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DIVERGENT SYNTHESIS OF PHOTOAFFINITY PROBE CANDIDATES BY CLICK REACTIONS OF AZIDO-SUBSTITUTED ARYLTRIFLUOROMETHYLDIAZIRINES

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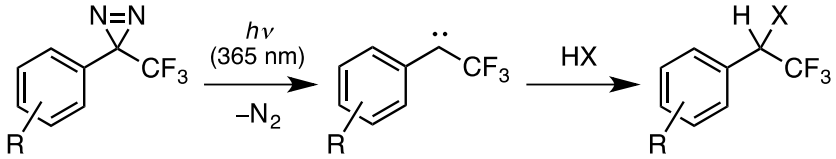
This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – Two types of azido-substituted aryltrifluoromethyldiazirine units have been designed and prepared for the divergent synthesis of photoaffinity probe (PAP) candidates. Using these azides, various aryltrifluoromethyldiazirine derivatives have been rendered easily synthesizable by several click reactions, as well as the Staudinger reduction affording the corresponding aniline. The triazole-conjugated aryltrifluoromethyldiazirine derivatives prepared in this study showed normal photoreactivity compared with those reported previously. These results indicate the utility of these azido-substituted aryltrifluoromethyldiazirine units for development of PAPs for target identification of bioactive compounds.

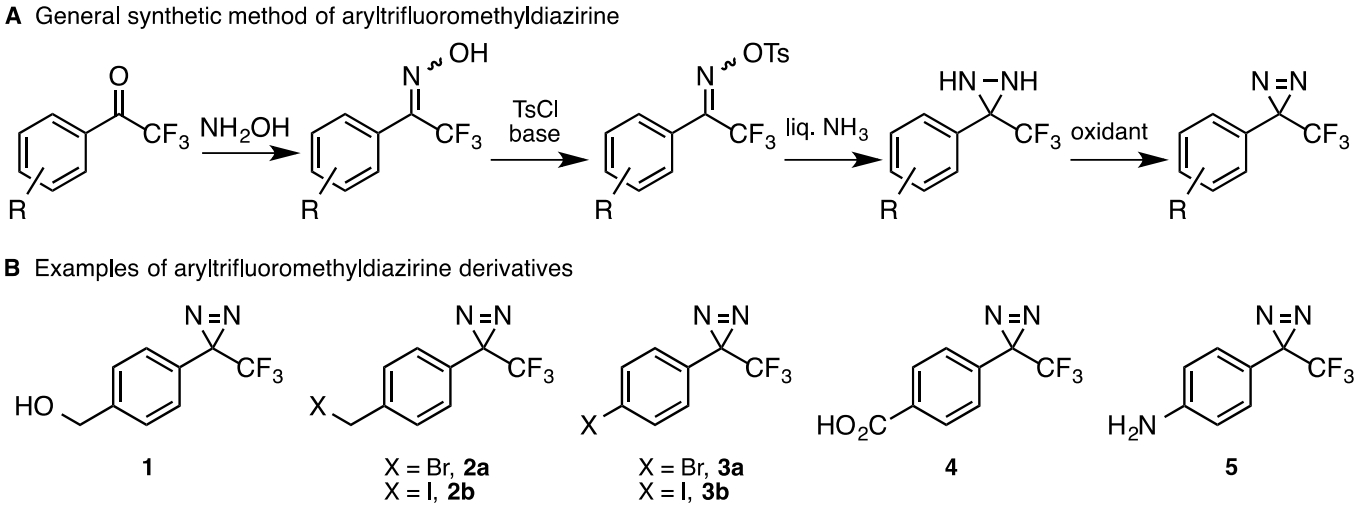
Photoaffinity labeling (PAL) is a suitable method for identifying target proteins and binding sites of bioactive compounds, providing valuable information for life science and drug discovery researches.[1] To implement a PAL study efficiently, designing and synthesizing an effective photoaffinity probe (PAP) is

one of the most critical issues. PAPs are usually derived from a bioactive compound by introducing a photoreactive functional group that enables covalent bond formation between the probe compound and its target proteins under photoirradiation. Aromatic azido, diazirinyl, diazo, and benzophenone groups are representative photoreactive groups used in PAL studies.[1] In particular, aryltrifluoromethyldiazirine derivatives are widely used as PAPs owing to the favorable photoreactive characters of the trifluoromethyldiazirinyl group. Carbene species that react with a variety of chemical bonds are generated by irradiation of the compounds under a long-wavelength (365 nm) ultraviolet (UV) light (Scheme 1).[2]



Scheme 1. Generation of carbene species from aryltrifluoromethyldiazirine by photoirradiation

Although aryltrifluoromethyldiazirine derivatives are very efficient for PAL studies, their syntheses are generally troublesome. They have been prepared from the corresponding 2,2,2-trifluoroacetophenone derivatives in a four-step sequence: oximation, *O*-tosylation, diaziridine ring formation by treatment with liquid ammonia, and oxidation (Scheme 2A).[2] To avoid this long-step transformation at the late stage of PAP synthesis, simple trifluoromethyldiazirinylbenzene derivatives bearing a connecting group, such as hydroxymethyl,[3] halomethyl,[3,4] halo,[5] carboxy,[6] and amino[7] groups, were prepared in advance and coupled with the main structure of bioactive compounds to afford the PAP candidates (Scheme 2B).[8]



Scheme 2. Synthetic method of aryltrifluoromethyldiazirines (**A**)
and their derivatives with a connecting group (**B**)

To prepare a diverse range of aryltrifluoromethyldiazirine-type PAP candidates more efficiently, simple trifluoromethyldiazirinylbenzene derivatives bearing a clickable group, such as azido and terminal alkyne groups, would serve as useful building blocks. Indeed, various bioactive compounds have been identified from screening assays of chemical libraries comprising 1,2,3-triazole derivatives prepared by click reactions between azides and alkynes that show high compatibility with a wide range of functional groups (Figure 1A).[9] The tolerance of diazirine derivatives under thermal,[10] acidic,[3b] and basic conditions,[11] as well as to transition metals,[12] has been demonstrated in previous studies; however, to the best of our knowledge, the compatibility of aryltrifluoromethyldiazirine derivatives to various transformations involving azido groups is left largely unexplored. Although the other groups along with us have developed several compact diazirine derivatives bearing azido or terminal alkyne groups as building blocks for PAP synthesis, the clickable groups were employed as a tag for the post-introduction of detectable functional groups in these cases.[13] Herein, we report that *p*-azido- and *p*-azidomethyl-substituted trifluoromethyldiazirinylbenzene **6** and **7** (Figure 1B) serve as common intermediates for the preparation of diverse aryltrifluoromethyldiazirine derivatives through the transformations of the azido groups.

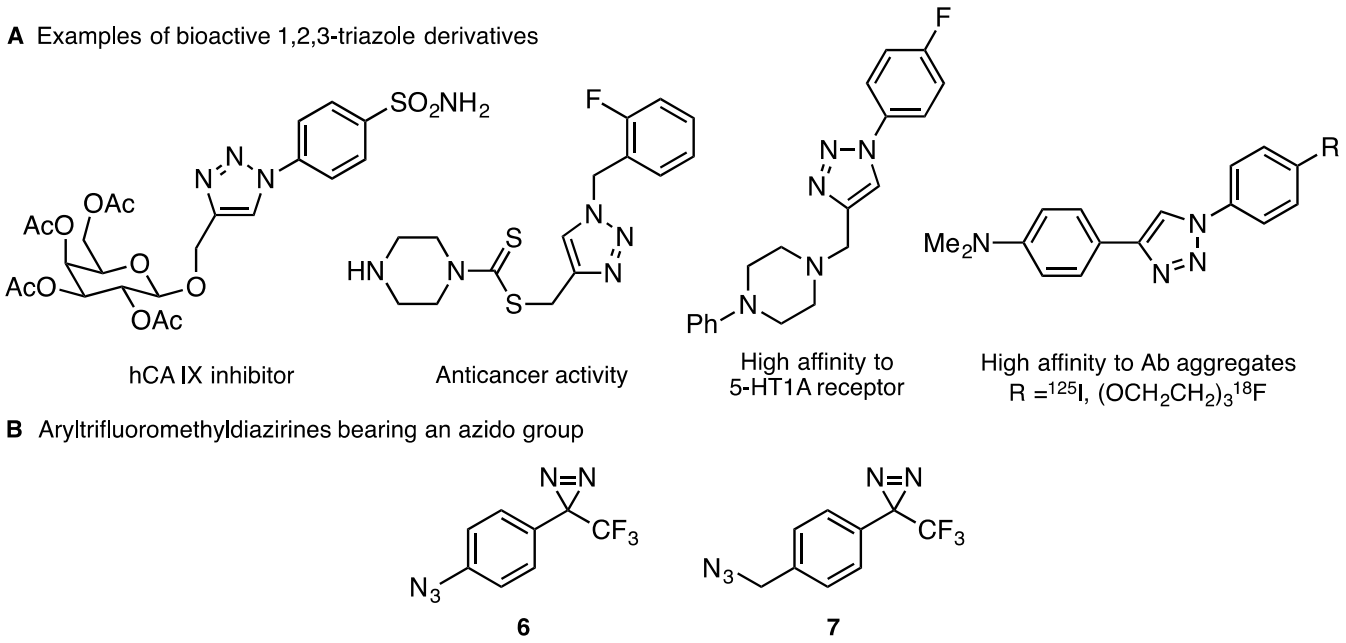
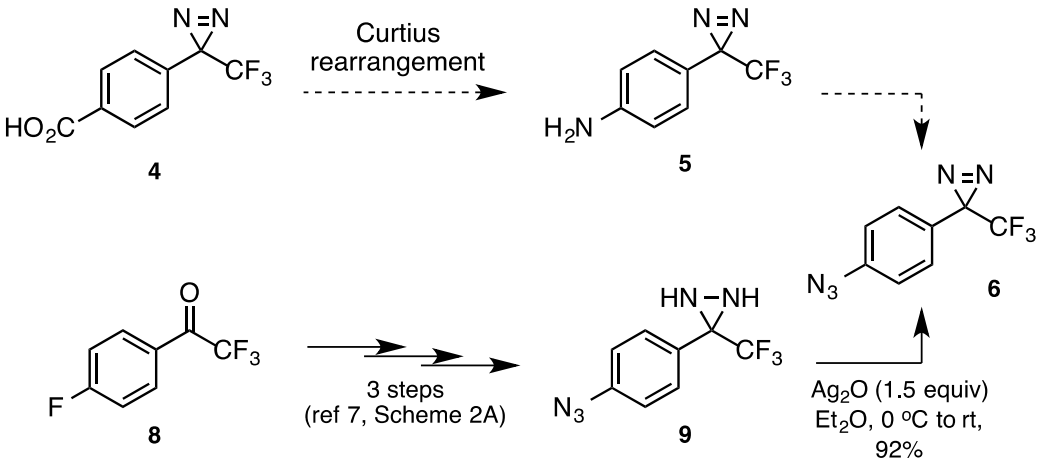


