3-Azidodifluoromethyl-3*H*-diazirin-3-yl group as an all-in-one functional group for radioisotope-free photoaffinity labeling

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Supplementary Data

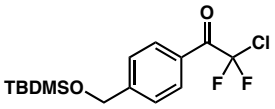
General remarks

THF (anhydrous; Wako Pure Chemical), $NaBD_4$ (CIL, sodium borodeuteride (D4, 99%), Cat. No. DML-226-1) and CD_3I (CIL, methyl iodide + copper wire (D3, 99.5%), Cat. No. DML-362-5) were used as received. All other chemical reagents used were commercial grade. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (MERCK, Silica Gel 60 F_{254}, Cat. No. 1.05715.0009). Preparative TLC was carried out using precoated (0.5 mm) silica-gel plates (MERCK, Silica Gel 60 F_{254}, Cat. No. 1.05744.0009). Column chromatography was conducted using silica-gel (Kanto, Silica Gel 60N, Cat. No. 37563-84). ^1H, ^{13}C and ^{19}F NMR were obtained with a Varian MERCURY 300 spectrometer. $CDCl_3$ (CIL) or CD_3OD (CIL) was used as a solvent for obtaining NMR spectra. Chemical shifts (δ) are given in parts per million (ppm) downfield from $(CH_3)_4Si$ (δ 0.00 for ^1H NMR in $CDCl_3$), hexafluorobenzene (δ 0.00 for ^{19}F NMR), or solvent (for ^{13}C NMR) as (internal) references with coupling constants (*J*) in Hz. The abbreviations s, d, t, q, m, and br signify singlet, doublet, triplet, quartet, multiplet, and broad respectively. IR spectra were measured by diffuse reflectance method on a SHIMADZU IRPrestige-21 spectrometer attached with DRS-8000A with the absorption band given in cm^{-1}. Elemental analyses were performed with a YANACO CHN CORDER MT-5 at the Center for Advanced Materials Analysis, Technical Department, Tokyo Institute of Technology. High-resolution mass spectra (HRMS) were measured on a JEOL JMS-700 mass spectrometer under electron impact ionization (EI) or positive fast atom bombardment (FAB^+) conditions at the Center for Advanced Materials Analysis, Technical Department, Tokyo Institute of Technology. Melting point (mp) was measured on a YANACO MP-J3 instrument.

CAUTION ! **Azido-containing compounds are presumed to be potentially explosive. Although we have never experienced such an explosion with azido-functionalized compounds used in this study, all manipulations should be carefully carried out behind a safety shield in a hood.**

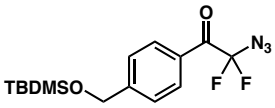
Synthesis of (3-azidodifluoromethyl-3H-diazirin-3-yl)benzene derivative 10.

1-{4-[(*tert*-Butyldimethylsilyloxy)methyl]phenyl}-2-chloro-2,2-difluoroethanone (**5**).



Under Ar atmosphere, to a solution of 4-bromobenzyl *tert*-butyldimethylsilyl ether (**4**) (4.34 g, 14.4 mmol) in THF (25 mL) was added *n*-C_4H_9Li (1.58 M *n*-hexane solution, 10.0 mL, 15.8 mmol) at –78 ˚C, and the mixture was stirred for 5 min at the same temperature. To this was added ethyl chlorodifluoroacetate (2.19 mL, 17.3 mmol) at the same temperature. After stirring for 10 min at the same temperature, the mixture was poured into 1.0 M aqueous HCl solution and the mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with water (×1) and brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/Et_2O = 9/1) to give 1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2-chloro-2,2-difluoroethanone (**5**) (4.50 g, 93.3%); pale yellow oil; TLC a tailing spot (*n*-hexane/Et_2O = 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.96 (s, 9H), 4.83 (s, 2H), 7.48–7.50 (AA'BB', 2H), 8.09–8.12 (AA'BB', 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ –5.4 (2C), 18.3, 25.8 (3C), 64.2, 120.2 (t, $^1J_{C–F}$ = 305.1 Hz), 126.0 (2C), 127.9, 130.7 (t, 2C, $^4J_{C–F}$ = 2.9 Hz), 149.7, 180.8 (t, $^2J_{C–F}$ = 28.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 101.1 (s, 2F); IR (KBr, cm^{-1}) 669, 733, 777, 814, 843, 893, 988, 1005, 1045, 1101, 1128, 1140, 1159, 1184, 1211, 1258, 1285, 1375, 1418, 1464, 1472, 1609, 1715, 2340, 2359, 2857, 2886, 2930, 2955; Anal. Calcd. for $C_{15}H_{21}O_2ClF_2Si$: C, 53.80; H, 6.32. Found: C, 53.94; H, 6.33.

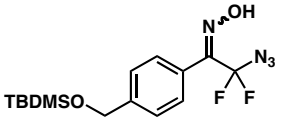
2-Azido-1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2,2-difluoroethanone (**6**).



To a solution of **5** (4.39 g, 13.1 mmol) in DMSO (15 mL) was added sodium azide (1.19 g, 18.3 mmol) at room temperature, and the mixture was stirred for 10 min at 100 ˚C. After cooling the mixture to room temperature, water was added and the mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with water (×1) and brine (×1), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography

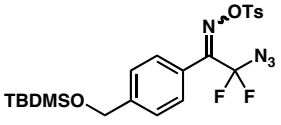
(*n*-hexane/EtOAc = 9/1) to give 2-azido-1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2,2-difluoroethanone (**6**) (3.98 g, 88.9%); pale yellow oil; TLC a tailing spot (*n*-hexane/Et_2O = 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.96 (s, 9H), 4.83 (s, 2H), 7.45–7.52 (AA'BB', 2H), 8.04–8.11 (AA'BB', 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ –5.4 (2C), 18.4, 25.8 (3C), 64.2, 115.5 (t, $^1J_{C–F}$ = 273.5 Hz), 125.9 (2C), 128.9, 130.5 (t, 2C, $^4J_{C–F}$ = 2.9 Hz), 149.7, 182.8 (t, $^2J_{C–F}$ = 34.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 83.9 (s, 2F); IR (KBr, cm^{-1}) 669, 743, 777, 814, 841, 895, 920, 1007, 1018, 1055, 1101, 1125, 1159, 1184, 1258, 1310, 1362, 1375, 1389, 1418, 1464, 1472, 1609, 1709, 2145, 2857, 2886, 2930, 2955; Anal. Calcd. for $C_{15}H_{21}N_3O_2F_2Si$: C, 52.77; H, 6.20; N, 12.31. Found: C, 52.83; H, 6.40; N, 11.97.

