HHS Public Access

Author manuscript

Synthesis (Stuttg). Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Synthesis (Stuttg). 2019 December ; 51(23): 4401–4407. doi:10.1055/s-0039-1690012.

Synthesis of [^{18}F]-γ-fluoro-α,β,-unsaturated esters and ketones via vinylogous ^{18}F-fluorination of α-diazoacetates with [^{18}F]AgF

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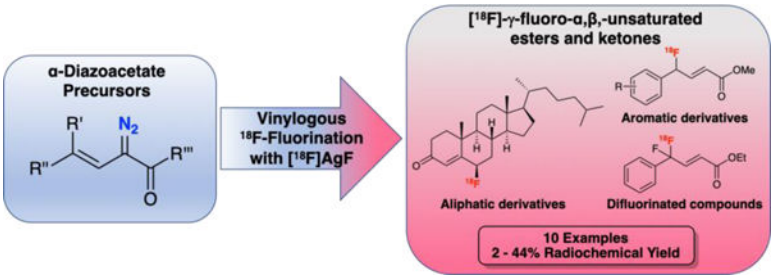
Abstract

This communication reports a method for the vinylogous radiofluorination of α-diazoacetates to generate γ-[^{18}F]fluoro-α,β-unsaturated esters and ketones in moderate to good radiochemical yields. The method uses no-carrier-added [^{18}F]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 5-cholesten-3-one derivative as well as a difluorinated product pertinent to drug discovery.

Graphical Abstract



Keywords

Fluorine-18; late-stage fluorination; PET radiochemistry; diazonium 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 (^{18}F) 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

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Supporting Information

Yes

new methods for the fluorination of a diverse array of substrates in recent years.[3] New C–^{18}F bond-forming reactions need to be compatible with the unique challenges of working with ^{18}F, 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–^{18}F bonds.[4]

Incorporation of ^{18}F at an sp^3 carbon is one of the most widely used labelling strategies. This is typically achieved via nucleophilic displacement of an appropriate leaving group with [^{18}F]fluoride, such as in the production of 2-[^{18}F]fluoro- 2-deoxy-D-glucose ([^{18}F]FDG) by the reaction of mannose triflate with K[^{18}F]F, one of the most commonly used labelling reactions in PET radiochemistry.[5] However, this approach is not compatible with all substrates and new methods for generating C(sp^3)–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 [^{18}F]fluoride.[6] Key to developing such reactions has been our discovery that different forms of [^{18}F]fluoride (beyond traditional [^{18}F]KF) are easily accessible by simple adjustment of the solution used to elute [^{18}F]fluoride from the quaternary methylammonium (QMA) cartridge employed to reprocess [^{18}F]fluoride obtained from cyclotron-irradiated [^{18}O]H_2O.[6] For example, we recently reported a new method for generating [^{18}F]AgF[6a] and utilized it in the C(sp^3)–H radiofluorination of a series of 8-methyl quinoline derivatives.[6d] This work demonstrated that new fluorine-18 radiochemistry could be accessed using [^{18}F]AgF, and we were interested to explore whether we could use [^{18}F]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 co-workers (Scheme 1a).[7] This paper describes our efforts towards translating Ag-mediated vinylogous fluorination to radio-fluorination using [^{18}F]AgF (Scheme 1b). The transformation was particularly attractive as (1) gamma (γ) functionalization of carbonyl compounds generally remains challenging,[8] relying primarily on S_N2' reactions with α-substituted-β,γ-unsaturated esters, reaction of activated enol ethers with electrophiles, or Wittig-type reactions with prefunctionalised reagents, all of which are challenging transformations to accomplish with [^{18}F]fluoride; (2) while diazo compounds have been demonstrated as useful precursors for radiofluorination[9] and related methods for allylic ^{18}F-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,[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 diazonium reagent. In PET radiochemistry, [^{18}F]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, [^{18}F]fluoride is used in under basic conditions.