Figure 1. Reported bioactive 1,2,3-triazole derivatives prepared by click reaction (**A**) and azido-substituted aryltrifluoromethyldiazirines **6** and **7** investigated in this study (**B**)

The benzyl azide-type trifluoromethyldiazirine derivative **7**[14] was prepared from the corresponding benzyl alcohol **1** in 81% yield by a reported mesylation–azidation sequence[14b] under slightly modified conditions. Since the synthesis of phenyl azide-type **6** has not been reported, we initially attempted to prepare it

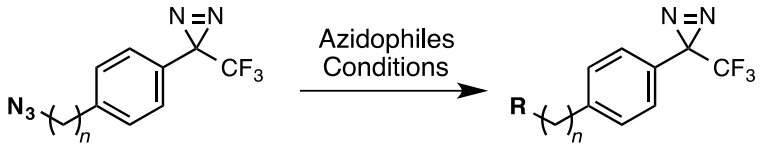
straightforwardly via the Curtius rearrangement of commercially available trifluoromethyldiazirinyl-benzoic acid **4**, followed by the azidation of the resulting aniline **5** (Scheme 3). However, the desired aniline **5** was not obtained under the typical conditions for the Curtius rearrangement. Although clean formation of the corresponding acyl azide by treating **4** with several azidation agents was observed,[15] heating it in the presence of water afforded a complex mixture. Thus, we changed the route to prepare the desired **6** by the oxidation of the corresponding diaziridine **9**, which was prepared according to the reported procedure.[7] The oxidation proceeded smoothly using silver(I) oxide to afford **6** in 91% yield.



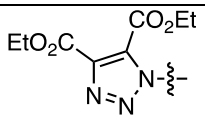
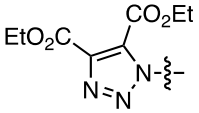
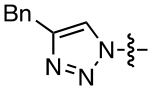
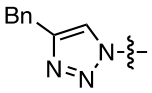
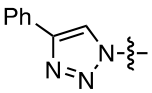
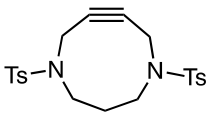
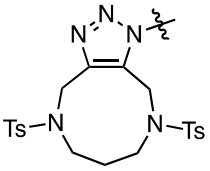
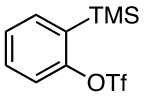
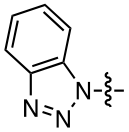
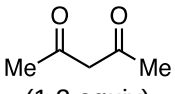
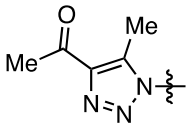
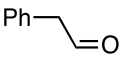
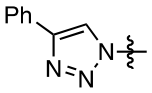
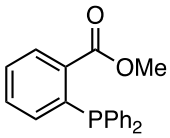
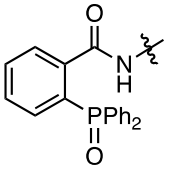
Scheme 3. Synthesis of *p*-azido-substituted trifluoromethyldiazirinylbenzene **6**

Using *p*-azido- and *p*-azidomethyl-substituted trifluoromethyldiazirinylbenzene **6** and **7**, we examined several click and related reactions with various azidophiles (Table 1). Initially, the Huisgen cycloaddition[16] of azide **6** with diethyl acetylenedicarboxylate was examined with heating the THF solution of the mixture at 85 °C.[17] Although a 61% conversion of **6** was observed after 4 h, the reaction afforded a complex mixture of uncharacterized byproducts, indicating that **6** had not tolerated the high-temperature heating conditions (entry 1). Performing the reaction at 50 °C with a large excess of diethyl acetylenedicarboxylate afforded a 76% yield to the cycloadduct **10** (entry 2). The copper-catalyzed azide-alkyne cycloaddition (CuAAC)[18] of **6** with 3-phenyl-1-propyne proceeded smoothly at room temperature to afford triazole **11** in high yield (entry 3). CuAAC of **7** with terminal alkynes also efficiently afforded triazoles **12** and **13** (entries 4 and 5). The strain-promoted azide-alkyne cycloaddition (SPAAC)[19] of azide **6** with *N,N'*-bis(*p*-toluenesulfonyl)-4,8-diazacyclononyne, which is a nine-membered alkyne developed by Tomooka and Igawa *et al.*,[20] proceeded smoothly to afford **14** in 75% yield (entry 6). In particular, benzyne, generated from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate using CsF,[21] reacted with azide **6** to afford benzotriazole **15** in 83% yield

Table 1. Reactions of azido-substituted aryltrifluoromethyldiazirines **6** and **7** with various azidophiles



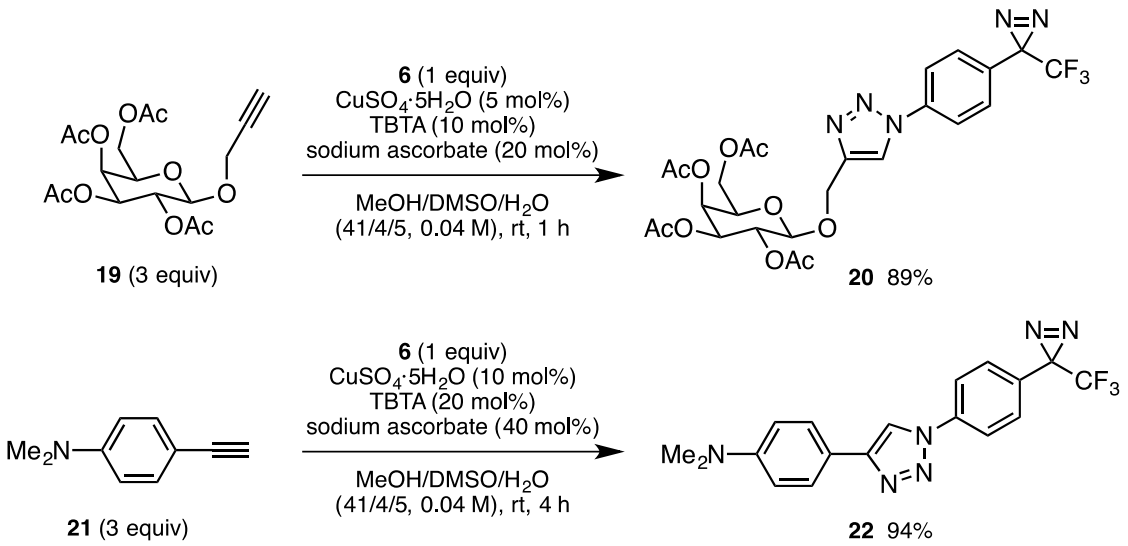
6 $n = 0$
7 $n = 1$

Entry	n	Azidophile	Conditions	R		Yield (%)[a]
1	0	EtO_2C—≡—CO_2Et (3 equiv)	THF (0.1 M) 85 °C, 4 h		**10**	0
2	0	EtO_2C—≡—CO_2Et (3 equiv)	neat 50 °C, 12 h		**10**	76
3	0	Bn—≡ (3 equiv)	$CuSO_4·5H_2O$ (5 mol%) TBTA[b] (10 mol%) sodium ascorbate (20 mol%) MeOH/DMSO/H_2O (41/4/5, 0.04 M) rt, 2 h		**11**	96
4	1	Bn—≡ (3 equiv)	$CuSO_4·5H_2O$ (5 mol%) TBTA[b] (10 mol%) sodium ascorbate (20 mol%) MeOH/DMSO/H_2O (41/4/5, 0.04 M) rt, 1 h		**12**	94
5	1	Ph—≡ (3 equiv)	$CuSO_4·5H_2O$ (5 mol%) TBTA[b] (10 mol%) sodium ascorbate (20 mol%) MeOH/DMSO/H_2O (41/4/5, 0.04 M) rt, 1 h		**13**	98
6	0	 (1.2 equiv)	MeCN/THF (2/1, 0.07 M) rt, 24 h		**14**	75
7	0	 (1.2 equiv)	CsF (2 equiv) MeCN (0.1 M) rt, 12 h		**15**	83
8	0	 (1.2 equiv)	K_2CO_3 (20 mol%) DMF (0.1 M) rt, 22 h		**16**	92
9	0	 (3 equiv)	DBU (10 mol%) DMSO (0.25 M) rt, 1 h		**17**	80
10	1	 (3 equiv)	$MeCN/H_2O$ (10/1, 0.05 M) rt, 2 h		**18**	95

[a] Isolated yields. [b] TBTA: Tris((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amine.

