JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

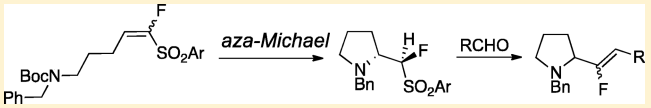
Access to Fluoropyrrolidines by Intramolecular Aza-Michael Addition Reaction

Clothilde Le Guen, Minh-Loan Tran Do, Aurélien Chardon, Cyril Lebargy, Jean-François Lohier, Emmanuel Pfund, and Thierry Lequeux*

Normandie University, LCMT, ENSICAEN, UNICAEN, CNRS, 14000 Caen, France

Supporting Information

ABSTRACT: Study of the intramolecular aza-Michael addition reaction from an aminofluorovinylsulfone opens a new route for the synthesis of pyrrolidine derivatives. An unexpected diastereoselective cyclization reaction was observed, leading preferentially to the *anti*-*N*-benzylpyrrolidine sulfone. The resulting sulfone was reacted with aldehydes to access β-substituted α-fluoroalkenyl pyrrolidines in one step.



INTRODUCTION

Pyrrolidine derivatives, in particular, fluorine-containing pyrrolidines, play a major role in organic synthesis.[1−3] Fluoroalkenyl pyrrolidines are employed as peptide isosteres to design enzyme inhibitors or a new generation of organocatalysts.[4,5] In both cases, the amide bond of the N-terminal or C-terminal proline is replaced by a fluoroalkene moiety (Figure 1).[6] The N-terminal modification has been extensively applied

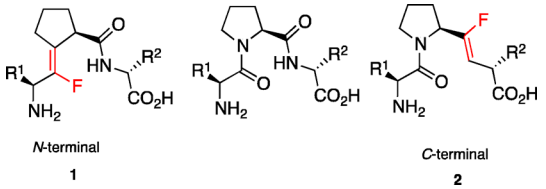


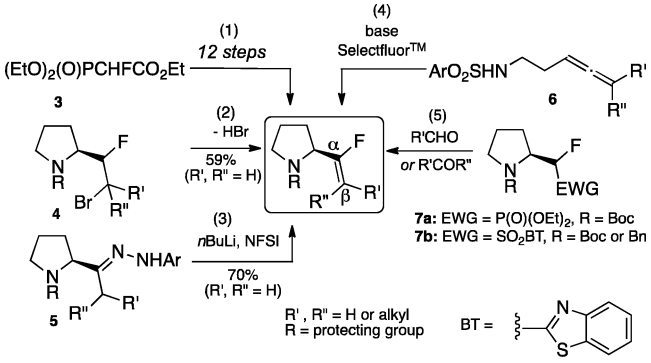
Figure 1. Tripeptide and fluoroalkene isosteres.

since the first report of the related synthesis of peptidase inhibitors containing fluoroalkene amide surrogates **1**.[7,8] However, the corresponding C-terminal modification is quite rare and was reported for the preparation of organocatalysts **2**.[9,10]

Peptide precursor **2** was prepared by a linear approach from phosphonate **3** (Scheme 1, eq 1).[11] Convergent synthesis of fluoroalkenyl C-terminal proline isosteres is conditioned by the available routes to prepare fluoroalkenyl pyrrolidine derivatives. Few works were reported in this field. For the preparation of α-fluoroethenyl pyrrolidines (R′, R″ = H), two expeditious methods required the dehalogenation reaction and the Shapiro fluorination reaction of pyrrolidines **4** and **5**, respectively (Scheme 1, eqs 2 and 3).[12,13]

The preparation of β,β-disubstituted α-fluoroalkenyl pyrrolidines (R′, R″ ≠ H) was realized exclusively by the cyclization reaction of allenoic sulfonamides **6** mediated by electrophilic fluorinating reagent (Scheme 1, eq 4).[14] Obviously, a most general route was explored from carbonyl compounds and phosphonate **7a**.[15] Nevertheless, this phosphonate involved in

Scheme 1. Synthesis of Alkylidene Prolines



the Horner−Wadsworth−Emmons (HWE) reaction failed to react with aldehydes (Scheme 1, eq 5). Indeed, the dehydrofluorination reaction of **7a** led to the corresponding vinylphosphonate in basic medium instead of the formation of the expected fluoroalkenes.

Previously, the modified Julia reaction was applied with success to the synthesis of fluoroalkylidenes, and it is established that this reaction is efficient where the HWE reaction is not.[16] We therefore sought to explore the synthesis of fluoroalkenyl pyrrolidines based on the modified Julia reaction from sulfone **7b** (Scheme 1) and report our results in this field.

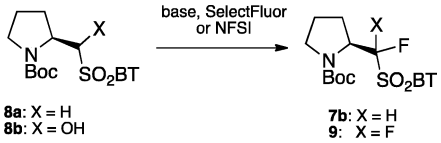
RESULTS AND DISCUSSION

To prepare a benzothiazolylsulfone, such as compound **7b**, the fluorination of sulfone **8a** with *N*-fluorobenzenesulfonimide (NFSI) was explored in the presence of LDA or LiHMDS following reported procedures (Scheme 2).[17] At best, after several tests, the fluorination step afforded a mixture of starting sulfone **8a** and mono- and difluorosulfones **7b** and **9** (ratio **8a**/

Received: June 6, 2016
Published: July 18, 2016

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720

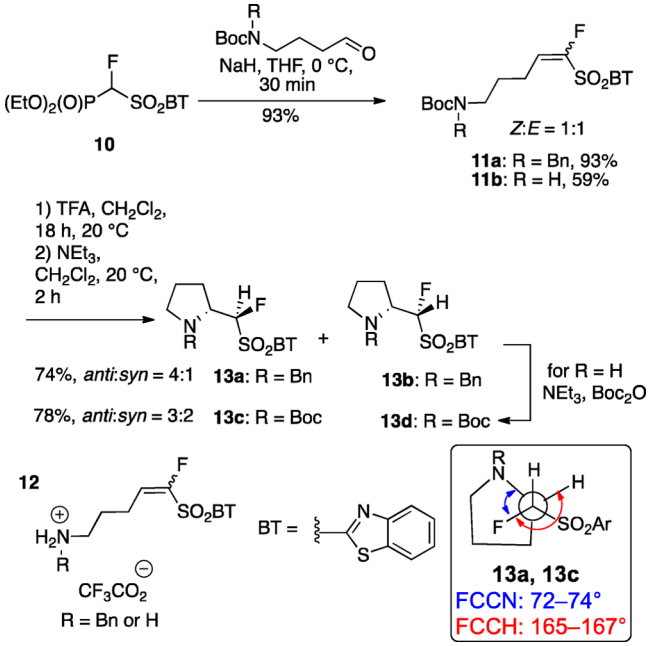
Scheme 2. Fluorination of Pyrrolidinosulfone 8



7b/**9** = 0.2:0.58:0.22). In the presence of SelectFluor and NaH, similar results were observed, and a complex mixture of products was obtained when the anion was formed at −78 °C with LiHMDS prior to the addition of the electrophilic fluorinating reagent (NFSI or SelectFluor). The other possibility for introduction of a fluorine atom consists of displacing a hydroxyl function with a nucleophilic fluorinating reagent.[15] However, the corresponding hydroxysulfone **8b** was not available, and we were not able to obtain the sulfide precursor of **8b** by addition of 2-mercaptobenzothiazole onto *N*-Boc-prolinal (Scheme 2).

The difficulties occurring for the introduction of a fluorine atom prompted us to explore the intramolecular aza-Michael reaction from unsaturated aminosulfone. Aza-Michael addition reaction has been largely developed in the literature to prepare substituted amines, including cyclic and linear amines.[18,19] Having in hand the fluorophosphonosulfone **10** as a potent HWE reagent for the preparation of α-fluoro α,β-unsaturated benzothiazolylsulfones,[20] we explored the synthesis of alkenes **11** as a precursor of fluoropyrrolidines **13** (Scheme 3).

