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Titration of Nonstabilized Diazoalkane Solutions by Fluorine NMR

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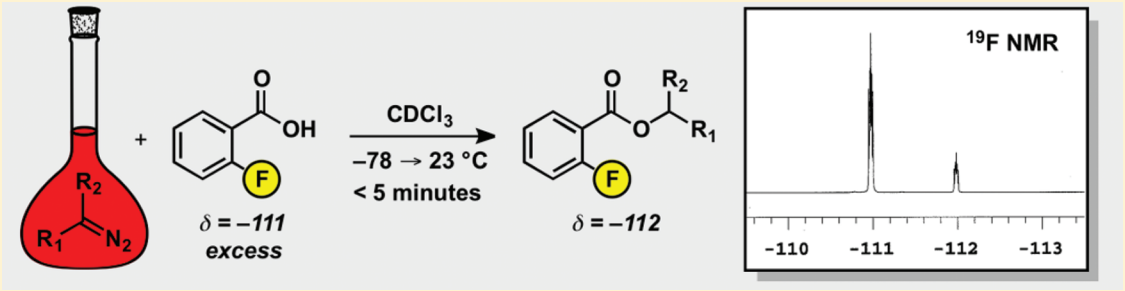
Supporting Information



ABSTRACT: A new protocol for titrating nonstabilized diazoalkane solutions by quantitative ^{19}F NMR is reported. An excess of 2-fluorobenzoic acid dissolved in $CDCl_3$ is treated with the diazoalkane solution at a low temperature, immediately forming the corresponding 2-fluorobenzoate ester upon warming. A significant difference in the ^{19}F chemical shift between the ester and acid is seen, allowing facile and accurate integration to determine titer. The procedure is safe, rapid, and indicates the active diazoalkane concentration with high precision.

The handling of noncarbonyl-stabilized diazoalkanes as neat compounds is often impractical and potentially hazardous. For this reason, diazoalkanes have been generated for use in situ by Bamford–Stevens decomposition,[1] iodine(III)-mediated oxidation of *N*-silylhydrazones,[2] or the decomposition of *N*-aziridinylimines.[3] Alternatively, mild methods based on free hydrazone oxidation[4,5] or diazo transfer[6] give pure solutions that can be stored at low temperatures.[7] During recent developments in our laboratory aimed at catalytic insertion of nonstabilized diazoalkanes into simple carbonyl feedstocks, we needed a rapid and accurate method to assay the active diazoalkane concentration in toluene solutions.[8−10] Although a number of methods have been reported in the literature, none offer a simple procedure that can be executed quickly and with small quantities of the diazoalkane reagent. Those based on acid-mediated decomposition and collection of evolved nitrogen gas require large quantities of the diazoalkane and elaborate experimental setups.[4] Spectrophotometric methods require preparation of calibration standards and calculation of extinction coefficients for compounds that can readily decompose at room temperature or by light-induced pathways.[11−13] Esterification with excess benzoic acid and titration of the unreacted carboxylic acid is time-consuming, requiring preparation and calibration of stock base solutions in order to obtain accurate results.[14] Esterification with benzoic acid and calculation of concentration on the basis of the unpurified yield of the benzoate ester is also possible, but at times it will provide concentration results of questionable accuracy due to common diazoalkane impurities.[12,13,15] Herein, we report the use of inexpensive and commercially available 2-fluorobenzoic acid as a new reagent to titrate diazoalkane solutions by quantitative ^{19}F NMR spectroscopy. The new protocol requires minimal experimental time and can be performed safely at low temperatures with micromolar quantities of the diazoalkane.

In a typical experimental procedure, an accurately weighed quantity of excess 2-fluorobenzoic acid is dissolved in 700 μL of $CDCl_3$, enough solvent to prepare a single NMR sample. After cooling to −78 °C, which causes the solution to freeze, a 100 μL aliquot of the diazoalkane solution is added rapidly in a single portion.[16] Upon warming of the mixture to room temperature, the reaction is complete as indicated by the absence of the characteristic diazoalkane color and the lack of further nitrogen gas evolution. The reaction mixture is swirled gently to ensure homogeneity and then transferred without rinsing to a standard NMR tube for analysis. Table 1 summarizes our findings for the titration of various alkyl, aryl, and vinyl diazoalkane solutions. In every case, the reaction quickly and cleanly produced the corresponding 2-fluorobenzoate esters. The difference in ^{19}F NMR chemical shift between the unreacted 2-fluorobenzoic acid and 2-fluorobenzoate esters is approximately 1.0 ppm. Conversion, and ultimately concentration, is calculated on the basis of integration of the two fluorine signals. Attempts to use ^{1}H NMR spectroscopy with various substituted benzoic acid derivatives were successful in certain cases, but it did not prove to be a general solution because of problems with overlapping resonances. Recourse to ^{19}F NMR spectroscopy avoids this complication in all cases tested thus far. Our spectra have been referenced relative to hexafluorobenzene (δ −164.9 ppm) as an internal standard; however, the use of a reference standard is not necessary due to