2-Azido-1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2,2-difluoroethanone oxime (**7**).



To a solution of **6** (3.98 g, 11.7 mmol) in pyridine (20 mL) was added hydroxylamine hydrochloride (2.26 g, 35.0 mmol) at room temperature, and the mixture was stirred for 14 h at 60 ˚C. After cooling the mixture to room temperature, to this was added 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed 1.0 M aqueous HCl solution (×1), water (×2) and brine (×1), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 9/1) to give 2-azido-1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2,2-difluoroethanone oxime (**7**) (3.81 g, 91.6%); pale yellow oil; TLC R_f = 0.52 (*n*-hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 and 0.12 (s, 6H), 0.95 and 0.96 (s, 9H), 4.77 and 4.79 (s, 2H), 7.34–7.47 (m, 4H), 8.14 and 8.41 (s, 1H); ^{13}C NMR (75.5 MHz) δ –5.3 (2C), 18.4, 25.9 (3C), 64.6, 115.9 (t, $^1J_{C–F}$ = 268.3 Hz) and 118.5 (t, $^1J_{C–F}$ = 262.0 Hz), 125.0 and 129.1, 125.8 and 125.9 (2C), 128.4 and 128.6 (2C), 143.5 and 143.8, 149.2 (t, $^2J_{C–F}$ = 31.7 Hz) and 150.1 (t, $^2J_{C–F}$ = 30.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 89.9 and 91.5 (s, 2F); IR (KBr, cm^{-1}) 669, 723, 737, 779, 816, 837, 932, 1005, 1065, 1094, 1119, 1173, 1233, 1258, 1306, 1362, 1375, 1391, 1410, 1464, 1472, 1514, 2147, 2859, 2886, 2930, 2955, 3059, 3227; Anal. Calcd. for $C_{15}H_{22}N_4O_2F_2Si$: C, 50.54; H, 6.22; N, 15.72. Found: C, 50.36; H, 6.07; N, 15.48.

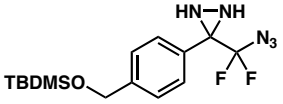
2-Azido-1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2,2-difluoroethanone *O*-tosyl oxime (**8**).



Under Ar atmosphere, to a solution of **7** (2.68g, 7.52 mmol) in CH_2Cl_2 (20 mL) were

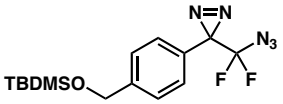
successively added Et_3N (1.26 mL, 9.02 mmol), *p*-toluenesulfonyl chloride (1.72 g, 9.02 mmol) and (4-dimethylamino)pyridine (46.3 mg, 379 μmol) at 0 ˚C. After stirring for 1.5 h at the same temperature, the mixture was poured into water and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with water (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 25/1) to give 2-azido-1-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-2,2-difluoroethanone *O*-tosyl oxime (**8**) (3.73 g, 97.2%); pale yellow oil; TLC R_f = 0.59 (*n*-hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 and 0.12 (s, 6H), 0.95 and 0.96 (s, 9H), 2.46 and 2.48 (s, 3H), 4.76 and 4.78 (s, 2H), 7.32–7.45 (m, 6H), 7.86–7.93 (m, 2H); ^{13}C NMR (75.5 MHz) δ –5.5 (2C), 18.2, 21.6, 25.7 (3C), 64.1, 115.1 and 117.2 (t, $^1J_{C–F}$ = 271.8 and 262.6 Hz), 123.4 and 126.6, 125.7 and 125.8 (2C), 128.3 and 128.8 (2C), 128.96 and 129.02 (2C), 129.7 and 129.8 (2C), 131.2 and 131.4, 145.2 and 145.4, 145.8 and 146.0, 156.3 (t, $^2J_{C–F}$ = 31.7 Hz) and 156.5 (t, $^2J_{C–F}$ = 34.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 88.5 and 93.1 (s, 2F); IR (KBr, cm^{-1}) 550, 567, 581, 615, 664, 706, 719, 777, 814, 839, 876, 949, 976, 1007, 1020, 1067, 1094, 1119, 1180, 1196, 1217, 1231, 1256, 1308, 1391, 1462, 1472, 1597, 2149, 2857, 2886, 2930, 2953; Anal. Calcd. for $C_{22}H_{28}N_4O_4F_2SSi$: C, 51.75; H, 5.53; N, 10.97. Found: C, 51.81; H, 5.60; N, 10.99.

3-(Azidodifluoromethyl)-3-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}diaziridine (**9**).



Under Ar atmosphere, to a solution of **8** (294 mg, 576 μmol) in CH_2Cl_2 (5 mL) was added liquid NH_3 (3 mL) at –78 ˚C and the mixture was allowed to warm up to room temperature. After stirring for 12 h at the same temperature, water was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with water (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/Et_2O/CH_2Cl_2 = 8/1/1) to give 3-(azidodifluoromethyl)-3-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}diaziridine (**9**) (195 mg, 95.3%); pale yellow oil; TLC R_f = 0.23 (*n*-hexane/Et_2O/CH_2Cl_2 = 7/1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 2.20 (d, 1H, *J* = 8.79 Hz), 2.79 (d, 1H, *J* = 8.79 Hz), 4.76 (s, 2H), 7.34–7.39 (AA'BB', 2H), 7.54–7.60 (AA'BB', 2H); ^{13}C NMR (75.5 MHz) δ –5.5 (2C), 18.3, 25.8 (3C), 59.4 (t, $^2J_{C–F}$ = 35.1 Hz), 64.3, 121.1 (dd, $^1J_{C–F}$ = 264.9, 268.9 Hz), 125.8 (2C), 128.4 (2C), 130.7, 143.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ 80.3 (d, 1F, *J* = 187.7 Hz), 81.1 (d, 1F, *J* = 187.7 Hz); IR (KBr, cm^{-1}) 419, 669, 731, 752, 777, 839, 941, 1007, 1020, 1069, 1080, 1094, 1113, 1142, 1177, 1258, 1298, 1362, 1375, 1414, 1464, 1472, 2156, 2361, 2857, 2886, 2930, 2955, 3215, 3252; Anal. Calcd. for $C_{15}H_{23}N_5OF_2Si$: C, 50.68; H, 6.52; N, 19.70. Found: C, 50.80; H, 6.55; N, 19.56.

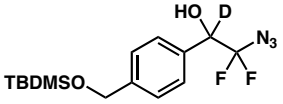
3-(Azidodifluoromethyl)-3-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-3*H*-diazirine (**10**).



