Special Topic

Synthesis of [¹⁸F]- γ -Fluoro- α , β -unsaturated Esters and Ketones via Vinylogous ¹⁸F-Fluorination of α -Diazoacetates with [¹⁸F]AgF

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Published as part of the Special Topic Halogenation methods (with a view towards radioimaging applications)

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Abstract This communication reports a method for the vinylogous radiofluorination of α -diazoacetates to generate [¹⁸F]- γ -fluoro- α , β -unsaturated esters and ketones in moderate to good radiochemical yields. The method uses no-carrier-added [¹⁸F]AgF and is compatible with aromatic and non-aromatic substrates and a number of different functional groups. The labeling method is showcased in the synthesis of a fluorinated cholest-5-en-3-one derivative as well as a difluorinated product pertinent to drug discovery.

Key words fluorine-18, late-stage fluorination, PET radiochemistry, diazo chemistry, positron emission tomography

Positron emission tomography (PET) is a functional imaging technique that is used for clinical diagnostic imaging as well as research applications in academic medical centers and pharmaceutical companies.^{1,2} Fluorine-18 (¹⁸F) is one of the most commonly used PET radionuclides because of its useful half-life (110 min) and favorable imaging properties. Reflecting this, the development of new methods for accessing novel radiotracer motifs using fluorine-18 is an exciting area of research that has led to development of numerous new methods for the fluorination of a diverse array of substrates in recent years.³ New C-¹⁸F bond-forming reactions need to be compatible with the unique challenges of working with ¹⁸F, such as short reaction times (usually ≤20 min), automated synthesis and purification, and cGMP compliant dose-on-demand production. In this context, transition-metal-mediated nucleophilic radiofluorination methods have emerged as particularly practical approaches for forming new C-18F bonds.4

Incorporation of ¹⁸F at an sp³ carbon is one of the most widely used labeling strategies. This is typically achieved via nucleophilic displacement of an appropriate leaving group with [¹⁸F]fluoride, such as in the production of 2-[¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) by the reaction of mannose triflate with [¹⁸F]KF, one of the most commonly used labeling reactions in PET radiochemistry.⁵ However, this approach is not compatible with all substrates and new methods for generating C(sp³)–F bonds are essential to simplify production of diverse libraries of PET radiotracers for preclinical and clinical evaluation.

In recent years we, and others, have reported new reactions for generating both $C(sp^2)$ -F and $C(sp^3)$ -F bonds that have proven challenging using traditional nucleophilic substitution reactions with [¹⁸F]fluoride.^{4,6} Key to developing such reactions has been our discovery that different forms of [18F]fluoride (beyond traditional [18F]KF) are easily accessible by simple adjustment of the solution used to elute [¹⁸F]fluoride from the quaternary methylammonium (QMA) cartridge employed to reprocess [18F]fluoride obtained from cyclotron-irradiated [180]H₂O.⁶ For example, we recently reported a new method for generating [¹⁸F]AgF^{6a} and utilized it in the C(sp³)-H radiofluorination of a series of 8-methylquinoline derivatives.^{6d} This work demonstrated that new fluorine-18 radiochemistry could be accessed using [¹⁸F]AgF, and we were interested to explore whether we could use [18F]AgF in the development of other novel radiofluorination methodology. In particular, vinylogous fluorination is quite challenging, and we were particularly interested in the Ag-catalyzed vinylogous fluorination of α-diazoacetates recently described by Davies and Qin (Scheme 1a).⁷ This paper describes our efforts towards translating Ag-mediated vinylogous fluorination to radiofluorination



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using [¹⁸F]AgF (Scheme 1b). The transformation was particularly attractive as (1) gamma (γ) functionalization of carbonyl compounds generally remains challenging,⁸ relying primarily on $S_N 2'$ reactions with α -substituted- β . γ -unsaturated esters, reaction of activated enol ethers with electrophiles, or Wittig-type reactions with prefunctionalized reagents, all of which are challenging transformations to accomplish with [18F]fluoride; (2) while diazo compounds have been demonstrated as useful precursors for radiofluorination⁹ and related methods for allylic ¹⁸F-fluorination have been reported,¹⁰ both remain unexploited as methods for accessing candidate PET radiotracers and radioligands; (3) the resultant γ -fluoro- α , β -unsaturated esters are useful synthons for further reaction; and (4) difluorinated moieties are attracting attention as bioisosteres and for the synthesis of PET imaging agents.^{11,12}

Initial examination of the reaction, as reported by Davies and Qin,⁷ identified two parameters which could potentially make such a reaction challenging to adapt for use with fluorine-18. Firstly, the reaction requires the use of an excess of fluoride (15 equivalents) with respect to the diazo reagent. In PET radiochemistry, [¹⁸F]fluoride is produced in pmol to nmol amounts and, under no-carrier-added conditions, is always the limiting reagent, often by several orders of magnitude. Secondly, the reaction requires a proton source as the reaction involves the (formal) addition of HF and in most cases, [¹⁸F]fluoride is used under basic conditions.