Scheme 3. Preparation of fluoropyrrolidine 13



The olefination of *N*-benzyl-*N*-Boc-4-aminobutanal was realized by deprotonation of phosphonate **10** with NaH. The reaction in THF at 20 °C afforded a nonseparable mixture of the expected vinylsulfones **11a,b** in 93% yield. The reaction was realized with other bases, including NaHMDS, LDA, *t*BuOK, or K_2CO_3, in THF at −78 or 20 °C.[21] In all cases, a 1:1 mixture of *Z*/*E* alkenes **11a,b** was obtained, in contrast to previous works done in nonfluorinated series.

Deprotection of the resulting protected amines **11a,b** was realized in the presence of CF_3COOH (TFA) to afford the intermediate crude ammonium salt **12**. The latter was treated with NEt_3 (10 equiv) in CH_2Cl_2 at 20 °C. After being stirred for 2 h, pyrrolidines **13a,b** were obtained in 74% yield. The cyclization step from a 1:1 mixture of salts *Z*/*E*-**12** was selective, leading to isomers **13a** and **13b** in a 4:1 ratio. A sample of the major isomer **13a** was isolated and identified as the *anti* isomer by X-ray analysis (see the Supporting Information).[22] The major isomer **13a** adopted a conformation where a torsion angle between the fluorine atom and the nitrogen atom of 72° (N−C−C−F torsion angle) was observed, resulting of a fluorine gauche effect.[4,5,23] This preference for a fluorine gauche conformation was also detected in solution with typical values of the ^{19}F NMR coupling constant observed for the major isomer **13a** ($^3J_{HF}$ 25.9 Hz vs 11.7 Hz in **13b**). In contrast, the cyclization reaction performed with **11b** was less selective and led to a 3:2 diastereomeric mixture of *N*-Boc-protected analogues **13c,d** in 78% yield. In this case, the intermediate pyrrolidines were difficult to handle and were characterized after treatment of the crude with excess Boc_2O. A sample of the *anti* major isomer **13c** was obtained and characterized by X-ray analysis (see the Supporting Information).[22] As mentioned in the benzyl series, this isomer also presented a typical conformation induced by the fluorine gauche effect with a N−C−C−F torsion angle of 74°.

A series of experiments were then carried out to rationalize the stereochemical *anti* selectivity outcome observed in the formation of **13a**. First, epimerization experiments of **13b** were realized in the presence of NEt_3 or DBU in THF and with *t*BuOK in isopropyl alcohol at 0 and 20 °C. In all cases, no change of the initial ratio of isomers was observed. A similar result was observed when deprotonation−reprotonation of a mixture of sulfones **13a,b** with a strong base such as LiHMDS in THF at −78 °C followed by a quench with NH_4Cl_{aq} was realized (at higher temperature, partial decomposition of **13a,b** was observed). An additional experiment realized with 10% MeONa in MeOH at 20 °C induced a decomposition of **13a,b**.

Second, no effect of the temperature on the isomer ratio was observed when the cyclization step was performed under refluxed solvent by slow addition of NEt_3 to the ammonium salts **12** or when a mixture of isomers **13a,b** was maintained under refluxed THF for 24 h. In addition, acidic medium had no effect on this ratio, as demonstrated by an experiment performed at 20 °C up to 70 °C (DMSO-d_6) in the presence of a catalytic amount of *para*-toluene sulfonic acid (10%).

The course of the reaction was monitored by ^{19}F NMR analysis from 5 to 20 °C after treatment of the crude ammonium *E*,*Z*-**12** (1:1 ratio) with NEt_3 in $CDCl_3$. The graph of the evolution of the percentage of each compound was plotted according to time (Figure 2). The percentage of alkenes dropped progressively with increasing time, and the two isomers **13a** and **13b** were formed in a constant ratio of 85:15.

In addition, after separation of alkenes *E*-**11** and *Z*-**11**,[24] the cyclization reaction was performed in the presence of NEt_3 from each isomer separately. From ammonium salt *E*-**12** the *anti* isomer **13a** was formed exclusively (Scheme 4). From ammonium salt *Z*-**12**, a mixture of pyrrolidines **13a** and **13b** was obtained in a 62:38 ratio, again with a preference for the *anti* isomer (Scheme 4). This suggests that no isomerization of starting alkenes *Z*,*E*-**12** occurred during the cyclization step, but a conformational change of intermediate II into I occurred to afford **13a** as the main product of the reaction. This change was driven by steric repulsions between the benzyl and the benzothiazol groups during the cyclization step (Scheme 4).

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720

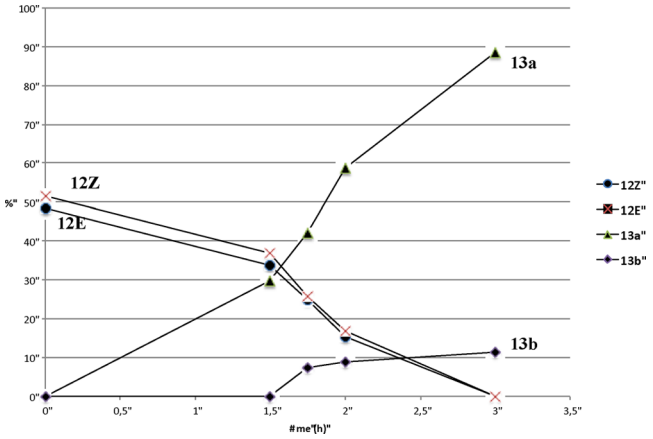
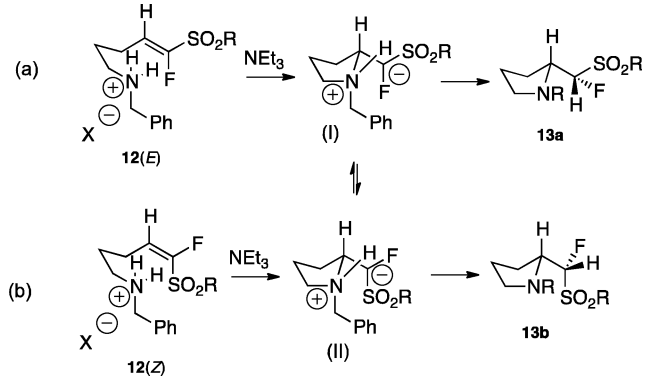
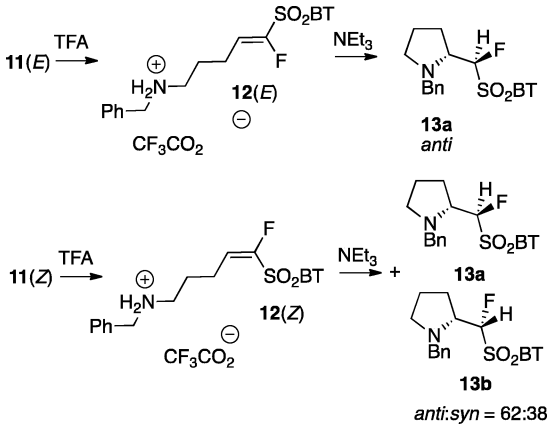


Figure 2. Evolution of the percentage of **13a,b** and *Z,E*-**12** by ^{19}F NMR.

Scheme 4. Selective Formation of 13 and Hypothetical Mechanism

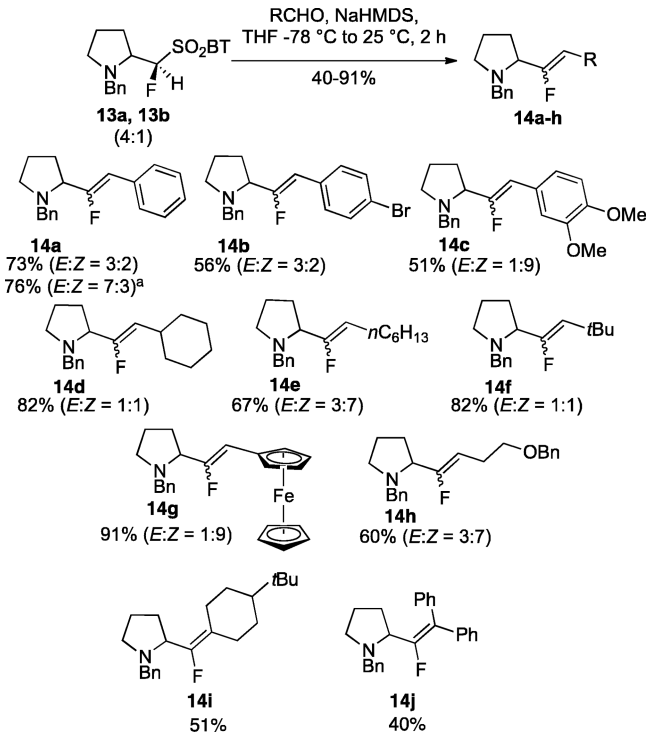


Indeed, as mentioned previously, the cyclization reaction performed with **11b** (*Z*/*E* = 1:1) led to a 3:2 diastereomeric mixture of *N*-Boc-protected analogues **13c** and **13d**.



