**: mp 168.0−174.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56 (1H, bs), 3.89 (1H, dd, J = 15.1, 2.4 Hz), 4.70 (1H, d, J = 4.6 Hz), 4.89 (1H, d, J = 15.1 Hz), 5.19 (1H, d, J = 8.3 Hz), 6.89−6.92 (2H, m), 7.06−7.09 (2H, m), 7.25−7.29 (8H, m), 7.34−7.36 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2 (d, J = 2 Hz), 61.5 (d, J = 23 Hz), 70.2 (d, J = 28 Hz), 103.2 (d, J = 227 Hz), 127.7 (d, J = 1 Hz), 127.8, 128.1, 128.1 (d, J = 2 Hz), 128.4, 128.4, 128.6, 128.6, 131.6 (d, J = 2 Hz), 133.7, 134.2, 135.8 165.0 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −111.3 (1F, m); MS m/z = 395 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{23}H_{20}ClFNO_2$, 396.1167 ([M + H]$^+$); found, 396.1167 ([M + H]$^+$); IR (KBr) cm^{-1} 3372, 1751. Minor isomer **9c**: mp 146.0−147.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (1H, bs), 3.68 (1H, dd, J = 14.9, 2.3 Hz), 4.56 (1H, d, J = 4.0 Hz), 4.74 (1H, d, J = 14.9 Hz), 5.29 (1H, d, J = 11.1 Hz), 6.50−6.52 (2H, m), 7.13−7.17 (2H, m), 7.20−7.26 (4H, m), 7.30−7.32 (2H, m), 7.39−7.40 (3H, m), 7.46−7.48 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.7 (d, J = 2 Hz), 60.3 (d, J = 23 Hz), 72.0 (d, J = 26 Hz), 104.2 (d, J = 228 Hz), 127.7, 127.8, 128.0 (d, J = 1 Hz), 128.4 (d, J = 1 Hz), 128.6, 128.6, 128.7, 128.9, 131.9 (d, J = 1 Hz), 133.1, 133.8 (d, J = 8 Hz), 134.5, 163.6 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.0 (1F, m); MS m/z = 395 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{23}H_{20}ClFNO_2$, 396.1167 ([M + H]$^+$); found, 396.1167 ([M + H]$^+$); IR (KBr) cm^{-1} 3483, 1751.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(naphthalen-1-yl)methyl}-4-phenylazeti-din-2-one ***8d*** *and* ***9d***. Compounds **8d** and **9d** were obtained as a colorless solid in 83% yield (**8d**/**9d** = 79/21). Major isomer **8d**: mp 201.0−202.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (1H, d, J = 4.8 Hz), 3.83 (1H, dd, J = 15.6, 2.6 Hz), 4.81 (1H, d, J = 4.4 Hz), 4.88 (1H, d, J = 15.6 Hz), 6.12 (1H, dd, J = 7.9, 4.8 Hz), 6.88−6.91 (2H, m), 7.01−7.03 (2H, m), 7.15−7.26 (6H, m), 7.45−7.54 (3H, m), 7.84−7.89 (3H, m), 8.05−8.07 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.0 (d, J = 2 Hz), 61.7 (d, J = 23 Hz), 67.6 (d, J = 29 Hz), 104.1 (d, J = 229 Hz), 123.0 (d, J = 3 Hz), 124.8 (d, J = 1 Hz), 125.1, 125.7, 126.4, 127.6, 127.9, 128.1 (d, J = 1 Hz), 128.4, 128.5, 128.6, 128.7, 129.3, 131.3, 131.8 (d, J = 1 Hz), 133.2 (d, J = 2 Hz), 133.5, 133.7, 164.9 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.4 (1F, m); MS m/z = 411 (M^+); HRMS (EI) Calcd for $C_{27}H_{22}FNO_2$, 411.1635 (M^+); found, 411.1634 (M^+); IR (KBr) cm^{-1} 3370, 1743. Minor isomer **9d**: mp 199.0−203.