(entry 7). The generation of benzyne under the same conditions in the presence of benzotriazole **15** resulted in the quantitative recovery of **15**, suggesting that the diazirinyl group had tolerated a highly reactive benzyne. According to the previous reports,[20,21] the SPAAC using these alkynes with benzyl azide proceeds smoothly under the same conditions, indicating that the benzyl azide-type trifluoromethyldiazirine derivative **7** would be also applicable to these transformations. The base-catalyzed dehydrative annulation of **6** with acetylacetone under the conditions reported by Chiba *et al.*[22] afforded 1,4,5-trisubstituted triazole **16** in 92% yield leaving the diazirine group untouched (entry 8). A similar reaction catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), reported by Ramachary *et al.*,[23] was also applicable to the reaction of **6** with phenylacetaldehyde to afford triazole **17** in 80% yield (entry 9). In contrast to the SPAAC, these annulative transformation with alkyl azides typically requires heating,[23b] suggesting that the reaction with **7** would result in decomposition of the diazirine moiety. Moreover, the modified Staudinger reaction developed by Bertozzi *et al.*[19c,24] between **7** and methyl 2-(diphenylphosphanyl)benzoate proceeded smoothly to afford amide **18** in 95% yield (entry 10). In this case, using aryl azides such as **6** instead of **7** would be unsuitable because it was reported that formation of *O*-alkyl imidates instead of the desired amides predominantly proceeded.[24d] These results indicated that the click reactions and related transformations of azido-substituted aryltrifluoromethyldiazirines **6** and **7** would be suitable for the preparation of bioactive PAP candidates with highly functionalized structures.

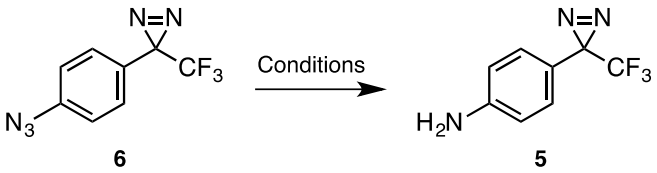
To demonstrate the utility of azido-substituted trifluoromethyldiazirinylbenzene derivatives as synthetic intermediates for PAP candidates, we prepared trifluoromethyldiazirinyl-substituted analogs of bioactive compounds containing a 1,2,3-triazole motif, as shown in Figure 1A. Thus, triazoles **20** and **22** were easily prepared in high yields by CuAAC between azide **6** and terminal alkyne **19** or **21** under standard conditions (Scheme 4).



Scheme 4. Synthesis of trifluoromethyldiazirinyl-substituted analogs of bioactive compounds by CuAAC of **6** with terminal alkynes

To expand the synthesizable aryltrifluoromethyldiazirine derivatives using azide **6**, we considered the corresponding aniline **5** serving as an efficient synthetic intermediate for various PAP candidates via the diverse transformations of the amino group. Indeed, the synthesis of aniline **5** had been achieved previously via the reduction of the azido group of diaziridine **9** followed by oxidation and was used to prepare a bioactive PAP.[7] To achieve the direct synthesis of aniline **5** through the selective reduction of the azido group in **6** while leaving the diazirine moiety untouched, we screened for the reduction conditions (Table 2). The use of typical reductants, such as lithium aluminum hydride (LAH) or triphenylphosphine (PPh_3), did not afford **5** at all (Table 2, entries 1 and 2). The desired **5** was observed when sodium borohydride ($NaBH_4$) was used, albeit in moderate yield (entry 3). We determined that the Staudinger reaction using tributylphosphine (P^nBu_3)[25] or its air-stable tetrafluoroborate salt[26] with triethylamine (Et_3N) afforded aniline **5** in superior yields (entries 4 and 5). Further optimization revealed that using a catalytic amount of Et_3N (10 mol%) afforded aniline **5** in 84% yield (entry 6). The selective reduction enabled the facile introduction of the diazirine group to various bioactive compounds, such as peptides, via an amide moiety. It should be noted that it is preferable to prepare **5** immediately before use because partial decomposition of **5** was observed during ^{13}C NMR analysis or storage in a freezer at −30 °C for a month.

Table 2. Optimization of the reduction conditions of azide **6** to aniline **5**



6 **5**

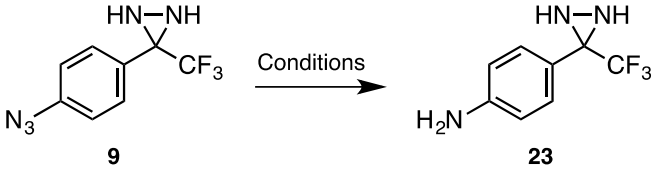
Entry	Conditions	Yield (%)
1	$LiAlH_4$ (1 equiv), THF (0.065 M), 0 °C, 2 h	0[a]
2	PPh_3 (1.5 equiv), THF/H_2O (6/5, 0.06 M), rt, 3 h	0[a]
3	$NaBH_4$ (1.5 equiv), EtOH (0.2 M), rt, 7 h	54[a]
4	P^nBu_3 (1.2 equiv), THF/H_2O (10/1, 0.09 M), rt, 30 min	69[a]
5	P^nBu_3·HBF_4 (1.2 equiv), Et_3N (1.2 equiv), THF/H_2O (10/1, 0.2 M), rt, 30 min	69[b]
6	P^nBu_3·HBF_4 (1.1 equiv), Et_3N (10 mol%), THF/H_2O (10/1, 0.2 M), rt, 30 min	84[b]

[a] ^1H NMR yields using CH_2Br_2 as an internal standard. [b] Isolated yields.

We also examined in detail the reduction of the azido group in diaziridine **9** to afford aniline **23** (Table 3), which had been achieved previously using LAH as the reductant (entry 1).[7] Although the Staudinger reduction using PPh_3 afforded only robust aza-ylide **24** that could not transform into aniline **23** under the conditions (entry 2), the treatment of **9** with P^nBu_3 smoothly afforded the desired **23** in 93% yield (entry 3). When the tetrafluoroborate salt of P^nBu_3 with the catalytic amount of Et_3N was employed, the reduction of the azido group and ring-opening of the diaziridine moiety occurred simultaneously to afford

25, indicating the susceptibility of the diaziridine moiety to acid (entry 4). Similar to the case for the reduction of the azido group in diazirine **6**, the use of $NaBH_4$ afforded the product albeit in moderate yields (entries 5 and 6). In addition, the hydrogenation of **9** in the presence of palladium–charcoal afforded the over-reduced product **26** via the cleavage of the C−N bonds (entry 7).

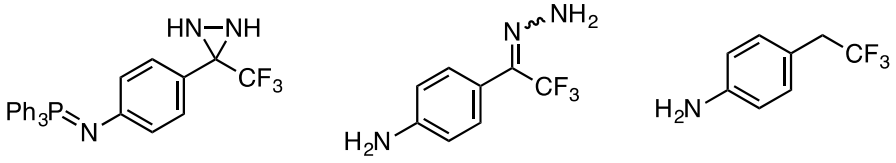
Table 3. Optimization of the reduction conditions of azide **9** to aniline **23**



9 **23**

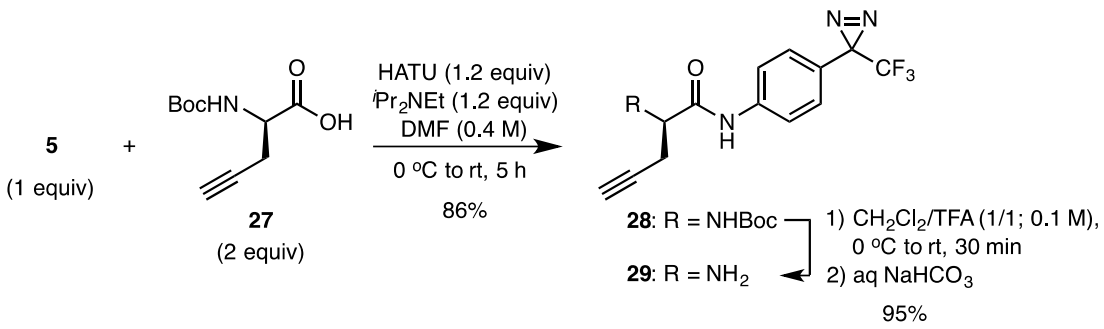
Entry	Conditions	Yield (%)[a]
1	$LiAlH_4$ (1 equiv), THF (0.065 M), 0 °C, 2 h	70[b]
2	PPh_3 (1.5 equiv), THF/H_2O (6/5, 0.06 M), rt, 3 h	0
3	P^{n}Bu$_3$ (2 equiv), THF/H_2O (10/1, 0.18 M), rt, 12 h	93
4	P^{n}Bu$_3$·HBF_4 (1.1 equiv), Et_3N (10 mol%), THF/H_2O (10/1, 0.09 M), rt, 30 min	0
5	$NaBH_4$ (1.5 equiv), EtOH (0.2 M), rt, 7 h	50
6	$NaBH_4$ (2 equiv), LiCl (2 equiv), DME (0.1 M), rt, 26 h	33
7	H_2 (1 atm), Pd/C (wet, 20 mol%), EtOH (0.1 M), rt, 3 h	0

[a] Isolated yields. [b] The yield reported in ref. 7.