Sulfones **13a** and **13b** (4:1 ratio) were then engaged in the modified Julia reaction to check if direct access to β-substituted α-fluoroalkenyl pyrrolidines was possible (Scheme 5). The reaction was conducted in the presence of base at −78 or 20 °C by addition of the base to a mixture of sulfone **13** and aldehyde.[20] No reaction was observed with DBU, TMG (20 °C or THF reflux), or *t*BuOK (20 °C). In contrast to the phosphonate **7a**, the olefination reaction proceeded smoothly with NaHMDS (−78 to 20 °C) from aliphatic and aromatic

Scheme 5. Formation of β-Substituted α-Fluoroalkenyl Pyrrolidines



[a]Reaction performed in the presence of KHMDS.

aldehydes, affording the expected alkenes **14a−h** in 51−91% yields. From benzaldehyde, *p*-bromobenzaldehyde, or veratraldehyde, pyrrolidines **14a−c** were obtained in 51−73% yield, and *Z*-selectivity increased with the electronic density of the aromatic ring up to a 9:1 *Z*/*E* ratio. From aliphatic aldehydes, such as cyclohexylcarboxaldehyde, dimethylpropanal, or heptanal, alkenes **14d−f** were obtained in 67−82% yields. Best selectivity was observed with ferrocenecarboxyldehyde. The corresponding *Z*-alkene was obtained as a major product in a 9:1 *Z*/*E* ratio and was isolated in 91% yield. From 3-benzyloxypropanal, the expected alkene **14h** was obtained in 60% yield with a preference for the *Z*-alkene. The olefination of ketones was more difficult; nevertheless, compounds **14i,j** were isolated in non-optimized yields of 40−51%. No improvement of the selectivity was observed in the presence of additive ($MgBr_2$) or when the reaction was performed in DMF instead of THF. In addition, the experiment was realized with other bases (LDA and KHMDS). A preference for the *E*-alkene was noticed with KHMDS, and compound **14a** was obtained in a 3:7 *Z*/*E* ratio and isolated in 76% yield. The selectivity of the reaction is strongly dependent on the reagents, the solvent, and the bases involved, as observed for the Julia−Kocienski reaction performed with a fluorinated tetrazolylsulfone.[25] Finally, deprotection of alkene **14b** was explored by catalytic hydrogenation (Pd(C) and $Pd(OH)_2$) at 20 °C in acetic acid. However, the reaction did not reach completion after 18 h, and a mixture of products was observed after prolonged reaction time. Optimization of the *N*-Boc-protected synthesis of pyrrolidinesulfones **13c,d** is underway to apply the present strategy to the preparation of modified biomolecules.

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720

CONCLUSION

In conclusion, we report the preparation of a fluorobenzothiazolylsulfone as olefinating reagent for the preparation of pyrrolidines. This sulfone was obtained in three steps from a phosphonate in good yield and excellent selectivity in the *N*-benzyl series. This sulfone involved in the modified Julia reaction allowed a direct access to β-substituted α-fluoroalkenyl pyrrolidine derivatives in good yields from either aliphatic or aromatic aldehydes, and this approach represents an issue in the HWE reaction.

EXPERIMENTAL SECTION

General Details. Unless otherwise specified, all reagents were obtained from commercial suppliers and were used without purification. For anhydrous conditions, the glassware was flamed under a continuous nitrogen flow and cooled to room temperature before the experiment was performed. Anhydrous solvents (THF and CH_2Cl_2) were purified by passing the degassed solvents (N_2) through a column of activated alumina. Flash column chromatography was performed on silica gel (60, 40−63 μm) with air pressure. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a 400 or 500 MHz apparatus in deuterated solvent. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in hertz (Hz). Mass spectra and high-resolution mass spectra (HRMS) were obtained on a Q-TOF (quadrupole time-of-flight) micro instrument with an electrospray source in the EI or ESI mode.

(*Z*/*E*)-*tert*-Butyl[5-(benzothiazol-2-ylsulfonyl]-5-fluoropent-4-enyl)-(benzyl)carbamate (11a). To a solution of diethyl[(1,3-benzothiazole-2-sulfonyl)fluoro)methyl]phosphonate **10**[20] (1.40 g, 3.81 mmol, 1.0 equiv) and 4-[*N*-benzyl-*N*-(*tert*-butyloxycarbonyl)]-amino-1-butanal[26] (1.55 g, 5.72 mmol, 1.5 equiv) in THF (15 mL) at 0 °C was added portionwise sodium hydride (60% in oil, 177 mg, 4.57 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h at room temperature, quenched with a saturated aqueous solution of NH_4Cl, and extracted three times with Et_2O (3 × 5 mL). Combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded compound **11a** (1.87 g, 93%, yellow oil) as a nonseparable mixture of stereoisomers (*Z*/*E* = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) (*Z*)-**11** δ 8.21−8.19 (m, 1H), 8.02−8.00 (m, 1H), 7.65−7.59 (m, 2H), 7.33−7.30 (m, 2H), 7.27−7.23 (m, 3H), 6.22−6.04 (m, 1H), 4.44 (br s, 2H), 3.23−3.30 (m, 2H), 2.67 (br s, 2H), 1.74 (br s, 2H), 1.49 and 1.44 (s, 9H); (*E*)-**11** δ 8.20−8.17 (m, 1H), 7.98−7.96 (m, 1H), 7.62−7.55 (m, 2H), 7.27−7.24 (m, 2H), 7.21−7.16 (m, 3H), 6.42 (dt, $^3J_{HF}$ = 31.5 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.36 (s, 2H), 3.21−3.14 (m, 2H), 2.22 (br s, 2H), 1.64 (br s, 2H), 1.44, and 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*/*E*)-**11** δ 163.9, 163.9, 155.7, 152.9 (d, $^1J_{CF}$ = 288.4 Hz), 152.6, 149.9 (d, $^1J_{CF}$ = 287.8 Hz), 138.2, 134.4, 137.3, 128.5, 128.4, 128.3, 127.8, 127.2, 127.1, 125.8, 124.0 (m), 122.2, 79.9, 79.8, 50.6, 50.0, 45.8, 28.3, 28.4, 27.8, 27.5, 26.4, 22.3, 22.2; ^{19}F NMR (376 MHz, $CDCl_3$) (*Z*)-**11** δ −115.6 (d, $^3J_{FH}$ = 21.4 Hz, 1F), −115.7 (d, $^3J_{FH}$ = 21.4 Hz, 1F); (*E*)-**11** δ −127.0 (d, $^3J_{FH}$ = 31.5 Hz, 1F), −127.2 (d, $^3J_{FH}$ = 31.5 Hz, 1F); MS (ESI$^+$) *m*/*z* 491 [M + H]$^+$, 32%), 436 (3), 435 (100), 391 (58); HRMS (ESI$^+$) *m*/*z* $C_{24}H_{27}FN_2O_4S_2$ ([M + H]$^+$) requires 491.1475; found 491.1457.