To a solution of **9** (270 mg, 760 μmol) in Et_2O (5 mL) was added Ag_2O (264 mg, 1.14 mmol) at room temperature. After stirring for 1.5 h at the same temperature, the precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/Et_2O = 50/1) to give 3-(azidodifluoromethyl)-3-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-3*H*-diazirine (**10**) (251 mg, 93.5%); pale yellow oil; TLC R_f = 0.62 (*n*-hexane/Et_2O = 20/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.94 (s, 9H), 4.74 (s, 2H), 7.18–7.23 (AA'BB', 2H), 7.31–7.36 (AA'BB', 2H); ^{13}C NMR (75.5 MHz) δ –5.4 (2C), 18.3, 25.9 (3C), 29.7 (t, $^2J_{C\text{-}F}$ = 36.3 Hz), 64.2, 120.0 (t, $^1J_{C\text{-}F}$ = 265.5 Hz), 126.1 (2C), 126.8 (2C), 128.4, 143.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ 91.3 (s, 2F); IR (KBr, cm^{-1}) 739, 777, 808, 839, 891, 916, 1007, 1030, 1098, 1196, 1252, 1329, 1362, 1377, 1412, 1462, 1470, 1518, 1612, 2145, 2359, 2859, 2886, 2930, 2955; Anal. Calcd. for $C_{15}H_{21}N_5OF_2Si$: C, 50.97; H, 5.99; N, 19.81. Found: C, 51.01; H, 5.84; N, 19.77.

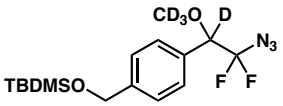
Synthesis of 12-d_4 from ketone 6.

1-(2-Azido-2,2-difluoro-1-hydroxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene.



Under Ar atmosphere, to a solution of **6** (133 mg, 390 μmol) in EtOH (2 mL) was added $NaBD_4$ (4.1 mg, 98 μmol) at 0 ˚C. After stirring for 1 h at the same temperature, water was added and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with water (×3) and brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 10/1) to give 1-(2-azido-2,2-difluoro-1-hydroxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (121 mg, 90.2%); pale yellow oil; TLC R_f = 0.28 (*n*-hexane/Et_2O = 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 2.54 (s, 1H), 4.76 (s, 2H), 7.33–7.39 (AA'BB', 2H), 7.40–7.46 (AA'BB', 2H); ^{13}C NMR (75.5 MHz) δ –5.4 (2C), 18.4, 25.9 (3C), 64.6, 121.4 (t, $^1J_{C\text{-}F}$ = 270.1 Hz), 125.9 (2C), 127.5 (2C), 133.2, 142.4, (one carbon in neighbor to deuterium was not observed); ^{19}F NMR (282 MHz, $CDCl_3$) δ 76.1 (d, 1F, *J* = 182 Hz), 77.3 (d, 1F, *J* = 182 Hz); IR (KBr, cm^{-1}) 569, 592, 669, 739, 777, 837, 908, 939, 982, 989, 1005, 1020, 1084, 1211, 1260, 1362, 1373, 1391, 1416, 1464, 1514, 2149, 2857, 2886, 2930, 2955, 3374; HRMS (EI) m/z 344.1587 (M^+, $C_{15}H_{22}DF_2N_3O_2Si$ requires 344.1590).

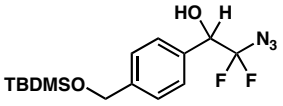
1-(2-Azido-2,2-difluoro-1-[$^2H_3$]methoxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (**12**-d_4).



Under Ar atmosphere, to a solution of 1-(2-azido-2,2-difluoro-1-hydroxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (726 mg, 2.11 mmol) in DMF (6 mL) was added NaH (60% oil suspension, 88.8 mg, 2.22 mmol) at 0 ˚C, and the mixture was stirred for 5 min at the same temperature. To this was added CD_3I (160 μL, 2.57 mmol) at the same temperature. After stirring for 1.5 h at the same temperature, water was added and the mixture was extracted with Et_2O (×3). The combined organic extracts were successively washed with water (×3) and brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 30/1) to give 1-(2-azido-2,2-difluoro-1-[$^2H_3$]methoxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (**12**-d_4) (731 mg, 95.9%); pale yellow oil; TLC R_f = 0.56 (*n*-hexane/Et_2O = 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 4.77 (s, 2H), 7.34–7.40 (m, 4H); ^{13}C NMR (75.5 MHz) δ –5.3 (2C), 18.4, 25.9 (3C), 64.5, 120.7 (t, $^1J_{C\text{-}F}$ = 268.3 Hz), 125.9 (2C), 128.2 (2C), 131.4 (d, $^3J_{C\text{-}F}$ = 1.7 Hz), 142.8, (two carbons in neighbor to deuterium were not observed); ^{19}F NMR (282 MHz, $CDCl_3$) δ 76,7 (d, 1F, *J* = 185 Hz), 78.8 (d, 1F, *J* = 185 Hz); IR (KBr, cm^{-1}) 669, 777, 839, 941, 970, 995, 1030, 1092, 1119, 1134, 1157, 1223, 1256, 1292, 1362, 1375, 1416, 1462, 1470, 2064, 2147, 2857, 2886, 2930, 2955; HRMS (EI) m/z 361.1933 (M^+, $C_{16}H_{21}D_4F_2N_3O_2Si$ requires 361.1935).

Synthesis of 12 from ketone 6.

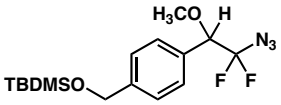
1-(2-Azido-2,2-difluoro-1-hydroxyethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene.



Under Ar atmosphere, to a solution of **6** (159 mg, 466 μmol) in EtOH (2 mL) was added $NaBH_4$ (4.6 mg, 0.12 mmol) at 0 ˚C. After stirring for 1 h at the same temperature, water was added and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with water (×1) was brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 10/1) to give 1-(2-azido-2,2-difluoro-1-hydroxyethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (147 mg, 91.9%); pale yellow oil; TLC R_f = 0.36 (*n*-hexane/EtOAc = 7/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 2.53 (d, 1H, *J* = 4.4 Hz), 4.76 (s, 2H), 4.92 (ddd, 1H, *J* = 4.4, 7.7, 7.7 Hz), 7.33–7.39 (AA'BB', 2H), 7.41–7.46 (AA'BB', 2H); ^{13}C NMR (75.5 MHz) δ –5.4 (2C), 18.4, 25.9 (3C), 64.7, 74.5 (t, $^2J_{C\text{-}F}$ = 30.5 Hz), 121.5 (t, $^1J_{C\text{-}F}$ = 270.1 Hz), 125.9 (2C), 127.5 (2C), 133.3, 142.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ 76.1

(dd, 1F, J = 7.6, 181.6 Hz), 77.4 (dd, 1F, J = 7.6, 181.6 Hz); IR (KBr, cm^{-1}) 478, 490, 554, 571, 598, 633, 669, 692, 731, 777, 816, 839, 907, 939, 1005, 1018, 1069, 1121, 1192, 1211, 1256, 1362, 1375, 1391, 1412, 1423, 1464, 1516, 1616, 1915, 2151, 2340, 2359, 2712, 2739, 2857, 2886, 2930, 2955, 3024, 3059, 3102, 3374; Anal. Calcd. for $C_{15}H_{23}N_3O_2F_2Si$: C, 52.46; H, 6.75; N, 12.23. Found: C, 52.25; H, 6.67; N, 12.19.