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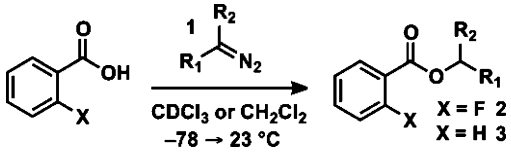
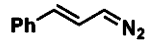
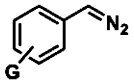
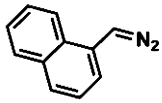
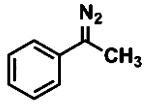
Table 1. Scope of Titration by Formation of the 2-Fluorobenzoate Ester and Comparison to the Gravimetric Benzoate Ester Method



entry	diazoalkane	2-fluorobenzoic acid (M)[a]	benzoic acid (M)[b]
a	CH_2N_2	0.49 ± 0.05	0.34
b		0.133 ± 0.003	0.40
c		0.43 ± 0.01	1.26
			
d	G = H	1.16 ± 0.03	1.23
e	G = *o*-CH_3	1.19 ± 0.01	1.33
f	G = *o*-Br	0.62 ± 0.01	0.68
g	G = *p*-CH_3	0.60 ± 0.01	0.64
h	G = *p*-CF_3	0.56 ± 0.02	0.69
i	G = *m*-OCH_3	0.227 ± 0.002	0.29
j	G = *m*-Br	0.826 ± 0.006	1.05
k		0.57 ± 0.02	0.64
l		0.53 ± 0.02	0.55
m		0.310 ± 0.009	0.38

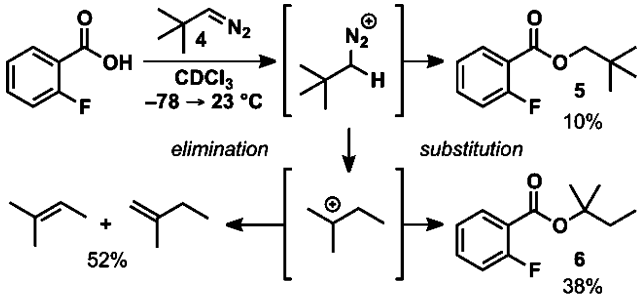
[a]Average of three trials ± standard deviation. [b]By yield of unpurified benzoate ester.

the uniform upfield shift of the esters. Also, noteworthy of the assay is the high reproducibility. Data are reported in Table 1 as the average of three trials ± standard deviations.

Results for esterification with benzoic acid and weighing of the unpurified benzoate ester after a basic aqueous workup are also provided in Table 1 for comparison. With the exception of methyl benzoate **3a**, isolation of the benzoate esters leads to concentration values that exceed those obtained with the new procedure. The volatility of **3a** is likely responsible for the lower value obtained in entry **a**. Certain diazoalkanes can undergo decomposition upon prolonged storage or warming,[12,13] and nonvolatile impurities can be introduced during preparative procedures. Either of these complications can account for the higher concentration values observed with the crude benzoylation method. The new titration procedure does not require isolation of the esters and is not affected by the presence of impurities.[17]

The accuracy of the method described herein, and previous methods based on esterification, relies on quantitative conversion of the diazoalkanes to their corresponding esters.[18] In certain cases, diazonium ions formed after the initial protonation event can undergo spontaneous rearrangement or elimination, ultimately leading to byproducts that would not be observed by ^{19}F NMR spectroscopy.[19] When 1-diazo-2,2-dimethylpropane (**4**) was subjected to 2-fluorobenzoic acid, rapid rearrangement to the tertiary carbocation occurred, affording predominantly ester **6** and two elimination byproducts (Scheme 1). For diazoalkanes that undergo

Scheme 1. Production of Elimination Byproducts Not Observed by ^{19}F NMR Spectroscopy with Diazoalkane 4



elimination, the use of ^{19}F NMR spectroscopy alone will not provide accurate concentration values. The concentration of **4** could still be determined from the combined ^{1}H and ^{19}F NMR data, although likely not with the same level of accuracy and precision as diazoalkanes which cleanly afford a single ester product.

