JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis and Use of a Trifluoromethylated Azomethine Ylide Precursor

Gaël Tran,[†] Robin Meier,[†] Lawrence Harris,[‡] Duncan L. Browne,[†] and Steven V. Ley[†,*]

[†]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

[‡]Industrial Research Limited, Gracefield Road, Lower Hutt 5040, PO Box 31310, New Zealand

Supporting Information

ABSTRACT: The presence of fluorous substituents can impart a dramatic effect on the efficacy of molecules used for a range of applications in society. Here, we describe the preparation and use of a new trifluoromethylated azomethine ylide precursor, which leads to a series of fluorinated pyrrolidine, 3-pyrroline, and pyrrole building blocks.

INTRODUCTION

The incorporation of fluorine, the trifluoromethyl group, and other fluorinated functionalities into organic molecules is of current interest.[1] In its various forms, fluorine can provide improved biological profiles, often through imparting greater metabolic stability to pharmaceutical[2] or agrochemical[3] agents. Furthermore, in the materials area, such substituents have been found to improve switching times and broaden working temperature ranges of LCD devices.[4] Driven by these potential rewards, there is considerable research interest and activity pursuing general methods for the introduction of fluorine substituents, as well as searching for novel reagents for such processes.[5] The current trends are being focused on the *late stage* introduction of fluorine-bearing functionalities.[5] Such a strategy allows laboratories possessing large chemical collections to rapidly generate and assess fluorous congeners, perhaps in some cases leading to the discovery of improved materials. On the other hand, access to new simple fluorous building blocks that can be quickly introduced to build complexity is an alternative approach.[6] For these reasons, we decided to investigate a new approach for the reliable and potentially scalable preparation of a series of α-trifluoromethylated pyrrolidines. Initially, we considered the preparation and use of a new azomethine ylide bearing just a single pendant trifluoromethyl group as a suitable precursor to achieve this goal. Azomethine ylides, which participate in rapid complexity generating 1,3 dipolar cycloaddition reactions, have been well explored, reviewed, and utilized in numerous ways, and this area of research is still very active.[7,8] However, with specific regard to α-trifluoromethylated variants we could only find a few approaches, all of which describe attractive but somewhat limited methods to generate trifluoromethylated pyrrolidine derivatives. Originally, Meffert and co-workers described the cycloaddition of a geminally disubstituted trifluoromethylated azomethine ylide with DMAD (dimethyl acetylenedicarboxylate).[9] The ylide was generated by the thermal degradation of a parent azalactone, whereas Tanaka et al. reported the one–pot thermal ring-opening and subsequent cycloaddition of acyl trifluoromethylated aziridines with a small range of alkenes, including styrene and butyl vinyl ether.[10] The aziridines themselves were derived from a four-step procedure designed around the ring-opening and reclosure of an isoxazole derived from a trifluoromethylated nitrile oxide.[11] Finally, Viehe et al. explored the cycloaddition of azomethine ylides derived from pyrrolidine trifluorothioamide with electron-poor alkenes.[12] In the reported cases, the bicyclic, geminally disubstituted thioether–trifluoromethyl products were produced as single regioisomers. In addition, this particular process was studied computationally by Domingo.[13]

RESULTS AND DISCUSSION

Following consideration of these early examples, a number of criteria became important in the design of our approach, namely (1) the need to deliver an azomethine ylide precursor that could be accessed readily from inexpensive starting materials and was both easy to handle and had good shelf life, (2) that the ylide could be unveiled under relatively straightforward and simple conditions, (3) that the scope and performance of the azomethine ylide in cycloadditions could be explored with a wide range of dipolarophiles, paying particular attention to the yield and regio- and diastereoselectivities.

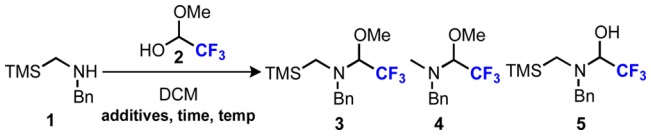
Of the many possibilities available to access azomethine ylide precursors via condensation reactions that we considered, the one between amine **1** and trifluoromethylated hemiacetal **2**[14] proved to be the most profitable. We began by stirring amine **1** and hemiacetal **2** in the presence of a variety of acids. This screen quickly established that the desired product (**3**) was indeed being formed in various quantities along with desilylated derivative **4** and hemiaminal **5** (Table 1).

With the aim of finding an efficient process to *rapidly* access *clean* precursor material, we examined a variety of acids. Specifically, we devised a workup procedure whereby the mixture of hemiaminal ether **3** and hemiaminal **5** could be

Received: October 2, 2012
Published: November 26, 2012

dx.doi.org/10.1021/jo302052m | J. Org. Chem. 2012, 77, 11071–11078

Table 1. Optimization of Azomethine Ylide Precursor Preparation

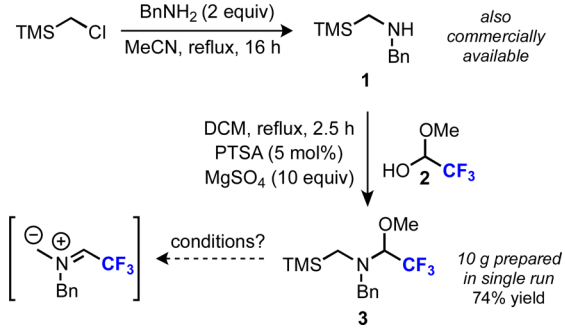


entry	additives	temp (°C)	time (h)	ratio **3**:**4**:**5**	conversion[a,b] (%)
1	PTSA (5 mol %)	rt	16	39:0:61	62
2	TFA (5 mol %)	rt	16	78:8:14	80
3	QP-SA (5 mol %)	rt	24	80:8:12	78
4	K10 Clay (10% w/w)	rt	16	85:8:7	65
5	Dowex 50WX8 (100% w/w)	rt	16	80:8:12	31
6	Nafion-H NR50 (40% w/w)	rt	16	79:5:16	81
7	CSA (5 mol %) $MgSO_4$ (1 equiv)	rt	24	77:15:8	77
8	**PTSA (5 mol %) $MgSO_4$ (1 equiv)**[c]	**40**	**2.5**	**91:0:9**	**82 (74)**

[a]Calculated by analysis of the 1H NMR spectra, using DMF as an internal standard. [b]Number in parentheses represents isolated yield of pure product. [c]PTSA was dried by azeotropic distillation with toluene on a rotary evaporator prior to use.

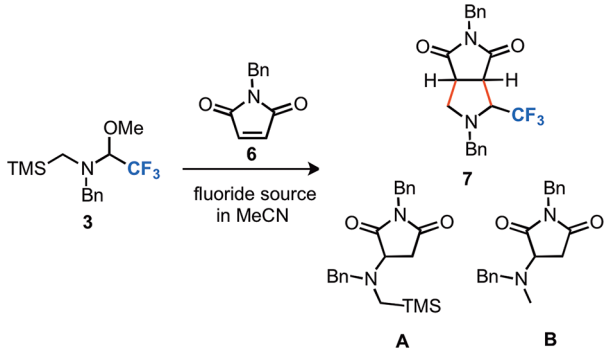
separated by a simple filtration through a plug of neutral alumina (where hemiaminal was retained on the support). However, the presence of the undesired desilylated hemiaminal ether **4** could only be removed from product **3** via flash chromatography on silica gel, which, as well as being more labor intensive also resulted in further desilylation of **3** to **4**. Following further experimentation we found optimal conditions consisted of refluxing the mixture for 150 min in the presence of PTSA and $MgSO_4$, affording no observed desilylation product in the crude reaction mixture which was then filtered through a pad of neutral alumina (entry 8, Table 1). Indeed, this process could be applied readily for the preparation of 10 g of material (Scheme 1).