(*Z*/*E*)-*tert*-Butyl[5-(benzothiazol-2-ylsulfonyl]-5-fluoropent-4-enyl)-carbamate (11b). To a solution of 4-[*N*-(*tert*-butyloxycarbonyl)]amino-1-butanal[27] (491 mg, 2.62 mmol, 1.0 equiv) and diethyl[(1,3-benzothiazole-2-sulfonyl)fluoro)methyl]phosphonate **10**[20] (867 mg, 2.36 mmol, 0.9 equiv) in THF (15 mL) at 0 °C was added portionwise sodium hydride (60% in oil, 123 mg, 3,07 mmol, 1.3 equiv). The reaction mixture was stirred for 2 h at room temperature, quenched with a saturated aqueous solution of NH_4Cl, and extracted three times with Et_2O (3 × 5 mL). Combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash column chromatography (pentane/Et_2O, 3:2) afforded compound **11b** (591.5 mg, 59%, yellow oil) as a nonseparable mixture of stereoisomers (*Z*/*E* = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 1H), 8.01 (m, 1H), 7.67−7.58 (m, 2H), 6.51 (dt, $^2J_{HF}$ = 31.5 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, *E*), 6.17 (dt, $^2J_{HF}$ = 20.8 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, *Z*), 5.14 (s,1H), 4.69 (s, 1H), 3.23−3.12 (m, 2H), 2.78 (q, $^3J_{HH}$ = 8.4 Hz, 1H), 2.36 (q, $^3J_{HH}$ = 7.8 Hz, 1H), 1.73 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 163.5, 156.1, 155.9, 153.0 (d, $^1J_{CF}$ = 182.9 Hz, *E*), 150.1 (d, $^1J_{CF}$ = 173.8 Hz, *Z*), 152.7, 137.4, 128.4, 127.9, 125.8, 124.4, 122.4, 122.2, 79.3, 39.9, 39.5, 29.3, 28.41, 22.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.5 (d, $^3J_{FH}$ = 20.8 Hz, *Z*), −127.1 (d, $^3J_{FH}$ = 31.5 Hz, *E*); MS (ESI$^+$) *m*/*z* (calc) ([M + H]$^+$), 401 (40), 345 (100), 301 (20); HRMS (ESI$^+$) *m*/*z* $C_{17}H_{21}FN_2O_4S_2Na$ ([M + Na]$^+$) requires 423.0824; found 423.0809.

2-[(Fluoro-2-benzothiazolylsulfonyl)-methyl]-1-benzylpyrrolidine (13a,b). To a solution of (*Z*/*E*)-*tert*-butyl[5-(benzothiazol-2-ylsulfonyl]-5-fluoropent-4-enyl)-(benzyl)carbamate **11a** (3.00 g, 6.11 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added trifluoroacetic acid (14.73 mL, 192.07 mmol, 31 equiv). The reaction mixture was stirred for 18 h at room temperature. The crude product was concentrated under reduced pressure to remove mainly the excess CF_3CO_2H, then diluted in CH_2Cl_2 (30 mL), and cooled at 0 °C. Et_3N (8.51 mL, 61.10 mmol, 10 equiv) was added dropwise, and the reaction mixture was stirred for 2 h at 20 °C. The crude was washed with a saturated aqueous solution of NH_4Cl (2 × 5 mL), a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The yellow solid was purified by crystallization (MeOH) to afford compounds **13a**,**b** (1.76 g, 74%, white solid) as a nonseparable mixture of diastereoisomers (dr = 4:1). A sample of the major isomer was obtained by crystallization in Et_2O/pentane (1:9) and was submitted to X-ray analysis: mp 79−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.21 (m, 1H), 8.00−7.97 (m, 1H), 7.64−7.56 (m, 2H), 7.31−7.11 (m, 5H), 5.50 (dd, $^2J_{HF}$ = 48.3 Hz, $^3J_{HH}$ = 1.6 Hz, 1H, *major*), 5.44 (dd, $^2J_{HF}$ = 48.0 Hz, $^3J_{HH}$ = 8.2 Hz, 1H, *minor*), 4.11 (d, $^3J_{HH}$ = 13.2 Hz, 1H, *minor*), 3.99 (d, $^3J_{HH}$ = 13.2 Hz, 1H, *major*), 3.66−3.61 (m, 2H, *major*), 3.48 (d, $^3J_{HH}$ = 13.2 Hz, 1H, *minor*), 3.42 (m, 1H, *minor*), 2.96−2.93 (m, 1H), 2.36−2.24 (m, 1H), 2.20−2.10 (m, 1H), 1.99−1.89 (m, 1H), 1.79−1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (*minor*), 163.2 (*major*), 152.8 (*minor*), 152.7 (*major*), 139.1 (*major* and *minor*), 138.4 (*major* and *minor*), 137.4 (*major* and *minor*), 128.8 (*major*), 128.7 (*minor*), 128.5 (*major* and *minor*), 128.4 (*major* and *minor*), 127.8 (*major* and *minor*), 127.2 (*major*), 126.9 (*minor*), 122.4 (*major* and *minor*), 104.6 (d, $^1J_{CF}$ = 222.2 Hz, *minor*), 101.6 (d, $^1J_{CF}$ = 227.8 Hz, *major*), 60.7 (d, $^2J_{CF}$ = 19.0 Hz, *major*), 60.5 (d, $^2J_{CF}$ = 12.1 Hz, *minor*), 60.4 (*minor*), 59.0 (*major*), 53.7 (*minor*), 53.6 (*major*), 28.0 (d, $^3J_{CF}$ = 5.3 Hz, *minor*), 25.6 (d, $^3J_{CF}$ = 6.5 Hz, *major*), 24.4 (*major* and *minor*); ^{19}F NMR (376 MHz, $CDCl_3$) δ −177.5 (dd, $^2J_{FH}$ = 48.0, $^3J_{FH}$ = 11.7, 1F, *minor*), −189.5 (dd, $^2J_{FH}$ = 48.3, $^3J_{FH}$ = 25.9, 1F, *major*); MS (ESI$^+$) *m*/*z* 413 ([M + Na]$^+$, 100%), 391 ([M + H]$^+$, 68%), 322 (4), 192 (18), 160 (100); HRMS (ESI$^+$) *m*/*z* $C_{19}H_{20}FN_2O_2S_2$ ([M + H]$^+$) requires 391.0950; found 391.0948.

***tert*-Butyl-2-[(fluoro-2-benzothiazolylsulfonyl)-methyl]-1-pyrrolidine Carboxylate (13c,d).** To a solution of (*Z*/*E*)-*tert*-butyl[5-(benzothiazol-2-ylsulfonyl]-5-fluoropent-4-enyl)-carbamate **11b** (376 mg, 0.939 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (1.1 mL, 14.08 mmol, 15 equiv). The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was concentrated under reduced pressure to remove mainly the excess CF_3CO_2H. The crude product (560 mg) was diluted in CH_2Cl_2 (10 mL) and cooled at 0 °C. Et_3N (1.12 mL, 8.34 mmol, 8.9 equiv) was added dropwise, and the reaction mixture was stirred for 2 h at 20 °C, followed by addition of Boc_2O (1.12 mL, 4.86 mmol, 5.2 equiv). The mixture was then stirred for 18 h at 20 °C and quenched with a saturated aqueous solution of NH_4Cl (5 mL). The crude product was washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (pentane/Et_2O = 3:2) to afford compound **13c** (163.4 mg, 43%, white solid) and compound **13d** (134.0 mg, 35%, yellow oil). A sample of the major isomer was obtained by crystallization in Et_2O/pentane (1:9) and