24 **25** **26**

Conjugation of trifluoromethyldiazirinylaniline **5** with *N*-Boc-protected propargyl glycine **27** using 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU)[27] as the coupling reagent afforded amide **28** in high yield (Scheme 5). The subsequent treatment of **28** with trifluoroacetic acid (TFA) quantitatively afforded the deprotected amine **29**. This compound would serve as a useful unit for PAP synthesis because it bears three functional groups; a photoreactive



Scheme 5. Derivatization of aniline **5** to trifunctional unit **29**

trifluoromethyldiazirinyl group, an amino group that can be connected to a bioactive compound, and a clickable terminal alkyne moiety, where a detectable tag can be installed after the formation of a covalent bond with a target protein.

Finally, the photoreactivity of aryltrifluoromethyldiazirine derivatives **11** and **13** that contain 1,2,3-triazole structure was examined (Figure 2). A 1 mM solution of **11** or **13** dissolved in methanol-d_4 was placed in a quartz NMR tube and was irradiated with 365 nm of UV light (light source, SLUV-4) at room temperature. The time course of the consumption of diazirine **11** or **13** and formation of methanol-d_4 adduct **11′** or **13′** were monitored by ^{19}F NMR spectroscopy (Figure 2A). Authentic samples for **11′** and **13′** were efficiently prepared by heating a methanol-d_4 solution of **11** and **13**, respectively (Figure 2B). Similar to the photoreaction of the aryltrifluoromethyldiazirine derivatives reported previously,[28] the clean consumption of both substrates **11** and **13** accompanied with the gradual formation of methanol-d_4

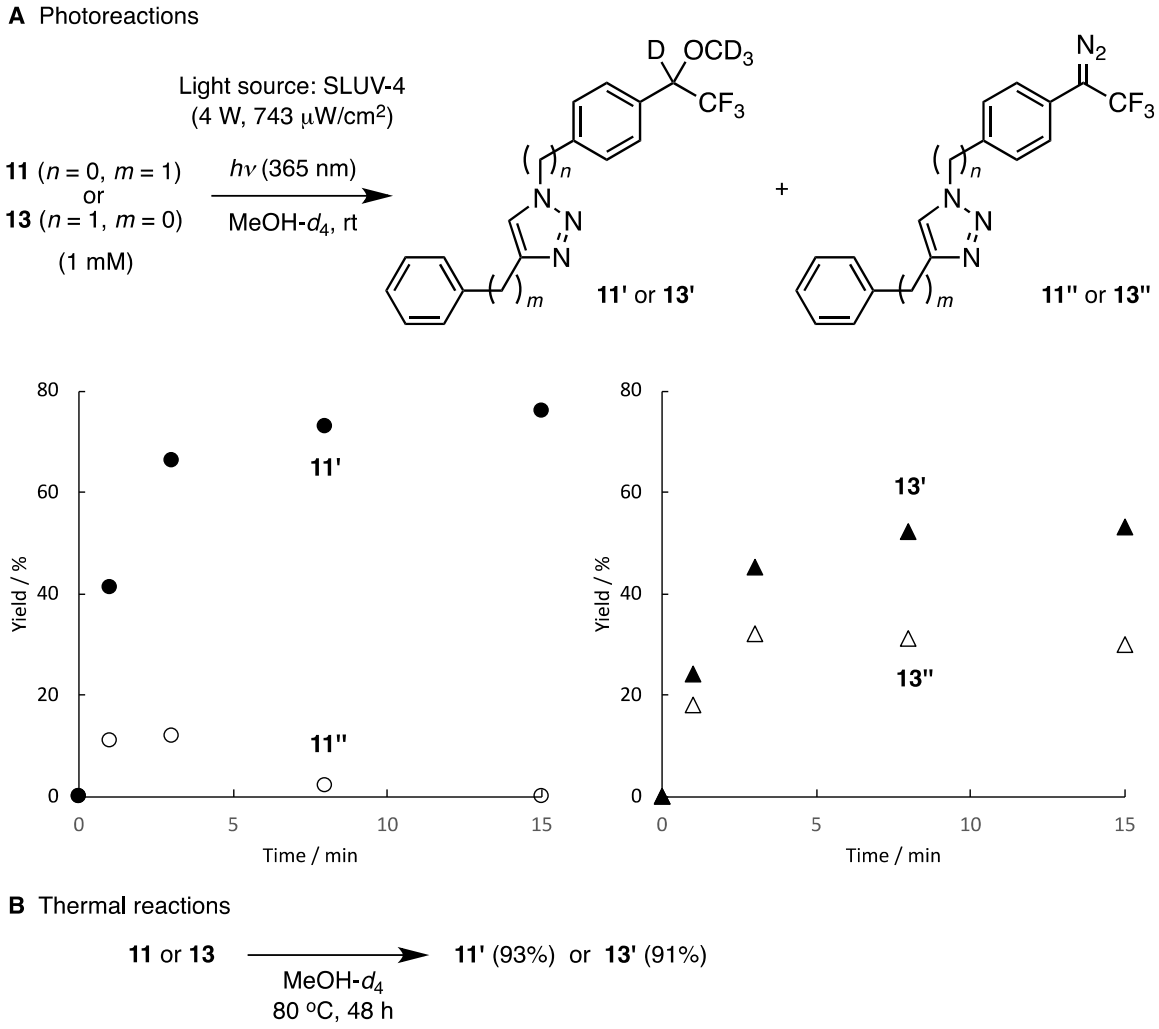


Figure 2. Photo (**A**) and thermal (**B**) reactions of diazirines **11** and **13** in methanol-d_4

adducts **11′** and **13′**, respectively, within 15 min was observed. Interestingly, while the initially formed linear diazo compound **11′′** was also converted to **11′**, resulting in the high overall conversion of **11** to **11′**, a certain amount of linear diazo compound **13′′** remained under the same conditions and only a partial conversion of **13′′** to **13′** was observed. Currently, it is difficult to rationalize the difference between the photoreactivities of **11** and **13**.

In summary, we have demonstrated that azido-substituted aryltrifluoromethyldiazirines are promising intermediates for the divergent synthesis of PAP candidates using click reactions. The trifluoromethyldiazirinyl group tolerated various transformations involving the azido group, including CuAAC, SPAAC, cycloaddition with benzyne and enolates, and modified Staudinger ligation. The reduction of the azido group was achieved by the Staudinger reduction using tributylphosphine to efficiently afford the aniline derivative, which also serves as a useful intermediate for PAP synthesis. The photoreactive study of aryltrifluoromethyldiazirines that contained triazole structures indicated that these types of compounds show usual photoreactivity that is applicable to PAL experiments.

EXPERIMENTAL

All reactions were performed under argon atmosphere unless otherwise indicated. All manipulations of air- and/or moisture-sensitive compounds were performed either using standard Schlenk techniques or in a MIWA DBO-1KH-NYWS glovebox under an atmosphere of argon. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck, Merck Silica Gel 60 F_{254}). Column chromatography was conducted on a YAMAZEN Automated Flash Chromatography System that consists of AI-580 and Parallel Frac FR-360 with silica-gel-packed column (Biotage Zip cartridge). Melting points (mp) were measured with an OptiMelt automated melting point apparatus (Stanford Research Systems, Inc.) and were uncorrected. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (373 MHz) and ^{31}P NMR (161 MHz) spectra were obtained from measurements at ambient temperature on a JEOL AS400 or a JEOL 400SS spectrometers. Chloroform-d_1 ($CDCl_3$) containing 0.05% tetramethylsilane (TMS) (99.8%D, Cambridge Isotope Laboratories, Inc.), methanol-d_4 (CD_3OD, 99.8%D, Merck, Inc.), and dimethyl sulfoxide-d_6 (DMSO-d_6, 99.9%D, Cambridge Isotope Laboratories, Inc.) were used as solvents for NMR measurements at room temperature. Chemical shifts (δ) for ^{1}H NMR are given in parts per million (ppm) downfield from signal of residual $CHCl_3$ (δ 7.26 ppm), methanol (δ 3.31 ppm), and DMSO (δ 2.50 ppm) as internal standards with coupling constants (*J*) in hertz (Hz). Chemical shifts (δ) for ^{13}C NMR are given in parts per million (ppm) downfield from signal of residual $CDCl_3$ (δ 77.2 ppm) and dimethylsulfoxide-d_6 (δ 39.5 ppm) as internal standards with coupling constants (*J*) in hertz (Hz). Chemical shifts (δ) for ^{19}F NMR are given in parts per million (ppm) downfield from signal of α,α,α-trifluorotoluene (δ −62.6 ppm in $CDCl_3$, δ −64.1 ppm in CD_3OD, and δ −61.3 ppm in