In summary, we have developed a safe and convenient procedure to assay the concentration of nonstabilized diazoalkane solutions. We hope that this procedure, coupled with milder methods for the preparation of diazoalkanes,[4−6] will permit these powerful reagents to be used routinely and safely.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. 2-Fluorobenzoic acid was purchased from Aldrich, sublimed at 100 °C under high vacuum (approximately 1 mmHg), and dried in vacuo over P_2O_5 at room temperature for 24 h before use. All nonstabilized diazoalkanes were prepared according to the previously reported procedures.[4,5,8,20] Silica gel chromatography was performed with ZEOPrep 60 Eco 40−63 μm silica gel. ^{1}H NMR spectra were recorded on a 500 MHz instrument and referenced using the residual solvent as an internal standard ($CHCl_3$: δ 7.26). ^{13}C spectra were recorded on a 125 MHz instrument and referenced using the solvent as an internal standard ($CDCl_3$: δ 77.16). ^{19}F NMR spectra were recorded on a 470 MHz spectrometer with complete carbon decoupling using hexafluorobenzene as an internal standard (C_6F_6 in $CDCl_3$: δ −164.9). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry facility.

Representative Procedure for ^{19}F NMR Titration. A stock solution of 2-fluorobenzoic acid in $CDCl_3$ was prepared by weighing 1.2591 g directly into a 25.00 mL volumetric flask. The flask was diluted to the total volume with $CDCl_3$, affording a 0.3595 M solution. The stock solution was sealed with a ground glass stopper and stored in the dark.[21] In an oven-dried 1 dram glass vial, the 2-fluorobenzoic acid solution (700 μL, 0.252 mmol, 0.359 M in $CDCl_3$, excess) was added and cooled to −78 °C, causing the solution to freeze. A 100 μL aliquot of phenyldiazomethane (**1d**) in toluene was added in a single portion, and the reaction was allowed to warm to room temperature. Upon reaching room temperature, the reaction was complete as judged by the absence of color and gas evolution. Approximately 5 μL of hexafluorobenzene was added as an internal standard for spectrum calibration.[22] The homogeneous colorless solution was transferred via glass pipet to an NMR tube for analysis. ^{19}F NMR data (8 scans) were recorded with a relaxation delay time of 10 s (d1 = 10),[23] and integration of the two signals (δ = −111 acid, δ = −112 ester) showed the aliquot to contain 0.117 mmol of diazoalkane on the basis of 46.4%

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conversion of the acid to the corresponding ester. The procedure was repeated in triplicate to give a concentration value of 1.16 ± 0.03 M.

General Procedure for Isolation of 2-Fluorobenzoate Esters. The three samples from the general ^{19}F NMR titration procedure were transferred to a separatory funnel with 25 mL of Et_2O. The organic layer was washed with 1 N NaOH (2 × 15 mL) and saturated NaCl (15 mL), dried over Na_2SO_4, filtered, and then concentrated. The product was purified by flash column chromatography on silica gel (ethyl acetate in hexanes) to afford the desired ester.

Methyl 2-Fluorobenzoate (2a). Colorless oil: R_f = 0.28 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.54−7.49 (m, 1H), 7.21 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.14 (ddd, J_{C-F} = 11.0, 8.3, 1.2 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9 (d, J_{C-F} = 3.7 Hz), 162.0 (d, J_{C-F} = 259.6 Hz), 134.5 (d, J_{C-F} = 9.3 Hz), 132.2 (d, J_{C-F} = 0.9 Hz), 124.0 (d, J_{C-F} = 4.2 Hz), 118.7 (d, J_{C-F} = 9.8 Hz), 117.0 (d, J_{C-F} = 22.3 Hz), 52.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.73 (dddd, J_{F-H} = 5.5, 5.5, 5.5, 5.5 Hz, 1F); IR (neat) 3000, 2955, 1719, 1613, 1489, 1457, 1435, 1301, 1262, 1125, 1086, 756, 693 cm^{-1}. HRMS (ESI+) Calcd. for $C_8H_8FO_2$ $[M + H]^+$: 155.0508. Found: 155.0513.