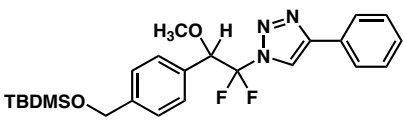
1-(2-Azido-2,2-difluoro-1-methoxyethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (**12**).



Under Ar atmosphere, to a solution of 1-(2-azido-2,2-difluoro-1-hydroxyethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (1.06 g, 3.09 mmol) in DMF (6 mL) was added NaH (60% oil suspension, 130 mg, 3.25 mmol) at 0 ˚C, and the mixture was stirred for 5 min at the same temperature. To this was added CH_3I (230 μL, 3.69 mmol) at the same temperature. After stirring for 1 h at the same temperature, water was added and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with water (×3) and brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/Et_2O = 49/1) to give 1-(2-azido-2,2-difluoro-1-methoxyethyl)-4-[(*tert*-butyldimethylsilyloxy)-methyl]benzene (**12**) (1.05 g, 95.2%); pale yellow oil; TLC R_f = 0.56 (*n*-hexane/Et_2O = 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 3.39 (s, 3H), 4.44 (t, 1H, J = 7.7 Hz), 4.77 (s, 2H), 7.34–7.40 (AA'BB', 4H); ^{13}C NMR (75.5 MHz) δ –5.4 (2C), 18.3, 25.8 (3C), 57.8, 64.4, 83.6 (t, $^2J_{C\text{-}F}$ = 30.5 Hz), 120.6 (t, $^1J_{C\text{-}F}$ = 268.3 Hz), 125.9 (2C), 128.2 (2C), 131.4 (d, $^3J_{C\text{-}F}$ = 1.7 Hz), 142.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ 76.7 (d, 1F, J = 7.6, 184.6 Hz), 78.8 (d, 1F, J = 7.6, 184.6 Hz); IR (KBr, cm^{-1}) 492, 540, 571, 610, 669, 702, 748, 777, 814, 841, 939, 984, 1005, 1020, 1057, 1096, 1155, 1211, 1256, 1275, 1350, 1360, 1375, 1389, 1422, 1462, 1472, 1514, 1915, 2149, 2330, 2833, 2857, 2930, 2953, 2995, 30553374; Anal. Calcd. for $C_{16}H_{25}N_3O_2F_2Si$: C, 53.76; H, 7.05; N, 11.75. Found: C, 53.88; H, 6.98; N, 11.66.

Huisgen 1,3-dipolar cycloaddition of 12 with phenylacetylene.

1-(2-{4-[(*tert*-Butyldimethylsilyloxy)methyl]phenyl}-1,1-difluoro-2-methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole (**16**).



Under Ar atmosphere, to a solution of **12** (30.0 mg, 83.9 μmol) in CH_3OH (672 μL) was

successively added phenylacetylene (27.6 μL, 252 μmol), TBTA (50 mM CH_3OH solution, 168 μL, 8.39 μmol), $CuSO_4$ (100 mM aqueous solution, 42.0 μL, 4.20 μmol) and sodium ascorbate (100 mM aqueous solution, 168 μL, 16.8 μmol) at room temperature. After shaking for 1 h at the same temperature, water was added and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with water (×1) and brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 15/1) to give 1-(2-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-1,1-difluoro-2-methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole (**16**) (38.5 mg, 99.8%); colorless solid; TLC R_f = 0.58 (*n*-hexane/EtOAc = 4/1); mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 3.34 (s, 3H), 4.76 (s, 2H), 5.28 (dd, 1H, J = 6.3, 15.4 Hz), 7.34–7.48 (m, 7H), 7.83–7.88 (AA'BB', 2H), 8.02 (d, 1H, J = 1.1 Hz); ^{13}C NMR (75.5 MHz) δ –5.4 (2C), 18.3, 25.8 (3C), 57.9, 64.4, 82.0 (dd, $^2J_{C\text{-}F}$ = 23.6, 32.2 Hz), 117.7 (dd, $^1J_{C\text{-}F}$ = 262.6, 265.5 Hz), 117.9, 125.8 (2C), 126.0 (2C), 128.4 (2C), 128.6, 128.8 (2C), 129.4, 130.3, 143.0, 147.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ 63.9 (dd, 1F, J = 15.3, 212.1 Hz), 77.3 (dd, 1F, J = 6.1, 212.1 Hz); IR (KBr, cm^{-1}) 694, 764, 779, 839, 914, 976, 1005, 1022, 1036, 1059, 1092, 1115, 1136, 1198, 1256, 1352, 1425, 1456, 2857, 2884, 2928, 2953; Anal. Calcd. for $C_{24}H_{31}N_3O_2F_2Si$: C, 62.72; H, 6.80; N, 9.14. Found: C, 62.86; H, 6.77; N, 9.11.

Photoreaction of 10 in CD_3OD by irradiation of UV with wavelength of 365 nm.

A 12.3 mM solution of **10** in deaerated CD_3OD (800 μL, 9.84 μmol) was placed in a quartz NMR tube (Nihon Seimitsu Kagaku, N-5Q) under Ar atmosphere. The mixture was continuously irradiated side-by-side with 365-nm-wavelength UV light (UVP, UVL-56, 6W) for 8 min at 20 ˚C. The course of the reaction was monitored by ^{1}H (Fig. S1) and ^{19}F NMR (Fig. S2 and Fig. S3).