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.71 (1H, bd, J = 3.5 Hz), 3.67 (1H, dd, J = 15.2, 2.6 Hz), 4.74 (1H, d, J = 15.2 Hz), 4.78 (1H, d, J = 4.1 Hz), 5.29 (1H, dd, J = 12.5, 3.4 Hz), 6.49−6.51 (2H, m), 7.07−7.10 (2H, m), 7.16−7.18 (3H, m), 7.36−7.38 (3H, m), 7.43−7.46 (1H, m), 7.52−7.55 (2H, m), 7.87−7.91 (3H, m), 8.14−8.17 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.7 (d, J = 2 Hz), 61.4 (d, J = 23 Hz), 69.3 (d, J = 25 Hz), 103.9 (d, J = 230 Hz), 123.5, 124.8 (d, J = 1 Hz), 125.1, 125.6 (d, J = 3 Hz), 125.9, 126.3, 127.5, 127.7, 128.0 (d, J = 1 Hz), 128.5, 128.6, 128.8 129.4, 130.7, 131.7 (d, J = 4 Hz), 132.2 (d, J = 1 Hz), 133.5, 133.6, 163.8 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −111.6 (1F, m); MS m/z = 411 (M^+); HRMS (EI) Calcd for $C_{27}H_{22}FNO_2$, 411.1635 (M^+); found, 411.1638 (M^+); IR (KBr) cm^{-1} 3419, 1750.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(naphthalen-2-yl)methyl}-4-phenylazeti-din-2-one ***8e*** *and* ***9e***. Compounds **8e** and **9e** were obtained as a colorless solid in 78% yield (**8e**/**9e** = 80/20). Major isomer **8e**: mp 164.0−165.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.34 (1H, d, J = 4.7 Hz), 3.88 (1H, dd, J = 15.2, 2.4 Hz), 4.81 (1H, d, J = 4.6 Hz), 4.90 (1H, d, J = 15.2 Hz), 5.37 (1H, dd, J = 8.5, 4.7 Hz), 6.92−6.97 (4H, m), 7.07−7.11 (2H, m), 7.16−7.25 (4H, m), 7.48−7.55 (3H, m), 7.79−7.84 (3H, m), 7.91 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.0 (d, J = 2 Hz), 61.5 (d, J = 23 Hz), 71.4 (d, J = 28 Hz), 103.4 (d, J = 227 Hz), 124.4 (d, J = 2 Hz), 126.1, 126.1, 127.5, 127.5, 127.8 (d, J = 1 Hz), 127.9, 128.0, 128.0, 128.3, 128.4, 128.5, 131.7 (d, J = 2 Hz), 132.8, 133.2, 133.6, 134.5 (d, J = 1 Hz), 164.9 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −111.2 (1F, m); MS m/z = 411 (M^+); HRMS (EI) Calcd for $C_{27}H_{22}FNO_2$, 411.1635 (M^+); found, 411.1631 (M^+); IR (KBr) cm^{-1} 3362, 1747. Minor isomer **9e**: mp 173.0−173.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72 (1H, bs), 3.62 (1H, dd, J = 15.3, 2.6 Hz), 4.69 (2H, m), 5.51 (1H, d, J = 10.9 Hz), 6.13−6.15 (2H, m), 6.44−6.48 (2H, m), 6.83−6.87 (1H, m), 7.26−7.29 (2H, m), 7.36−7.41 (3H, m), 7.52−7.67 (3H, m), 7.84−7.91 (3H, m), 8.04 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.5 (d, J = 2 Hz), 60.3 (d, J = 23 Hz), 72.7 (d, J = 25 Hz), 104.5 (d, J = 227 Hz), 124.7, 126.2 (d, J = 1 Hz), 126.3, 126.4, 127.2, 127.3, 127.7, 128.0 (d, J = 1 Hz), 128.0, 128.3, 128.4, 128.6, 128.8, 132.2 (d, J = 1 Hz), 132.8, 132.9, 133.1, 133.4, 163.9 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.4 (1F, m); MS m/z = 411 (M^+); HRMS (EI) Calcd for $C_{27}H_{22}FNO_2$, 411.1635 (M^+); found, 411.1637 (M^+); IR (KBr) cm^{-1} 3445, 1748.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxy-1-phenylethyl)-4-phenylazetidin-2-one ***8f*** *and* ***9f***. Compounds **8f** and **9f** were obtained as a colorless solid in 92% yield (**8f**/**9f** = 81/19). Major isomer **8f**: mp 180.0−181.