DMSO-d_6) as an external standard. Chemical shifts (δ) for ^{31}P NMR are given in parts per million (ppm) downfield from signal of triphenylphosphine (δ −4.8 ppm in $CDCl_3$) as an external standard. 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 with the absorption band given in cm^{-1}. High-resolution mass spectra (HRMS) were measured on a Thermo Fisher Scientific Exactive^{TM} Plus Orbitrap mass spectrometer under positive (ESI^+) conditions. 3-(4-Azidophenyl)-3-(trifluoromethyl)diaziridine (**9**),[7] 2-(diphenylphosphanyl)benzoic acid,[29] and (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**19**)[30] were synthesized according to the literatures. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

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

3-(4-Azidophenyl)-3-(trifluoromethyl)-3*H*-diazirine (6) (Scheme 3)

To a 200 mL round-bottom flask equipped with a magnetic stir bar and charged with 3-(4-azidophenyl)-3-(trifluoromethyl)diaziridine **9** (1.15 g, 5.02 mmol, 1 equiv) and Et_2O (40 mL) was added silver(I) oxide (1.74 g, 7.51 mmol, 1.5 equiv) at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 h. After completion of the reaction as judged from the TLC analysis, the mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 10:1) to give **6** (1.04 g, 4.58 mmol, 91.2%) as a colorless oil; TLC R_f = 0.58 (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.02–7.06 (AA′BB′, 2H), 7.17–7.20 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2 (q, $^2J_{C–F}$ = 40.3 Hz, 1C), 119.5 (2C), 122.0 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 125.5 (1C), 128.2 (2C), 141.8 (1C); ^{19}F NMR ($CDCl_3$) δ −65.3 (s); IR (ZnSe, cm^{-1}) 937, 1150, 1184, 1233, 1298, 1344, 1512, 1612, 2095, 2129; HRMS (ESI^+) *m*/*z* 228.0489 (228.0492 calcd for $C_8H_5F_3N_5^+$, $[M+H]^+$).

3-(4-(Azidomethyl)phenyl)-3-(trifluoromethyl)-3*H*-diazirine (7)

This compound was synthesized according to the reported procedure with a minor modification.[14b]

To a 100 mL round-bottom flask equipped with a magnetic stir bar and charged with (4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)methanol (**1**) (1.08 g, 5.00 mmol, 1 equiv), Et_2O (40 mL), and triethylamine (1.74 mL, 12.5 mmol, 2.5 equiv) was dropwise added methanesulfonyl chloride (776 μL, 10.0 mmol, 2 equiv) at 0 °C. The mixture was warmed up to room temperature and stirred for 20 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added brine (ca. 50 mL) and extracted with CH_2Cl_2 (ca. 50 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue containing

4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzyl methanesulfonate was directly used in the next reaction.

To a 100 mL round-bottom flask equipped with a magnetic stir bar and charged with a solution of the crude 4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzyl methanesulfonate (ca. 1.5 g) in DMF (10 mL) and tetrabutylammonium iodide (185 mg, 0.501 mmol, 10 mol%) was added sodium azide (358 mg, 5.51 mmol, 1.1 equiv) at 0 °C. The mixture was warmed up to room temperature and stirred for 5 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added brine (ca. 50 mL) and extracted with EtOAc (ca. 50 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 10:1) to give **7** (972 mg, 4.03 mmol, 80.7%) as a colorless oil; TLC R_f = 0.60 (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 4.37 (s, 2H), 7.20–7.23 (AA′BB′, 2H), 7.35–7.37 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3 (q, $^2J_{C–F}$ = 40.3 Hz, 1C), 54.1 (1C), 122.1 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 127.0 (2C), 128.5 (2C), 129.2 (1C), 137.2 (1C); ^{19}F NMR ($CDCl_3$) δ −65.1 (s). The chemical shifts were consistent with those reported in the literature.[14a]

3-(4-(4,5-Bis(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-3-(trifluoromethyl)-3*H*-diazirin-1-ium (10) (Table 1, entry 2)

To a capped 4 mL vial equipped with a magnetic stir bar were added **6** (90.8 mg, 0.400 mmol, 1 equiv) and diethyl acetylenedicarboxylate (191 μL, 1.20 mmol, 3 equiv). The mixture was stirred with heating at 50 °C for 12 h. After completion of the reaction as judged from the TLC analysis, the mixture was cooled to room temperature, diluted with hexane (ca. 2 mL), and subjected to silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 1:1) to give **10** (121 mg, 0.305 mmol, 76.2%) as a colorless solid (mp 47–48 °C); TLC R_f = 0.42 (*n*-hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$) δ 1.29 (t, $J_{H–H}$ = 3.2 Hz, 3H), 1.43 (t, $J_{H–H}$ = 3.2 Hz, 3H), 4.39 (q, $J_{H–H}$ = 3.2 Hz, 2H), 4.47 (q, $J_{H–H}$ = 3.2 Hz, 2H), 7.37–7.40 (AA′BB′, 2H), 7.61–7.64 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 1□□□□(1C), 14.2 (1C), 28.2 (q, $^2J_{C–F}$ = 41.2 Hz, 1C), 62.1 (1C), 63.6 (1C), 121.9 (q, $^1J_{C–F}$ = 275.9 Hz, 1C), 124.5 (2C), 127.8 (2C), 131.6 (1C), 132.4 (1C), 136.6 (1C), 139.4 (1C), 158.8 (1C), 159.6 (1C); ^{19}F NMR ($CDCl_3$) δ −64.9 (s); IR (ZnSe, cm^{-1}) 829, 939, 1084, 1182, 1153, 1344, 1522, 1732, 2987; HRMS (ESI^+) *m*/*z* 398.1071 (398.1071 calcd for $C_{16}H_{15}F_3N_5O_4^+$, $[M+H]^+$).

4-Benzyl-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1*H*-1,2,3-triazole (11) (Table 1, entry 3)

To a 50 mL round-bottom flask equipped with a magnetic stir bar were sequentially added a solution of TBTA (26.5 mg, 49.9 μmol, 10 mol%) in DMSO (1 mL), a solution of copper(II) sulfate pentahydrate (6.2 mg, 25 μmol, 5 mol%) in water (0.25 mL), MeOH (10 mL), L-ascorbic acid sodium salt (19.8 mg, 99.9 μmol, 20 mol%) in water (1 mL), 3-phenyl-1-propyne (185 μL, 1.50 mmol, 3 equiv), and a solution of **6** (114 mg, 0.502 mmol, 1 equiv) in MeOH (0.25 mL). The mixture was stirred at room temperature for 2 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added water (ca.

30 mL) and extracted with EtOAc (ca. 30 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 1:1) to give **11** (165 mg, 0.481 mmol, 95.8%) as a colorless solid (mp 82–84 °C); TLC R_f = 0.53 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 4.17 (s, 2H), 7.23–7.27 (m, 1H), 7.29–7.35 (m, 6H), 7.61 (s, 1H), 7.73–7.76 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2 (q, $^2J_{C–F}$ = 40.3 Hz, 1C), 32.3 (1C), 119.4 (1C), 120.4 (2C), 121.9 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 126.7 (1C), 127.99 (1C), 128.01 (1C), 128.8 (2C + 2C), 129.2 (1C), 137.9 (1C), 138.6 (1C), 149.0 (1C); ^{19}F NMR ($CDCl_3$) δ −65.0 (s); IR (ZnSe, cm^{-1}) 1049, 1153, 1180, 1234, 1346, 1526, 1614, 3134; HRMS (ESI^+) *m*/*z* 344.1115 (344.1118 calcd for $C_{17}H_{13}F_3N_5^+$, $[M+H]^+$).

4-Benzyl-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzyl)-1*H*-1,2,3-triazole (12) (Table 1, entry 4)

This compound was synthesized according to the procedure for **11** using **7** (121 mg, 0.502 mmol, 1 equiv) and 3-phenyl-1-propyne (185 μL, 1.50 mmol, 3 equiv) with stirring for 1 h; Yield: 93.7% (168 mg, 0.470 mmol); Colorless solid (mp 108–110 °C); Eluent for column chromatographic purification: *n*-hexane:EtOAc = 2:1; TLC R_f = 0.54 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 2H), 5.46 (s, 2H), 7.08 (s, 1H), 7.15–7.17 (AA′BB′, 2H), 7.21–7.30 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 28.1 (q, $^2J_{C–F}$ = 41.2 Hz, 1C), 32.2 (1C), 53.2 (1C), 121.4 (1C), 121.9 (q, $^1J_{C–F}$ = 273.4 Hz, 1C), 126.0 (1C), 127.06 (1C), 127.08 (1C), 128.2 (2C), 128.5 (2C), 128.6 (2C), 129.5 (1C), 136.6 (1C), 138.8 (1C), 148.2 (1C); ^{19}F NMR ($CDCl_3$) δ −65.1 (s); IR (ZnSe, cm^{-1}) 1049, 1152, 1193, 1342, 1454, 1519, 1614, 3126; HRMS (ESI^+) *m*/*z* 358.1274 (358.1274 calcd for $C_{18}H_{15}F_3N_5^+$, $[M+H]^+$).