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720

identified by X-ray analysis: mp 56−58 °C. **13c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.21 (m, 1H), 8.00−7.97 (m, 1H), 7.64−7.56 (m, 2H), 6.65 and 6.25 (d, $^2J_{HF}$ = 49.1 Hz, 1H), 4.70 (d, $^3J_{HH}$ = 30.7 Hz, 1H), 3.60−3.40 (m, 2H), 2.50−2.30 (m, 1H), 2.20−2.05 (m, 1H), 2.00−1.80 (m, 2H), 1.52 and 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 162.7, 154.3, 153.5, 152.8, 137.4, 128.5, 128.4, 127.9, 127.8, 125.9, 125.8, 122.4, 122.3, 101.1, and 99.9 (d, $^1J_{CF}$ = 229.6 Hz), 81.1, 80.4, 55.2, and 55.1 (d, $^2J_{CF}$ = 18.2 Hz), 46.6, 46.1, 28.5, 28.4, 26.3, 26.2, 25.5, 24.8, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −194.5 and −194.8 (dd, $^2J_{FH}$ = 49.1, $^3J_{FH}$ = 30.7, 1F); MS (ESI$^+$) m/z 423 ([M + Na]$^+$), 80%), 367 (30), 303 (38), 231 (100), 158 (40), 135 (40); HRMS (ESI$^+$) m/z $C_{17}H_{21}FN_2NaO_4S_2$ ([M + Na$^+$) requires 423.0824; found 423.0827. **13d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.30 (m, 1H), 8.10−8.00 (m, 1H), 7.70−7.50 (m, 2H), 6.00 and 5.55 (d, $^2J_{HF}$ = 47.7 Hz, 1H), 4.70 (m,1H), 3.60−3.30 (m, 2H), 2.70−1.80 (m, 4H), 1.42 and 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 154.3, 152.8, 137.5, 128.4, 127.8, 127.8, 126,0, 125.8, 124,8,122.7, 122.3, 121.7, 100.5 and 99,4 (d, $^1J_{CF}$ = 226.4 Hz), 80.5, 56.4, 55.0, 50.8, 46.8 (d, $^2J_{CF}$ = 25.1 Hz), 46.2, 28.4, 28.2, 26.4, 23.9, 22.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −179.4 and −179.5 (d, $^2J_{FH}$ = 47.7, 1F); MS (ESI$^+$) m/z 423 ([M + Na]$^+$, 80%), 323 (50), 232 (100), 158 (68), 136 (40); HRMS (ESI$^+$) m/z $C_{17}H_{21}FN_2NaO_4S_2$ ([M + Na$^+$) requires 423.0824; found 423.0827.

General Procedure A: Preparation of Fluorinated Allylamines (14a−h). To a solution of fluoroaminosulfones **13a,b** (200 mg, 0.51 mmol, 1.0 equiv) and aldehyde (1.05 equiv) in THF (5 mL) was added dropwise NaHMDS (1 M in THF, 1.5 equiv) at −78 °C. After 30 min at −78 °C, the reaction mixture was slowly warmed from −78 to 0 °C over 2 h under stirring and then quenched with a saturated aqueous solution of NH_4Cl and extracted three times with Et_2O. Combined organic layers were washed with an aqueous solution of NaOH (10%) and a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give fluorinated allylamines.

(*Z*/*E*)-1-Benzyl-2-(1-fluoro-2-phenylvinyl)pyrrolidine (14a). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (200 mg, 0.51 mmol, 1.0 equiv), benzaldehyde (54 μL, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.76 mL, 0.76 mmol, 1.5 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14a** (105 mg, 73%, colorless oil) as a nonseparable mixture of stereoisomers (*E*/*Z* = 3:2). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (200 mg, 0.51 mmol, 1.0 equiv), benzaldehyde (54 μL, 0.54 mmol, 1.05 equiv), and KHMDS (1 M in THF, 1.1 mL, 1.1 mmol, 2.0 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14a** (110 mg, 76%, colorless oil) as a nonseparable mixture of stereoisomers (*E*/*Z* = 7:3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.08 (m, 10H), 6.35 (d, $^3J_{HF}$ = 21.0 Hz, 1H, *E*), 5.74 (d, $^3J_{HF}$ = 39.3 Hz, 1H, *Z*), 4.04 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.86 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.52 (dt, $^3J_{HF}$ = 29.3 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, *E*), 3.28 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.18 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.10 (dt, $^3J_{HF}$ = 19.7 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *Z*), 2.96−2.86 (m, 1H), 2.28−1.10 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4 (d, $^1J_{CF}$ = 267.7 Hz, *Z*), 160.3 (d, $^1J_{CF}$ = 256.8 Hz, *E*), 139.1, 138.4, 133.5 (m), 133.4 (m,), 129.0, 128.8 (d, $^4J_{CF}$ = 2.6 Hz), 128.7, 128.5 (d, $^4J_{CF}$ = 7.3 Hz), 128.4, 128.3, 128.2, 128.0, 127.0, 126.9, 126.8, 111.3 (d, $^2J_{CF}$ = 27.3 Hz, *E*), 106.8 (d, $^2J_{CF}$ = 7.3 Hz, *Z*), 65.4 (d, $^2J_{CF}$ = 27.8 Hz, *Z*), 60.1 (d, $^2J_{CF}$ = 23.6 Hz, *E*), 58.2, 57.3, 53.3, 52.9, 29.2, 28.3, 22.8, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.5 (dd, $^3J_{FH}$ = 39.3 Hz, $^3J_{FH}$ = 19.7 Hz, 1F, *Z*), −116.6 (dt, $^3J_{FH}$ = 29.3 Hz, $^3J_{FHcis}$ = 21.0 Hz, 1F, *E*); MS (ESI$^+$) m/z 282 ([M + H]$^+$, 100%), 262 (15), 190 (17), 181 (10), 174 (23), 133 (15), 120 (13), 120 (5); HRMS (ESI$^+$) $C_{19}H_{21}FN$ ([M + H]$^+$) requires 282.1658; found 282.1666.

(*Z*/*E*)-1-Benzyl-2-(2-(4-bromophenyl)-1-fluorovinyl)pyrrolidine (14b). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (200 mg, 0.51 mmol, 1.0 equiv), *para*-bromobenzaldehyde (100 mg, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.76 mL, 0.76 mmol, 1.5 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14b** (102.80 mg, 56%, colorless oil) as a nonseparable mixture of stereoisomers (*E*/*Z* = 3:2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−6.83 (m, 9H), 6.13 (d, $^3J_{HF}$ = 20.6 Hz, 1H, *E*), 5.57 (d, $^3J_{HF}$ = 38.8 Hz, 1H, *Z*), 3.89 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.71 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.35 (dt, $^3J_{HF}$ = 29.2 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, *E*), 3.20 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.08 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.00 (dt, $^3J_{HF}$ = 19.1 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, *Z*), 2.86−2.77 (m, 1H), 2.24−1.52 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, $^1J_{CF}$ = 268.9 Hz, *Z*), 161.0 (d, $^1J_{CF}$ = 258.2 Hz, *E*), 139.0, 138.4, 132.4 (m), 132.3 (m), 131.5, 130.5 (d, $^4J_{CF}$ = 2.7 Hz), 130.1 (d, $^4J_{CF}$ = 7.7 Hz), 128.9, 128.7, 128.2, 128.0, 127.0, 126.9, 120.9, 120.6 (d, $^6J_{CF}$ = 3.4 Hz), 110.2 (d, $^2J_{CF}$ = 28.4 Hz, *E*), 105.6 (d, $^2J_{CF}$ = 7.1 Hz, *Z*), 65.2 (d, $^2J_{CF}$ = 27.9 Hz, *Z*), 60.0 (d, $^2J_{CF}$ = 23.6 Hz, *E*), 58.3, 57.4, 53.4, 53.3, 53.1, 29.3, 28.4, 22.9, 22.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.9 (dd, $^3J_{FH}$ = 38.8 Hz, $^3J_{FH}$ = 19.1 Hz, 1F, *Z*), −100.6 (dt, $^3J_{FH}$ = 29.2 Hz, $^3J_{FH}$ = 20.6 Hz, 1F, *E*); MS (ESI$^+$) m/z 362 ([M($C_{19}H_{19}{}^{80}$BrFN) + H]$^+$, 100%), 360 ([M($C_{19}H_{19}{}^{79}$BrFN) + H]$^+$, 100%), 340 (7), 268 (12), 253 (4), 211 (5), 174 (8), 120 (5), 91 (50); HRMS (ESI$^+$) $C_{19}H_{20}{}^{79}$BrFN ([M + H]$^+$) requires 360.0763; found 360.0752.