Scheme 1. Bulk Synthesis of Precursor



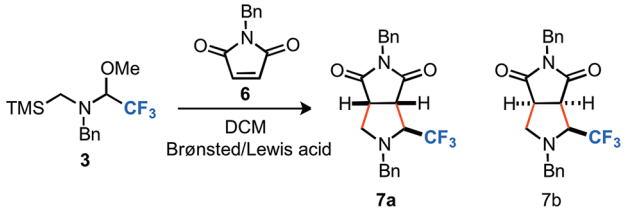
Next the generation of a trifluoromethylated azomethine ylide was studied using *N*-benzylmaleimide (**6**) as a dipole trap. The use of this reactive, symmetrical, cyclic alkene as a trap simplified both regio- and diastereoselectivity considerations in our preliminary studies. Initially, the use of fluoride sources for the unveiling of the azomethine ylide were investigated.[15] This approach, however, was met with no success; the use of CsF, TBAF and TBAT (tetrabutylammonium triphenyldifluorosilicate) provided none of the anticipated cycloaddition products. On exposure of the ylide precursor (**3**) to LiF, KF or AgF for more than 24 h at room temperature only a poor yield of the desired product was realized (**7**, up to 11% with AgF, 70 h) and this was accompanied by large amounts of amine conjugate addition products **A** and **B** (Scheme 2).

Scheme 2. Fluoride Sources Provide Poor Results



We reasoned that a strong Lewis acid should be more appropriate for the generation of an inherently unstable iminium species. Therefore, in the presence of *N*-benzylmaleimide, azomethine ylide precursor **3** was treated with a variety of acids until complete consumption of one of the starting materials was observed. Invariably, under a 1:1 ratio of ylide precursor to dipolarophile, residual alkene was always present suggesting some instability of the trifluoromethylated ylide. Notably, in all cases, only the all-syn isomer **7a** was observed and isomer **7b** was never witnessed. Pleasingly by altering of the reaction conditions such that the ylide was available in a slight excess (1.2 equiv) in the presence of catalytic trimethylsilyl triflate (0.2 equiv), complete conversion of the alkene occurred (Table 2, entry 6) and resulted in the formation of a single diastereomer (**7a**) in excellent yield.[16]

Table 2. Lewis/Bronsted Acid Screen



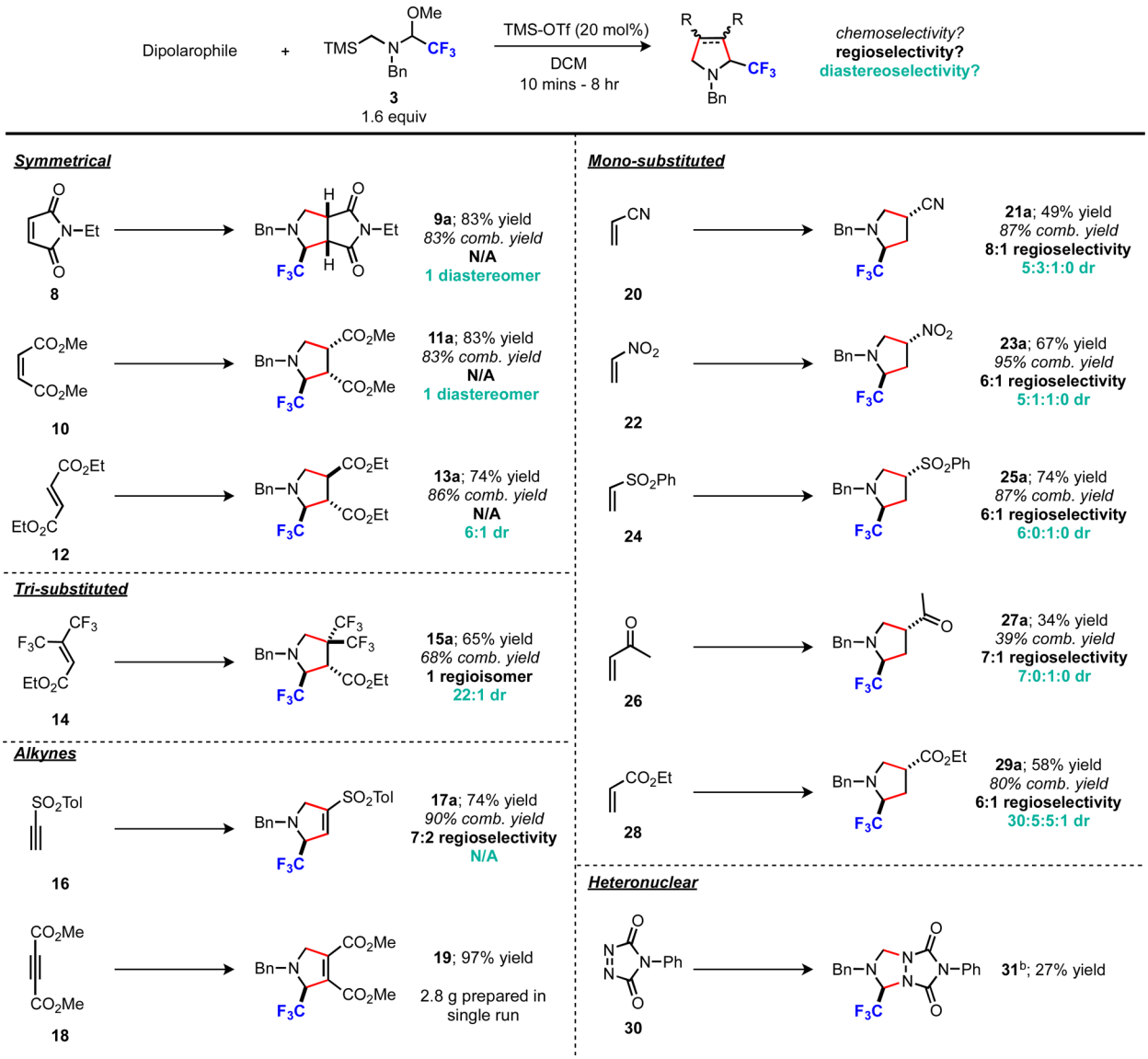
entry	additive	acid:**3**:**6**	isolated yield (%)[a]
1	BF_3·THF	1:1:1	61
2	AgOTf	1:1:1	44
3	TFA	1:1:1	54
4	TMSOTf	1:1:1	65
5	BF_3•THF	1.6:1.6:1	81
6	**TMSOTf**	**0.2:1.2:1**	**92**

[a]Only isomer **7a** was isolated.

Next, attention was turned to exploring the generality of the process. First, we assessed the use of other symmetrical alkenes as dipolar traps. It was found that both *N*-ethylmaleimide (**8**) and dimethyl maleate (**10**) led to trifluoromethylated pyrrolidines in excellent yield and as single diastereomers (Scheme 3, **9a** and **11a**, respectively). Cycloaddition with diethyl fumarate (**12**) provided excellent overall yield and good but not full diastereoselectivity (6:1) in favor of the 2,3-anti

dx.doi.org/10.1021/jo302052m | J. Org. Chem. 2012, 77, 11071−11078

Scheme 3. Scope of Dipolarophiles Compatible with the Azomethine Ylide Generated Using Trimethylsilyl Triflate[a]



[a]Only major product isomers are shown for clarity; in nearly all cases, all isomers were separated and characterized. A full list is available in the Supporting Information, dr reported as 2,4-anti:2,4 syn:2,3-anti:2,3-syn. [b]prepared using $BF_3{\cdot}Et_2O$.