4-Phenyl-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzyl)-1*H*-1,2,3-triazole (13) (Table 1, entry 5)

This compound was synthesized according to the procedure for **11** using **7** (121 mg, 0.502 mmol, 1 equiv) and phenylacetylene (185 μL, 1.50 mmol, 3 equiv) with stirring for 1 h; Yield: 97.5% (168 mg, 0.489 mmol); Colorless solid (mp 115–117 °C); Eluent for column chromatographic purification: *n*-hexane:EtOAc = 1:1; TLC R_f = 0.53 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 5.60 (s, 2H), 7.20–7.23 (AA′BB′, 2H), 7.31–7.35 (m, 3H), 7.41–7.43 (m, 2H), 7.67 (s, 1H), 7.78–7.81 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2 (q, $^2J_{C–F}$ = 41.2 Hz, 1C), 53.5 (1C), 119.5 (1C), 122.0 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 125.7 (2C), 127.3 (2C), 128.3 (1C), 128.29 (1C), 128.31 (1C), 128.8 (2C), 129.7 (1C), 130.3 (1C), 136.4 (1C), 148.5 (1C); ^{19}F NMR ($CDCl_3$) δ −65.1 (s); IR (ZnSe, cm^{-1}) 937, 1051, 1082, 1148, 1177, 1227, 1342, 1611, 3090; HRMS (ESI^+) *m*/*z* 344.1120 (344.1118 calcd for $C_{17}H_{13}F_3N_5^+$, $[M+H]^+$).

5,9-Di(*p*-toluenesulfonyl)-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1,4,5,6,7,8,9,10-octahydro[1,2,3]triazolo[4,5-*g*][1,5]diazonine (14) (Table 1, entry 6)

To a capped 4 mL vial equipped with a magnetic stir bar were added **6** (45.4 mg, 0.200 mmol, 1 equiv), MeCN (2 mL), THF (1 mL), and *N*,*N*-di(*p*-toluenesulfonyl)-4,8-diazacyclononyne (104 mg, 0.240 mmol, 1.2 equiv). The mixture was stirred at room temperature for 24 h. After completion of the reaction as

judged from the TLC analysis, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:1 to 0:1) to give **14** (98.8 mg, 0.150 mmol, 74.9%) as a colorless solid (decomposed at 119 °C); TLC R_f = 0.48 (*n*-hexane:EtOAc = 1:1); ^{1}H NMR ($CDCl_3$) δ 2.04–2.07 (m, 2H), 2.42 (s, 3H), 2.47 (s, 3H), 3.20 (t, $J_{H–H}$ = 5.6 Hz, 2H), 3.43 (t, $J_{H–H}$ = 5.6 Hz, 2H), 4.43 (s, 2H), 4.49 (s, 2H), 7.20 (s, 2H + 2H), 7.36–7.39 (AA′BB′, 2H), 7.42–7.45 (AA′BB′, 2H), 7.56–7.59 (AA′BB′, 2H), 7.73–7.76 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4 (1C), 21.5 (1C), 28.2 (q, $^2J_{C–F}$ = 41.2 Hz, 1C), 30.4 (1C), 43.1 (1C), 47.3 (1C), 49.2 (1C), 49.8 (1C), 121.9 (q, $^1J_{C–F}$ = 273.4 Hz, 1C), 126.7 (2C), 127.0 (2C), 127.60 (2C), 127.64 (2C), 129.8 (2C), 129.9 (2C), 130.7 (1C), 131.7 (1C), 133.3 (1C), 134.4 (1C), 137.1 (1C), 143.1 (1C), 144.1 (1C),144.2 (1C); ^{19}F NMR ($CDCl_3$) δ −64.9 (s); IR (ZnSe, cm^{-1}) 763, 814, 1090, 1153, 1339, 1454, 1524, 2926; HRMS (ESI^+) *m*/*z* 660.1669 (660.1669 calcd for $C_{29}H_{29}F_3N_7O_4S_2^+$, $[M+H]^+$).

1-(4-(3-(Trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1*H*-benzo[*d*][1,2,3]triazole (15) (Table 1, entry 7)

To a capped 4 mL vial equipped with a magnetic stir bar were added **6** (68.1 mg, 0.300 mmol, 1 equiv), MeCN (2 mL), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (87.3 μL, 0.359 mmol, 1.2 equiv), and cesium fluoride (91.4 mg, 0.601 mmol, 2 equiv) in a glovebox. The mixture was stirred at room temperature for 12 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added brine (ca. 10 mL) and extracted with EtOAc (ca. 10 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 1:1) to give **15** (85.0 mg, 0.247 mmol, 82.5%) as a colorless solid (mp 112–114 °C); TLC R_f = 0.55 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 7.44–7.48 (m, 3H), 7.59 (dd, $J_{H–H}$ = 8.8, 8.0 Hz, 1H), 7.74 (d, $J_{H–H}$ = 8.0 Hz, 1H), 7.86–7.90 (AA′BB′, 2H), 8.16 (d, $J_{H–H}$ = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (q, $^2J_{C–F}$ = 40.4 Hz, 1C), 110.1 (1C), 120.6 (1C), 121.9 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 122.7 (2C), 124.7 (1C), 128.1 (2C), 128.7 (1C), 129.3 (1C), 131.9 (1C), 138.1 (1C), 146.7 (1C); ^{19}F NMR ($CDCl_3$) δ −65.0 (s); IR (ZnSe, cm^{-1}) 937, 1041, 1153, 1180, 1192, 1225, 1342, 1524, 1618, 3123; HRMS (ESI^+) *m*/*z* 304.0807 (304.0805 calcd for $C_{14}H_9F_3N_5^+$, $[M+H]^+$).

1-(5-Methyl-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-one (16) (Table 1, entry 8)

To a capped 10 mL vial equipped with a magnetic stir bar were added **6** (113 mg, 0.497 mmol, 1 equiv), DMF (5.0 mL), acetylacetone (0.06 mL, 0.6 mmol, 1.2 equiv), and potassium carbonate (13.9 mg, 0.101 mmol, 20 mol%). The mixture was stirred at room temperature for 22 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added water (ca. 5 mL) and extracted with EtOAc (ca. 5 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was

concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 0:1) to give **16** (141 mg, 0.456 mmol, 91.6%) as a colorless solid (mp 85–87 °C); TLC R_f = 0.40 (*n*-hexane:EtOAc = 4:1); ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 2.76 (s, 3H), 7.41–7.44 (AA′BB′, 2H), 7.53–7.56 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 10.1 (1C), 27.8 (1C), 28.2 (q, $^2J_{C–F}$ = 41.2 Hz, 1C), 121.8 (q, $^1J_{C–F}$ = 274.1 Hz, 1C), 125.5 (2C), 127.9 (2C), 131.0 (1C), 136.3 (1C), 137.3 (1C), 143.8 (1C), 194.1 (1C); ^{19}F NMR ($CDCl_3$) δ −64.9 (s); IR (ZnSe, cm^{-1}) 756, 827, 937, 1144, 1163, 1182, 1229, 1344, 1414, 1520, 1680; HRMS (ESI$^+$) *m*/*z* 310.0910 (310.0910 calcd for $C_{13}H_{11}F_3N_5O^+$, $[M+H]^+$).

4-Phenyl-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1*H*-1,2,3-triazole (17) (Table 1, entry 9)

To a capped 4 mL vial equipped with a magnetic stir bar were added **6** (114 mg, 0.502 mmol, 1 equiv), DMSO (2 mL), phenylacetaldehyde (181 mg, 0.502 mmol, 3 equiv), and DBU (7.5 μL, 50 μmol, 10 mol%). The mixture was stirred at room temperature for 1 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added brine (ca. 10 mL) and extracted with CH_2Cl_2 (ca. 10 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:1 to 0:1) to give **17** (132 mg, 0.401 mmol, 79.9%) as a colorless solid (decomposed at 126 °C); TLC R_f = 0.64 (*n*-hexane:EtOAc = 4:1); ^{1}H NMR (DMSO-d_6) δ 7.37–7.41 (AA′BB′C, 1H), 7.48–7.52 (AA′BB′C, 2H), 7.56–7.59 (AA′BB′C, 2H), 7.93–7.95 (AA′BB′, 2H), 8.10–8.12 (AA′BB′, 2H), 9.37 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 119.7 (1C), 120.6 (2C), 121.7 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 125.4 (2C), 127.5 (1C), 128.4 (2C+1C), 129.0 (2C), 129.9 (1C), 137.7 (1C), 147.5 (1C) (one quaternary carbons was not observed due to low solubility of the sample); ^{19}F NMR (DMSO-d_6) δ −64.5 (s); IR (ZnSe, cm^{-1}) 937, 1041, 1153, 1180, 1192, 1225, 1342, 1524, 1618, 3123; HRMS (ESI$^+$) *m*/*z* 330.0959 (330.0961 calcd for $C_{16}H_{11}F_3N_5^+$, $[M+H]^+$).