3-Phenylpropyl 2-Fluorobenzoate (2b). Colorless oil: R_f = 0.31 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.55−7.50 (m, 1H), 7.32−7.28 (m, 2H), 7.24−7.18 (m, 4H), 7.15 (ddd, J = 11.0, 8.3, 1.0 Hz, 1H), 4.36 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 2.13−2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6 (d, J_{C-F} = 3.6 Hz), 162.1 (d, J_{C-F} = 260.0 Hz), 141.3, 134.5 (d, J_{C-F} = 9.2 Hz), 132.2 (d, J_{C-F} = 0.9 Hz), 128.6, 126.2, 124.1 (d, J_{C-F} = 4.1 Hz) 119.1 (d, J_{C-F} = 9.7 Hz), 117.1 (d, J_{C-F} = 22.6 Hz), 64.7, 32.3, 30.4; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.49 (dddd, J_{F-H} = 6.6, 6.6, 4.4, 4.4 Hz, 1F); IR (neat) 3027, 2955, 2927, 1713, 1612, 1488, 1455, 1294, 1249, 1157, 1126, 1082, 1032, 754, 698 cm^{-1}. HRMS (ESI+) Calcd. for $C_{16}H_{16}FO_2$ $[M + H]^+$: 259.1134. Found: 259.1135.

Cinnamyl 2-Fluorobenzoate (2c).[17] Colorless oil: R_f = 0.31 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.98 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.56−7.50 (m, 1H), 7.44−7.41 (m, 2H), 7.36−7.31 (m, 2H), 7.29−7.25 (m, 1H), 7.21 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.15 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 6.77 (d, J = 15.9 Hz, 1H), 6.41 (dt, J = 15.9, 6.4 Hz, 1H), 5.01 (dd, J = 6.4, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 (d, J_{C-F} = 3.6 Hz), 162.0 (d, J_{C-F} = 260.2 Hz), 136.2, 134.6 (d, J_{C-F} = 8.7 Hz), 134.4, 132.2, 128.6, 128.1, 126.7, 124.0 (d, J_{C-F} = 3.6 Hz), 123.0, 118.8 (d, J_{C-F} = 9.7 Hz), 117.0 (d, J_{C-F} = 22.5 Hz), 65.8; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.39 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3059, 3027, 2943, 1715, 1612, 1488, 1454, 1289, 1247, 1157, 1122, 1075, 1032, 964, 910, 754, 690 cm^{-1}. HRMS (ESI+) Calcd. for $C_{16}H_{17}FNO_2$ $[M + NH_4]^+$: 274.1243. Found: 274.1231.

Benzyl 2-Fluorobenzoate (2d). Colorless oil: R_f = 0.36 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.97 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.55−7.50 (m, 1H), 7.49−7.45 (m, 2H), 7.41−7.37 (m, 2H), 7.37−7.32 (m, 1H), 7.20 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.14 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (d, J_{C-F} = 3.7 Hz), 162.2 (d, J_{C-F} = 260.5 Hz), 135.9, 134.7 (d, J_{C-F} = 9.3 Hz), 132.3 (d, J_{C-F} = 0.9 Hz), 128.7, 128.4, 128.2, 124.1 (d, J_{C-F} = 3.7 Hz), 118.8 (d, J_{C-F} = 9.8 Hz), 117.1 (d, J_{C-F} = 22.3 Hz), 67.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.26 (dddd, J_{F-H} = 7.3, 7.3, 4.4, 4.4 Hz, 1F); IR (neat) 3066, 3034, 2954, 1714, 1612, 1488, 1455, 1292, 1247, 1120, 1075, 1030, 752, 693 cm^{-1}. HRMS (ESI+) Calcd. for $C_{14}H_{12}FO_2$ $[M + H]^+$: 231.0821. Found: 231.0817.