(*Z*/*E*)-1-Benzyl-2-(2-(3,4-dimethoxyphenyl)-1-fluorovinyl)pyrrolidine (14c). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidine **13a,b** (200 mg, 0.51 mmol, 1.0 equiv), 2,4-dimethoxybenzaldehyde (90 mg, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.76 mL, 0.76 mmol, 1.5 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14c** (88.0 mg, 51%, yellow oil) as a nonseparable mixture of stereoisomers (*E*/*Z* = 1:9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−6.63 (m, 8H), 6.28 (d, $^3J_{HF}$ = 21.0 Hz, 1H, *E*), 5.64 (d, $^3J_{HF}$ = 39.3 Hz, 1H, *Z*), 4.02 (d, $^3J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.87 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.82 (s, 3H), 3.80 (s, 3H), 3.52 (dt, $^3J_{HF}$ = 29.2 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, *E*), 3.27 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.17 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.07 (dt, $^3J_{HF}$ = 20.6 Hz, $^3J_{HH}$ = 7.6 Hz, 1H, *Z*), 2.95−2.88 (m, 1H), 2.23−1.12 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, $^1J_{CF}$ = 255.6 Hz, *E*), 158.9 (d, $^1J_{CF}$ = 265.6 Hz, *E*), 148.6, 148.1, 148.0, 139.0, 138.5, 129.0, 128.8, 128.1, 128.0, 126.8, 126.4 (d, $^3J_{CF}$ = 2.5 Hz), 126.3, 121.3 (d, $^4J_{CF}$ = 6.3 Hz), 121.2 (d, $^4J_{CF}$ = 2.6 Hz), 112.2 (m), 111.4 (d, $^2J_{CF}$ = 9.1 Hz, *Z*), 111.2 (m), 111.0, 110.9, 106.7 (d, $^2J_{CF}$ = 7.3 Hz), 65.5 (d, $^2J_{CF}$ = 27.6 Hz, *Z*), 60.3 (d, $^2J_{CF}$ = 23.9 Hz, *E*), 58.1, 57.4, 55.9, 55.8, 55.7, 53.2, 52.9, 29.1, 28.3, 22.8, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.5 (dd, $^3J_{FH}$ = 39.3 Hz, $^3J_{FH}$ = 20.6 Hz, 1F, *Z*), −117.3 (dt, $^3J_{FH}$ = 29.2 Hz, $^3J_{FH}$ = 21.0 Hz, 1F, *E*); MS (ESI$^+$) m/z 342 ([M + H]$^+$, 93%), 322 (95), 320 (10), 305 (4), 294 (10), 244 (20), 235 (82), 222 (17), 215 (17), 207 (21), 193 (75), 189 (12), 184 (10), 169 (5), 151 (100), 146 (8), 120 (18), 91 (79); HRMS (ESI$^+$) $C_{21}H_{25}FNO_2$ ([M + H]$^+$) requires 342.1869; found 342.1870.

(*Z*/*E*)-1-Benzyl-2-(2-cyclohexyl-1-fluorovinyl)pyrrolidine (14d). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (200 mg, 0.51 mmol, 1.0 equiv), cyclohexane carboxaldehyde (65.00 μL, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.76 mL, 0.76 mmol, 1.5 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14d** (120.50 mg, 82%, colorless oil) as a nonseparable mixture of stereoisomers (*E*/*Z* = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.18 (m, 5H), 5.04 (dd, $^3J_{HF}$ = 22.4 Hz, $^3J_{HH}$ = 10.2 Hz, 1H, *E*), 4.61 (dd, $^3J_{HF}$ = 38.1 Hz, $^3J_{HH}$ = 9.2 Hz, 1H, *Z*), 3.98 (d, $^2J_{HH}$ = 12.9 Hz, 1H, *Z*), 3.97 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.33 (dt, $^3J_{HF}$ = 29.6 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, *Z*), 3.18 (d, $^2J_{HH}$ = 13.0 Hz, 1H), 2.92−2.82 (m, 1H), 2.78−2.82 (m, 1H, *E*), 2.46−2.38 (m, 1H), 2.23−0.98 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (d, $^1J_{CF}$ = 254.7 Hz), 156.5 (d, $^1J_{CF}$ = 250.6 Hz), 139.1, 139.0, 128.7, 128.6, 127.9, 126.7, 126.6, 115.2 (d, $^2J_{CF}$ = 18.4 Hz), 113.4 (d, $^2J_{CF}$ = 14.2 Hz), 64.7 (d, $^2J_{CF}$ = 28.0 Hz), 60.5 (d, $^2J_{CF}$ = 25.6 Hz), 57.7, 57.5, 53.0, 52.9, 34.4 (d, $^3J_{CF}$ = 8.4 Hz), 34.0 (d, $^4J_{CF}$ = 2.3 Hz), 33.7 (d, $^4J_{CF}$ = 1.7 Hz), 33.2 (d, $^5J_{CF}$ = 1.2 Hz), 32.9 (m), 28.4, 27.7, 25.6−25.5 (m), 22.3, 22.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −124.0 (dt, $^3J_{FH}$ = 38.1 Hz, $^3J_{FH}$ = 22.2 Hz, 1F), −122.5 (dt, $^3J_{FH}$ = 29.0 Hz, $^3J_{FHcis}$ = 22.4

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720

Hz, 1F); MS (ESI$^+$) m/z 288 ([M + H]$^+$, 100%), 268 (5), 196 (9), 192 (3), 120 (7), 91 (28); HRMS (ESI$^+$) $C_{19}H_{27}FN$ ([M + H]$^+$) requires 288.2128; found 288.2121.

(*Z*/*E*)-1-Benzyl-2-(1-fluorooct-1-en-1-yl)pyrrolidine (14e). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (220 mg, 0.56 mmol, 1.0 equiv), heptanal (84.00 μL, 0.59 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.84 mL, 0.84 mmol, 1.5 equiv) in THF (6 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14e** (110.00 mg, 67%, yellow oil) as a nonseparable mixture of stereoisomers (E/Z = 3:7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.15 (m, 5H), 5.15 (dt, $^2J_{HF}$ = 22.2 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, *E*), 4.72 (dt, $^2J_{HF}$ = 37.5 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, *Z*), 3.97 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *Z*), 3.95 (d, $^2J_{HH}$ = 12.8 Hz, 1H, *E*), 3.31 (dt, $^3J_{HF}$ = 29.4 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *E*), 3.18 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *Z*), 3.16 (d, $^2J_{HH}$ = 12.8 Hz, 1H, *E*), 2.88 (m, 1H, *Z*), 2.18−1.57 (m, 8H), 1.29−1.21 (m, 8H), 0.84−0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (d, $^1J_{CF}$ = 254.5 Hz, *Z*), 157.6 (d, $^1J_{CF}$ = 249.6 Hz, *E*), 139.3, 139.2, 128.9, 128.1, 126.7 (m), 109.5 (d, $^2J_{CF}$ = 20.7 Hz, *E*), 107.5 (d, $^2J_{CF}$ = 14.9 Hz, *Z*), 65.0 (d, $^2J_{CF}$ = 28.1 Hz, *Z*), 60.4 (d, $^2J_{CF}$ = 25.7 Hz, *E*), 58.0, 57.8, 53.2, 53.1, 31.6, 30.1 (d, $^4J_{CF}$ = 2.1 Hz), 29.4 (d, $^4J_{CF}$ = 1.5 Hz), 28.8, 28.7, 28.6, 27.6, 24.9 (d, $^3J_{CF}$ = 8.7 Hz), 23.4 (d, $^3J_{CF}$ = 4.5 Hz), 22.7, 22.6, 22.5, 22.4, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.9 (dd, $^2J_{FHtrans}$ = 37.5 Hz, $^3J_{FH}$ = 21.8, 1F), −120.7 (dd, $^3J_{FH}$ = 29.4 Hz, $^2J_{FHcis}$ = 22.2 Hz, 1F); MS (ESI$^+$) m/z 290 ([M + H]$^+$, 100%), 270 (12), 198 (22), 178 (3), 120 (9), 91 (59); HRMS (ESI$^+$) m/z $C_{19}H_{29}FN$ ([M + H]$^+$) requires 290.2284; found 290.2285.