2-(Diphenylphosphoryl)-*N*-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzyl)benzamide (18) (Table 1, entry 10)

To a capped 50 mL round-bottom flask equipped with a magnetic stir bar were added **7** (72.4 mg, 0.300 mmol, 1 equiv), MeCN (9 mL), water (1 mL), and methyl 2-(diphenylphosphanyl)benzoate (275 mg, 0.899 mmol, 3 equiv). The mixture was stirred at room temperature for 2 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added water (ca. 10 mL) and extracted with EtOAc (ca. 10 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 2:1 to 0:1) to give **18** (148 mg, 0.285 mmol, 94.9%) as a colorless solid (mp 51–53 °C); TLC R_f = 0.35 (*n*-hexane:EtOAc = 1:2); ^{1}H NMR ($CDCl_3$) δ 4.12 (d, $J_{H–H}$ = 5.6 Hz, 2H), 6.99–7.05 (m, 3H), 7.19–7.21 (AA′BB′, 2H), 7.36–7.40 (AA′BB′C, 1H), 7.44–7.47 (m, 4H), 7.55–7.60 (m, 6H), 7.62–7.66 (AA′BB′C, 1H), 8.06 (ddd, $J_{H–H}$ = 4.8, 0.8 Hz, $J_{H–P}$ = 4.0 Hz, 1H), 9.40 (t, $J_{H–H}$

= 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (q, $^2J_{C–F}$ = 40.3 Hz, 1C), 43.4 (1C), 122.1 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 126.52 (1C), 126.54 (1C) , 127.6 (1C), 128.3 (2C), 128.6 (2C), 128.8 (2C), 129.0 (d, $J_{C–P}$ = 98.7 Hz, 1C), 129.9 (d, $J_{C–P}$ = 12.3 Hz, 1C), 130.9 (d, $J_{C–P}$ = 105.3 Hz, 2C), 131.6 (d, $J_{C–P}$ = 9.9 Hz, 4C), 132.0 (d, $J_{C–P}$ = 9.1 Hz, 1C), 132.34 (1C), 132.37 (1C), 132.6 (d, $J_{C–P}$ = 2.5 Hz, 1C), 133.3 (d, $J_{C–P}$ = 12.4 Hz, 1C), 139.6 (1C), 140.7 (d, $J_{C–P}$ = 7.4 Hz, 1C), 167.3 (d, $J_{C–P}$ = 3.3 Hz, 1C); ^{19}F NMR ($CDCl_3$) δ −65.1 (s); ^{31}P NMR ($CDCl_3$) δ 36.7 (1P); IR (ZnSe, cm^{-1}) 937, 1152, 1233, 1306, 1344, 1437, 1537, 1651, 3057; HRMS (ESI^+) *m*/*z* 542.1216 (542.1216 calcd for $C_{28}H_{21}F_3N_3NaO_2P^+$, $[M+Na]^+$).

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (20) (Scheme 4)

This compound was synthesized according to the procedure for **11** using **6** (114 mg, 0.502 mmol, 1 equiv) and alkyne **19** (580 mg, 1.50 mmol, 3 equiv) with stirring for 1 h; Yield: 89.0% (274 mg, 0.447 mmol); colorless solid (decomposed at 121 °C); Eluent for column chromatographic purification: *n*-hexane:EtOAc = 1:1 to 0:1; TLC R_f = 0.44 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 2.16 (s, 3H), 3.97 (td, $J_{H–H}$ = 6.4, 0.8 Hz, 1H), 4.13–4.23 (m, 2H), 4.70 (d, $J_{H–H}$ = 8.0 Hz, 1H), 4.90 (d, $J_{H–H}$ = 12.8 Hz, 1H), 5.03–5.08 (m, 2H), 5.26 (dd, $J_{H–H}$ = 10.8, 8.0 Hz, 1H), 5.42 (dd, $J_{H–H}$ = 3.6, 0.8 Hz, 1H), 7.37–7.39 (AA′BB′, 2H), 7.80–7.82 (AA′BB′, 2H), 7.99 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.5 (1C), 20.58 (1C), 20.60 (1C), 20.7 (1C), 28.1 (q, $^2J_{C–F}$ = 41.2 Hz, 1C), 61.3 (1C), 62.9 (1C), 67.0 (1C), 68.8 (1C), 70.7 (1C), 70.9 (1C), 100.7 (1C), 120.5 (2C), 120.6 (1C), 121.9 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 128.1 (2C), 129.6 (1C), 137.7 (1C), 145.5 (1C), 169.5 (1C), 170.0 (1C), 170.1 (1C), 170.3 (1C); ^{19}F NMR ($CDCl_3$) δ −65.0 (s); IR (ZnSe, cm^{-1}) 1042, 1219, 1396, 1526, 1746; HRMS (ESI^+) *m*/*z* 636.1524 (636.1524 calcd for $C_{25}H_{26}F_3N_5NaO_{10}^+$, $[M+Na]^+$); Optical rotation $[\alpha]^{25}_D$ +32.3 (c 1.00, $CHCl_3$).

***N*,*N*-Dimethyl-4-(1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)aniline (22) (Scheme 4)**

This compound was synthesized according to the procedure for **11** using **6** (114 mg, 0.502 mmol, 1 equiv) and 4-ethynyl-*N*,*N*-dimethylaniline (**21**, 218 μL, 1.50 mmol, 3 equiv) in the presence of $CuSO_4·5H_2O$ (10 mol%), TBTA (20 mol%), and sodium ascorbate (40 mol%) with stirring for 4 h; Yield: 93.6% (175 mg, 0.470 mmol); Colorless solid (decomposed at 118 °C); Eluent for column chromatographic purification: *n*-hexane:EtOAc = 1:1 to 0:1; TLC R_f = 0.38 (*n*-hexane:EtOAc = 1:1); ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 6H), 6.79–6.81 (AA′BB′, 2H), 7.36–7.39 (AA′BB′, 2H), 7.76–7.78 (AA′BB′, 2H), 7.85–7.87 (AA′BB′, 2H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (q, $^2J_{C–F}$ = 40.3 Hz, 1C), 40.4 (2C), 112.4 (2C), 115.5 (1C), 117.9 (1C), 120.4 (2C), 122.0 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 126.9 (2C), 128.1 (2C), 129.1 (1C), 138.0 (1C), 149.3 (1C), 150.7 (1C); ^{19}F NMR ($CDCl_3$) δ −65.0 (s); IR (ZnSe, cm^{-1}) 937, 1034, 1152, 1179, 1223, 1344, 1504, 1614, 2812, 2859, 2897; HRMS (ESI^+) *m*/*z* 373.1383 (373.1383 calcd for $C_{18}H_{16}F_3N_6^+$, $[M+H]^+$).

4-(3-(Trifluoromethyl)-3*H*-diazirin-3-yl)aniline (5) (Table 2, entry 6)

To a 50 mL round-bottom flask equipped with a magnetic stir bar were added **6** (227 mg, 0.999 mmol, 1 equiv), THF (4 mL), water (0.4 mL), tributylphosphine tetrafluoroborate (319 mg, 1.10 mmol, 1.1 equiv), and triethylamine (14 μL, 0.10 mmol, 10 mol%). The mixture was stirred at room temperature for 30 min. After completion of the reaction as judged from the TLC analysis, to the mixture was added water (ca. 10 mL) and extracted with EtOAc (ca. 10 mL × 3). The combined organic extract was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 3:1) to give **5** (169 mg, 0.840 mmol, 84.0%) as a yellow oil; TLC R_f = 0.37 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 3.83 (br s, 2H), 6.63–6.66 (AA′BB′, 2H), 6.98–7.01 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 28.4 (q, $^2J_{C–F}$ = 39.5 Hz, 1C), 114.8 (2C), 118.3 (1C), 122.4 (q, $^1J_{C–F}$ = 272.5 Hz, 1C), 127.9 (2C), 147.8 (1C) (An unidentified byproduct formed during the acquisition of ^{13}C NMR data at room temperature for 5 hours); ^{19}F NMR ($CDCl_3$) δ −65.6 (s); IR (ZnSe, cm^{-1}) 935, 1144, 1179, 1234, 1300, 1350, 1522, 1624, 3391; HRMS (ESI^+) *m*/*z* 202.0587 (202.0587 calcd for $C_8H_7F_3N_3^+$, $[M+H]^+$). The chemical shifts were consistent with those reported in the literature.[7]

4-(3-(Trifluoromethyl)diaziridin-3-yl)aniline (23) (Table 3, entry 3)

To a 50 mL round-bottom flask equipped with a magnetic stir bar were added 3-(4-azidophenyl)-3-(trifluoromethyl)diaziridine **9** (458 mg, 2.00 mmol, 1 equiv), THF (10 mL), water (1 mL), and P^{n}Bu$_3$ (0.99 mL, 4.0 mmol, 2.0 equiv). The mixture was stirred at room temperature for 12 h. After completion of the reaction as judged from the TLC analysis, to the mixture was added water (ca. 30 mL) and extracted with EtOAc (ca. 30 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 1:1) to give **23** (379 mg, 1.87 mmol, 93.3%) as a colorless solid (mp 105–108 °C); TLC R_f = 0.42 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 2.12 (d, $J_{H–H}$ = 8.4 Hz, 1H), 2.70 (d, $J_{H–H}$ = 8.4 Hz, 1H), 3.83 (s, 2H), 6.66–6.69 (AA′BB′, 2H), 7.36–7.39 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 57.7 (q, $^2J_{C–F}$ = 35.4 Hz, 1C), 114.7 (2C), 121.2 (1C), 123.7 (q, $^1J_{C–F}$ = 276.6 Hz, 1C), 129.3 (2C), 148.0 (1C); ^{19}F NMR ($CDCl_3$) δ −75.8 (s); IR (ZnSe, cm^{-1}); 818, 1134, 1178, 1396, 1524, 1628, 3194; HRMS (ESI^+) *m*/*z* 204.0743 (204.0743 calcd for $C_8H_9F_3N_3^+$, $[M+H]^+$). The chemical shifts were consistent with those reported in the literature.[7]