Our initial investigations focused on the radiofluorination of model α -diazoacetate substrate $\mathbf{1N_2}$ using the previously-described preparation of [¹⁸F]AgF, with kryptofix-222 (K₂₂₂) as a phase transfer catalyst (Table 1).^{6d} Early experiments focused on the reaction of [¹⁸F]AgF·K₂₂₂·AgOTf with $\mathbf{1N_2}$ at 40 °C in dichloromethane in the dark, using a protocol similar to that described by Davies and Qin.⁷ Under these conditions, radiochemical yields (RCY)¹³ of [¹⁸F]**1**F were found to be $\leq 0.5\%$ (Table 1, entry 1), which was not unexpected considering the lack of a proton source in this system. Screening of protic additives in the reaction identified imidazolium triflate (Im·HOTf) as an additive that led to improved RCYs (Table 1, entry 2). RCYs were further increased to $23 \pm 11\%$ (*n* = 7) upon addition of 3 equivalents of acetic acid (Table 1, entry 3). Further optimization of the reaction revealed that higher temperatures [which necessitated changing the reaction solvent from DCM to dichloroethane (DCE)] also led to improved yields. At 40 °C in DCE in the presence of Im·HOTf and HOAc, [¹⁸F]**1F** was produced in $12 \pm 6\%$ RCY (n = 4) (Table 1, entry 4), which was lower than the observed RCY in DCM at that temperature. However, increasing the temperature of the reaction to 100 °C increased the RCY of $[^{18}F]$ **1F** to 40 ± 12% (*n* = 26) (Table 1, entry 5). Further increases in temperature under these conditions led to erosion of the observed RCY. Interestingly, RCYs for the transformation when [18F]KF·K₂₂₂·KOTf was used as a source of [18F]fluoride are similar to those observed when using [18F]AgF·K₂₂₂·AgOTf (Table 1, entries 5 and 6). Since the transformation using [18F]AgF·K₂₂₂·AgOTf requires 1 equivalent of AgOAc for the reaction to proceed, it is perhaps not surprising that the reaction proceeds equally well with [18F]AgF and [18F]KF. Omitting AgOAc from the reaction greatly suppressed RCY, regardless of whether [18F]AgF or [18F]KF was used as the [18F]fluoride source (Table 1, entries 7 and 8). Ultimately however, in order to maintain a common counterion, we elected to move forward with [¹⁸F]AgF·K₂₂₂·AgOTf for further development of this methodology. Other variables, including the identity and loading of a variety of silver and imidazolium salts, and weak acids as well as the concentration of 1N₂ and AgOAc were optimized for their effect on the reaction (see Supporting Information). Ultimately, the optimal conditions for the conversion of **1N₂** to [¹⁸F]**1F** were as follows: **1N₂** (10 μmol), AgOAc (10 μmol), Im·HOTf (10 μmol), HOAc (30 μmol), [¹⁸F]AgF·K₂₂₂·AgOTf in DCE (100 µL, 100-1000 µCi) in a total volume of 1 mL DCE, heated to 100 °C for 30 minutes. These optimal conditions generated [¹⁸F]**1F** RCY of $40 \pm 12\%$ (*n* = 26) (Table 1, entry 5). Analysis of a typical radiosynthesis employing 328 µCi of [18F]fluoride provided 151 μ Ci of [₁₈F]**1F** (46% RCY) with a molar activity of 0.5 Ci/mmol (typical for a lower activity synthesis run in our laboratory^{6d}).

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Table 1 Optimization of Radiofluorination of $\alpha\mbox{-Diazoacetates Using $|^{18}F|AgF^a$}$

			[¹⁸ F]MF• AgOAc additive acid (solvent temperat	K ₂₂₂ •MOTf (1 equiv) (1 equiv) 3 equiv) t (0.01 M) ure, 30 min	C	¹⁸ F OMe
Entry	М	Additive	Acid	Solvent	Temp	RCY ^b (%) ¹³
1	Ag	-	-	DCM	40	0.5 ± 0.1 (n = 3)
2	Ag	Im·HOTf	-	DCM	40	8 ± 3 (n = 3)
3	Ag	Im·HOTf	HOAc	DCM	40	23 ± 11 (n = 7)
4	Ag	Im·HOTf	HOAc	DCE	40	12 ± 6 (n = 4)
5	Ag	Im·HOTf	HOAc	DCE	100	40 ± 12 (n = 26)
6	К	Im∙HOTf	HOAc	DCE	100	$40 \pm 3 (n = 3)$
7 ^c	Ag	Im·HOTf	HOAc	DCE	100	3 ± 2 (n = 3)
8 ^c	К	Im·HOTf	HOAc	DCE	100	1 ± 0 (n = 3)

 a Conditions: $1N_2$ (10 μ mol), AgOAc (10 μ mol), additive (10 μ mol), acid (30 μ mol), [18 F]MF-K_{222}-MOTf in solvent (100 μ L, 100–1000 μ Ci) in a total volume of 1 mL solvent, heat, 30 min.

^b RCY is the non-isolated yield estimated by radioTLC and reported as mean ± standard deviation for *n* runs.

^c Reactions run without any AgOAc.