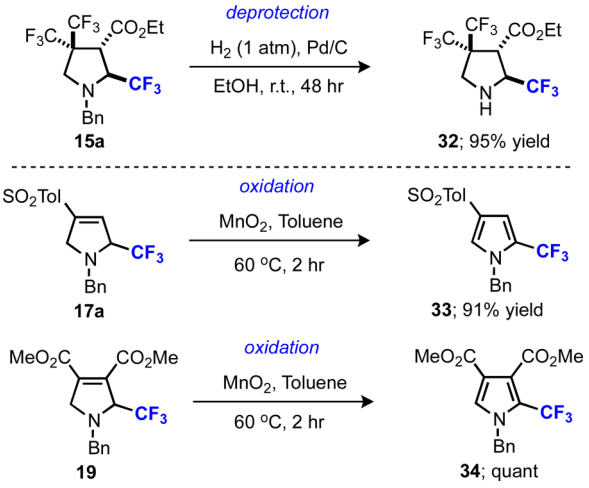
relationship (**13a**). Importantly, both isomers could be isolated separately; thus, isomer **13a** was isolated as a racemic but diastereomerically pure material in 74% yield following flash column chromatography; similarly, **13b** was isolated cleanly in 12% yield from the same column.[15] Cycloaddition with a trisubstituted alkene (**14**) furnished the polyfluorinated product **15a** as a single regioisomer and favoring the 2,3-anti configuration (22:1). Again, the diastereoisomers were separable, furnishing pure **15a** in 65% yield. Furthermore, the trifluoromethylated ylide reacted well with electron-deficient alkynes; for example, sulfonyl 3-pyrrolines **17a** and **17b** were isolated separately in a 7:2 ratio favoring a 2,4 disposition of substituents from cycloaddition with alkyne **16**. Cycloaddition with DMAD (**18**) proceeded very smoothly to provide 3-pyrroline **19** in excellent yield (97%). With regard to monosubstituted alkenes, the ylide participated in successful cycloaddition with acrylonitrile (**20**), nitroethylene (**22**), phenyl vinyl sulfone (**24**), butenone (**26**), and ethyl acrylate (**28**). While most of the cycloadditions with these substrates were achievable in good overall yield and the major isomers could be isolated separately, performance of butenone was poor, resulting in just 39% yield of cycloaddition products. However, regioselectivity for all examples was good, showing a clear preference for the sterically less demanding 2,4 relationship (which appears to be at worst 6:1, 2,4:2,3). In addition, a clear preference for an anti configuration is also witnessed experimentally. Finally, cycloaddition of the trifluoromethylated azomethine ylide with phenyltriazolinedione (**30**) proceeded in excellent conversion but isolation was hampered by the sensitive aminal functionality providing heterobicycle **31** in 27% isolated yield.

Finally, we briefly studied further manipulation of the cycloadducts. Deprotection of an exemplary trifluoromethylated pyrrolidine **15a** by hydrogenation delivered the free amine **32** in excellent yield and now available for further analogue preparation (Scheme 4). The adducts derived from cycloaddition with alkynes could be readily oxidized to the

dx.doi.org/10.1021/jo302052m | J. Org. Chem. 2012, 77, 11071−11078

corresponding trifluoromethylated pyrroles (**33** and **34**) by treatment with manganese dioxide.

Scheme 4. Further Manipulations of Trifluoromethylated Cycloadducts



CONCLUSION

We have presented a practical and robust approach for the preparation and use of a new trifluoromethyl bearing azomethine ylide precursor (**3**) which can be obtained in up to 10 g batches. The resulting ylide itself undergoes cycloaddition with a wide spectrum of electron poor alkenes and alkynes and displays useful levels of regio- and diastereoselectivities. It has also been demonstrated that the series of pyrrolidine products can be further manipulated by oxidation and reduction reactions.

EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were conducted under anhydrous conditions under an atmosphere of argon. ^{1}H NMR spectra were collected on a 400 or 500 MHz NMR spectrometer using the deuterated solvent as an internal deuterium reference. Chemical shift data are given in units δ calibrated with residual protic solvent (e.g., $CHCl_3$ at 7.26 ppm). The multiplicity of a signal is indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sep, septet. Coupling constants (J) are recorded to the nearest 0.1 Hz. ^{13}C NMR spectra were collected on a 125 MHz spectrometer with proton decoupling and fluorine coupling using the deuterated solvent as an internal carbon reference. Chemical shift data are given in units δ calibrated with residual solvent (e.g., 77.23 ppm for $^{13}CDCl_3$). ^{19}F NMR spectra were recorded with ^{1}H decoupling on a 376 MHz spectrometer. Only selected absorbances (ν_{max}) are reported in the IR spectra. The strength and shape of IR signals is designated by the following abbreviations: w, weak; m, medium; s, strong; br, broad. Melting points are uncorrected. HRMS analysis was performed in ESI-TOF or EI-TOF mode.

Preparation of the Azomethine Ylide Precursor 3. Magnesium sulfate was oven-dried overnight at 200 °C, p-toluenesulfonic acid was dried by azeotropic distillation of its hydrate with toluene, and *N*-[(trimethylsilyl)methyl]benzylamine was dried under high vacuum (0.6 Torr) overnight. Under argon atmosphere, to a suspension of *p*-toluenesulfonic acid (317 mg, 1.84 mmol) and magnesium sulfate (4.5 g, 37.4 mmol) in dichloromethane (17 mL) was added trifluoroacetaldehyde methyl hemiaminal (**2**, 13.5 mL, 141 mmol). The resulting suspension was stirred under argon at 40 °C for 10 min. *N*-[(Trimethylsilyl)methyl]benzylamine (**1**,[17] 7.25 g, 37.5 mmol) was then added dropwise over 10 min, and the reaction mixture was stirred under argon at 40 °C and monitored by ^{1}H NMR until total consumption of *N*-[(trimethylsilyl)methyl]benzylamine. The reaction mixture was then filtered through cotton wool, and the filtrate was concentrated in vacuo to give the crude product as a yellow oil. This oil was then purified by filtration through a plug of neutral alumina, using 1:20 EtOAc/hexanes as eluent. The desired fractions were combined and concentrated in vacuo to give compound **3** as a clear, colorless oil in 74% yield (8.5 g). On scaling the reaction the product was obtained in 66% yield (22.2 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.24 (m, 5H), 4.13 (q, J = 5.7 Hz, 1H), 3.92 (d, J = 13.9 Hz, 1H), 3.79 (d, J = 13.9 Hz, 1H), 3.46 (s, 3H), 2.36 (d, J = 15.1 Hz, 1H), 2.28 (d, J = 15.1 Hz, 1H), 0.06 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 128.7, 128.5, 127.3, 124.1 (q, J = 289.8 Hz), 89.3 (q, J = 30.5 Hz), 57.6, 56.4, 40.0, −1.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.70 (s) ppm. IR (neat film): 3032 (w), 2956 (m), 2901 (w), 2833 (w), 1496 (w), 1455 (m), 1375 (w), 1272 (m), 1250 (s), 1154 (s), 1123 (s), 1094 (s), 1093 (s), 1075 (s), 1028 (w) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{14}H_{22}F_3NOSi$ m/z = 306.1496 (found m/z = 306.1490).

General Procedure for the 1,3-Dipolar Cycloaddition of Electron-Poor Alkenes and Alkynes with Ylide Precursor 3. Under an argon atmosphere, to a stirred solution of dry azomethine ylide precursor **3** (1.2 equiv) and a dipolarophile (1.0 equiv) in DCM (0.8 M) was slowly added trimethylsilyl trifluoromethanesulfonate (0.2 equiv). The resulting reaction mixture was stirred under argon at room temperature until completion of the reaction (determined by TLC), followed by dilution with DCM and saturated $NaHCO_3$. The layers were separated, the aqueous layer was extracted with DCM, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography gave the desired cycloadducts. The structural identity of all of the minor isomers can be found in the Supporting Information.