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (3H, d, J = 2.5 Hz), 2.51 (1H, bs), 3.93 (1H, dd, J = 15.2, 2.4 Hz), 4.64 (1H, d, J = 4.8 Hz), 4.93 (1H, d, J = 15.2 Hz), 6.67−6.69 (2H, m), 7.12−7.33 (11H, m), 7.48−7.51 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8 (d, J = 4 Hz), 44.1, 61.9 (d, J = 23 Hz), 73.7 (d, J = 25 Hz), 105.3 (d, J = 231 Hz), 125.7, 125.7, 127.6, 127.7, 128.1, 128.1, 128.2, 128.3, 128.6, 132.1, 134.1, 141.7, 165.1 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −112.3 (1F, m); MS m/z = 375 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{24}H_{23}FNO_2$, 376.1713 ([M + H]$^+$); found, 376.1719 ([M + H]$^+$); IR (KBr) cm^{-1} 3433, 1747. Minor isomer **9f**: mp 152.0−153.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (3H, d, J = 2.2 Hz), 2.30 (1H, bs), 3.72 (1H, dd, J = 15.1, 2.8 Hz), 4.50 (1H, d, J = 4.4 Hz), 4.72 (1H, d, J = 15.1 Hz), 6.38−6.39 (2H, m), 7.01−7.39 (11H, m), 7.67−7.69 (2H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.3 (d, J = 4 Hz), 43.6 (d, J = 2 Hz), 61.6 (d, J = 23 Hz), 74.9 (d, J = 24 Hz), 105.8 (d, J = 228 Hz), 126.5, 127.5, 127.9, 128.0, 128.2 (d, J = 1 Hz), 128.5, 128.5, 128.5, 128.7, 132.6 (d, J = 2 Hz), 133.2, 140.1 (d, J = 4 Hz), 164.1 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −115.4 (1F, m); MS m/z = 375 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{24}H_{23}FNO_2$, 376.1713 ([M + H]$^+$); found, 376.1714 ([M + H]$^+$); IR (KBr) cm^{-1} 3386, 1737.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxyethyl)-4-phenylazetidin-2-one ***8g*** *and* ***9g***. Compounds **8g** and **9g** were obtained as a colorless solid in 65% yield (**8g**/**9g** = 56/44). This reaction was conducted in 1 mmol scale. Both isomers **8g** and **9g**: mp 87.0−88.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (1.7H, dd, J = 6.6, 1.1 Hz), 1.33 (1.3H, dd, J = 6.3, 1.3 Hz), 2.27 (0.56H, d, J = 4.3 Hz), 2.32 (0.44H, d, J = 7.0 Hz), 4.13−4.25$_{\text{both isomers}}$ (1H, m), 4.64 (0.56H, d, J = 3.9 Hz), 4.76 (0.44H, d, J = 4.1 Hz), 4.91$_{\text{both isomers}}$ (1H, d, $J_{\text{one isomer}}$ = 14.6, $J_{\text{the other isomer}}$ = 14.9 Hz), 7.14−7.17$_{\text{both isomers}}$ (2H, m), 7.26−7.32$_{\text{both isomers}}$ (5H, m), 7.36−7.41$_{\text{both isomers}}$ (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.8 (d, J = 6.1 Hz), 17.4 (d, J = 2.3 Hz), 44.2, 61.7 (d, J = 23 Hz), 62.5 (d, J = 23 Hz), 66.4 (d, J = 28 Hz), 67.2 (d, J = 26 Hz), 103.8 (d, J = 228 Hz), 103.9 (d, J = 227 Hz), 128.0, 128.1, 128.5, 128.6, 128.6, 128.7, 128.8, 128.8, 128.9, 132.4, 132.5, 134.2, 164.6 (d, J = 24 Hz), 165.1 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −114.8 (0.56F, d, J = 14.0 Hz), −118.3 (0.44F, d, J = 11.0 Hz); MS m/z = 299 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{18}H_{19}FNO_2$, 300.1400 ([M + H]$^+$); found, 300.1397 ([M + H]$^+$); IR (KBr) cm^{-1} 3453, 1758.