Following optimization of the reaction conditions using simple unsubstituted arene substrate 1N₂, the substrate scope of the reaction was explored using a series of substituted arene precursors without further optimization of the reaction conditions (Scheme 2). Electron-deficient ([¹⁸F]**2F**) and electron-neutral arenes [¹⁸F]**3F**-[¹⁸F]**6F** were well tolerated in the reaction. Contrastingly, electron-rich arenes, such as anisoles [¹⁸F]**7F** and *N*,*N*-dimethylanilines [¹⁸F]**8F**, proved poor substrates presumably due to instability of the ¹⁸F-fluorinated product, which is implied by the in situ analysis of such substrates in the original reaction.^{7,14} While most substrates tested contained *para*-substituents, the reaction was also tolerant of ortho- and meta-substituents on the phenyl ring. RCYs of the para- [¹⁸F]**4**F, meta- [¹⁸F]**5**F, and ortho-bromo-substituted [¹⁸F]**6F** products were comparable, with the slightly lower RCYs of the ortho- and meta-substituted products likely attributable to steric effects. Using a fluorovinvl- α -diazo precursor **9N**₂, it was found that the difluorinated product [18F]9F could be obtained in $45 \pm 5\%$ (*n* = 4) RCY, suggesting that this transformation may be useful for the synthesis of $[^{18}F]CF_2$ groups which is of interest as the CF₂ motif is being explored for PET imaging and as a bioisostere in drug design.^{11,12} Finally, it was demonstrated that this method was suitable for radiolabeling non-aromatic precursors, whereby 4-diazo-



Scheme 2 Substrate scope of AgOAc-mediated radiofluorination of α-diazoacetates using [18 F]AgF. *Reagents and conditions*: **1N**₂-**10N**₂ (10 μmol), AgOAc (10 μmol), Im-HOTf (10 μmol), HOAc (30 μmol), [18 F]AgF·K₂₂₂·AgOTf in DCE (100 μL, 100–1000 μCi) in a total volume of 1 mL DCE, 100 °C, 30 min. Non-isolated RCYs were estimated by radioTLC and product identities were confirmed by radioHPLC.

functionalized cholest-5-en-3-one was successfully radiofluorinated using [¹⁸F]AgF·K₂₂₂·AgOTf to generate [¹⁸F]**10F** in modest radiochemical yield (15 ± 8%, n = 4). The latter compound is of interest for our program radiolabeling steroid derivatives for applications, such as use of PET to quantify cholesterol metabolism.^{6e,15}

In conclusion, we have developed a simple method for the vinylogous radiofluorination of substituted α -diazoacetates in moderate to good radiochemical yield using [¹⁸F]AgF. This method provides access to [¹⁸F]- γ -fluoro- α , β unsaturated esters which are useful synthons for further elaboration. These labeled substrates are challenging to access via traditional radiochemistry, and this method has potential for labeling drug molecules and preparing new PET radiotracers. In the latter case, we are in the process of using the new methodology to label steroids such as [¹⁸F]**10F** for pre-clinical PET imaging and anticipated translation into clinical trials.

Reagents were purchased from Sigma Aldrich, Alfa Aesar, Oakwood, Fisher Scientific, EMD Millipore Corporation and Acros Organics. ¹H NMR spectra were obtained on a Varian 400 MHz MR NMR (399.7 MHz for ¹H, 100.5 MHz for ¹³C and 376.1 MHz for ¹⁹F) and Varian 500 MHz VNMRS (499.5 MHz for ¹H, 125.6 MHz for ¹³C) spectrometers. Spectra were referenced to TMS as an internal standard (¹H: δ = 0.00) or residual solvent peak (CDCl₃: ¹H: δ = 7.26, ¹³C: δ = 77.16). ¹⁹F NMR spectra are referenced to an external standard CFCl₃ (CFCl₃: δ = 0.00 for ¹⁹F). NMR spectra were recorded at r.t. HRMS were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Flash column chromatography was conducted using a Biotage Isolera Prime system with SNAP KP-Sil column cartridges (10 g or 25 g).

Ultrapure water was obtained from a Millipore MilliQ Gradient A10 system. Sterile vials were purchased from Hollister-Stier.

QMA-light Sep-Paks were purchased form Waters Corporation, and were preconditioned with EtOH (10 mL), followed by water (10 mL), followed by 0.5 M aq KOTf (10 mL), followed by water (10 mL) before use.

Glass-backed TLC plates coated with silica gel $60F_{254}$ were used for TLC and radioTLC analysis and were purchased from EMD-Millipore. TLC plates were visualized with KMnO₄ or anisaldehyde stain. RadioTLC analysis was performed using a Bioscan AR 2000 RadioTLC scanner (Ekert and Ziegler).

Activity in vials was counted using a CRC-15 (Capintec) detector, calibrated for fluorine-18.

HPLC was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector in series. A 0.2 min offset was applied to all traces below to account for the detectors being in series. Specific HPLC conditions are specified in the Supporting Information.