2-Methylbenzyl 2-Fluorobenzoate (2e). Colorless oil: R_f = 0.28 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.54−7.49 (m, 1H), 7.47−7.43 (m, 1H), 7.29−7.18 (m, 4H), 7.14 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.40 (s, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (d, J_{C-F} = 3.7 Hz), 162.2 (d, J_{C-F} = 260.1 Hz), 137.2, 134.6 (d, J_{C-F} = 9.4 Hz), 133.8, 132.3 (d, J_{C-F} = 0.9 Hz), 130.5, 129.4, 128.7, 126.2, 124.0 (d, J_{C-F} = 4.2 Hz), 118.8 (d, J_{C-F} = 9.7 Hz), 117.1 (d, J_{C-F} = 22.3 Hz), 65.6, 19.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.23 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3025, 2957, 1716, 1613, 1488, 1456, 1292, 1248, 1123, 1077, 755, 691 cm^{-1}. HRMS (ESI+) Calcd. for $C_{15}H_{14}FO_2$ $[M + H]^+$: 245.0978. Found: 245.0989.

2-Bromobenzyl 2-Fluorobenzoate (2f). White solid: mp 39−41 °C; R_f = 0.27 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.60 (dd, J = 7.8, 1.2 Hz, 1H), 7.58−7.52 (m, 2H), 7.35 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.24−7.19 (m, 2H), 7.16 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0 (d, J_{C-F} = 3.2 Hz), 162.2 (d, J_{C-F} = 260.5 Hz), 135.2, 134.8 (d, J_{C-F} = 9.2 Hz), 133.0, 132.4 (d, J_{C-F} = 0.9 Hz), 129.9, 129.8, 127.7, 124.2 (d, J_{C-F} = 3.7 Hz), 123.3, 118.6 (d, J_{C-F} = 9.7 Hz), 117.2 (d, J_{C-F} = 22.1 Hz), 66.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.06 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3071, 2952, 1717, 1612, 1488, 1455, 1291, 1247, 1158, 1120, 1029, 748, 691 cm^{-1}. HRMS (ESI+) Calcd. for $C_{14}H_{11}BrFO_2$ $[M + H]^+$: 308.9926. Found: 308.9923.

4-Methylbenzyl 2-Fluorobenzoate (2g). Colorless oil: R_f = 0.31 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.54−7.48 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.21−7.11 (m, 4H), 5.35 (s, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4 (d, J_{C-F} = 3.7 Hz), 162.2 (d, J_{C-F} = 260.5 Hz), 138.2, 134.6 (d, J_{C-F} = 9.3 Hz), 132.9, 132.3 (d, J_{C-F} = 1.0 Hz), 129.4, 128.4, 124.0 (d, J_{C-F} = 3.7 Hz), 118.9 (d, J_{C-F} = 9.7 Hz), 117.1 (d, J_{C-F} = 22.4 Hz), 67.0, 21.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.38 (dddd, J_{F-H} = 6.6, 6.6, 6.6, 6.6 Hz, 1F); IR (neat) 3027, 2951, 1725, 1613, 1488, 1456, 1295, 1250, 1123, 1078, 807, 757 cm^{-1}. HRMS (ESI+) Calcd. for $C_{15}H_{14}FO_2$ $[M + H]^+$: 245.0978. Found: 245.0971.

4-(Trifluoromethyl)benzyl 2-Fluorobenzoate (2h). White solid: mp 45−47 °C; R_f = 0.25 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.98 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.56−7.52 (m, 1H), 7.22 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.16 (ddd, J_{C-F} = 10.8. 9.3, 1.0 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, J_{C-F} = 4.2 Hz), 162.2 (d, J_{C-F} = 260.5 Hz), 139.3 (d, J_{C-F} = 0.9 Hz), 135.0 (d, J_{C-F} = 9.3 Hz), 132.4, 130.6 (q, J_{C-F} = 32.6 Hz), 128.2, 125.7 (q, J_{C-F} = 3.7 Hz), 124.2 (d, J_{C-F} = 3.7 Hz), 124.2 (q, J_{C-F} = 272.2 Hz), 118.4 (d, J_{C-F} = 9.8 Hz), 117.2 (d, J_{C-F} = 22.3 Hz), 66.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −65.82 (s, 3F), −111.92 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3086, 2956, 1722, 1614, 1489, 1457, 1326, 1295, 1251, 1164, 1124, 1067, 824, 757 cm^{-1}. HRMS (ESI+) Calcd. for $C_{15}H_{11}F_4O_2$ $[M + H]^+$: 299.0695. Found: 299.0682.