Our initial investigations focused on the radiofluorination of model α-diazoacetate substrate **1N$_2$** using the previously-described preparation of [^{18}F]AgF, with kryptofix-222 (K_{222}) as a phase transfer catalyst (Table 1).[6d] Early experiments focused on the reaction of Ag[^{18}F]F•K_{222}•AgOTf with **1N$_2$** at 40 °C in dichloromethane (DCM) in the dark, using a protocol similar to that described by Davies.[7] Under these conditions, radiochemical yields (RCY)[13] of [^{18}F]**1F** were found to be ≤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 ± 11 % (n = 7) upon addition of 3 equivalents of acetic acid (AcOH, 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 AcOH, [^{18}F]**1F** was produced in 12 ± 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 [^{18}F]KF•K_{222}•KOTf was used as a source of [^{18}F]fluoride are similar to those observed when using [^{18}F]AgF•K_{222}•AgOTf (Table 1, entries 5 and 6). Since the transformation using [^{18}F]AgF•K_{222}•AgOTf requires 1 equivalent of AgOAc for the reaction to proceed, it is perhaps not surprising that the reaction proceeds equally well with [^{18}F]AgF and [^{18}F]KF. Omitting AgOAc from the reaction greatly suppressed RCY, regardless of whether [^{18}F]AgF or [^{18}F]KF was used as the [^{18}F]fluoride source (Table 1, entries 7 and 8). Ultimately however, in order to maintain a common counter ion, we elected to move forward with [^{18}F]AgF•K_{222}•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 **1N$_2$** and AgOAc were optimized for their effect on the reaction (see Supporting Information). Ultimately, the optimal conditions for the conversion of **1N$_2$** to [^{18}F]**1F** were as follows: 10 μmol of **1N$_2$**, 10 μmol AgOAc, 10 μmol of Im•HOTf, 30 μmol AcOH, [^{18}F]AgF•K_{222}•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 [^{18}F]**1F** RCY of 40 ± 12 % (n = 26) (Table 1, entry 5). Analysis of a typical radiosynthesis employing 12 MBq of [^{18}F]fluoride provided 151 MBq of [^{18}F]**1F** (46% RCY) with a molar activity of 18 GBq / mmol (typical for a lower activity synthesis run in our laboratory[6d]).

Following optimization of the reaction conditions using simple unsubstituted arene substrate **1N$_2$**, the substrate scope of the reaction was explored using a series of substituted arene precursors without further optimization of the reaction conditions (Figure 1). Electron-deficient ([^{18}F]**2F**) and electron-neutral arenes ([^{18}F]**3F** – [^{18}F]**6F**) were well tolerated in the reaction. Contrastingly, electron rich arenes, such as anisoles ([^{18}F]**7F**) and *N,N*-dimethylanilines ([^{18}F]**8F**)proved poor substrates presumably due to instability of the ^{18}F-

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*- ([^{18}F]**4F**), *meta*- ([^{18}F]**5F**) and *ortho*-bromo ([^{18}F]**6F**) substituted products were comparable, with the slightly lower RCYs of the *ortho*- and *meta*-substituted products likely attributable to steric effects. Using a fluorovinyl-α-diazo precursor (**9N$_2$**), it was found that the difluorinated product [^{18}F]**9F** could be obtained in 45 ± 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 CF_2 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-functionalized 5-cholesten-3-one was successfully radiofluorinated using Ag[^{18}F]F•K_{222}•AgOTf to generate [^{18}F]**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 [^{18}F]AgF. This method provides access to 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 [^{18}F]**10F** for pre-clinical PET imaging and anticipated translation into clinical trials.

General Considerations

Reagents were purchased from Sigma Aldrich, Alfa Aesar, Oakwood, Fisher Scientific, EMD Millipore Corporation and Acros Organics. ^{1}H NMR spectra were obtained on a Varian 400 MHz MR NMR (399.7 MHz for ^{1}H, 100.5 MHz for ^{13}C and 376.1 MHz for ^{19}F) and Varian 500 MHz VNMRS (499.5 MHz for ^{1}H, 125.6 MHz for ^{13}C) spectrometers. Chemical shifts are reported in parts per million (ppm) and referenced to tetramethylsilane as in internal standard (^{1}H: δ = 0.00) or residual solvent peak ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm). ^{19}F NMR spectra are referenced to an external standard trichlorofluoromethane ($CFCl_3$: δ = 0.00 ppm for ^{19}F). NMR spectra were recorded at room temperature. The abbreviations for ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet of doublets (td), and multiplet (m). Broad signals are indicated by “br”. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Thin layer chromatography (TLC) was performed on Merck KGaA. pre-coated TLC Silica gel 60 F_{254} plates. Flash column chromatography was conducted using a Biotage Isolera Prime system with SNAP KP-Sil column cartridges (10 g or 25 g).

Reagents were purchased from Sigma Aldrich, Alfa Aesar, Oakwood, Fisher Scientific, EMD Millipore Corporation and Acros Organics. 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 10 ml ethanol, followed by 10 mL of water, followed by 10 mL of 0.5 M aqueous potassium triflate solution, followed by 10 mL of water before use.

Glass backed thin layer chromatography (TLC) plates coated with silica gel $60F_{254}$ were used for TLC- and radio-TLC analysis and were purchased from EMD-Millipore. TLC plates were visualized with $KMnO_4$ or anisaldehyde stain. Radio-TLC analysis was performed using a Bioscan AR 2000 Radio-TLC scanner (Ekert and Ziegler).