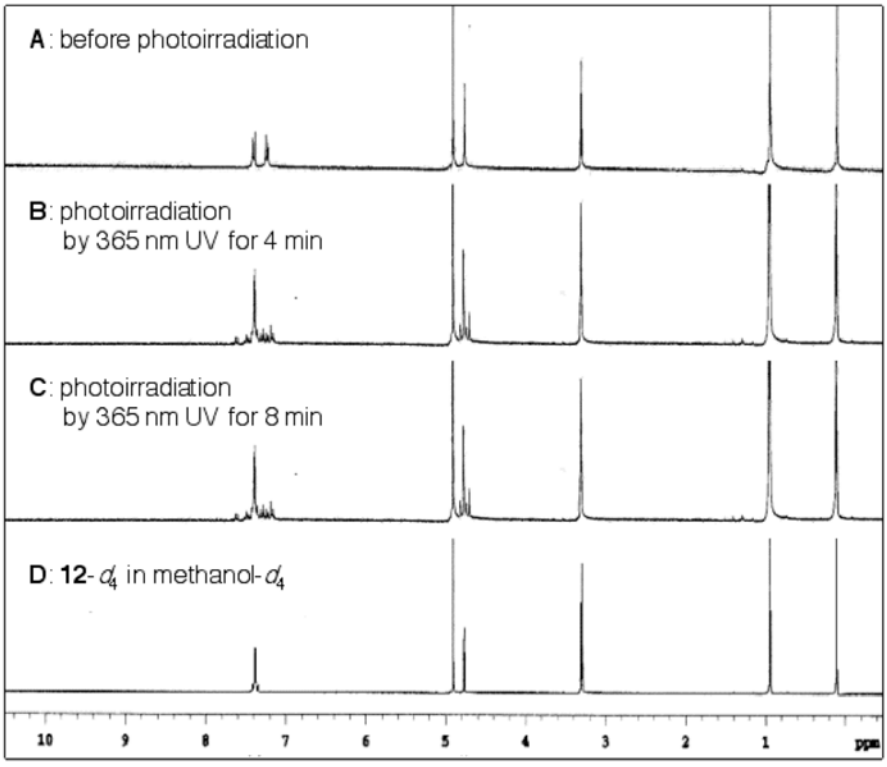


Figure S1. Photoreaction of **10** in CD_3OD monitored by ^{1}H NMR. The reaction was carried out at 20 ˚C using quartz NMR tube.

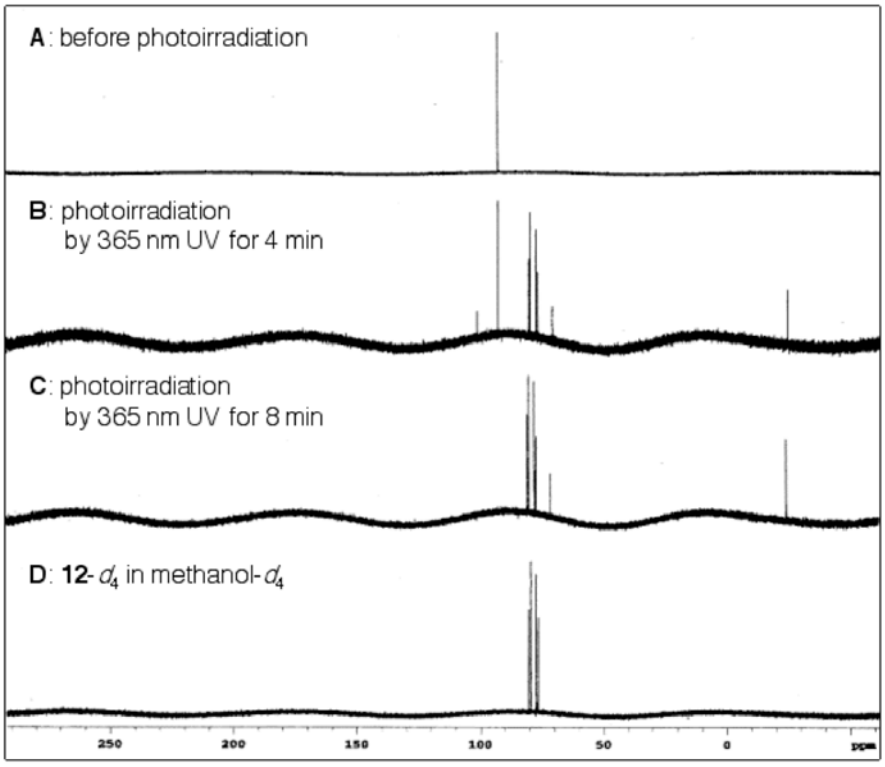


Figure S2. Photoreaction of **10** in CD_3OD monitored by ^{19}F NMR. The reaction was carried out at 20 ˚C using quartz NMR tube.

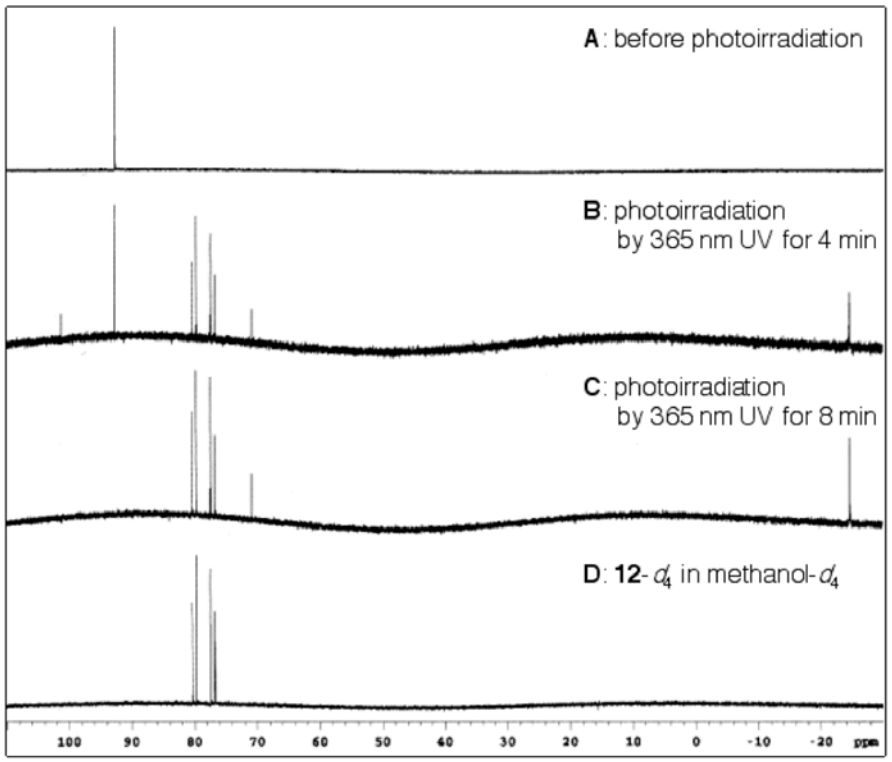


Figure S3. Magnified view of Fig. S2 from –30 to 110 ppm.

Photoreaction of 13 in CD_3OD by irradiation of UV with wavelength of 365 nm.