3-Methoxybenzyl 2-Fluorobenzoate (2i).[17] Colorless oil: R_f = 0.21 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.97 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.55−7.50 (m, 1H), 7.32−7.28 (m, 1H), 7.20 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.15 (ddd, J = 10.9, 8.5, 1.1 Hz, 1H), 7.06−7.00 (m, 2H), 6.88 (dd, J = 8.3, 2.7 Hz, 1H), 5.37 (s, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, J_{C-F} = 3.7 Hz), 162.1 (d, J_{C-F} = 260.0 Hz), 159.8, 137.4, 134.7 (d, J_{C-F} = 8.8 Hz), 132.3, 129.7, 124.0 (d, J_{C-F} = 4.2 Hz), 120.2, 118.7 (d, J_{C-F} = 9.6 Hz), 117.1 (d, J_{C-F} = 22.1 Hz), 113.8, 113.5, 66.8, 55.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.23 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3002, 2954, 2837, 1717, 1612, 1488, 1455, 1373, 1291, 1247, 1156, 1121, 1077, 1050, 867, 754, 690 cm^{-1}. HRMS (ESI+) Calcd. for $C_{15}H_{17}FNO_3$ $[M + NH_4]^+$: 278.1192. Found: 278.1182.

3-Bromobenzyl 2-Fluorobenzoate (2j). White solid: mp 30−32 °C; R_f = 0.35 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.97 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.62−7.60 (m, 1H), 7.57−7.51 (m, 1H), 7.49−7.45 (m, 1H), 7.41−7.37 (m, 1H), 7.28−7.24 (m, 1H), 7.22 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.16 (ddd, J_{C-F} = 10.8, 8.3, 1.0 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (d, J_{C-F} = 3.7 Hz), 162.2 (d, J_{C-F} = 260.5 Hz), 138.1, 134.9 (d, J_{C-F} = 9.2 Hz), 132.3 (d, J_{C-F} = 1.0 Hz), 131.4, 131.1, 130.3, 126.7, 124.2 (d, J_{C-F} = 4.2 Hz), 122.7, 118.5 (d, J_{C-F} = 9.6 Hz), 117.2 (d, J_{C-F} = 22.6 Hz), 66.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −111.98 to −112.08 (m, 1F); IR (neat) 3067, 2952, 1716, 1612, 1487, 1455, 1291, 1246, 1120, 1071, 753, 689 cm^{-1}. HRMS (ESI+) Calcd. for $C_{14}H_{11}BrFO_2$ $[M + H]^+$: 308.9926. Found: 308.9918.

Naphthalen-1-ylmethyl 2-Fluorobenzoate (2k). White solid: mp 40−43 °C; R_f = 0.25 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, J = 8.6 Hz, 1H), 7.93 (ddd, J = 7.6, 7.6,

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1.7 Hz, 1H), 7.92−7.86 (m, 2H), 7.67 (d, J = 6.6 Hz, 1H), 7.59 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.56−7.46 (m, 3H), 7.16 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.12 (ddd, J = 10.8, 9.3, 1.0 Hz, 1H), 5.85 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (d, J_{C-F} = 4.1 Hz), 162.2 (d, J_{C-F} = 260.5 Hz), 134.7 (d, J_{C-F} = 9.2 Hz), 133.9, 132.3, 131.8, 131.4, 129.5, 128.8, 127.6, 126.7, 126.1, 125.4, 124.1 (d, J_{C-F} = 4.1 Hz), 123.8, 118.8 (d, J_{C-F} = 9.2 Hz), 117.1 (d, J_{C-F} = 22.6 Hz), 65.5; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.26 (dddd, J_{F-H} = 7.4, 7.4, 5.2, 5.2 Hz, 1F); IR (neat) 3054, 2960, 1724, 1613, 1488, 1456, 1295, 1248, 1122, 1076, 756 cm^{-1}. HRMS (ESI+) Calcd. for $C_{18}H_{17}FNO_2$ $[M + NH_4]^+$: 298.1243. Found: 298.1248.