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

High performance liquid chromatography (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. The following set of HPLC conditions were used, as specified in the Supporting Information.

Chemistry

Synthesis of α-diazoacetate substrates ($\mathbf{1N_2}$ – $\mathbf{10N_2}$); General Procedure for Diazo Transfer

α-diazoacetate substrates (**$\mathbf{1N_2}$ – $\mathbf{10N_2}$**) were prepared through adaptation of literature methods reported by Davies.[7] Briefly, the appropriate ester (1 eq., see precursors S1 – S10 in Supporting Information) and *p*-acetamidobenzenesulfonyl azide (1.1 eq.) were taken up in dry MeCN and the suspension cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.1 eq) was taken up in dry MeCN, and added to the suspension dropwise over 10 minutes. 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 mins, and at RT for a further 30–60 minutes, 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 ethyl acetate in hexanes (20% v/v). The product was further purified by automated silica gel chromatography using a hexane-ethyl acetate gradient to yield the corresponding diazo ester.

The isolated diazo products are unstable at RT, 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 ^{13}C 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 (1N$_2$)

Synthesised according to the general procedure to yield **1N$_2$** (766 mg, 83%) as an orange-red oil that solidified upon storage at −20 °C. δ_H (399.7 MHz, $CDCl_3$): 7.36–7.29 (4 H, m, Ar*H*), 7.22–7.17 (1 H, m, Ar*H*), 6.48 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.19 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.85 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 165.7, 136.9, 128.8, 127.2, 126.0, 123.1, 111.3, 52.5; HRMS (ESI$^+$) calc. for $C_{11}H_{11}O_2N_2$ $[M+H]^+$ 203.0815, found 203.0813.

Methyl (*E*)-2-diazo-4-(4'-(trifluoromethyl)phenyl)but-3-enoate (2N$_2$)

Synthesised according to the general procedure to yield **2N$_2$** (184 mg, 83%) as an orange solid. δ_H (399.7 MHz, $CDCl_3$): 7.55 (2 H, app. d, *J* = 8.3, Ar*H*), 7.43 (2 H, app. d, *J* = 8.3, Ar*H*), 6.61 (1 H, *J* = 16.3 Hz, ArC*H*=CH), 6.22 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.87 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −62.46 (3F, s, CF_3); HRMS (ESI$^+$) calc. for $C_{12}H_{10}O_2F_3N_2$ $[M+H]^+$ 271.0689, found 271.0687.

Methyl (*E*)-2-diazo-4-([1',1''-biphenyl]-4'-yl)but-3-enoate (3N$_2$)

Synthesised according to the general procedure to yield **3N$_2$** (107 mg, 65%) as an orange solid. δ_H (399.7 MHz, $CDCl_3$): 7.61–7.55 (4 H, m, Ar*H*), 7.46–7.42 (4 H, m, Ar*H*), 7.36–7.32 (1 H, m, Ar*H*), 6.52 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.24 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.87 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 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$^+$) calc. for $C_{17}H_{15}O_2$ $[M+H]^+$ 279.1128, found 279.1127.

Methyl (*E*)-2-diazo-4-(4'-bromophenyl)but-3-enoate (4N$_2$)

Synthesised according to the general procedure to yield **4N$_2$** (134 mg, 61%) as an orange-red oil that solidified upon storage at −20 °C. δ_H (399.7 MHz, $CDCl_3$): 7.44–7.41 (2 H, m, Ar*H*), 7.22–7.20 (2 H, m, Ar*H*), 6.48 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.13 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.85 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 165.4, 135.7, 131.8, 127.3, 121.6, 120.7, 112.3, 52.4; HRMS (EI$^+$) calc. for $C_{11}H_{10}O_2N_2Br$ $[M]^+$ 279.9847, found 298.9847.

Methyl (*E*)-2-diazo-4-(3'-bromophenyl)but-3-enoate (5N$_2$)

Synthesised according to the general procedure to yield **5N$_2$** (206 mg, 75%) as an orange-red oil which solidified upon standing. δ_H (399.7 MHz, $CDCl_3$): 7.49–7.47 (1 H, m, Ar*H*), 7.31–7.29 (1 H, m, Ar*H*), 7.25–7.23 (1 H, m, Ar*H*), 7.17–7.13 (1 H, m, Ar*H*), 6.41 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.11 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.85 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 165.3, 139.0, 130.2, 129.9, 128.7, 124.5, 123.0, 121.4, 113.2, 52.5; HRMS (ESI$^+$) calc. for $C_{11}H_{11}O_2N_2Br$ $[M+H]^+$ 280.9920, found 280.9918.