dx.doi.org/10.1021/jo401072h | J. Org. Chem. 2013, 78, 7903−7911

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxy-2-methylpropyl)-4-phenylazetidin-2-one ***8h*** *and* ***9h***. Compounds **8h** and **9h** were obtained as a colorless solid in 76% yield (**8h**/**9h** = 51/49). Both isomers **8h** and **9h**: mp 115.0−116.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.93−1.02$_{\text{both isomers}}$ (6H, m), 1.96−2.04 $_{\text{both isomers}}$ (1H, m), 2.21−2.22 (0.51H, m), 2.37−2.38 (0.49H, m), 3.71 (0.49H, ddd, 17.0, 6.4, 5.6 Hz), 3.86−3.91 (1.51H, m), 4.60 (0.44H, d, J = 4.1 Hz), 4.82 (0.51H, d, J = 4.6 Hz), 4.86−4.90$_{\text{both isomers}}$ (1H, d, $J_{\text{one isomer}}$ = 15.2, $J_{\text{the other isomer}}$ = 14.8 Hz), 7.13−7.16$_{\text{both isomers}}$ (2H, m), 7.25−7.31$_{\text{both isomers}}$ (5H, m), 7.37−7.39$_{\text{both isomers}}$ (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.3 (d, J = 2 Hz), 17.9 (d, J = 1 Hz), 19.5 (d, J = 3 Hz), 19.7 (d, J = 2 Hz), 29.9 (d, J = 3 Hz), 29.9, 44.1 (d, J = 2 Hz), 62.8 (d, J = 22 Hz), 63.8 (d, J = 23 Hz), 73.9 (d, J = 26 Hz), 76.5 (d, J = 25 Hz), 103.7 (d, J = 230 Hz), 104.2 (d, J = 228 Hz), 127.8, 127.9, 128.3, 128.4, 128.5, 128.5, 128.6, 128.7, 128.7, 128.8, 128.8, 129.0, 131.9 (d, J = 1 Hz), 132.3 (d, J = 1 Hz), 134.1, 134.2, 164.8 (d, J = 24 Hz), 165.3 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −114.9 (0.51F, d, J = 4.0 Hz), −117.5 (0.49F, d, J = 17.0 Hz); MS m/z = 327 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{20}H_{23}FNO_2$, 328.1713 ([M + H]$^+$); found, 328.1710 ([M + H]$^+$); IR (KBr) cm^{-1} 3409, 1748.