Synthesis of $\alpha\mbox{-Diazoacetate}$ Substrates $1N_2\mbox{--}10N_2\mbox{;}$ General Procedure for Diazo Transfer

 α -Diazoacetate substrates **1N**₂-**10N**₂ were prepared through adaptation of literature methods reported by Davies and Qin.⁷ Briefly, the ester (1 equiv, see precursors **S1–S10** in Supporting Information) and *p*-acetamidobenzenesulfonyl azide (1.1 equiv) were taken up in dry MeCN and the suspension cooled to 0 °C. DBU (1.1 equiv) was taken

up in dry MeCN and added to the suspension dropwise over 10 min. The total volume of MeCN used gave a final concentration of the ester of 0.25 M; two thirds of the total volume of MeCN was used to dissolve the ester/ketone, and the remaining third used for the DBU. The suspension was stirred at 0 °C for a further 30 min, and at r.t. for a further 30–60 min until the reaction was found to be complete by TLC. The deep orange solution was concentrated, and the residue was taken up into DCM, and dry loaded onto silica gel, before being passed through a short (5 cm) silica plug, eluting with 20% EtOAc/hexanes. The product was further purified by automated silica gel chromatography (hexane/EtOAc gradient) to yield the corresponding diazo ester.

The isolated diazo products are unstable at r.t., and are best stored at -20 °C in the dark. Prolonged storage under vacuum (i.e., to remove residual solvents) was found to accelerate decomposition. If stored for long periods (>1–2 months), diazo precursors should be re-purified before use. The ¹³C NMR signal for the diazo carbon is not observed, due to the long T1 for such carbons.

Methyl (E)-2-Diazo-4-phenylbut-3-enoate (1N₂)

Synthesized according to the general procedure to yield $1N_2$ (766 mg, 83%) as an orange-red oil that solidified upon storage at -20 °C.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.36–7.29 (m, 4 H, ArH), 7.22–7.17 (m, 1 H, ArH), 6.48 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.19 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.85 (s, 3 H, COOCH₃).

 ^{13}C NMR (100.5 MHz, CDCl₃): δ = 165.7, 136.9, 128.8, 127.2, 126.0, 123.1, 111.3, 52.5.

HRMS (ESI*): m/z [M + H]⁺ calcd for C₁₁H₁₁O₂N₂: 203.0815; found: 203.0813.

Methyl (E)-2-Diazo-4-[4-(trifluoromethyl)phenyl]but-3-enoate $(2N_2)$

Synthesized according to the general procedure to yield $2N_2$ (184 mg, 83%) as an orange solid.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.55 (app. d, *J* = 8.3 Hz, 2 H, ArH), 7.43 (app. d, *J* = 8.3 Hz, 2 H, ArH), 6.61 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.22 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.87 (s, 3 H, COOCH₃).

¹³C NMR (100.5 MHz, CDCl₃): δ = 165.1, 140.2 (q, *J* = 1.5 Hz), 128.6 (q, *J* = 32.5 Hz), 125.8, 125.6 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.8 Hz), 121.2, 114.4, 52.5.

¹⁹F NMR (376.1 MHz, CDCl₃): δ = -62.46 (s, 3 F, CF₃).

HRMS (ESI*): m/z [M + H]* calcd for $C_{12}H_{10}O_2F_3N_2$: 271.0689; found: 271.0687.

Methyl (E)-4-(Biphenyl-4-yl)-2-diazobut-3-enoate (3N₂)

Synthesized according to the general procedure to yield $3N_2$ (107 mg, 65%) as an orange solid.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.61–7.55 (m, 4 H, ArH), 7.46–7.42 (m, 4 H, ArH), 7.36–7.32 (m, 1 H, ArH), 6.52 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.24 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.87 (s, 3 H, COOCH₃).

 ^{13}C NMR (100.5 MHz, CDCl_3): δ = 165.7, 140.7, 140.0, 135.9, 128.9, 127.5, 127.4, 127.0, 126.4, 122.7, 111.4, 52.0.

HRMS (ESI*): m/z [M + H]⁺ calcd for C₁₇H₁₅O₂: 279.1128; found: 279.1127.

Methyl (E)-4-(4-Bromophenyl)-2-diazobut-3-enoate (4N2)

Synthesized according to the general procedure to yield $4N_2$ (134 mg, 61%) as an orange-red oil that solidified upon storage at -20 °C.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.44–7.41 (m, 2 H, ArH), 7.22–7.20 (m, 2 H, ArH), 6.48 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.13 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.85 (s, 3 H, COOCH₃).

 ^{13}C NMR (100.5 MHz, CDCl₃): δ = 165.4, 135.7, 131.8, 127.3, 121.6, 120.7, 112.3, 52.4.

HRMS (EI⁺): m/z [M]⁺ calcd for $C_{11}H_9O_2N_2^{79}Br$: 279.9847; found: 279.9847.

Methyl (E)-4-(3-Bromophenyl)-2-diazobut-3-enoate (5N₂)

Synthesized according to the general procedure to yield $5N_2$ (206 mg, 75%) as an orange-red oil that solidified upon standing.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.49–7.47 (m, 1 H, ArH), 7.31–7.29 (m, 1 H, ArH), 7.25–7.23 (m, 1 H, ArH), 7.17–7.13 (m, 1 H, ArH), 6.41 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.11 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.85 (s, 3 H, COOCH₃).