Methyl (*E*)-2-diazo-4-(2'-bromophenyl)but-3-enoate (6N$_2$)

Synthesised according to the general procedure to yield **6N$_2$** (150 mg, 68%) as an orange-red oil. δ_H (399.7 MHz, $CDCl_3$): 7.54–7.51 (2 H, m, Ar*H*), 7.28–7.23 (1 H, m, Ar*H*), 7.07–7.03

(1 H, m, Ar*H*), 6.55 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.47 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.85 (3 H, s, COOCH_3); δ_C (126 MHz, $CDCl_3$):165.4, 136.6, 133.2, 128.4, 127.8, 126.6, 123.3, 121.5, 114.7, 52.6; HRMS (ESI^+) calc. for $C_{11}H_{11}O_2N_2Br$ $[M+H]^+$ 280.9920, found 280.9921.

Methyl (*E*)-2-diazo-4-(4'-methoxyphenyl)but-3-enoate ($7N_2$)

Synthesised according to the general procedure to yield **$7N_2$** (59 mg, 49%) as an orange-red oil that solidified upon storage at −20 °C. δ_H (399.7 MHz, $CDCl_3$): 7.30–7.28 (2 H, m, Ar*H*), 6.87–6.85 (2 H, m, Ar*H*), 6.30 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.14 (1 H, d, *J* = 16.3 Hz, ArCH=C*H*), 3.85 (3 H, s, COOCH_3), 3.81 (3 H, s, ArOCH_3); δ_C (100.5 MHz, $CDCl_3$): 165.9, 158.9, 129.7, 127.0, 122.8, 114.3, 108.7, 55.3, 52.3; HRMS (ESI^+) calc. for $C_{12}H_{13}O_3N_2$ $[M+H]^+$ 233.0921, found 233.0914.

Methyl (*E*)-2-diazo-4-(4'-(dimethylamino)-phenyl)but-3-enoate ($8N_2$)

Synthesised according to the general procedure to yield **$8N_2$** (44 mg, 85%) as an orange-red oil which solidified upon standing. δ_H (399.7 MHz, $CDCl_3$): 7.27–7.24 (2 H, m, Ar*H*), 6.69–6.67 (2 H, m, Ar*H*), 6.19 (1 H, d, *J* = 16.3 Hz, ArC*H*=CH), 6.11 (1 H, d, *J* = 16.3. Hz, ArCH=C*H*), 3.84 (3 H, s, COOCH_3), 2.96 (6H, s, ArN(CH_3)$_2$; δ_C (100.5 MHz, $CDCl_3$): 149.9, 127.0, 125.5, 123.7, 112.6, 105.9, 52.4, 40.6 (C=O not observed); HRMS (ESI^+) calc. for $C_{13}H_{15}O_2N_3$ $[M+H]^+$ 246.1237, found 246.1236.

Ethyl (*Z*)-2-diazo-4-fluoro-4-phenylbut-3-enoate ($9N_2$)

Synthesised according to the general procedure to yield **$9N_2$** (102 mg, 93%) as a pale orange solid. δ_H (399.7 MHz, $CDCl_3$): 7.48–7.46 (2 H, m, Ar*H*), 7.38–7.34 (2 H, m, Ar*H*), 7.29–7.25 (1 H, m, Ar*H*), 5.71 (1 H, d, *J* = 37.2, CFC*H*CN_2), 4.30 (2 H, q, *J* = 7.1 Hz, C$H_2$$CH_3$), 1.32 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); δ_C (100.5 MHz, $CDCl_3$): 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, *C*F resonance as well as *C*N_2 resonance not observed); δ_F (376.1 MHz, $CDCl_3$): −117.77 (1F, br s, C*F*CHCN_2). HRMS (ESI^+) calc. for $C_{12}H_{12}FO_2$ $[M-N_2+H]^+$ 207.0816, found 207.0815.

5-Cholesten-4-diazo-3-one ($10N_2$)