***tert*-Butyl (*R*)-(1-oxo-1-((4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)amino)pent-4-yn-2-yl)carbamate (28) (Scheme 5)**

To a capped 4 mL vial equipped with a magnetic stir bar were added (*R*)-2-((tert-butoxycarbonyl)amino)-pent-4-ynoic acid (**27**, 85.2 mg, 0.400 mmol, 2 equiv), DMF (0.5 mL), HATU (91.3 mg, 0.240 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (41.3 μL, 0.241 mmol, 1.2 equiv), and **5** (40.2 mg, 0.200 mmol, 1

equiv) at 0 °C. The mixture was warmed up to room temperature and stirred for 5 h. After completion of the reaction as judged from the TLC analysis, to the reaction mixture was added brine (ca. 10 mL) and extracted with EtOAc (ca. 10 mL × 3). The combined organic extract was dried over Na_2SO_4, and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 1:1) to give **28** (68.4 mg, 0.173 mmol, 86.3%) as a colorless solid (mp 53–55 °C); TLC R_f = 0.50 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.13 (t, $J_{H–H}$ = 2.4 Hz, 1H), 2.69 (ddd, $J_{H–H}$ = 16.8, 6.4, 2.0 Hz, 1H), 2.87 (ddd, $J_{H–H}$ = 16.8, 6.4, 2.0 Hz, 1H), 4.41 (br d, $J_{H–H}$ = 2.4 Hz, 1H), 5.29 (br s, 1H), 7.14–7.17 (AA′BB′, 2H), 7.55–7.58 (AA′BB′, 2H), 8.51 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8 (1C), 28.2 (q, $^2J_{C–F}$ = 40.3 Hz, 1C), 28.3 (3C), 53.6 (1C), 72.0 (1C), 79.0 (1C), 81.3 (1C), 119.9 (2C), 122.1 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 124.8 (1C), 127.3 (2C), 138.7 (1C), 156.1 (1C), 168.8 (1C); ^{19}F NMR ($CDCl_3$) δ −65.3 (s); IR (ZnSe, cm^{-1}) 937, 1053, 1150, 1520, 1603, 1668, 3298; HRMS (ESI^+) *m*/*z* 419.1301 (419.1301 calcd for $C_{18}H_{19}F_3N_4NaO_3^+$, $[M+Na]^+$); Optical rotation $[\alpha]^{25}_D$ +38.6 (c 1.00, $CHCl_3$).

(*R*)-2-Amino-*N*-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)pent-4-ynamide (29) (Scheme 5)

To a capped 4 mL vial equipped with a magnetic stir bar and charged with **28** (19.8 mg, 50 μmol, 1 equiv) and CH_2Cl_2 (0.25 mL) was added TFA (0.25 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. After completion of the reaction as judged from the TLC analysis, the mixture was cooled to 0 °C and to this was added water (ca. 5 mL) and saturated aqueous $NaHCO_3$ (ca. 5 mL). The mixture was extracted with EtOAc (ca. 10 mL × 3) and the combined organic extract was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc:triethylamine = 1:1:0.01) to give **29** (14.0 mg, 47.3 μmol, 94.6%) as a colorless solid; TLC R_f = 0.30 (*n*-hexane:EtOAc:triethylamine = 1:1:0.01); ^{1}H NMR ($CDCl_3$) δ 1.91 (br s, 2H), 2.07 (t, $J_{H–H}$ = 2.4 Hz, 1H), 2.72 (ddd, $J_{H–H}$ = 16.8, 4.8, 2.4 Hz, 1H), 2.83 (ddd, $J_{H–H}$ = 16.8, 7.2, 2.4 Hz, 1H), 3.65 (dd, $J_{H–H}$ = 7.2, 4.8 Hz, 1H), 7.15–7.18 (AA′BB′, 2H), 7.63–7.66 (AA′BB′, 2H), 9.65 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7 (1C), 28.3 (q, $^2J_{C–F}$ = 40.4 Hz, 1C), 53.8 (1C), 71.7 (1C), 79.8 (1C), 119.5 (2C), 122.1 (q, $^1J_{C–F}$ = 273.3 Hz, 1C), 124.5 (1C), 127.4 (2C), 138.8 (1C), 171.0 (1C); ^{19}F NMR ($CDCl_3$) δ −65.3 (s); IR (ZnSe, cm^{-1}) 937, 1144, 1171, 1233, 1344, 1415, 1542, 1668, 1690, 2926, 3273; HRMS (ESI^+) *m*/*z* 297.0960 (297.0958 calcd for $C_{13}H_{12}F_3N_4O^+$, $[M+H]^+$); Optical rotation $[\alpha]^{25}_D$ +54.0 (c 0.73, $CHCl_3$).

Photoreactions of 11 and 13 in CD_3OD by irradiation of UV with wavelength of 365 nm (Figure 2A)

A solution of **11** (1 mM, 7 μmol) and methyl trifluoroacetate (an internal standard, 0.1 mM, 0.7 μmol) in 0.7 mL of CD_3OD was placed in a quartz NMR tube (Shigemi Co., SS-002) under argon atmosphere. The mixture was continuously irradiated side-by-side with 365-nm-wavelength UV light (AS ONE, SLUV-4, 4 W) for 15 min at room temperature. The course of the reaction was monitored by ^{19}F NMR, and the

yields were determined by comparison of an integrated value of the peak that corresponds to a trifluoromethyl group of **11** (δ −67.0 ppm) with that corresponds to a trifluoromethyl group of methyl trifluoroacetate (δ −76.8 ppm) (Figure S1). After the photoirradiation, a singlet signal appeared at δ −78.2 ppm that corresponds to the methanol-d_4 adduct **11′**, which was confirmed by comparison with the authentic sample prepared by the thermal reaction of **11**.

The photoreaction of **13** (1 mM in CD_3OD) was also performed according to this procedure. The generation of **13′** was also confirmed by comparison with the authentic sample prepared by the thermal reaction of **13** (Figure S2).

4-Benzyl-1-(4-(1-deuterio-1-(trideuteriomethoxy)-2,2,2-trifluoroethyl)phenyl)-1*H*-1,2,3-triazole (11′) (Figure 2B)

To a capped 4 mL vial equipped with a magnetic stir bar were added **11** (68.6 mg, 0.200 mmol, 1 equiv) and CD_3OD (2 mL) and the mixture was stirred at 80 °C for 48 h. After completion of the reaction as judged from the TLC analysis, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane:EtOAc = 1:0 to 1:1) to give **11′** (65.2 mg, 0.173 mmol, 92.9%) as a colorless solid (mp 53–55 °C); TLC R_f = 0.44 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 2H), 7.23–7.27 (m, 1H), 7.32–7.34 (m, 4H), 7.55–7.57 (AA′BB′, 2H), 7.62 (s, 1H), 7.73–7.76 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 32.2 (1C), 119.3 (1C), 120.4 (2C), 123.5 (q, $^1J_{C–F}$ = 280.7 Hz, 1C), 126.7 (2C), 128.74 (2C), 128.71 (1C), 129.5 (2C), 132.9 (1C), 138.0 (1C), 138.7 (1C), 148.7 (1C) (two carbons in neighbor to deuterium atoms were not observed); ^{19}F NMR ($CDCl_3$) δ −76.6 (s); IR (ZnSe, cm^{-1}) 988, 1042, 1169, 1315, 1520, 1612, 2066, 3030; HRMS (ESI$^+$) *m*/*z* 352.1573 (352.1569 calcd for $C_{18}H_{13}D_4F_3N_3O^+$, $[M+H]^+$).

4-Phenyl-1-(4-(1-deuterio-1-(trideuteriomethoxy)-2,2,2-trifluoroethyl)benzyl)-1*H*-1,2,3-triazole (13′) (Figure 2B)

This compound was synthesized according to the procedure for **11′** using **13** (68.6 mg, 0.200 mmol, 1 equiv); Yield: 90.9% (63.8 mg, 0.182 mmol); Colorless solid (mp 115–117 °C); Eluent for column chromatographic purification: *n*-hexane:EtOAc = 1:0 to 1:1; TLC R_f = 0.60 (*n*-hexane:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$) δ 5.61 (s, 2H), 7.33–7.36 (m, 3H), 7.39–7.47 (m, 4H), 7.71 (s, 1H), 7.81–7.82 (AA′BB′, 2H); ^{13}C NMR ($CDCl_3$) δ 53.8 (1C), 119.6 (2C), 123.6 (q, $^1J_{C–F}$ = 280.7 Hz, 1C), 125.8 (2C), 128.1 (2C), 128.3 (1C), 128.8 (2C), 129.0 (1C), 130.5 (1C), 133.2 (1C), 136.2 (1C), 148.4 (1C) (two carbons in neighbor to deuterium atoms were not observed); ^{19}F NMR ($CDCl_3$) δ −76.6 (s); IR (ZnSe, cm^{-1}) 3086, 1317, 1171, 1144, 1049, 761; HRMS (ESI$^+$) *m*/*z* 352.1572 (352.1569 calcd for $C_{18}H_{13}D_4F_3N_3O^+$, $[M+H]^+$).

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