1-Phenylethyl 2-Fluorobenzoate (2l). Colorless oil: R_f = 0.37 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.54−7.49 (m, 1H), 7.48−7.44 (m, 2H), 7.40−7.35 (m, 2H), 7.33−7.28 (m, 1H), 7.20 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.14 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 6.15 (q, J = 6.6 Hz, 1H), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8 (d, J_{C-F} = 3.2 Hz), 162.2 (d, J_{C-F} = 260.1 Hz), 141.7, 134.5 (d, J_{C-F} = 9.3 Hz), 132.3, 128.7, 128.0, 126.2, 124.0 (d, J_{C-F} = 4.2 Hz), 119.2 (d, J_{C-F} = 9.6 Hz), 117.1 (d, J_{C-F} = 22.6 Hz), 73.6, 22.7; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.27 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 3035, 2982, 2932, 1710, 1613, 1488, 1455, 1291, 1248, 1126, 1061, 1030, 754, 697, 540 cm^{-1}. HRMS (ESI+) Calcd. for $C_{15}H_{17}FNO_2$ $[M + NH_4]^+$: 262.1243. Found: 262.1247.

Furan-2-ylmethyl 2-Fluorobenzoate (2m).[24] Pale yellow oil: R_f = 0.24 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.54−7.49 (m, 1H), 7.45 (dd, J = 2.0, 1.0 Hz, 1H), 7.19 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.13 (ddd, J = 10.7, 8.3, 0.7 Hz, 1H), 6.51−6.49 (m, 1H), 6.39 (dd, J = 3.4, 1.9 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9 (d, J_{C-F} = 3.7 Hz), 162.1 (d, J_{C-F} = 260.5 Hz), 149.3, 143.4, 134.7 (d, J_{C-F} = 9.2 Hz), 132.2, 124.0 (d, J_{C-F} = 4.1 Hz), 118.5 (d, J_{C-F} = 9.7 Hz), 117.0 (d, J_{C-F} = 22.1 Hz), 111.0, 110.7, 58.7; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.40 (dddd, J_{F-H} = 6.6, 6.6, 4.4, 4.4 Hz, 1F); IR (neat) 3124, 2956, 1719, 1613, 1488, 1455, 1292, 1246, 1118, 1070, 918, 819, 751, 599 cm^{-1}. HRMS (ESI+) Calcd. for $C_{12}H_{13}FNO_3$ $[M + NH_4]^+$: 238.0879. Found: 238.0876.

Neopentyl 2-Fluorobenzoate (5). Colorless oil: R_f = 0.39 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.55−7.49 (m, 1H), 7.21 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.14 (ddd, J = 11.0, 8.3, 1.0 Hz, 1H), 4.03 (s, 2H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.68 (d, J_{C-F} = 3.7 Hz), 162.1 (d, J_{C-F} = 260.1 Hz), 134.4 (d, J_{C-F} = 9.2 Hz), 132.2 (d, J_{C-F} = 0.9 Hz), 124.0 (d, J_{C-F} = 3.6 Hz), 119.1 (d, J_{C-F} = 9.7 Hz), 117.1 (d, J_{C-F} = 22.5 Hz), 74.8, 31.5, 26.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −112.18 (dddd, J_{F-H} = 7.3, 7.3, 4.4, 4.4 Hz, 1F); IR (neat) 2959, 2871, 1713, 1613, 1456, 1296, 1126, 1083, 754, 691 cm^{-1}. HRMS (ESI+) Calcd. for $C_{12}H_{16}FO_2$ $[M + H]^+$: 211.1134. Found: 211.1137.

***tert*-Amyl 2-Fluorobenzoate (6).** Colorless oil: R_f = 0.44 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.50−7.44 (m, 1H), 7.17 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.10 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 1.91 (q, J = 7.6 Hz, 2H), 1.57 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.7 (d, J_{C-F} = 3.7 Hz), 162.0 (d, J_{C-F} = 259.1 Hz), 133.9 (d, J_{C-F} = 8.7 Hz), 132.0 (d, J_{C-F} = 0.9 Hz), 123.9 (d, J_{C-F} = 3.7 Hz), 120.7 (d, J_{C-F} = 9.7 Hz), 117.0 (d, J_{C-F} = 22.5 Hz), 84.5, 33.9, 25.8, 8.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −113.25 (dddd, J_{F-H} = 7.3, 7.3, 5.1, 5.1 Hz, 1F); IR (neat) 2976, 2933, 1708, 1613, 1487, 1369, 1126, 838, 755 cm^{-1}. HRMS (ESI+) Calcd. for $C_{12}H_{16}FO_2$ $[M + H]^+$: 211.1134. Found: 211.1129.