*Cycloaddition with N-Benzylmaleimide (**6**).* *N*-Benzylmaleimide (123 mg, 0.655 mmol) and compound **3** (240 mg, 0.786 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:15 EtOAc/hexanes to 1:8 EtOAc/hexanes) gave compound **7a** as a colorless oil in 92% yield (235 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.32 (m, 5H), 7.25−7.19 (m, 3H), 6.98 (dd, J = 6.3, 2.7 Hz, 2H), 4.69 (s, 2H), 3.96−3.87 (m, 2H), 3.73 (d, J = 13.6 Hz, 1H), 3.39 (d, J = 7.9 Hz, 1H), 3.32 (td, J = 8.2, 1.5 Hz, 1H), 3.25 (td, J = 9.7, 0.8 Hz, 1H), 3.14 (dt, J = 9.9, 1.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 176.2, 137.4, 135.5, 128.8 (2C), 128.6, 128.2, 127.9, 127.5, 126.5 (q, J = 290 Hz), 64.6 (q, J = 28 Hz), 54.5, 53.1, 46.8, 44.1, 43.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −69.84 (s) ppm. IR (neat film): 3033 (w), 2853 (w), 1780 (w), 1702 (s),1605 (w), 1586 (w), 1496 (m), 1455 (m), 1434 (m), 1398 (m), 1345 (m), 1275 (m), 1246 (m), 1145 (s), 1123 (s) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{21}H_{19}F_3N_2O_2$ m/z = 411.1291 (found m/z = 411.1291)

*Cycloaddition with N-Ethylmaleimide (**8**).* *N*-Ethylmaleimide (82 mg, 0.655 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:8 EtOAc/hexanes to 1:6 EtOAc/hexanes) gave compound **9a** as a colorless oil in 83% yield (178 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.05 (m, 5H), 3.95 (d, J = 13.7 Hz, 1H), 3.86 (q, J = 8.4 Hz, 1H), 3.77 (d, J = 13.7 Hz, 1H), 3.53 (q, J = 7.1 Hz, 2H), 3.35−3.15 (m, 3H), 3.08 (d, J = 8.6 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 176.3, 137.5, 128.6, 127.9, 127.6, 126.4 (q, J = 290 Hz), 64.5 (q, J = 28 Hz), 54.2, 52.9, 46.7, 43.9, 34.3, 12.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −69.97 (s) ppm. IR (neat film): 2984 (w), 2940 (w), 2857 (w), 1779 (w), 1702 (s), 1498 (w), 1455 (m), 1403 (m), 1378 (m), 1348 (m), 1276 (m), 1226 (m), 1161 (s), 1123 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{16}H_{17}F_3N_2O_2$ m/z = 327.1315 (found m/z = 327.1309).

*Cycloaddition Using Dimethyl Maleate (**10**).* Dimethyl maleate (82 μL, 0.655 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:15 EtOAc/hexanes to 1:8 EtOAc/hexanes) gave compound **11a** as a colorless oil in 83% yield (180 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.16 (m, 5H), 4.11 (d, J = 13.0 Hz, 1H),

dx.doi.org/10.1021/jo302052m | J. Org. Chem. 2012, 77, 11071−11078

3.68 (d, J = 13.1 Hz, 1H), 3.66−3.57 (m, 7H), 3.32−3.23 (m, 2H), 3.13−3.07 (m, 1H), 2.90 (t, J = 9.6, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 170.8, 138.2, 128.6, 128.4, 127.4, 125.8 (q, J = 281 Hz), 66.8 (q, J = 30 Hz), 59.9, 53.9, 52.6, 52.1, 46.4, 45.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.64 (s) ppm. IR (neat film): 2955 (w), 2847 (w), 1737 (s), 1496 (w), 1438 (m), 1396 (w), 1353 (m), 1319 (m), 1278 (m), 1206 (s), 1159 (s), 1116 (s), 1050 (m), 1028 (m), 938 (m), 920 (m) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{16}H_{18}F_3NO_4$ m/z = 346.1261 (found m/z = 346.1258).

*Cycloaddition Using Diethyl Fumarate (**12**).* Diethyl fumarate (107 μL, 0.655 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:20 EtOAc/hexanes to 1:10 EtOAc/hexanes) gave compounds **13a** and **13b** as colorless oils in 86% combined yield (210 mg).

For **13a** (181 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.26 (m, 5H), 4.24 (q, J = 6.9 Hz, 2H), 4.20 (qd, J = 7.2, 0.7 Hz, 2H), 4.11 (d, J = 13.5 Hz, 1H), 3.82−3.67 (m, 3H), 3.33 (m, 2H), 2.90 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 171.6, 138.5, 128.8 (2C), 127.7, 126.4 (q, J = 281 Hz), 67.3 (q, J = 30 Hz), 62.2, 61.8, 59.6, 55.5, 48.4, 46.9, 14.5 (2C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.94 (d, J = 1.5 Hz) ppm. IR (neat film): 2983 (w), 1734 (s), 1497 (w), 1455 (m), 1370 (m), 1280 (s), 1161 (s), 1129 (s), 1028 (m) cm^{-1} HRMS (ESI+): $[M + Na]^+$ calcd for $C_{18}H_{22}F_3NO_4$ m/z = 396.1393 (found m/z = 396.1392).

For **13b** (29 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.27 (m, 5H), 4.19 (q, J = 7.1 Hz, 2H), 4.15−4.04 (m, 3H), 3.81 (m, 1H), 3.77 (d, J = 13.4 Hz, 1H), 3.64 (m, 1H), 3.53 (dd, J = 9.0, 11.4 Hz, 1H), 3.33 (t, J = 8.4 Hz, 1H), 2.59 (t, J = 9.6 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 168.6, 137.7, 128.5 (2C), 127.5, 125.6 (q, J = 283 Hz), 65.1 (q, J = 29 Hz), 61.4, 61.2, 59.7, 54.3, 47.2, 44.7, 14.1, 13.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.63 (s) ppm. IR (neat film): 2982 (w), 1733 (s), 1497 (w), 1455 (m), 1372 (m), 1329 (m), 1281 (m), 1261 (m), 1195 (s), 1164 (s), 1120 (s), 1029 (m) cm^{-1}. HRMS (ESI +): $[M + Na]^+$ calcd for $C_{18}H_{22}F_3NO_4$ m/z = 396.1393 (found m/z = 396.1391).

*Cycloaddition Using Ethyl 4,4,4-Trifluoro-3-(trifluomethyl)-crotonate (**14**).* Ethyl 4,4,4-trifluoro-3-(trifluomethyl)crotonate (155 mg, 0.656 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:50 EtOAc/hexanes to 1:40 EtOAc/hexanes) gave compounds **15a** and **15b** as colorless oils in 68% combined yield (191 mg).

For **15a** (183 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.18 (m, 5H), 4.27−4.11 (m, 4H), 3.63 (d, J = 13.8 Hz, 1H), 3.55 (d, J = 9.3 Hz, 1H), 3.41 (dd, J = 12.5, 1.6 Hz, 1H), 3.00 (d, J = 12.5 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 137.5, 128.7, 128.0, 127.7, 125.4 (q, J = 282 Hz), 123.9 (q, J = 284 Hz), 123.6 (q, J = 283 Hz), 67.1 (q, J = 30 Hz), 62.6, 58.8, 58.4 (sep, J = 27 Hz), 55.6, 47.1, 13.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.59 (q, J = 10.2 Hz), −70.53 (q, J = 10.2 Hz), −74.35 (s) ppm. IR (neat film): 3036 (w), 2988 (w),1751 (w), 1498 (w), 1456 (w), 1373 (m), 1345 (m), 1296 (m), 1272 (m), 1214 (s), 1146 (s), 1088 (m), 1054 (m) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{17}H_{16}F_9NO_2$ m/z = 438.1110 (found m/z = 438.1102).