A 12.3 mM solution of **13** in deaerated CD_3OD (800 μL, 9.84 μmol) was placed in a quartz NMR tube (Nihon Seimitsu Kagaku, N-5Q) under Ar atmosphere. The mixture was continuously irradiated side-by-side with 365-nm-wavelength UV light (UVP, UVL-56, 6W) for 60 min at 20 ˚C. The course of the reaction was monitored by ^{1}H (Fig. S4) and ^{19}F NMR (Fig. S5 and Fig. S6).

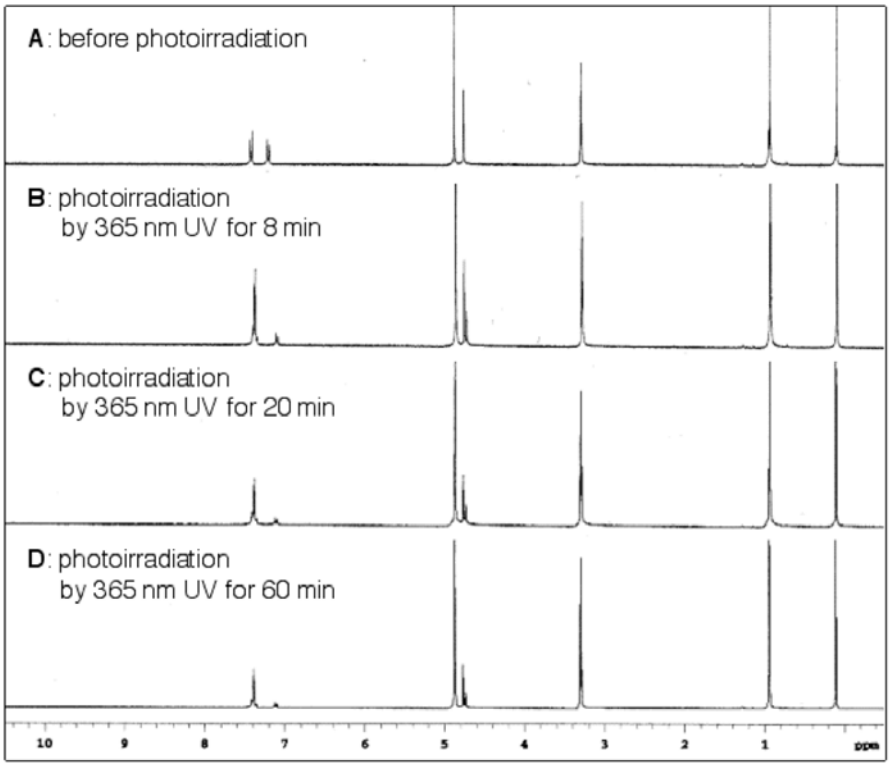


Figure S4. Photoreaction of **13** in CD_3OD monitored by ^{1}H NMR. The reaction was carried out at 20 ˚C using quartz NMR tube.

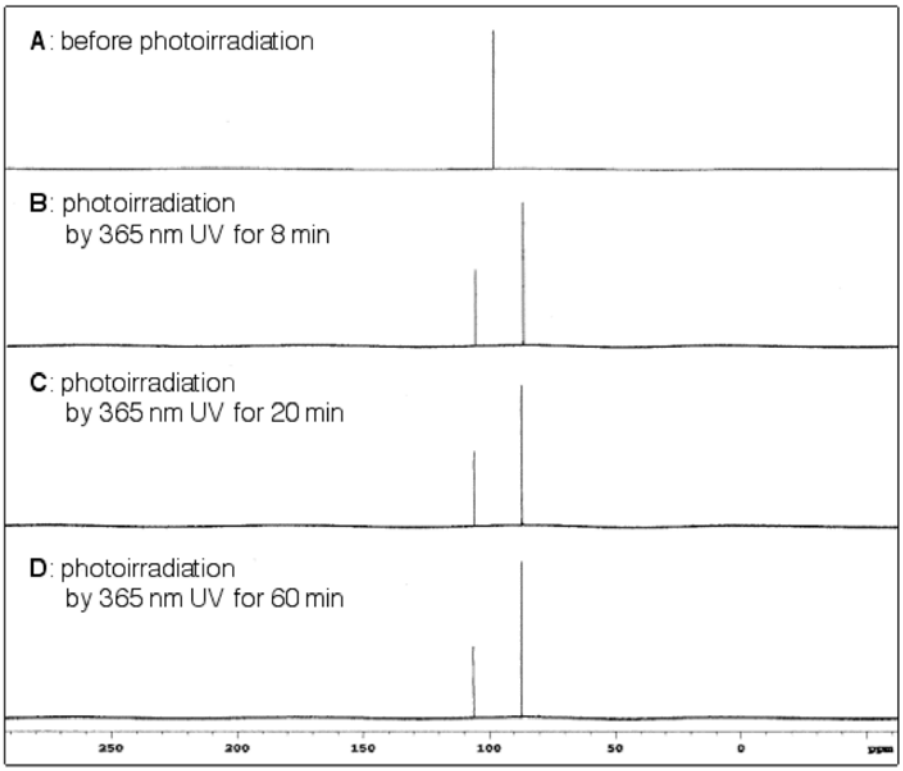


Figure S5. Photoreaction of **13** in CD_3OD monitored by ^{19}F NMR. The reaction was carried out at 20 ˚C using quartz NMR tube.

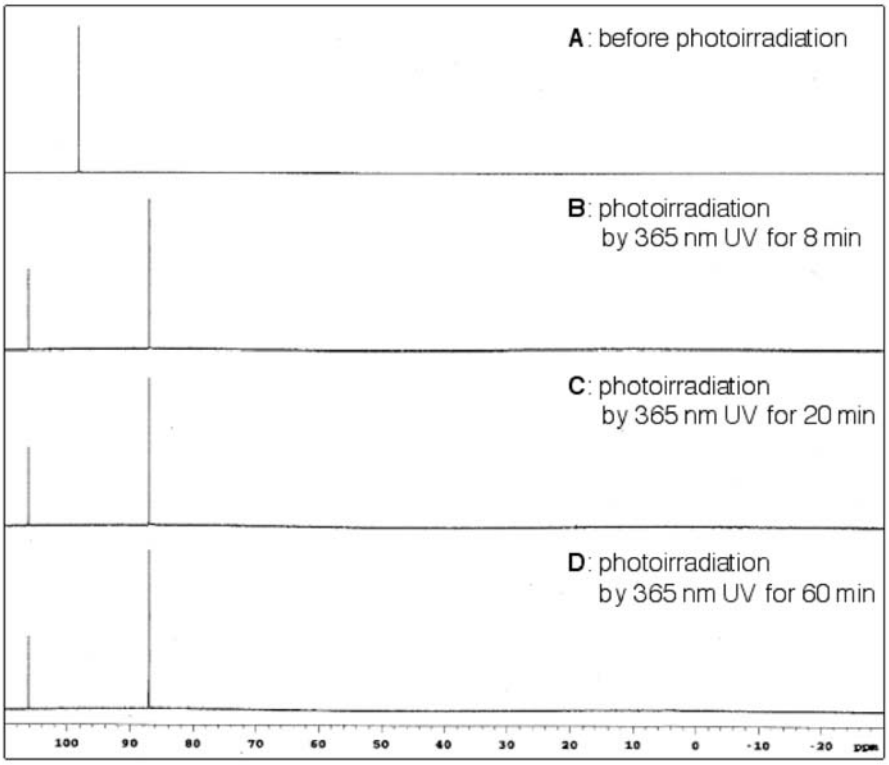
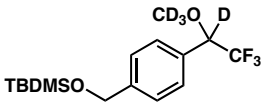