5-Cholesten-3-one (100 mg, 0.25 mmol, 1 eq.) and *p*-acetamidobenzenesulfonyl azide (70 mg, 0.29 mmol, 1.1 eq.) were taken up in dry MeCN (4 mL) and the suspension cooled to 0 °C. DBU (43 μL, 0.29 mmol, 1.1 eq) was taken up in dry MeCN (1 mL), and added to the suspension dropwise over 10 minutes. The suspension was stirred at 0 °C for a further 30 mins, and at RT for a further 90 minutes, 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 ethyl acetate in hexanes (20% v/v). The product was further purified by automated silica gel chromatography using a hexane-ethyl acetate gradient to give **$10N_2$** (13.7 mg, 13%) as a yellow oil. δ_H (399.7 MHz, $CDCl_3$): 5.18 (1 H, dd, *J* = 4.9, 2.8 Hz), 2.47–2.44 (2 H, m), 2.23 (1 H, dt, *J* = 18.0, 5.2 Hz), 2.05 (1 H, dt, *J* = 12.6, 3.3 Hz), 2.00–1.95 (1 H, m), 1.90–1.82 (1 H, m), 1.79–0.96 (23 H, m), 0.92 (3 H, d, *J* = 6.5 Hz), 0.87 (6 H, dd, *J* = 6.6, 1.7 Hz), 0.72 (3 H, s); δ_C (100.5 MHz, $CDCl_3$): 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^+) calc. for $C_{27}H_{43}O$ $[M\text{-}N_2+H]^+$ 383.3308, found 383.3308.

Synthesis of fluorinated reference standards; General Procedure[14]

AgOAc (0.2 eq.) was placed in a flame dried, foil-covered flask, and the flask evacuated and filled with Ar three times. Dry DCM (final concentration 0.075 M) was added to the flask under Ar, and $3HF.Et_3N$ was added to the suspension. The suspension was heated to reflux before the appropriate α-diazoacetate substrates (1 eq, in ca. 1 mL DCM) 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 reaction mixture was refluxed for a further 3 h. The reaction was cooled, the foil removed, and the reaction quenched with sat. aq. $NaHCO_3$ (10× the volume of $3HF.Et_3N$ 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 (Na_2SO_4), filtered and concentrated. The residue was taken up into DCM, dry-loaded onto silica gel, and purified by automated silica gel chromatography using a hexane-ethyl acetate gradient to yield the corresponding fluorinated product.

Methyl (*E*)-4-fluoro-4-phenylbut-2-enoate (1F)

Synthesised according to the general procedure to yield **1F** (27 mg, 36%) as a colourless oil. δ_H (399.7 MHz, $CDCl_3$): 7.43–7.26 (5 H, m, Ar*H*), 7.06 (1 H, ddd, *J* = 19.2, 15.7, 4.4 Hz, ArCHF-C*H*=CH), 6.19 (1 H, ddd, *J* = 15.7, 1.6, 1.6 Hz, ArCHF-CH=C*H*), 6.02 (1 H, ddd, *J* = 47.0, 19.2, 1.6 Hz, ArC*H*F-CH=CH), 3.76 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −173.50 (1F, dd, *J* = 47.0, 19.2 Hz, CH*F*CHCH); HRMS (ESI^+) calc. for $C_{11}H_{12}O_2F$ $[M+H]^+$ 195.0816, found 195.0811.

Methyl (*E*)-4-fluoro-4-(4'-(trifluoromethyl)phenyl)but-2-enoate (2F)

Synthesised according to the general procedure to yield **2F** (4.7 mg, 16%) as a colourless oil. δ_H (399.7 MHz, $CDCl_3$): 7.67 (2 H, d, *J* = 8.0 Hz, Ar*H*), 7.48 (2 H, d, *J* = 8.0 Hz, Ar*H*), 7.02 (1 H, ddd, *J* = 18.8, 15.7, 4.6 Hz, ArCHF-C*H*=CH), 6.20 (1 H, ddd, *J* = 15.7, 1.7, 1.7, ArCHF-CH=C*H*), 6.15–6.02 (1 H, m, ArC*H*F-CH=CH), 3.77 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 166.1, 143.3 (d, *J* = 21.2 Hz), 127.3 (app. d, *J* = 32.5 Hz), 126.8 (d, *J* = 6.2), 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*-CF_3 and C-*C*F_3 carbons were not observed due to the low mass of material isolated; δ_F (376.1 MHz, $CDCl_3$): −177.30 (1F, dd, *J* = 46.7, 18.8 Hz, CH*F*CHCH), −62.80 (3F, s, C*F*$_3$); HRMS (ESI^+) calc. for $C_{12}H_{11}O_2F_4$ $[M+H]^+$ 263.0690, found 263.0696.

Methyl (*E*)-4-fluoro-4-([1',1''-biphenyl]-4'-yl)but-2-enoate (3F)

Synthesised according to the general procedure to yield **3F** (15 mg, 30%) as a colourless oil. δ_H (399.7 MHz, $CDCl_3$): 7.64–7.57 (4 H, m, Ar*H*), 7.47–7.41 (4 H, m, Ar*H*), 7.39–7.35 (1

H, m, Ar*H*) 7.09 (1 H, ddd, *J* = 19.0, 15.7, 4.4 Hz, ArCHF-*H*=CH), 6.22 (1 H, ddd, *J* = 15.7, 1.6, 1.6 Hz, ArCHF-CH=C*H*), 6.07 (1 H, ddd, *J* = 47.0, 4.3, 1.6 Hz, ArC*H*F-CH=CH), 3.77 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −172.96 (1F, dd, *J* = 47.0, 19.0 Hz, CH*F*CHCH); HRMS (ESI^+) calc. for $C_{17}H_{16}O_2F$ $[M+Na]^+$ 293.0948, found 293.0946.