For **15b** (8 mg, 3%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.18 (m, 5H), 4.15 (q, J = 7.1 Hz, 2H), 4.07 (d, J = 13.5 Hz, 1H), 3.78 (quin, J = 7.9 Hz, 1H), 3.69 (d, J = 8.0 Hz, 1H), 3.59 (d, J = 13.5 Hz, 1H), 3.44 (d, J = 11.8 Hz, 1H), 2.86 (d, J = 11.7 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 136.6, 128.7, 128.1, 127.8, 124.6 (q, J = 282.2 Hz), 123.3 (q, J = 287 Hz), 66.7 (q, J = 30 Hz), 62.1, 57.9 (sep, J = 28 Hz), 56.6, 54.0, 48.1, 13.7 ppm. Seemingly one q signal missing due to small amount of sample. ^{19}F NMR (376 MHz, $CDCl_3$): δ-64.72 (q, J = 4.7 Hz), −64.95 (qq, J = 10.3, 4.7 Hz), −71.67 (q, J = 10.9 Hz) ppm. IR (neat film): 2985 (w), 2929 (w), 2845 (w), 1766 (m), 1498 (w), 1456 (w), 1378 (w), 1281 (m), 1250 (m), 1210 (s), 1144 (s), 1055 (m), 1014 (m) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{17}H_{16}F_9NO_2$ m/z = 460.0930 (found m/z = 460.0927).

*Cycloaddition Using Ethynyl p-Tolyl Sulfone (**16**).* Ethynyl p-Tolyl sulfone (118 mg, 0.655 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:15 EtOAc/hexanes to 1:4 EtOAc/hexanes) gave compounds **17a** and **17b** as a white solid and a yellow oil, respectively, in 90% combined yield (225 mg).

For **17a** (185 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.3 Hz, 2H), 7.36−7.22 (m, 7H), 6.52 (q, J = 2.0 Hz, 1H), 4.40 (m, 1H), 4.13 (d, J = 13.5 Hz, 1H), 3.82 (ddd, J = 14.6, 6.2, 2.0 Hz, 1H), 3.74 (d, J = 13.5 Hz, 1H), 3.56 (ddd, J = 14.6, 4.2, 2.1 Hz, 1H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 145.4, 137.5, 135.3, 131.3 (q, J = 2 Hz), 130.2, 128.6, 128.3, 128.1, 127.6, 124.4 (q, J = 281 Hz), 71.9 (q, J = 31 Hz), 59.8, 58.2, 21.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.45 (s) ppm. IR (solid state): 3091 (w), 3063 (w), 3032 (w), 2837 (w), 1596 (w), 1496 (w), 1454 (w), 1321 (m), 1274 (m), 1156 (s), 1128 (s), 1092 (s) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{19}H_{18}F_3NO_2S$: m/z = 404.0903 (found m/z = 404.0903). Mp: 79.1−79.5 °C.

For **17b** (40 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.36−7.23 (m, 7H), 7.12 (s, 1H), 4.45 (m, 1H), 4.04 (d, J = 13.4 Hz, 1H), 3.98 (ddd, J = 1.7, 5.5, 18.4 Hz 1H), 3.76 (d, J = 13.4 Hz, 1H), 3.50 (dt, J = 18.4, 2.6 Hz, 1H), 2.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 144.9, 138.9, 137.5, 136.1, 129.7, 128.6, 128.4, 128.2, 127.6, 124.2 (q, J = 282 Hz), 70.3 (q, J = 32 Hz), 60.6, 59.5, 21.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.52 (s) ppm. IR (neat film): 3095 (w), 3063 (w), 3036 (w), 2929 (w), 2853 (w),1598 (w), 1496 (w), 1455 (w), 1320 (m), 1272 (m), 1154 (s), 1132 (s), 1094 (s) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{19}H_{18}F_3NO_2S$ m/z = 404.0903 (found m/z = 404.0919).

*Cycloaddition Using Dimethyl Acetylenedicarboxylate (**18**).* Under an argon atmosphere, to a solution of dimethyl acetylenedicarboxylate (1.46 g, 9.18 mmol) in DCM (8 mL) was added trimethylsilyl trifluoromethanesulfonate (0.77 mL, 4.25 mmol) dropwise over 5 min. The resulting solution was then cooled to 10−15 °C, and a solution of compound **3** (4.10 g, 13.42 mmol) in DCM (4 mL) was added dropwise via a cannula over 1 h. At the end of the addition, the reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was then diluted with DCM and saturated $NaHCO_3$. The aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (1:5 EtOAc/hexanes) gave compound **19** as a clear colorless oil in 97% yield (2.82 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.25 (m, 5H), 4.68−4.64 (m, 1H), 4.12 (d, J = 16.9 Hz, 1H), 4.11 (d, J = 13.8 Hz, 1H), 3.84 (s, 3H), 3.81 (d, J = 13.6 Hz, 1H), 3.75 (s, 3H), 3.61 (dd, J = 16.7, 3.10 Hz, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.6, 162.4, 139.1, 137.6, 133.7, 128.6, 128.4, 127.6, 124.6 (q, J = 282 Hz), 73.3 (q, J = 31 Hz), 60.5, 60.2, 52.7, 52.4 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ −75.28 (s) ppm. IR (neat film): 3030 (w), 2956 (w), 1727 (s), 1665 (m), 1437 (m), 1257 (s), 1158 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{16}H_{17}F_3NO_4$ m/z = 344.1110 (found m/z = 344.1093).

*Cycloaddition Using Acrylonitrile (**20**).* Acrylonitrile (62 μL, 0.941 mmol) and compound **3** (460 mg, 1.506 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:9 EtOAc/hexanes to 1:3 EtOAc/hexanes) gave compounds **21a**, **21b** (white solids) and **21c** (colorless oil) in 88% combined yield (282 mg).

For **21a** (158 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.20 (m, 5H), 4.13 (d, J = 13.3 Hz, 1H), 3.64 (d, J = 13.3 Hz, 1H), 3.39−3.48 (m, 1H), 3.19 (dd, J = 8.9, 6.7 Hz, 1H), 3.05−2.96 (m, 1H), 2.67 (t, J = 9.5 Hz, 1H), 2.36 (ddd, J = 13.8, 7.3, 2.9 Hz, 1H), 2.27 (dt, J = 13.7, 10.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 128.6 (2C), 127.7, 126.0 (q, J = 280 Hz), 119.4, 62.2 (q, J = 29 Hz), 59.0, 56.0, 30.9, 26.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.48 (s) ppm. IR (neat film): 3035 (w), 2839 (w), 2249 (w), 1496 (w), 1455 (w), 1278 (s), 1140 (s) cm^{-1}. HRMS (ES): $[M]^+$ calcd for

$C_{13}H_{13}F_3N_2$ m/z = 254.1025 (found m/z = 254.1032). Mp: 83.4−85 °C.

For **21b** (97 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.20 (m, 5H), 4.11 (d, J = 13.7 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.39−3.20 (m, 1H), 3.15 (dd, J = 10.2, 4.1 Hz, 1H), 2.96−2.90 (m, 1H), 2.74 (dd, J = 10.2, 6.4 Hz, 1H), 2.40 (dt, J = 14.2, 9.0 Hz, 1H), 2.25 (dt, J = 14.2, 4.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 128.6, 128.5, 127.7, 126.0 (q, J = 281 Hz), 120.2, 62.5 (q, J = 30 Hz), 58.5, 56.2, 30.66, 26.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.69 (s) ppm. IR (neat film): 3035 (w), 2848 (w), 2242 (w), 1722 (w), 1497 (w), 1457 (w), 1280 (s), 1142 (s) cm^{-1}. HRMS (EI): $[M]^+$ calcd for $C_{13}H_{13}F_3N_2$ m/z = 254.1025 (found m/z = 254.1030). Mp: 65.5−66.8 °C.