(3S,4S)/(3R,4R)-1-Benzyl-3-{cyclohexyl(hydroxy)methyl}-3-fluoro-4-phenylazetidin-2-one ***8i*** *and* ***9i***. Compounds **8i** and **9i** were obtained as a colorless solid in 89% yield (**8i**/**9i** = 52/48). Both isomers **8i** and **9i**: mp 117.0−122.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07−1.21$_{\text{both isomers}}$ (5H, m), 1.57−1.99 $_{\text{both isomers}}$ (6H, m), 2.23 (0.48H, d, J = 7.2 Hz), 2.36 (0.52H, d, J = 5.0 Hz), 3.75 (0.52H, ddd, 18.1, 6.4, 5.0 Hz), 3.83−3.91 (1.48H, m), 4.59 (0.52H, d, J = 4.5 Hz), 4.81 (0.48H, d, J = 4.7 Hz), 4.85−4.91$_{\text{both isomers}}$ (1H, d, $J_{\text{one isomer}}$ = 15.0, $J_{\text{the other isomer}}$ = 14.8 Hz), 7.13−7.16$_{\text{both isomers}}$ (2H, m), 7.26−7.32$_{\text{both isomers}}$ (5H, m), 7.36−7.41$_{\text{both isomers}}$ (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8, 25.8, 26.0, 26.0, 26.1, 27.5 (d, J = 1 Hz), 28.0 (d, J = 1 Hz), 29.3 (d, J = 3 Hz), 29.6 (d, J = 1 Hz), 39.4 (d, J = 3 Hz), 39.7, 44.0 (d, J = 1 Hz), 44.0 (d, J = 1 Hz), 62.7 (d, J = 22 Hz), 63.6 (d, J = 23 Hz), 73.6 (d, J = 26 Hz), 76.0 (d, J = 25 Hz), 103.6 (d, J = 229 Hz), 104.9 (d, J = 229 Hz), 127.8, 127.9, 128.3, 128.5, 128.5, 128.5 (d, J = 1 Hz), 128.6, 128.6 (d, J = 1 Hz), 128.7, 128.7, 128.8, 129.0, 132.1 (d, J = 1 Hz), 132.4 (d, J = 1 Hz), 134.1, 134.2, 164.9 (d, J = 24 Hz), 165.4 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −114.2 (0.51F, m), −116.6 (0.49F, d, J = 18.1 Hz); MS m/z = 367 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{23}H_{27}FNO_2$, 368.2026 ([M + H]$^+$); found, 368.2026 ([M + H]$^+$); IR (KBr) cm^{-1} 3478, 2927, 2851, 1746.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxy-2,2-dimethylpropyl)-4-phenylazetidin-2-one ***8j*** *and* ***9j***. Compounds **8j** and **9j** were obtained as a colorless solid in 74% yield (**8j**/**9j** = 67/33). Both isomers **8j** and **9j**: mp 126.0−127.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96−0.98$_{\text{both isomers}}$ (9H, m), 2.33 (0.33H, d, J = 7.1 Hz), 2.75 (0.67H, d, J = 4.2 Hz), 3.66 (0.67H, dd, 24.3, 3.9 Hz), 3.80−3.87 (1.33H, m), 4.59 (0.67H, d, J = 4.4 Hz), 4.86$_{\text{both isomers}}$ (1H, d, J = 14.7 Hz), 4.91 (0.33H, d, J = 4.9 Hz), 7.11−7.16$_{\text{both isomers}}$ (2H, m), 7.26−7.30$_{\text{both isomers}}$ (5H, m), 7.36−7.40$_{\text{both isomers}}$ (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7 (d, J = 3 Hz), 26.8 (d, J = 3 Hz), 35.2 (d, J = 2 Hz), 35.5 (d, J = 2 Hz), 43.9, 43.9, 62.8 (d, J = 22 Hz), 64.7 (d, J = 23 Hz), 75.9 (d, J = 26 Hz), 79.0 (d, J = 22 Hz), 104.4 (d, J = 235 Hz), 105.1 (d, J = 229 Hz), 127.7, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9 (d, J = 2 Hz), 129.1, 129.1 (d, J = 2 Hz), 131.7, 132.2, 134.0, 134.2, 165.1 (d, J = 25 Hz), 165.6 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −112.5 (0.33F, m), −119.1 (0.67F, d, J = 24.3 Hz); MS m/z = 341 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{21}H_{25}FNO_2$, 342.1869 ([M + H]$^+$); found, 342.1877 ([M + H]$^+$); IR (KBr) cm^{-1} 3422, 2959, 1749, 1725.