 ^{13}C NMR (100.5 MHz, CDCl₃): δ = 165.3, 139.0, 130.2, 129.9, 128.7, 124.5, 123.0, 121.4, 113.2, 52.5.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₁₁H₁₀O₂N₂⁷⁹Br: 280.9920; found: 280.9918.

Methyl (E)-4-(2-Bromophenyl)-2-diazobut-3-enoate (6N₂)

Synthesized according to the general procedure to yield $6N_2$ (150 mg, 68%) as an orange-red oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.54–7.51 (m, 2 H, ArH), 7.28–7.23 (m, 1 H, ArH), 7.07–7.03 (m, 1 H, ArH), 6.55 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.47 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.85 (s, 3 H, COOCH₃). ¹³C NMR (126 MHz, CDCl₃): δ = 165.4, 136.6, 133.2, 128.4, 127.8, 126.6, 123.3, 121.5, 114.7, 52.6.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for $C_{11}H_{10}O_2N_2^{79}Br$: 280.9920; found: 280.9921.

Methyl (E)-2-Diazo-4-(4-methoxyphenyl)but-3-enoate (7N₂)

Synthesized according to the general procedure to yield $7N_2$ (59 mg, 49%) as an orange-red oil that solidified upon storage at -20 °C.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.30–7.28 (m, 2 H, ArH), 6.87–6.85 (m, 2 H, ArH), 6.30 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.14 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.85 (s, 3 H, COOCH₃), 3.81 (s, 3 H, ArOCH₃).

 ^{13}C NMR (100.5 MHz, CDCl₃): δ = 165.9, 158.9, 129.7, 127.0, 122.8, 114.3, 108.7, 55.3, 52.3.

HRMS (ESI*): m/z [M + H]* calcd for C₁₂H₁₃O₃N₂: 233.0921; found: 233.0914.

Methyl (E)-2-Diazo-4-[4-(dimethylamino)phenyl]but-3-enoate (8N₂)

Synthesized according to the general procedure to yield $8N_2$ (44 mg, 85%) as an orange-red oil that solidified upon standing.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.27–7.24 (m, 2 H, ArH), 6.69–6.67 (m, 2 H, ArH), 6.19 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 6.11 (d, *J* = 16.3 Hz, 1 H, ArCH=CH), 3.84 (s, 3 H, COOCH₃), 2.96 [s, 6 H, ArN(CH₃)₂].

¹³C NMR (100.5 MHz, CDCl₃): δ = 149.9, 127.0, 125.5, 123.7, 112.6, 105.9, 52.4, 40.6; (C=O not observed).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₁₃H₁₆O₂N₃: 246.1237; found: 246.1236.

Ethyl (Z)-2-Diazo-4-fluoro-4-phenylbut-3-enoate (9N₂)

Synthesized according to the general procedure to yield $9N_2$ (102 mg, 93%) as a pale orange solid.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.48–7.46 (m, 2 H, ArH), 7.38–7.34 (m, 2 H, ArH), 7.29–7.25 (m, 1 H, ArH), 5.71 (d, J = 37.2 Hz, 1 H, CF-CHCN₂), 4.30 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 1.32 (t, J = 7.1 Hz, 3 H, CH₂CH₃).

¹³C NMR (100.5 MHz, CDCl₃): δ = 165.7, 131.8 (d, *J* = 26.4 Hz), 128.7 (d, *J* = 2.4 Hz), 128.6, 123.5 (d, *J* = 7.3 Hz), 89.9 (d, *J* = 12.0 Hz), 61.7, 14.6; *note*: CF resonance as well as CN₂ resonance not observed.

¹⁹F NMR (376.1 MHz, CDCl₃): δ = -117.77 (br s, 1 F, CFCHCN₂).

HRMS (ESI⁺): m/z [M – N₂ + H]⁺ calcd for C₁₂H₁₂FO₂: 207.0816; found: 207.0815.

4-Diazocholest-4-en-3-one (10N₂)

Cholest-5-en-3-one (100 mg, 0.25 mmol, 1 equiv) and *p*-acetamidobenzenesulfonyl azide (70 mg, 0.29 mmol, 1.1 equiv) were taken up in dry MeCN (4 mL) and the suspension cooled to 0 °C. DBU (43 μ L, 0.29 mmol, 1.1 equiv) was taken up in dry MeCN (1 mL), and added to the suspension dropwise over 10 min. The suspension was stirred at 0 °C for a further 30 min, and at r.t. for a further 90 min, until the reaction was found to be complete by TLC. The deep orange solution was concentrated, and the residue was taken up into DCM, and dry loaded onto silica gel, before being passed through a short (5 cm) silica plug, eluting with 20% EtOAc/hexanes. The product was further purified by automated silica gel chromatography (hexane/EtOAc acetate gradient) to give **10N**₂ (13.7 mg, 13%) as a yellow oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 5.18 (dd, *J* = 4.9, 2.8 Hz, 1 H), 2.47–2.44 (m, 2 H), 2.23 (dt, *J* = 18.0, 5.2 Hz, 1 H), 2.05 (dt, *J* = 12.6, 3.3 Hz, 1 H), 2.00–1.95 (m, 1 H), 1.90–1.82 (m, 1 H), 1.79–0.96 (m, 23 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.87 (dd, *J* = 6.6, 1.7 Hz, 6 H), 0.72 (s, 3 H).