(*Z*/*E*)-1-Benzyl-2-(1-fluoro-3,3-dimethylbutenyl)pyrrolidine (14f). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (200 mg, 0.51 mmol, 1.0 equiv), pivaldehyde (60.00 μL, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.76 mL, 0.76 mmol, 1.5 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14f** (110.00 mg, 82%, yellow oil) as a nonseparable mixture of stereoisomers (E/Z = 45:55): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.15 (m, 5H), 5.30 (d, $^2J_{HFcis}$ = 28.5 Hz, 1H, *E*), 4.64 (d, $^2J_{HFtrans}$ = 42.9 Hz, 1H, *Z*), 4.02 (d, $^2J_{HH}$ = 12.6 Hz, 1H, *E*), 3.95 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *Z*), 3.51 (dt, $^3J_{HF}$ = 30.9 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, *E*), 3.19 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *Z*), 3.15 (d, $^2J_{HH}$ = 12.6 Hz, 1H, *E*), 2.91−2.86 (m, 1H), 2.91−2.86 (m, 1H), 2.82 (dt, $^3J_{HF}$ = 21.8 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *Z*), 2.14 (q, $^3J_{HH}$ = 8.8 Hz, 1H), 1.99−1.60 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1 (d, $^1J_{CF}$ = 259.0 Hz, *Z*), 156.8 (d, $^1J_{CF}$ = 247.0 Hz, *E*), 139.6, 139.3, 128.9, 128.7, 128.2, 128.1, 126.8, 126.7, 120.5 (d, $^2J_{CF}$ = 21.4 Hz, *E*), 117.0 (d, $^2J_{CF}$ = 10.0 Hz, *Z*), 65.5 (d, $^2J_{CF}$ = 28.2 Hz, *Z*), 62.0 (d, $^2J_{CF}$ = 25.6 Hz, *E*), 58.1, 57.9, 53.3, 31.9, 31.8, 31.2, 30.6 (d, $^3J_{CF}$ = 3.2 Hz), 29.7 (d, $^3J_{CF}$ = 10.2 Hz), 28.6, 28.3, 22.5, 22.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.9 (dd, $^2J_{FHtrans}$ = 42.9 Hz, $^3J_{FH}$ = 21.8, 1F), −118.8 (dd, $^3J_{FH}$ = 30.9 Hz, $^2J_{FHcis}$ = 28.5 Hz, 1F); MS (ESI$^+$) m/z 262 ([M + H]$^+$, 100%), 242(4), 206 (3), 186 (2), 170 (10), 120 (12), 91 (70); HRMS (ESI$^+$) m/z $C_{17}H_{25}FN$ ([M + H]$^+$) requires 262.1971; found 262.1976.

(*Z*/*E*)-1-Benzyl-2-(2-cyclohexyl-1-fluorovinyl)-pyrrolidine (14g). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (100 mg, 0.26 mmol, 1.0 equiv), ferrocenecarboxaldehyde (58.00 mg, 0.27 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.38 mL, 0.38 mmol, 1.5 equiv) in THF (2.5 mL), purification by flash column chromatography (pentane/EtOAc, 95:5) afforded compound **14g** (91.00 mg, 91%, red oil) as a nonseparable mixture of stereoisomers (E/Z = 1:9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.15 (m, 5H), 5.98 (d, $^3J_{HF}$ = 21.3 Hz, 1H, *E*), 5.47 (d, $^3J_{HF}$ = 39.2 Hz, 1H, *Z*), 4.43−4.36 (m, 2H), 4.19−4.11 (m, 2H), 4.04−4.00 (m, 6H), 3.55 (dt, $^3J_{HF}$ = 29.8 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *E*), 3.43 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *E*), 3.23 (d, $^2J_{HH}$ = 13.0 Hz, 1H, *Z*), 2.99 (dt, $^3J_{HF}$ = 20.9 Hz, $^3J_{HH}$ = 7.6 Hz, 1H, *Z*), 2.93 (m, 1H), 2.17 (q, $^3J_{HH}$ = 8.5 Hz, 1H), 1.98−1.64 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0 (d, $^1J_{CF}$ = 251.8 Hz, *E*), 158.2 (d, $^1J_{CF}$ = 262.0 Hz, *Z*), 139.1, 138.8, 129.0, 128.9, 128.2, 128.1, 127.0, 126.9, 108.3 (d, $^2J_{CF}$ = 29.5 Hz, *E*), 104.7 (d, $^2J_{CF}$ = 11.1 Hz, *Z*), 78.3 (d, $^3J_{CF}$ = 14.9 Hz, *E*), 77.6 (m, *Z*), 69.1, 69.0, 68.8, 68.7, 68.6, 68.5, 68.3, 65.4 (d, $^2J_{CF}$ = 27.2 Hz, *Z*), 61.1 (d, $^2J_{CF}$ = 24.1 Hz, *E*), 58.1, 57.7, 53.3, 53.1, 53.0, 30.9, 28.9, 28.1, 27.8, 22.7, 22.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.8 (dd, $^3J_{FH}$ = 39.2 Hz, $^3J_{FH}$ = 20.9 Hz, 1F), −117.8 (dt, $^3J_{FH}$ = 29.8 Hz, $^3J_{FH}$ = 21.3 Hz, 1F); MS (ESI$^+$) m/z 390 ([M + H]$^+$, 100%), 389 (27), 370 (21), 369 (8), 368 (4), 324 (13), 299 (16), 289 (48), 283 (24), 263 (3), 250 (10), 236 (12), 233 (3), 199 (16), 167 (4), 143 (7); HRMS (ESI$^+$) $C_{23}H_{25}FFeN$ ([M + H]$^+$) requires 390.1320; found 390.1333.

(*Z*/*E*)-1-Benzyl-2-[4-(benzyloxy)-1-fluorobutenyl]pyrrolidine (14h). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidines **13a,b** (500 mg, 0.51 mmol, 1.00 equiv), 3-benzyloxypropanal (253 mg, 1.54 mmol, 1.20 equiv), and NaHMDS (1 M in THF, 1.92 mL, 1.92 mmol, 1.50 equiv) in THF (13 mL), purification by flash column chromatography (pentane/EtOAc, 95:5) afforded compound **14h** (259.00 mg, 60%, yellow oil) as a nonseparable mixture of stereoisomers (E/Z = 3:7) (*Z*)-**14h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.15 (m, 10H), 5.19 (dt, $^3J_{HF}$ = 21.6 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, *E*), 4.85 (dt, $^3J_{HF}$ = 37.3 Hz, $^3J_{HH}$ = 7.4 Hz, 1H, *Z*), 4.46 (s, 2H, *Z*), 4.44 (s, 2H, *E*), 3.96 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.95 (d, $^2J_{HH}$ = 12.9 Hz, 1H, *E*), 3.43 (t, $^3J_{HH}$ = 6.7 Hz, 2H, *Z*), 3.40−3.36 (m, 2H, *E*), 3.21 (d, $^2J_{HH}$ = 13.1 Hz, 1H, *Z*), 3.17 (d, $^2J_{HH}$ = 12.9 Hz, 1H), 2.92−2.88 (m, 2H), 2.40−1.60 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (d, $^1J_{CF}$ = 256.4 Hz, *Z*), 159.1 (d, $^1J_{CF}$ = 251.1 Hz, *E*), 139.1, 138.4, 138.2, 128.8, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4 126.8, 126.7, 105.5 (d, $^2J_{CF}$ = 23.3 Hz, *E*), 103.6 (d, $^2J_{CF}$ = 14.3 Hz, *Z*), 72.9, 72.7, 69.8 (d, $^4J_{CF}$ = 2.8 Hz), 69.5 (d, $^4J_{CF}$ = 1.7 Hz), 64.8 (d, $^2J_{CF}$ = 27.9 Hz, *Z*), 60.4 (d, $^2J_{CF}$ = 25.6 Hz), 58.0, 57.8, 53.3, 53.2, 28.6, 27.7, 25.7 (d, $^3J_{CF}$ = 9.0 Hz), 24.3 (d, $^3J_{CF}$ = 4.7 Hz), 22.6, 22.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −121.6 (dd, $^2J_{FH}$ = 37.3 Hz, $^3J_{FH}$ = 21.2, 1F), −117.8 (dd, $^3J_{FH}$ = 28.9, $^2J_{FH}$ = 21.6, 1F); MS (ESI$^+$) m/z 340 ([M + H]$^+$, 100%), 320 (9), 248 (48), 232 (9), 230.2 (4), 210 (7), 181 (23), 172 (3), 160 (3), 120 (6), 91 (61); HRMS (ESI$^+$) m/z $C_{22}H_{27}FNO$ ([M + H]$^+$) requires 340.2077; found 340.2072.