Methyl (*E*)-4-fluoro-4-(4'-bromophenyl)but-2-enoate (4F)

Synthesised according to the general procedure to yield **4F** (15 mg, 30%) as a colourless oil. δ_H (399.7 MHz, $CDCl_3$): 7.54 (2 H, d, *J* = 8.3 Hz, Ar*H*), 7.22 (2 H, d, *J* = 8.3 Hz, Ar*H*), 7.00 (1 H, ddd, *J* = 19.0, 15.7, 3.9 Hz, ArCHF-C*H*=CH), 6.19–6.15 (1 H, m, ArCHF-CH=C*H*), 6.04–5.92 (1 H, m, ArC*H*F-CH=CH), 3.77 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −174.13 (1F, dd, *J* = 46.8, 19.0 Hz, CH*F*CHCH); HRMS (ESI^+) calc. for $C_{11}H_{11}O_2FBr$ $[M+H]^+$ 272.9921, found 272.9916.

Methyl (*E*)-4-fluoro-4-(3'-bromophenyl)but-2-enoate (5F)

Synthesised according to the general procedure to yield **5F** (15 mg, 30%) as a colourless oil. δ_H (399.7 MHz, $CDCl_3$): 7.52–7.50 (2 H, m, Ar*H*), 7.29–7.27 (2 H, m, Ar*H*), 7.00 (1 H, ddd, *J* = 19.0, 15.7, 4.5 Hz, ArCHF-C*H*=CH), 6.19 (1 H, ddd, *J* = 15.7, 1.6, 1.6 Hz, ArCHF-CH=C*H*), 5.98 (1 H, ddd, *J* = 46.9, 4.4, 1.6 Hz, ArC*H*F-CH=CH), 3.77 (3 H, s, COOCH_3); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −175.29 (1F, dd, *J* = 46.9, 19.0 Hz, CH*F*CHCH); HRMS (ESI^+) calc. for $C_{11}H_{11}O_2FBr$ $[M+H]^+$ 272.9921, found 272.9918.

Methyl (*E*)-4-fluoro-4-(2'-bromophenyl)but-2-enoate (6F)

Synthesised according to the general procedure to yield **6F** (16 mg, 55%) as a pale yellow solid. δ_H (499 MHz, $CDCl_3$): 7.58 (1 H, dt, *J* = 8.1, 1.2 Hz, Ar*H*), 7.45 (1 H, dd, *J* = 7.8, 1.8 Hz, Ar*H*), 7.38 (1 H, td, *J* = 7.6, 1.2 Hz, Ar*H*), 7.26–7.21 (1 H, m, Ar*H*), 7.04 (1 H, ddd, *J* = 19.0, 15.7, 4.3 Hz, ArCHF-C*H*=CH), 6.42 (1 H, ddd, *J* = 45.7, 4.3, 1.8 Hz, ArCHF-CH=C*H*); 6.22 (1 H, dt, *J* = 15.7, 1.7 Hz, ArC*H*F-CH=CH), 3.76 (3 H, s, COOCH_3); δ_C (126 MHz, $CDCl_3$): 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; δ_F (470 MHz, $CDCl_3$): 1F, dd, *J* = −180.58, 19.3 Hz, CH*F*CHCH). HRMS (ESI^+) calc. for $C_{11}H_{10}BrFO_2$ $[M+H]^+$ 271.9848, found 271.9853.

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

Synthesised according to the general procedure to yield **9F** (14 mg, 48%) as a colourless oil. δ_H (399.7 MHz, $CDCl_3$): 7.51–7.43 (5 H, m, Ar*H*), 7.01 (1 H, dt, *J* = 15.7, 10.5, CF_2C*H*C), 4.30 (2 H, q, *J* = 7.1 Hz, C$H_2$$CH_3$), 1.32 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −117.77 (1F, br s, CF_2CHCH). HRMS (ESI^+) calc. for $C_{12}H_{13}F_2O_2$ $[M+H]^+$ 227.0878, found 227.0875.