 ^{13}C NMR (100.5 MHz, CDCl_3): δ = 192.90, 129.42, 114.87, 56.6, 56.0, 48.3, 42.4, 39.5, 39.5, 36.1, 35.8, 35.4, 33.4, 32.4, 31.5, 31.3, 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 21.2, 19.4, 18.7, 11.9.

HRMS (ESI⁺): m/z [M – N₂ + H]⁺ calcd for C₂₇H₄₃O: 383.3308; found: 383.3308.

Synthesis of Fluorinated Reference Standards; General Procedure $^{\rm 14}$

AgOAc (0.2 equiv) was placed in a flame dried, foil-covered flask, and the flask evacuated and filled with argon (3 ×). Drv DCM (final concentration 0.075 M) was added to the flask under argon, and 3HF·Et₃N was added to the suspension. The suspension was heated to reflux before the α -diazoacetate substrate [1 equiv, in DCM (ca. 1 mL)] was added to the refluxing suspension by syringe pump over 1 h. After addition was complete, a further aliquot of DCM (1 mL) was taken up into the syringe, and this added in one portion to the suspension. The mixture was refluxed for a further 3 h. The reaction was cooled, the foil removed, and the reaction guenched with sat. ag NaHCO₃ (10 × the volume of 3HF·Et₃N used), and the resultant mixture stirred for 30 min. The mixture was diluted with water (10 mL), then the resultant biphasic mixture was separated and the aqueous phase extracted with DCM (3 × 30 mL). The organic extracts were combined, dried (Na₂SO₄), filtered, and concentrated. The residue was taken up into DCM, dry loaded onto silica gel, and purified by automated silica gel chromatography (hexane/EtOAc gradient) to yield the corresponding fluorinated product.

F

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Methyl (E)-4-Fluoro-4-phenylbut-2-enoate (1F)

Synthesized according to the general procedure to yield 1F (27 mg, 36%) as a colorless oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.43–7.26 (m, 5 H, ArH), 7.06 (ddd, J = 19.2, 15.7, 4.4 Hz, 1 H, ArCHFCH=CH), 6.19 (ddd, J = 15.7, 1.6, 1.6 Hz, 1 H, ArCHFCH=CH), 6.02 (ddd, J = 47.0, 19.2, 1.6 Hz, 1 H, ArCHFCH=CH), 3.76 (s, 3 H, COOCH₃).

 ^{13}C NMR (100.5 MHz, CDCl₃): δ = 166.4, 144.5 (d, J = 22.0 Hz), 136.8 (d, J = 20.0 Hz), 129.4 (d, J = 2.4 Hz), 129.0, 126.8 (d, J = 5.7 Hz), 121.1 (d, J = 10.2 Hz), 91.9 (d, J = 175.3 Hz), 52.0.

¹⁹F NMR (376.1 MHz, CDCl₃): δ = -173.50 (dd, *J* = 47.0, 19.2 Hz, 1 F, CHFCHCH).

HRMS (ESI*): m/z [M + H]* calcd for C₁₁H₁₂O₂F: 195.0816; found: 195.0811.

Methyl (E)-4-Fluoro-4-[4-(trifluoromethyl)phenyl]but-2-enoate (2F)

Synthesized according to the general procedure to yield $\mathbf{2F}$ (4.7 mg, 16%) as a colorless oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.67 (d, *J* = 8.0 Hz, 2 H, ArH), 7.48 (d, *J* = 8.0 Hz, 2 H, ArH), 7.02 (ddd, *J* = 18.8, 15.7, 4.6 Hz, 1 H, ArCH-FCH=CH), 6.20 (ddd, *J* = 15.7, 1.7, 1.7 Hz, 1 H, ArCHFCH=CH), 6.15–6.02 (m, 1 H, ArCHFCH=CH), 3.77 (s, 3 H, COOCH₃).

¹³C NMR (100.5 MHz, CDCl₃): δ = 166.1, 143.3 (d, *J* = 21.2 Hz), 127.3 (app. d, *J* = 32.5 Hz), 126.8 (d, *J* = 6.2 Hz), 126.0 (q, *J* = 3.8 Hz), 122.0 (d, *J* = 10.5 Hz), 91.1 (d, *J* = 177.0 Hz), 52.1; *note*: quartets for C-CF₃ and C-CF₃ carbons were not observed due to the low mass of material isolated.

¹⁹F NMR (376.1 MHz, CDCl₃): δ = -177.30 (dd, *J* = 46.7, 18.8 Hz, 1 F, CHFCHCH), -62.80 (s, 3 F, CF₃).

HRMS (ESI*): m/z [M + H]⁺ calcd for C₁₂H₁₁O₂F₄: 263.0690; found: 263.0696.