Figure S6. Magnified view of Fig. S5 from –30 to 110 ppm.

Photoreaction of 13 in CD_3OD by irradiation of UV with wavelength of 365 and 302 nm.

1-(2,2,2-trifluoro-1-[$^2H_3$]methoxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (**14**).



A 12.3 mM solution of **13** in deaerated CD_3OD (800 μL, 9.84 μmol) was placed in a quartz NMR tube (Nihon Seimitsu Kagaku, N-5Q) under Ar atmosphere. The mixture was continuously irradiated side-by-side with 365-nm-wavelength UV light (UVP, UVL-56, 6W) for 8 min followed with 302-nm-wavelength UV light (UVP, UVM-57, 6W) for 5 min at 20 ˚C. The course of the reaction was monitored by ^{1}H (Fig. S7) and ^{19}F NMR (Fig. S8 and Fig. S9). After concentration of the reaction mixture under reduced pressure, the crude product was purified by preparative TLC (*n*-hexane/Et_2O = 9/1) to give 1-(2,2,2-trifluoro-1- [$^2H_3$]methoxy[1-^{2}H]ethyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]benzene (**14**) (2.5 mg, 75%); pale yellow oil; TLC R_f = 0.36 (*n*-hexane/ Et_2O = 20/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 4.77 (s, 2H), 7.35–7.42 (m, 4H); ^{13}C NMR (75.5 MHz) δ –5.4 (2C), 18.4, 25.9 (3C), 64.5, 123.8 (q, $^1J_{C\text{-}F}$ = 281.6 Hz), 126.1 (2C), 128.1 (2C), 130.9, 143.0, (two carbons in neighbor to deuterium were not observed); ^{19}F NMR (282 MHz, $CDCl_3$) δ 85.1 (s, 3F); IR (KBr, cm^{-1}) 509, 527, 567, 669, 685, 719, 739, 777, 802, 839, 907, 939, 974, 1001, 1049, 1096, 1117, 1140, 1173, 1192, 1236, 1256, 1319, 1362, 1375, 1391, 1416, 1462, 1470, 1512, 2066, 2210, 2857, 2886, 2930, 2955; HRMS (EI) m/z 338.1827 (M^+, $C_{16}H_{21}D_4F_3O_2Si$ requires 338.1827).

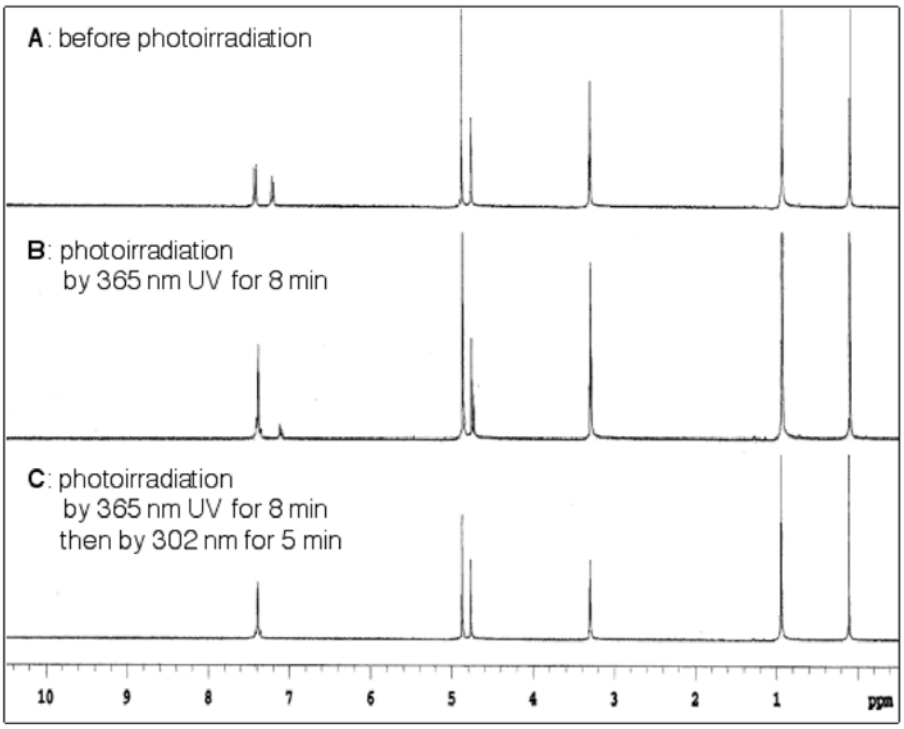


Figure S7. Photoreaction of **13** in CD_3OD monitored by ^1H NMR. The reaction was carried out at 20 ˚C using quartz NMR tube.