(6*R*)-4-Cholesten-6-fluoro-3-one (10F)

Synthesised according to the general procedure, replacing AgOAc with AgOTf, and using 10 equivalents of 3HF.Et_3N, to yield **10F** (14 mg, 30%) as a colourless solid, as a single diastereomer. δ_H (399.7 MHz, $CDCl_3$): 5.87 (1 H, d, J = 4.9 Hz), 4.99 (1 H, ddd, J = 49.2, 2.5, 2.5 Hz), 2.55 (1 H, ddd, J = 16.8, 15.1, 4.9 Hz), 2.40 (1 H, ddd, J = 16.8, 3.3, 3.3 Hz), 2.25–2.16 (2 H, m), 1.91–1.81 (2 H, m), 1.73 (1 H, J = 14.3, 14.3, 4.4), 1.65–0.94 (22 H, m), 0.92 (3 H, d, J = 6.5 Hz), 0.87 (6 H, dd, J = 6.6, 1.7 Hz), 0.74 (3 H, s); δ_C (100.5 MHz, $CDCl_3$): 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; δ_F (376.1 MHz, $CDCl_3$): −165.07– −165.58 (1F, m, CCFHCH_2). HRMS (ESI^+) calc. for $C_{27}H_{44}FO$ $[M+H]^+$ 404.3371, found 404.3375.

Davies et al. 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 ^{18}F-fluorination

To a 4 mL vial were added AgOAc (1.6 mg, 10 μmol, 1.0 eq.) and imidazolium triflate (2.2 mg,10 μmol, 1.0 eq.), followed by anhydrous dichloroethane (DCE) (700 μL) and acetic acid solution (100 μL of a stock solution in DCE (18 μL HOAc/1 mL DCE), 30 μmol, 3 eq.) The solution was briefly vortexed. The reaction vial was capped with a PTFE/Silicone septum cap and a 100 μL aliquot of $[^{18}F]AgF•K_{222}•AgOTf$ complex in DCE (typically 60–1000 μCi; see Supporting Information) was added to the reaction vial by syringe. Finally the diazo compound (10 μmol in 100 μL DCE) was added by syringe. The reaction 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 room temperature before analysis by radio-TLC and radio-HPLC to confirm RCY and identity, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Information

We acknowledge US DOE/NIBIB (DE-SC0012484 to PJHS) and NIH (R01EB021155 to MSS and PJHS) for financial support.

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(13). Radiochemical yields (RCY) are non-isolated and were calculated by % integrated area of the ^{18}F product versus ^{18}F- in a radio-TLC trace. Product identities were confirmed by radio-HPLC.

(14). In addition to low RCYs, we were not able to synthesize reference standards to confirm the identity of [^{18}F]**7F** and [^{18}F]**8F** because of stability issues, which is consistent with Davies' results. For example, they reported an NMR yield for the -OMe product but did not isolate it, suggesting that the compound is unstable.7

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(16). Lights in the fumehood where the reactions occurred were turned off as a general precaution. However, ambient laboratory lighting was left on and we do not believe the chemistry is light sensitive.