Methyl (E)-4-Fluoro-4-(biphenyl-4-yl)but-2-enoate (3F)

Synthesized according to the general procedure to yield 3F (15 mg, 30%) as a colorless oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.64–7.57 (m, 4 H, ArH), 7.47–7.41 (m, 4 H, ArH), 7.39–7.35 (m, 1 H, ArH), 7.09 (ddd, *J* = 19.0, 15.7, 4.4 Hz, 1 H, ArCHFCH=CH), 6.22 (ddd, *J* = 15.7, 1.6, 1.6 Hz, 1 H, ArCHFCH=CH), 6.07 (ddd, *J* = 47.0, 4.3, 1.6 Hz, 1 H, ArCHFCH=CH), 3.77 (s, 3 H, COOCH₃).

¹³C NMR (100.5 MHz, CDCl₃): δ = 166.4, 144.4 (d, *J* = 22.1 Hz), 142.44, 140.5, 135.7 (d, *J* = 20.1 Hz), 129.0, 127.8 (d, *J* = 6.5 Hz), 127.8, 127.3 (d, *J* = 5.5 Hz), 127.3, 121.3 (d, *J* = 10.0 Hz), 91.8 (d, *J* = 175.2 Hz), 52.0. ¹⁹F NMR (376.1 MHz, CDCl₃): δ = -172.96 (dd, *J* = 47.0, 19.0 Hz, 1 F, CHFCHCH).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₇H₁₆O₂F: 293.0948; found: 293.0946.

Methyl (E)-4-(4-Bromophenyl)-4-fluorobut-2-enoate (4F)

Synthesized according to the general procedure to yield $\mathbf{4F}$ (15 mg, 30%) as a colorless oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.54 (d, *J* = 8.3 Hz, 2 H, ArH), 7.22 (d, *J* = 8.3 Hz, 2 H, ArH), 7.00 (ddd, *J* = 19.0, 15.7, 3.9 Hz, 1 H, ArCH-FCH=CH), 6.19–6.15 (m, 1 H, ArCHFCH=CH), 6.04–5.92 (m, 1 H, ArCH-FCH=CH), 3.77 (s, 3 H, COOCH₃).

Special Topic

¹³C NMR (100.5 MHz, CDCl₃): δ = 166.2, 143.8 (d, J = 21.9 Hz), 135.8 (d, J = 20.5 Hz), 132.2, 128.4 (d, J = 5.7 Hz), 123.6 (d, J = 3.0 Hz), 121.6 (d, J = 10.2 Hz), 91.2 (d, J = 176.1 Hz), 52.1.

 $^{19}{\rm F}$ NMR (376.1 MHz, CDCl₃): δ = –174.13 (dd, J = 46.8, 19.0 Hz, 1 F, CHFCHCH).

HRMS (ESI*): m/z [M + H]* calcd for $C_{11}H_{11}O_2F^{79}Br$: 272.9921; found: 272.9916.

Methyl (E)-4-(3-Bromophenyl)-4-fluorobut-2-enoate (5F)

Synthesized according to the general procedure to yield **5F** (15 mg, 30%) as a colorless oil.

¹H NMR (399.7 MHz, CDCl₃): δ = 7.52–7.50 (m, 2 H, ArH), 7.29–7.27 (m, 2 H, ArH), 7.00 (ddd, *J* = 19.0, 15.7, 4.5 Hz, 1 H, ArCHFCH=CH), 6.19 (ddd, *J* = 15.7, 1.6, 1.6 Hz, 1 H, ArCHFCH=CH), 5.98 (ddd, *J* = 46.9, 4.4, 1.6 Hz, 1 H, ArCHFCH=CH), 3.77 (s, 3 H, COOCH₃).

¹³C NMR (100.5 MHz, CDCl₃): δ = 166.2, 143.6 (d, *J* = 21.6 Hz), 139.00 (d, *J* = 20.4 Hz), 132.5, 130.6, 129.7 (d, *J* = 6.2 Hz), 125.2 (d, *J* = 5.8 Hz), 121.8 (d, *J* = 10.4 Hz), 91.0 (d, *J* = 177.1 Hz), 52.1.

¹⁹F NMR (376.1 MHz, CDCl₃): δ = -175.29 (dd, *J* = 46.9, 19.0 Hz, 1 F, CHFCHCH).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₁₁H₁₁O₂F⁷⁹Br: 272.9921; found: 272.9918.

Methyl (E)-4-(2-Bromophenyl)-4-fluorobut-2-enoate (6F)

Synthesized according to the general procedure to yield **6F** (16 mg, 55%) as a pale yellow solid.

¹H NMR (499 MHz, $CDCl_3$): δ = 7.58 (dt, *J* = 8.1, 1.2 Hz, 1 H, ArH), 7.45 (dd, *J* = 7.8, 1.8 Hz, 1 H, ArH), 7.38 (td, *J* = 7.6, 1.2 Hz, 1 H, ArH), 7.26–7.21 (m, 1 H, ArH), 7.04 (ddd, *J* = 19.0, 15.7, 4.3 Hz, 1 H, ArCHFCH=CH), 6.42 (ddd, *J* = 45.7, 4.3, 1.8 Hz, 1 H, ArCHFCH=CH), 6.22 (dt, *J* = 15.7, 1.7 Hz, 1 H, ArCH-CH=CH), 3.76 (s, 3 H, COOCH₃).