For **21c** (27 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.21 (m, 5H), 4.14 (d, J = 13.2 Hz, 1H), 3.67 (d, J = 13.2 Hz, 1H), 3.57 (qd, J = 6.8, 2.6 Hz, 1H), 3.13−3.11 (m, 1H), 3.00 (broad t, J = 7.9 Hz, 1H), 2.71 (td, J = 9.8, 6.3 Hz, 1H), 2.21−2.09 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 128.5, 128.5, 127.6, 125.1 (q, J = 280 Hz), 120.1, 67.7 (q, J = 30 Hz), 59.6, 52.2, 30.1, 29.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.07 (s) ppm. IR (neat film, cm^{-1}): 3030 (w), 2816 (w), 2246 (w), 1497 (w), 1455 (m), 1277 (s), 1124 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{13}H_{14}F_3N_2$ m/z = 255.1104 (found m/z = 255.1099).

*Cycloaddition Using Nitroethylene (**22**).* Nitroethylene (97 mg, 1.31 mmol) and compound **3** (400 mg, 1.31 mmol) were reacted together in toluene (1.2 mL) according to the general procedure. Purification was attempted by flash chromatography, which resulted in almost total epimerization of the stereogenic center α to the nitro moiety (later confirmed by subjection of a pure isomer to treatment with silica gel). Three of the four possible isomers could be isolated; however, the initial ratio had to be determined from the crude NMR. Ratio of compounds **23a**/**23b**/**23c** from the crude NMR: 70:15:15. Combined yield after column: 96% (348 mg).

For **23a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.09 (m, 5H), 4.81−4.87 (m, 1H), 4.00 (d, J = 13.4 Hz, 1H), 3.65−3.56 (m, 2H), 3.30 (dd, J = 11.4, 6.4 Hz, 1H), 3.00 (dd, J = 11.4, 5 Hz, 1H), 2.68 (ddd, J = 14.3, 8.9, 5.3 Hz, 1H), 2.30 (ddd, J = 14.5, 7.5, 5.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 128.2, 128.9, 127.3, 125.8 (q, J = 279 Hz), 82.7, 63.0 (q, J = 30 Hz), 58.6, 56.6, 31.0 (q, J = 2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.58 (s) ppm. IR (neat film): 3032 (w), 2845 (w), 2310 (w), 1551 (s), 1497 (w), 1451 (w), 1375 (m), 1279 (s), 1120 (br, s) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{12}H_{13}F_3N_2O_2$ m/z = 297.0827 (found m/z = 297.0828).

For **23b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.19 (m, 5H), 4.64−4.68 (m, 1H), 4.17 (d, J = 13.8 Hz, 1H), 3.72 (d, J = 11.7 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H), 3.37−3.29 (m, 1H), 2.96−2.90 (m, 1H), 2.76 (dd, J = 11.7, 5.7 Hz, 1H), 2.56 (ddd, J = 15.7, 9.7, 8.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 128.63, 128.4, 127.65, 125.8 (q, J = 279 Hz), 81.9, 62.0 (q, J = 30 Hz), 58.0, 56.3, 30.6 (q, J = 2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.43 (s) ppm. IR (neat film) 3031 (w), 2985 (w), 1547 (s), 1495 (m), 1451 (m), 1378 (m), 1275 (m), 1171 (s), 1147 (s), 1115 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{12}H_{13}F_3N_2O_2$ m/z = 275.1007 (found m/z = 275.1009). Mp: 65.6−67.3 °C.

For **23c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.25 (m, 5H), 5.02 (dt, J = 7.2, 1.3 Hz, 1H), 4.25 (d, J = 13.1, 1H), 4.08 (q, J = 7.3 Hz, 1H), 3.78 (d, J = 13.1 Hz, 1H), 3.07 (t, J = 8.3 Hz, 1H), 2.73 (ddd, J = 11.3, 9.5, 5.9 Hz, 2H), 2.47 (dd, J = 14.4, 5.8 Hz, 1H), 2.41−2.31 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.5, 128.4, 127.5, 124.9 (q, J = 280 Hz), 86.0, 68.1 (q, J = 30.0 Hz), 59.6, 51.5, 31.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.33 (s) ppm. IR (neat film): 3033 (w), 2843 (w), 1557 (s), 1497 (m), 1455 (m), 1375 (m), 1273 (s), 1165 (s), 1124 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{12}H_{13}F_3N_2O_2$ m/z = no mass found.

*Cycloaddition Using Phenyl Vinyl Sulfone (**24**).* Phenyl vinyl sulfone (148 mg, 0.880 mmol) and compound **3** (430 mg, 1.408 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:9 EtOAc/hexanes to 1:5 EtOAc/hexanes) gave compounds **25a** and **25b** as white solids in 87% combined yield (282 mg).

For **25a** (240 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.9 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.50(t, J = 7.7 Hz, 2H), 7.26−7.19(m, 5H), 4.09 (d, J = 13.3 Hz, 1H), 3.73−3.62 (m, 2H), 3.47−3.54 (m, 1H), 3.07 (dd, J = 9.5, 7.4 Hz, 1H), 2.89 (t, J = 9.4 Hz, 1H), 2.52 (dt, J = 13.7, 9.4 Hz, 1H), 2.14−2.08 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 137.7, 134.2, 129.5, 128.5, 128.4, 128.3, 127.5, 124.7, 63.3 (q, J = 30 Hz), 61.6, 59.2, 52.9, 27.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.04 (s) ppm. IR (neat film): 3063 (w), 2877 (w), 1495 (w), 1447 (m), 1310 (m) 1285 (m), 1126 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{18}H_{18}F_3NO_2S$ m/z = 370.1089 (found m/z = 370.1086). Mp: 89.9−90.7 °C.

For 25b (42 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 7.1 Hz, 3H), 7.73 (tt, J = 7.5, 1.5 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.38−7.24 (m, 5H), 8.21 (d, J = 13 Hz, 1H), 3.86 (qd, J = 7.0, 2.5 Hz, 1H), 3.78 (d, J = 13 Hz, 1H), 3.68 (dt, J = 8.8, 2.1 Hz, 1H), 3.00 (td, J = 8.4, 1.7 Hz, 1H), 2.86 (td, J = 10.0, 6.3 Hz, 1H), 2.42 (broad dd, J = 14.2, 6.2 Hz, 1H), 2.22−2.15 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 137.3, 134.3, 129.5, 128.7, 128.6, 128.4, 127.3, 125.4 (q, J = 281 Hz), 65.1, 64.8 (q, J = 30 Hz), 59.7, 52.6, 26.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.88 (s) ppm. IR (neat film): 3063 (w), 3030 (w), 2847 (w), 1586 (w), 1496 (w), 1447 (m), 1310 (m), 1262 (m), 1148 (s) cm^{-1}. HRMS(ESI+): $[M + H]^+$ calcd for $C_{18}H_{18}F_3NO_2S$ m/z = 370.1089 (found m/z = 370.1079). Mp: 65.1−66 °C.

*Cycloaddition Using Methyl Vinyl Ketone (**26**).* Methyl vinyl ketone (55 μL, 0.727 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:25 EtOAc/hexanes to 1:15 EtOAc/hexanes) gave compounds **27a** and **27b** as colorless oils in 39% combined yield (178 mg).