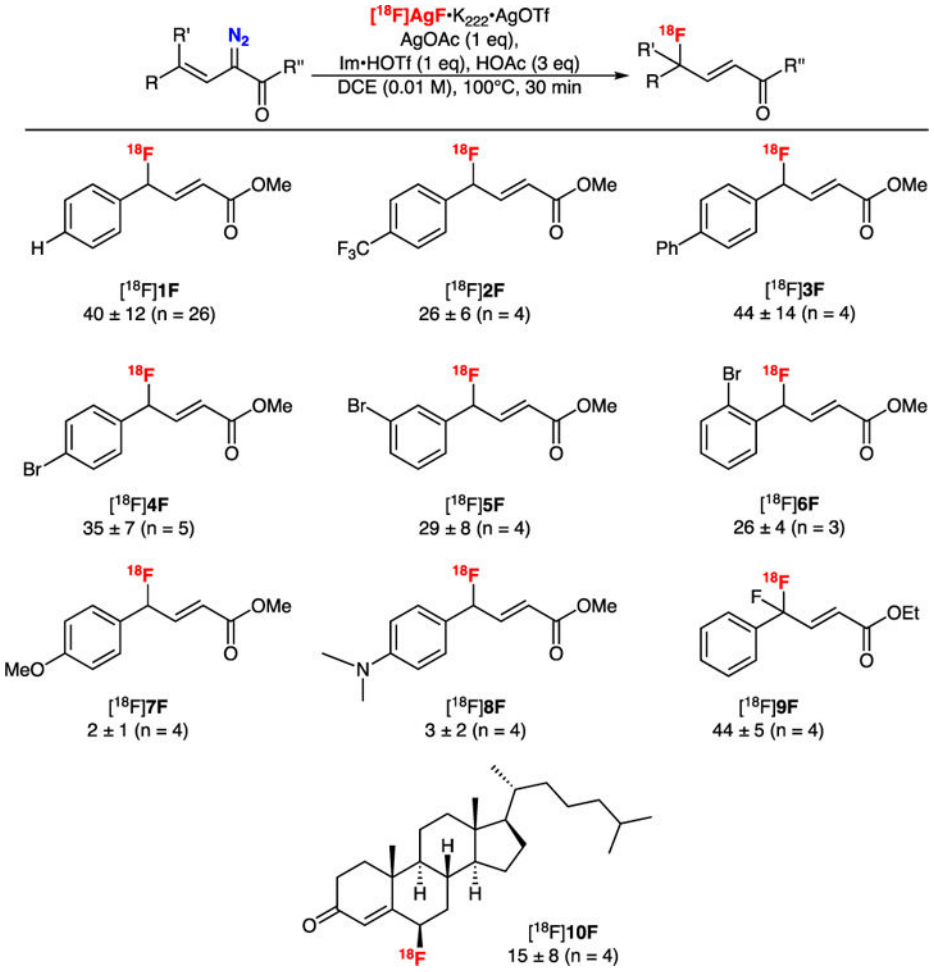
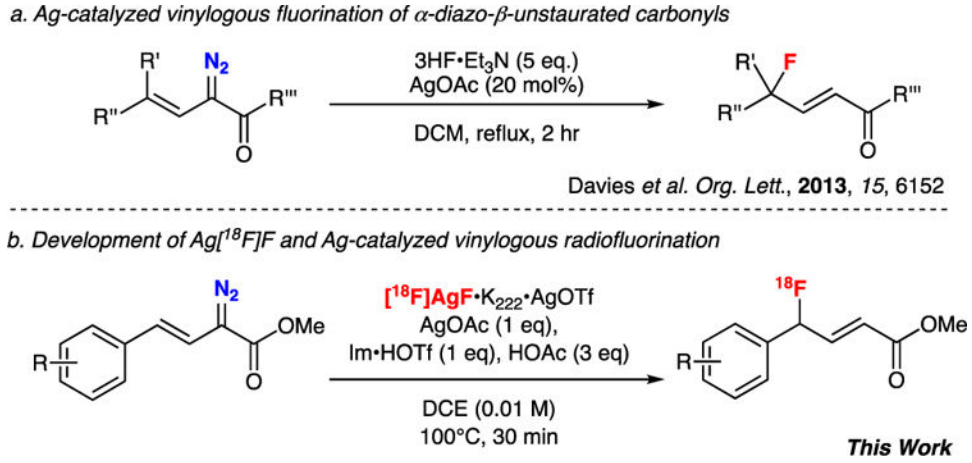


Figure 1.

Substrate scope of AgOAc-mediated radiofluorination of α-diazoacetates using Ag[^{18}F]F. Conditions: 10 μmol of **1N$_2$** – **8N$_2$**, 10 μmol AgOAc, 10 μmol of Im•HOTf, 30 μmol AcOH, Ag[^{18}F]F•K$_{222}$•AgOTf in DCE (100 μL, 100–1000 μCi) in a total volume of 1 mL DCE heated to 100 °C for 30 minutes. Non-isolated RCYs were estimated by radioTLC and product identities were confirmed by radioHPLC.

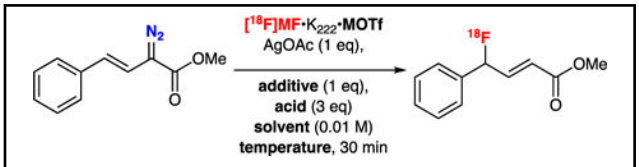


Scheme 1.

Strategies for (radio)fluorination of α-diazoacetates and motivation for this work

Table 1

Optimization of radiofluorination of α-diazoacetates using [^{18}F]AgF



Entry	M	Additive	Acid	Solvent	Temp	RCY (%)[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	K	Im•HOTf	HOAc	DCE	100	40±3 (n=3)
7[a]	Ag	Im•HOTf	HOAc	DCE	100	3±2 (n=3)
8[a]	K	Im•HOTf	HOAc	DCE	100	1±0 (n=3)

Conditons: 10 μmol of **1N2**, 10 μmol AgOAc, 10 μmol of **additive**, 30 μmol of **acid**, [^{18}F]MF•K$_{222}$•MOTf in **solvent** (100 μL, 100–1000 μCi) in a total volume of 1 mL **solvent** heated to the indicated **temperature** for 30 min. RCY are non-solated yield estimated by radioTLC and are reported as mean ± standard deviation for *n* runs;

[a]Reactions run without any AgOAc.