¹³C NMR (126 MHz, CDCl₃): δ = 166.4, 143 (d, J = 21.9 Hz), 136.5 (d, J = 21.5 Hz), 133.1, 131.7, 130.6 (d, J = 1.9 Hz), 127.9 (d, J = 8.3 Hz), 121.6 (d, J = 10.4 Hz), 90.5 (d, J = 176.5 Hz), 52.1.

 ^{19}F NMR (470 MHz, CDCl_3): δ = –180.58 (dd, J = 19.3 Hz, 1 F, CHFCHCH).

HRMS (ESI⁺): m/z [M]⁺ calcd for C₁₁H₁₀⁷⁹BrFO₂: 271.9848; found: 271.9853.

Ethyl (E)-4,4-Difluoro-4-phenylbut-2-enoate (9F)

Synthesized according to the general procedure to yield ${\bf 9F}$ (14 mg, 48%) as a colorless oil.

¹H NMR (399.7 MHz, $CDCl_3$): δ = 7.51–7.43 (m, 5 H, ArH), 7.01 (dt, *J* = 15.7, 10.5 Hz, 1 H, $CF_2CH=CH$), 6.26 (dt, *J* = 15.7, 2.3 Hz, 1 H, $CF_2CH=CH$), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 1.32 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

 ^{13}C NMR (100.5 MHz, CDCl₃): δ = 165.2, 140.1 (t, J = 30.7 Hz), 135.3 (t, J = 27.1 Hz), 130.6 (t, J = 1.7 Hz), 128.8, 125.4 (t, J = 5.8 Hz), 124.9 (t, J = 8.2 Hz), 118.5 (t, J = 240.4 Hz), 61.4, 14.3.

¹⁹F NMR (376.1 MHz, CDCl₃): δ = -117.77 (br s, 1 F, CF₂CHCH).

HRMS (ESI*): m/z [M + H]⁺ calcd for C₁₂H₁₃F₂O₂: 227.0878; found: 227.0875.

(6R)-6-Fluorocholest-4-en-3-one (10F)

Synthesized according to the general procedure, replacing AgOAc with AgOTf, and using $3HF\cdot Et_3N$ (10 equiv), to yield **10F** (14 mg, 30%) as a colorless solid, as a single diastereomer.

¹H NMR (399.7 MHz, CDCl₃): δ = 5.87 (d, *J* = 4.9 Hz, 1 H), 4.99 (ddd, *J* = 49.2, 2.5, 2.5 Hz, 1 H), 2.55 (ddd, *J* = 16.8, 15.1, 4.9 Hz, 1 H), 2.40 (ddd, *J* = 16.8, 3.3, 3.3 Hz, 1 H), 2.25–2.16 (m, 2 H), 1.91–1.81 (m, 2 H), 1.73 (td, *J* = 14.3, 14.3, 4.4 Hz, 1 H), 1.65–0.94 (m, 22 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.87 (dd, *J* = 6.6, 1.7 Hz, 6 H), 0.74 (s, 3 H).

¹³C NMR (100.5 MHz, CDCl₃): δ = 200.2, 162.3 (d, *J* = 12.3 Hz), 128.4 (d, *J* = 9.1 Hz), 93.7 (d, *J* = 166.0 Hz), 56.2, 55.9, 53.4, 42.7, 39.6, 38.0, 37.6, 37.4, 37.0, 36.3, 35.9, 34.4, 30.1, 28.3, 28.2, 24.2, 24.0, 23.0, 22.7, 21.0, 18.8, 18.5 (d, *J* = 0.9 Hz), 12.1.

 ^{19}F NMR (376.1 MHz, CDCl_3): δ = –165.07 to –165.58 (m, 1 F, CCF-HCH_2).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₇H₄₄FO: 404.3371; found: 404.3375.

Davies and Qin report the isolation of a single diastereomer with configuration as shown above.⁷ Data are in agreement with the reported data.

Radiochemistry

General Procedure for Vinylogous ¹⁸F-Fluorination

To a 4-mL vial were added AgOAc (1.6 mg, 10 μ mol, 1.0 equiv) and imidazolium triflate (2.2 mg, 10 μ mol, 1.0 equiv), followed by anhydrous DCE (700 μ L) and HOAc solution [100 μ L of a stock solution in DCE (18 μ L HOAc/1 mL DCE), 30 μ mol, 3 equiv) The solution was briefly vortexed. The reaction vial was capped with a PTFE/Silicone septum cap and a 100 μ L aliquot of [¹⁸F]AgF·K₂₂₂·AgOTf complex in DCE (typically 60–1000 μ Ci; see Supporting Information) was added to the reaction vial by syringe. Finally the diazo compound (10 μ mol in 100 μ L DCE) was added by syringe. The mixture was heated in an aluminum block at 100 °C for 30 min with the exclusion of light.¹⁶ After 30 min, the reaction was removed from the heat and allowed to cool to r.t. before analysis by radioTLC and radioHPLC to confirm RCY and identity, respectively.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690012.

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