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(2-hydroxybutan-2-yl)-4-phenylazetidin-2-one ***8k*** *and* ***9k***. Compounds **8k** and **9k** were obtained as a colorless solid in 73% yield (**8k**/**9k** = 57/43). This reaction was conducted in 1 mmol scale. Both isomers **8k** and **9k**: mp 112.5−113.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.91−0.94 (1.29H, m), 0.94−0.97 (1.71H, m), 1.20 (1.71H, d, J = 1.7 Hz), 1.36 (1.29H, d, J = 2.0 Hz), 1.57−1.60 (0.86H, m), 1.67−1.73 (0.57H, m), 1.74 (0.43H, bs), 1.79 (0.57H, bs), 1.81−1.87 (0.57H, m), 3.77−3.90$_{\text{both isomers}}$ (1H, m), 4.78 (0.57H, d, J = 4.5 Hz), 4.81 (0.43H, d, J = 4.6 Hz), 4.90−4.93$_{\text{both isomers}}$ (1H, d, $J_{\text{one isomer}}$ = 14.9, $J_{\text{the other isomer}}$ = 14.9 Hz), 7.15−7.17$_{\text{both isomers}}$ (2H, m), 7.26−7.30$_{\text{both isomers}}$ (5H, m), 7.36−7.40$_{\text{both isomers}}$ (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 6.9 (m), 20.2 (d, J = 2 Hz), 20.4 (d, J = 2 Hz), 28.6 (d, J = 2 Hz), 29.2 (d, J = 2 Hz), 44.1 (m), 61.9 (d, J = 22 Hz), 62.2 (d, J = 23 Hz), 73.3 (d, J = 24 Hz), 73.4 (d, J = 24 Hz), 106.2 (d, J = 230 Hz), 106.3 (d, J = 230 Hz), 127.9, 127.9, 128.4 (d, J = 1 Hz), 128.4 (d, J = 1 Hz), 128.6, 128.6, 128.6, 128.7, 128.8, 128.9, 132.7 (d, J = 1 Hz), 132.8 (d, J = 1 Hz), 134.3, 134.4, 164.9 (d, J = 24 Hz), 165.0 (d, J = 23 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ: −114.5 (0.57F, m), −114.8 (0.43F, m); MS m/z = 327 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{20}H_{23}FNO_2$, 328.1713 ([M + H]$^+$); found, 328.1715 ([M + H]$^+$); IR (KBr) cm^{-1} 3450, 1751.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(2-hydroxypropan-2-yl)-4-phenylazetidin-2-one ***8l***. Compound **8l** was obtained as a colorless solid in 76% yield. mp 173.0−173.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (3H, J = 1.5 Hz), 1.38 (3H, J = 1.5 Hz), 1.92 (1H, bs), 3.90 (1H, dd, J = 14.9, 2.4 Hz), 4.78 (1H, d, J = 4.3 Hz), 4.93 (1H, d, J = 14.9 Hz), 7.15−7.18 (2H, m), 7.26−7.31 (5H, m), 7.37−7.39 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2 (d, J = 3 Hz), 24.5 (d, J = 2 Hz), 44.1 (d, J = 2 Hz), 61.9 (d, J = 23 Hz), 71.1 (d, J = 25 Hz), 105.6 (d, J = 227 Hz), 127.9, 128.1 (d, J = 1 Hz), 128.5, 128.5, 128.6, 128.7, 132.6 (d, J = 1 Hz), 134.2, 164.7 (d, J = 24 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −114.7 (1F, m); MS m/z = 313 (M^+); HRMS (*pos*-FAB, Gly.) Calcd for $C_{19}H_{21}FNO_2$, 314.1556 ([M + H]$^+$); found, 314.1549 ([M + H]$^+$); IR (KBr) cm^{-1} 3451, 1755.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all starting substrates **3a**−**3g** (α-bromo-α-fluoro-β-lactams) and all products **4a**−**4h**, **5**, **6**, **7b**−**7g**, **8a**−**8l**, and **9a**−**9k** are provided. ^{19}F NMR spectra for all products **4a**−**4h**, **5**, **7b**−**7g**, **8a**−**8l**, and **9a**−**9k** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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