1-Benzyl-2-[(4-(*tert*-butyl)cyclohexylidene)fluoromethyl]-pyrrolidine (14i). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)ethyl]-1-benzylpyrrolidine **13** (200 mg, 0.51 mmol, 1.00 equiv), 4-*tert*-butylcyclohexanone (83.3 mg, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.87 mL, 0.87 mmol, 1.70 equiv) in THF (5 mL), purification by flash column chromatography (pentane/Et_2O, 98:2) afforded compound **14i** (85 mg, 51%, colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 3.96 and 3.89 (d, $^2J_{HH}$ = 13.0 Hz, 1H), 3.39 (dt, $^3J_{HF}$ = 29.4, $^3J_{HH}$ = 7.7 Hz, 1H), 3.21, and 3.20 (d, $^2J_{HH}$ = 12.9 Hz, 1H), 2.99−2.84 (m, 2H), 2.48 (m, 1H), 2.17 (m, 1H), 2.10−1.4 (m, 8H), 1.20−0.80 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (d, J_{CF} = 246 Hz), 139.6, 128.9, 128.8, 128.2, 128.1, 119.3 (d, J_{CF} = 14.4 Hz), 60.6 and 60.5 (d, J_{CF} = 26 Hz), 57.9, 57.8, 53.5, 53.4, 48.2, 32.4, 28.5, 26.0 (d, J_{CF} = 9 Hz), 22.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.1 (d, $^3J_{HF}$ 28.0 Hz); MS (ESI$^+$) m/z 330.2 ([M + H]$^+$, 100%), 310.2 (11), 120.1 (12), 91.1 (36); HRMS (ESI$^+$) m/z $C_{22}H_{33}NF$ ([M + H]$^+$) requires 330.2597; found 330.2602.

1-Benzyl-2-(1-fluoro-2,2-diphenylvinyl)pyrrolidine (14j). Following general procedure A with 2-[(fluoro-2-benzothiazolylsulfonyl)-ethyl]-1-benzylpyrrolidine **13** (200 mg, 0.51 mmol, 1.00 equiv), benzophenone (98.9 mg, 0.54 mmol, 1.05 equiv), and NaHMDS (1 M in THF, 0.78 mL, 0.78 mmol, 1.50 equiv) in THF (5 mL), purification by flash column chromatography (pentane/EtOAc, 98:2) afforded compound **14i** (73 mg, 40%, colorless oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−6.90 (m, 15H), 3.87 (d, $^2J_{HH}$ = 13.1 Hz, 1H), 3.25 (dt, $^3J_{HF}$ = 28.3 Hz, $^3J_{HH}$ = 7.9 Hz, 1H), 3.19 (d, $^2J_{HH}$ = 13.1 Hz, 1H), 2.93−2.85 (m, 1H), 2.40−1.50 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2 (d, J_{CF} = 269 Hz), 139.0, 138.3 (d, J_{CF} = 8 Hz), 137.4, 130.5 (d, J_{CF} = 3 Hz), 129.7 (d, J_{CF} = 5 Hz), 129.0, 128.4, 128.0, 127.5, 127.1, 126.9, 123.2 (d, J_{CF} = 14 Hz), 62.1 (d, J_{CF} = 23 Hz), 57.9, 53.5, 28.7, 23.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.5 (d, $^3J_{HF}$ = 28.3 Hz); MS (ESI$^+$) m/z 358.2 ([M + H]$^+$, 100%), 251.1 (7), 223.1 (10), 210.1 (16), 167.1 (9), 91.1 (39); HRMS (ESI$^+$) m/z $C_{25}H_{25}NF$ ([M + H]$^+$) requires 358.1971; found 358.1972.

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01363.

X-ray data for **13a** (CIF)
NMR study of the aza-Michael reaction, NMR data of ammonium **12**, HPLC separation of *Z*,*E*-**11**, NMR data for compounds **13a**−**d** and **14a**−**j** (PDF)
X-ray data for **13c** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: thierry.lequeux@ensicaen.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the excellence laboratory LabEx SYNORG (ANR-11-LABX-0029), the Conseil Régional de Normandie, and the European FEDER fundings. Mr F. Lecavelier is thanked for preparative HPLC optimization.

■ REFERENCES

(1) Shaitanova, E. N.; Gerus, I. I.; Kukhar, V.; Haufe, G. *J. Fluorine Chem.* **2014**, *160*, 8−11.
(2) Lam, Y.; Stanway, S. J.; Gouverneur, V. *Tetrahedron* **2009**, *65*, 9905−9933.
(3) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073−9174.
(4) Sparr, C.; Schweizer, W. B.; Senn, H. M.; Gilmour, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 3065−3068.
(5) Paul, S.; Schweizer, W. B.; Rugg, G.; Senn, H. M.; Gilmour, R. *Tetrahedron* **2013**, *69*, 5647−5659.
(6) Taguchi, T.; Yanai, H. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, U.K., 2009.
(7) Lin, J.; Toscano, P. J.; Welch, J. T. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 14020−14024.
(8) Dutheuil, G.; Pierry, C.; Villiers, E.; Couve-Bonnaire, S.; Pannecoucke, X. *New J. Chem.* **2013**, *37*, 1320−1325.
(9) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707−6711.
(10) Jakobsche, C. E.; Choudhary, A.; Miller, S. J.; Raines, R. T. *J. Am. Chem. Soc.* **2010**, *132*, 6651−6653.
(11) Sano, S.; Kuroda, Y.; Saito, K.; Ose, Y.; Nagao, Y. *Tetrahedron* **2006**, *62*, 11881−11890.
(12) Takeuchi, Y.; Yamada, A.; Suzuki, T.; Koizumi, T. *Tetrahedron* **1996**, *52*, 225−232.
(13) Yang, M.; Matikonda, S. S.; Altman, R. A. *Org. Lett.* **2013**, *15*, 3894−3897.
(14) Cui, H.; Chai, Z.; Zhao, G.; Zhu, S. *Chin. J. Chem.* **2009**, *27*, 189−194.
(15) Van der Veken, P.; Senten, K.; Kertèsz, I.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2003**, *44*, 969−972.
(16) Pfund, E.; Gueyrard, D.; Lequeux, T. *Synthesis* **2015**, *47*, 1534−1546.
(17) Ghosh, A. K.; Zajc, B. *Org. Lett.* **2006**, *8*, 1553−1556.
(18) Iradier, F.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2001**, *3*, 2957−2960.
(19) Fustero, S.; Jiménez, D.; Sanchez-Rosello, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700−6701.
(20) Calata, C.; Pfund, E.; Lequeux, T. *J. Org. Chem.* **2009**, *74*, 9399−9405.
(21) Mauleòn, P.; Alonso, I.; Rodriguez Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924−9935.
(22) The structures have been deposit at the Cambridge Crystallographic Data Centre for compound **13a** (CCDC 1428141) and for compound **13c** (CCDC 1492556).
(23) Buissonneaud, D. Y.; van Mourik, T.; O'Hagan, D. *Tetrahedron* **2010**, *66*, 2196−2202.
(24) Alkenes *Z*- and *E*-**14** were separated by semi-preparative HPLC.
(25) Ghosh, A. K.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 8531−8540.
(26) Crich, D.; Ranganathan, K. *J. Am. Chem. Soc.* **2002**, *124*, 12422−12423.
(27) Zhao, T.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Herdtweck, E.; Dömling, A. *Chem. - Eur. J.* **2016**, *22*, 3009−3018.

DOI: 10.1021/acs.joc.6b01363
J. Org. Chem. 2016, 81, 6714−6720