General Procedure for Titration by Isolation of the Unpurified Benzoate Ester. Benzoic acid (150 mg, 1.23 mmol, excess) was dissolved in 3 mL of CH_2Cl_2 and cooled to −78 °C. A 300 μL aliquot of the diazoalkane solution was added in a single portion, and the reaction mixture was allowed to warm to room temperature. After standing at room temperature for 30 min, the reaction mixture was transferred to a separatory funnel with 25 mL of Et_2O. The organic layer was washed with 1 N NaOH (2 × 15 mL) and saturated NaCl (15 mL), dried over Na_2SO_4, filtered, and then concentrated. The crude ester was dried under high vacuum (approximately 1 mmHg) for 12 h and weighed to determine yield. Analytically pure samples for new compounds were obtained by purification on silica gel (ethyl acetate in hexanes). Characterization data for benzoate esters **3a**,[25] **3b**,[26] **3c**,[27] **3d**,[28] **3e**,[29] **3g**,[30] **3i**,[29] **3k**,[31] **3l**,[27] and **3m**[32] have been reported previously.

2-Bromobenzyl Benzoate (3f). White solid: mp 33−35 °C; R_f = 0.30 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12−8.09 (m, 2H), 7.61 (dd, J = 8.1, 1.2 Hz, 1H), 7.58 (tt, J = 7.3, 1.5 Hz, 1H), 7.51 (dd, J = 7.6, 1.5 Hz, 1H), 7.48−7.44 (m, 2H), 7.34 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.22 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 135.6, 133.3, 133.0, 130.1, 130.0, 129.9, 129.9, 128.6, 127.7, 123.6, 66.4; IR (neat) 3034, 2956, 1717, 1450, 1374, 1264, 1176, 1096, 1069, 1025, 748, 706 cm^{-1}. HRMS (ESI+) Calcd. for $C_{14}H_{15}BrNO_2$ $[M + NH_4]^+$: 308.0286. Found: 308.0278.

4-(Trifluoromethyl)benzyl Benzoate (3h). White solid: mp 29−30 °C; R_f = 0.30 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10−8.07 (m, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.61−7.55 (m, 3H), 7.49−7.44 (m, 2H), 5.43 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 140.2 (q, J_{C-F} = 1.4 Hz), 133.4, 130.6 (q, J_{C-F} = 32.1 Hz), 129.9, 129.9, 128.6, 128.2, 125.7 (q, J_{C-F} = 3.7 Hz), 124.2 (q, J_{C-F} = 272.1 Hz), 65.8; IR (neat) 3065 (bw), 2949 (bw), 1720 (s), 1452 (w), 1323 (s), 1266 (bs), 1163 (m), 1106 (bs), 1064 (s), 1018 (m), 824 (m), 708 (s), 593 (m) cm^{-1}. HRMS (ESI+) Calcd. for $C_{15}H_{12}F_3O_2$ $[M + H]^+$: 281.0789. Found: 281.0776.

3-Bromobenzyl Benzoate (3j). Colorless oil: R_f = 0.38 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10−8.06 (m, 2H), 7.61−7.56 (m, 2H), 7.49−7.44 (m, 3H), 7.39−7.36 (m, 1H), 7.28−7.24 (m, 1H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 138.4, 133.3, 131.5, 131.2, 130.3, 130.0, 129.8, 128.6, 126.8, 122.8, 65.8; IR (neat) 3062 (bw), 3042 (bw), 2952 (bw), 1716 (s), 1601 (m), 1571 (m), 1450 (m), 1263 (bs), 1175 (m), 1095 (bs), 1068 (s), 1026 (m), 776 (m), 707 (bs) cm^{-1}. HRMS (ESI+) Calcd. for $C_{14}H_{12}BrO_2$ $[M + H]^+$: 291.0021. Found: 291.0031.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for new compounds, data tables for all titration trials, and NMR FID files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Addition of the internal standard was not necessary and done for characterization purposes only. In our experience, the esters always appear upfield (more negative shift) from the acid.
(23) The fluorine T_1 values for 2-fluorobenzoic acid and **2d** were determined to be 1.14 ± 0.03 and 1.73 ± 0.06 s, respectively. Relaxation delays of 10 s were sufficiently long to ensure accurate integration.
(24) The titration reaction with **1m** produced two distinct products on the ^{19}F spectrum in a 6.5:1 ratio. We believe the additional product (δ −111.5 ppm) was the result of $S_{N'}$ addition. However, attempts to isolate the compound led to decomposition. The titer reported is the result of integration of both signals.
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