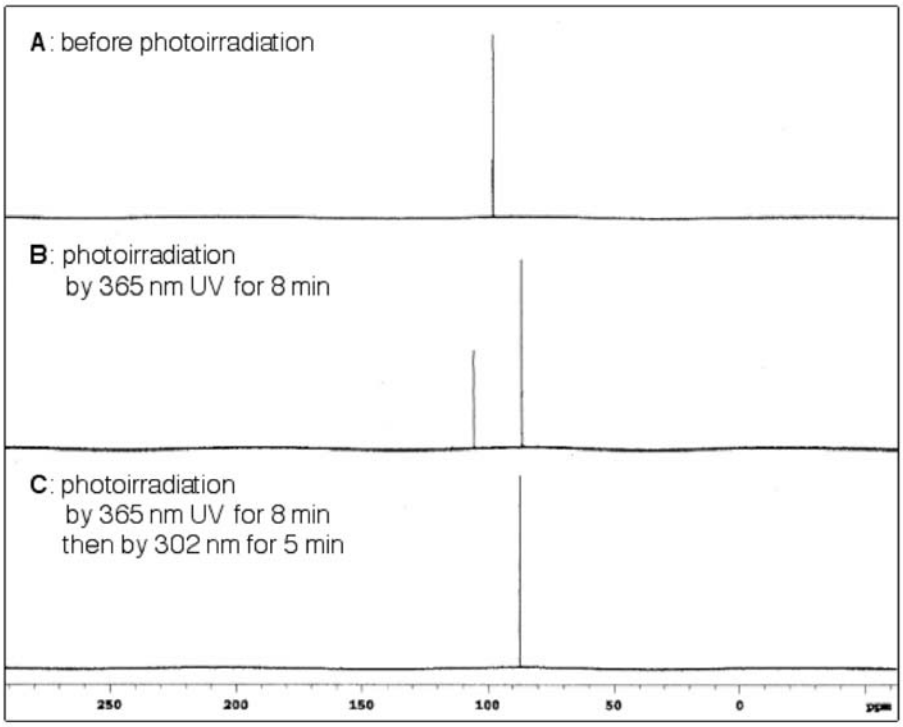


Figure S8. Photoreaction of **13** in CD_3OD monitored by ^{19}F NMR. The reaction was carried out at 22 ˚C using quartz NMR tube.

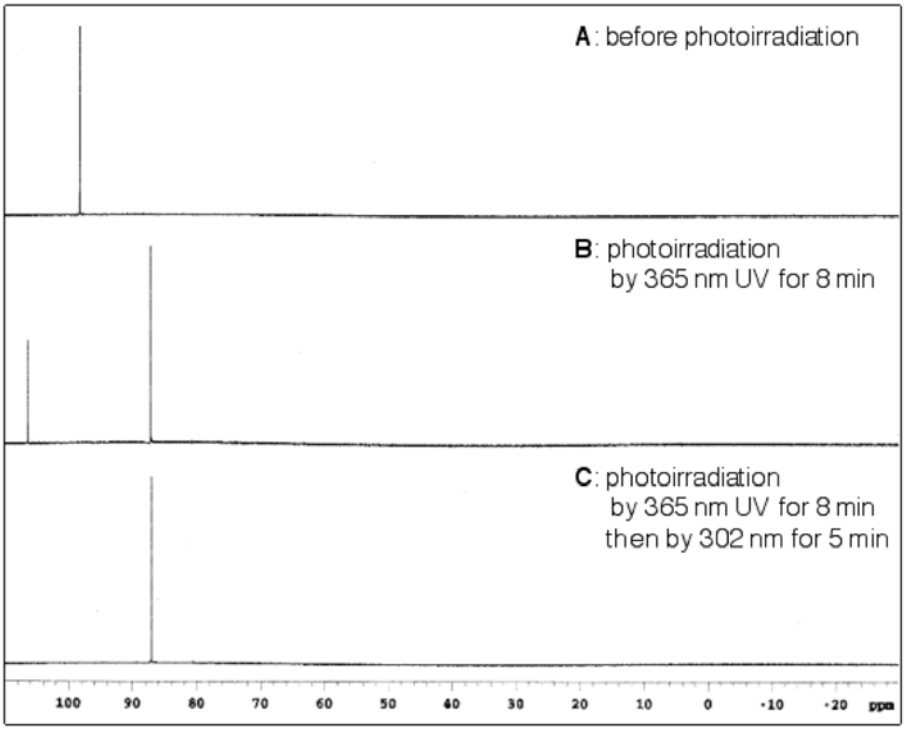


Figure S9. Magnified view of Fig. S8 from –30 to 110 ppm.

Photoreaction of 10 in CH_3OH followed by Huisgen 1,3-dipolar cycloaddition with phenylacetylene.

A 12.3 mM solution of **10** in deaerated CH_3OH (5.00 mL, 61.5 μmol) was dispensed in five quartz NMR tubes (Nihon Seimitsu Kagaku, N-5Q) under Ar atmosphere. The reaction mixture was continuously irradiated side-by-side with 365-nm-wavelength UV light (UVP, UVL-56, 6W) for 8 min at room temperature. After photoirradiation, the reaction mixture was collected and concentrated under reduce pressure to give crude **12**. Under Ar atmosphere, to this was successively added CH_3OH (493 μL), phenylacetylene (20.3 μL, 185 μmol), TBTA (50 mM CH_3OH solution, 123 μL, 6.15 μmol), $CuSO_4$ (100 mM aqueous solution, 30.8 μL, 3.08 μmol) and sodium ascorbate (100 mM aqueous solution, 123 μL, 12.3 μmol) at room temperature. After shaking for 1.5 h at the same temperature, to this was added water and the mixture was extracted with EtOAc (×3). The combined organic extracts were successively washed with water (×1) and brine (×1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 15/1) to give 1-(2-{4-[(*tert*-butyldimethylsilyloxy)methyl]phenyl}-1,1-difluoro-2-methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole (**16**) (14.8 mg, 52.4%).

Attempt on Staudinger–Bertozzi ligation of 12 with methyl 2-(diphenylphosphino)benzoate.

Under Ar atmosphere, to a solution of **12** (15.0 mg, 42.0 μmol) in a 10:1 mixture of THF–H_2O (2.2 mL) was added methyl 2-(diphenylphosphino)benzoate (20.2 mg, 63.0 μmol) at room temperature. After stirring for 12 h at the same temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/CH_3OH = 9/1) to give 2-[4-(hydroxymethyl)phenyl]-2-methoxyacetamide (**18**) (5.2 mg, 63%); colorless oil; TLC R_f = 0.31 (CH_2Cl_2/CH_3OH = 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (br s, 1H), 3.35 (s, 3H), 4.60 (s, 1H), 4.66 (d, 2H, *J* = 4.4 Hz), 5.93 (br s, 1H), 6.70 (br s, 1H), 7.32–7.42 (m, 4H); ^{13}C NMR (75.5 MHz) δ 57.1, 64.7, 83.4, 127.1 (2C), 127.2 (2C), 135.8, 141.5, 173.7; IR (KBr, cm^{-1}) 446, 478, 503, 521, 559, 588, 602, 611, 638, 669, 731, 799, 814, 908, 934, 955, 988, 1016, 1043, 1098, 1155, 1200, 1260, 1306, 1333, 1377, 1416, 1449, 1512, 1585, 1630, 1670, 2828, 2878, 2934, 2994, 3188, 3304, 3447; HRMS (FAB$^+$) m/z 196.0980 ($(M+H)^+$, $C_{10}H_{14}N_3O_3$ requires 196.0974).