For **27a** (160 mg, 35%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.26 (m, 5H), 4.21 (d, J = 13.2 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 3.45 (dqd, J = 10.1, 7.3, 2.9 Hz, 1H), 3.32−3.16 (m, 2H), 2.50 (t, J = 9.3 Hz, 1H), 2.33 (m, 1H), 2.16 (s, 3H), 2.13 (ddd, J = 2.9, 7.9, 13.8 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.2, 138.3, 128.6, 128.4, 127.3, 126.6 (q, J = 280 Hz), 64.3 (q, J = 29 Hz), 59.6, 55.6, 50.1, 29.6, 28.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.49 (s) ppm. IR (neat film): 3032 (w), 2925 (w), 2853 (w), 2810 (w), 1714 (m), 1496 (w), 1455 (m), 1357 (m), 1281 (m), 1167 (s), 1137 (s), 1112 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{14}H_{16}F_3NO$ m/z = 272.1257 (found m/z = 272.1248).

For **27b** (18 mg, 5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29−7.14 (m, 5H), 4.12 (d, J = 13.2 Hz, 1H), 3.69 (qd, J = 7.6, 2.6 Hz, 1H), 3.59 (d, J = 13.1 Hz, 1H), 3.19 (dt, J = 9.1, 2.5 Hz, 1H), 2.83 (m, 1H), 2.27 (td, J = 10.1, 9.3 Hz, 1H), 2.19 (s, 3H), 2.13(m, 1H), 1.85 (dd, J = 12.7, 7.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.3, 139.0, 128.5, 128.3, 127.1, 126.7 (q, J = 280 Hz), 64.6 (q, J = 29 Hz), 59.8, 52.3, 52.1, 28.4, 28.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.61 (s) ppm. IR (neat film): 3032 (w), 2948 (w), 2820 (w), 1717 (m), 1496 (w), 1454 (m), 1360 (m), 1278 (m), 1152 (s), 1118 (s) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{14}H_{16}F_3NO$ m/z = 272.1257 (found m/z = 272.1249).

*Cycloaddition Using Ethyl Acrylate (**28**).* Ethyl acrylate (80 μL, 0.727 mmol) and compound **3** (320 mg, 1.046 mmol) were reacted together according to the general procedure. Purification by flash chromatography (1:35 EtOAc/hexanes to 1:25 EtOAc/hexanes) gave compounds **29a**, **29b**, **29c**, and **29d** as colorless oils in 81% combined yield (178 mg).

For **29a** (128 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.17 (m, 5H), 4.12 (d, J = 13.2 Hz, 1H), 4.04 (qd, J = 7.1, 2.2 Hz, 2H), 3.57 (d, J = 13.2 Hz, 1H), 3.36 (dqd, J = 10.3, 7.2, 3.2 Hz 1H), 3.15−2.98 (m, 2H), 2.52 (t, J = 9.3 Hz, 1H), 2.27 (dt, J = 13.7, 10.1 Hz, 1H), 2.14 (ddd, J = 13.5, 7.6, 3.1 Hz, 1H), 1.16 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 138.3, 128.6, 128.4, 127.3, 126.6 (q, J = 281 Hz), 63.2 (q, J = 29 Hz), 60.9, 59.5, 56.1, 42.2, 29.4, 14.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.45 (s) ppm. IR (neat film): 3036 (w), 2983 (w), 2813 (w), 1732 (s), 1497 (w), 1455 (m), 1372 (m), 1339 (m), 1281 (s), 1173 (s), 1138 (s), 1111 (s), 1030 (m)

cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{15}H_{18}F_3NO_2$ m/z = 302.1362 (found m/z = 302.1355).

Compounds **29b** and **29d** were obtained as a mixture; therefore, the yield and the ratio for those two compounds were calculated from the NMR of the mixture.

For **29b** with **29d** (~13%, 6:1 b:d, data for b only). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.16 (m, 5H), 4.10−4.01 (m, 3H), 3.57 (d, J = 13.8 Hz, 1H), 3.34−3.20 (m, 2H), 2.90−2.81(m, 1H), 2.64 (dd, J = 10.2, 7.1 Hz, 1H), 2.40−2.22(m, 2H), 1.17(t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 138.3, 128.4 (2C), 127.2, 126.6 (q, J = 281 Hz), 63.5 (q, J = 30 Hz), 60.9, 59.1, 55.4, 41.7, 29.2, 14.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.74 (s) ppm. IR (neat film): 2983 (w), 2940 (w), 2813 (w), 1732 (m), 1496 (w), 1454 (m), 1373 (m), 1280 (m), 1183 (m), 1154 (s), 1122 (s), 1046 (m), 1030 (m) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{15}H_{18}F_3NO_2$ m/z = 302.1362 (found m/z = 302.1357).

For **29c** (20 mg, 9%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.30−7.15 (m, 5H), 4.14 (d, J = 13.2 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.68 (qd, J = 7.5, 2.8 Hz, 1H), 3.62 (d, J = 13.2 Hz, 1H), 3.03 (dt, J = 8.6, 2.5 Hz, 1H), 2.88 (m, 1H), 2.44 (td, J = 10.2, 6.1 Hz, 1H), 2.16−1.94 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 138.9, 128.6, 128.3, 127.1, 126.4 (q, J = 280 Hz), 65.4 (q, J = 29 Hz), 61.4, 60.0, 52.5, 45.0, 29.1, 14.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.87 (s) ppm. IR (neat film): 3032 (w), 2988 (w), 2927 (w), 2813 (w), 1733 (s), 1497 (w), 1455 (m), 1368 (m), 1333 (m), 1278 (m), 1155 (s), 1120 (s), 1083 (m), 1028 (m) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{15}H_{18}F_3NO_2$ m/z 302.1362 (found m/z=302.1356).

*Cycloaddition Using 4-Phenyl-1,2,4-triazoline-2,3-dione (**30**).* Under an argon atmosphere, to a stirred solution of compound **3** (160 mg, 0.523 mmol) and 4-phenyl-1,2,4-triazoline-2,3-dione (57 mg, 0.325 mmol) in CH_2Cl_2 (1.5 mL) was slowly added BF_3·THF (40 μL, 0.360 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 10 min, followed by dilution with DCM and saturated $NaHCO_3$. The aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography using Florisil (1:15 EtOAc/hexanes to 1:12 EtOAc/hexanes) gave compound **31** as a colorless oil in 27% yield (33 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.53−7.27 (m, 10H), 5.11 (q, J = 6.3 Hz, 1H), 4.95 (d, J = 11.0 Hz, 1H), 4.58 (d, J = 10.9 Hz, 1H), 3.86 (d, J = 12.9 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 157.2, 134.4, 131.2, 129.4, 129.2 (2C), 129.1, 128.7, 125.1, 121.9 (q, J = 281 Hz), 77.6 (q, J = 36 Hz), 67.8, 60.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.68 (s) ppm. IR (neat film): 2930 (w), 1790 (m), 1717 (s), 1598 (w), 1500 (m), 1457 (m), 1399 (s), 1287 (m), 1237 (m), 1207 (m), 1169 (s), 1127 (s), 1075 (m) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{18}H_{15}F_3N_4O_2$ m/z = 377.1220 (found m/z = 377.1217).

*Debenzylation of Compound **15a**.* Under an argon atmosphere, to a stirred suspension of 5% Pd/C (102 mg) in EtOH (4 mL) was added a solution of the cycloadduct **15a** (140 mg, 0.320 mmol) in EtOH (4 mL) at room temperature. After flushing the flask with H_2 gas the resulting reaction mixture was stirred at room temperature for 2 days. The reaction mixture was then filtered through Celite, and the filtrate was concentrated *in vacuo* to give the desired pyrrolidine **32** as a colorless oil in 95% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 4.42 (dquin, J = 10.3, 7.5 Hz, 1H), 4.19 (qq, J = 10.8, 7.2 Hz, 2H), 3.59 (dd, J = 13.6, 7.9 Hz, 1H), 3.52 (d, J = 7.9 Hz, 1H), 3.39 (m, 1H), 2.40 (q, J = 9.8 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 125.4 (q, J = 279 Hz), 124.1 (q, J = 285 Hz), 123.5 (q, J = 286 Hz), 63.4 (q, J = 31 Hz), 62.7, 61.9 (sep, J = 26 Hz), 51.9, 47.9, 13.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.46 (q, J = 9.7 Hz), −69.06 (q, J = 9.7 Hz), −77.00 (s) ppm. IR (neat film): 3393 (w), 2989 (w), 2917 (w), 1744 (m), 1452 (w), 1384 (w), 1374 (w), 1336 (w), 1278 (s), 1203 (s), 1169 (s), 1133 (s), 1108 (m) cm^{-1}. HRMS (ESI+): $[M + H]^+$ calcd for $C_{10}H_{10}F_9NO_2$ m/z = 348.0641, no mass found.

*Oxidation of 3-Pyrrolines **17a**.* Under an argon atmosphere, to a stirred solution of cycloadduct **17a** (20 mg, 0.052 mmol) in toluene (2 mL) was added MnO_2 (46 mg, 0.52 mmol) at room temperature. The resulting reaction mixture was then stirred at 60 °C for 2 h, followed by filtration through Celite. The filtrate was then concentrated in vacuo. Purification by flash chromatography (1:4 EtOAc/hexanes to 1:3 EtOAc/hexanes) gave compound **33** as a white solid in 91% yield (18 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.3 Hz, 2H), 7.42−7.34 (m, 3H), 7.29 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 6.4, 3.1 Hz, 2H), 6.86 (dd, J = 2.0, 1.0 Hz, 1H), 5.13 (s, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 139.6, 134.2, 129.8, 129.2, 128.9, 128.1, 127.9, 127.1, 125.4, 123.7 (q, J = 39 Hz), 120.2 (q, J = 268 Hz), 111.4 (q, J = 4 Hz), 52.4, 21.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −59.10 ppm. IR (solid state): 3152 (w), 3035 (w), 2926 (w), 2853 (w), 1597 (w), 1557 (m), 1500 (m), 1452 (m), 1404 (m), 1357 (m), 1318 (s), 1277 (m), 1210 (m), 1143 (s), 1102 (s), 1039 (s) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{19}H_{16}F_3NO_2S$ m/z = 402.0746 (found m/z = 402.0765). Mp: 108.0 −108.6 °C.

*Oxidation of 3-Pyrrolines **19**.* Under an argon atmosphere, to a stirred solution of cycloadduct **19** (80 mg, 0.233 mmol) in toluene (2.5 mL) was added MnO_2 (203 mg, 2.33 mmol) at room temperature. The resulting reaction mixture was stirred at 60 °C for 2 h, followed by filtration through Celite. The filtrate was then concentrated in vacuo to give a colorless oil. Purification by flash chromatography (1:2.5 EtOAc/hexanes) gave compound **34** as a colorless oil in quantitative yield (78 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.35 (m, 2H), 7.22 (s, 1H), 7.18−7.16 (m, 2H), 5.16 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 162.6, 134.4, 129.4, 129.2, 128.8, 127.7, 120.9 (q, J = 3 Hz), 120.2 (q, J = 267 Hz), 119.7 (q, J = 39 Hz), 114.1, 52.9, 52.4, 51.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.4 (s) ppm. IR (neat film): 3135 (w), 3036 (w), 2954 (w), 2857 (w), 1740 (s), 1717 (s), 1567 (m), 1530 (m), 1440 (m), 1265 (s), 1214 (s), 1172 (s), 1116 (s), 1043 (s), 910 (m) cm^{-1}. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{16}H_{15}F_3NO_4$ m/z = 402.0746 (found m/z = 402.0765).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full data and identity of the minor isomers along with ^1H and ^{13}C spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: svl1000@cam.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the EPSRC (award # EP/F069685/1) and Pfizer Global Research (D.L.B.) and the BP Endowment (S.V.L.). Industrial Research Ltd. is thanked for supporting a sabbatical placement in Cambridge (L.H.).

■ REFERENCES

(1) For some articles highlighting the state-of-the-art methods for fluorination, see: (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305−321. (b) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9322−9324. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470−477. (d) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048−5050.

(2) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330.

(3) Jeschke, P. *ChemBioChem* **2004**, *5*, 570−589.

(4) Kirsch, P.; Bremer, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4216−4235.

(5) For a selection of recent examples of interesting reagents and methods for late-stage fluorination reactions, see: (a) Knauber, T.; Arikan, F.; Röschenthaler, G.-V.; Gooßen, L. J. *Chem.—Eur. J.* **2011**, *17*, 2689−2697. (b) Khan, B. A.; Buba, A. E.; Gooßen, L. J. *Chem.—Eur. J.* **2012**, *18*, 1577−1581. (c) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901−20913. (d) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411−14415. (e) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909−1911. (f) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224−228. (g) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648−3649. (h) Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem.—Eur. J.* **2011**, *17*, 6039−6042. (i) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298−1304. (j) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494−1497. (k) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482−11484. (l) Huang, C.; Liang, T.; Harada, S.; Lee., E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 13308−13310. (m) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312−7314. (n) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767−7770.

(6) (a) Wilson, P. G.; Percy, J. M.; Redmond, J. M.; McCarter, A. W. *J. Org. Chem.* **2012**, *77*, 6384−6393. (b) Kyne, S. H.; Percy, J. M.; Pullin, R. D. C.; Redmond, J. M.; Wilson, P. G. *Org. Biomol. Chem.* **2011**, *9*, 8328−8339. (c) Audouard, C.; Garayt, M. R.; Kérouréden, E.; Percy, J. M.; Yang, H. *J. Fluor. Chem.* **2005**, *126*, 611−623.

(7) For some comprehensive reviews on azomethine ylide cycloadditions, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765−2809. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484−4517.

(8) For some recent examples of azomethine ylide cycloadditions, see: (a) Li, Q.-H.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2012**, *53*, 3650−3653. (b) Hernández-Toribio, J.; Padilla, S.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8854.

(9) Burger, K.; Meffert, A.; Bauer, S. *J. Fluor. Chem.* **1977**, *10*, 57−62.

(10) Tanaka, K.; Nagatani, S.; Ohsuga, M.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 589−591.

(11) Tanaka, K.; Ohsuga, M.; Sugimoto, Y.; Okafuji, Y.; Mitsuhashi, K. *J. Fluorine Chem.* **1988**, *39*, 39−45.

(12) (a) Laduron, F.; Ates, C.; Viehe, H. G. *Tetrahedron Lett.* **1996**, *37*, 5515−5518. (b) Laduron, F.; Viehe, H. G. *Tetrahedron* **2002**, *58*, 3543−3551.

(13) Domingo, L. R. *J. Org. Chem.* **1999**, *64*, 3922−3929.

(14) Mimura, H.; Kawada, K.; Yamashita, T.; Sakamoto, T.; Kikugawa, Y. *J. Fluorine Chem.* **2010**, *131*, 477−486.

(15) (a) Gerlach, K.; Hoffmann, H. M. R.; Wartchow, R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3867−3872. (b) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235−244. (c) Padwa, A.; Chen, Y. *Tetrahedron Lett.* **1983**, *24*, 3447−3450. (d) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 896−898. (e) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117−1120.

(16) Indentity of the diasteroisomers was made by FHOESY, NOESY, and coupling constant analysis, all of which can be found in the Supporting Information.

(17) Carey, J. S. *J. Org. Chem.* **2001**, *66*, 2526−2529.