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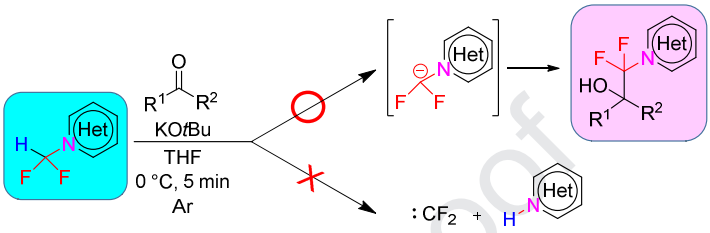
Heteroaryl-*N*-difluoromethyl anion pathway via deprotonation



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ABSTRACT

There has been great interest in the chemistry, syntheses and reactivities of heteroaryl-*N*-difluoromethane. The present work is based on the addition reaction of difluoromethyl anions, which are generated directly from difluoromethyl heterocycles, to benzophenone and benzaldehyde. As 1,2,3-triazoles and benzotriazoles can act as leaving groups, two reaction pathways are expected to exist: either the desired reaction route - deprotonation (formation of difluoromethyl anion) or the unfavored reaction route – the formation of difluorocarbene. We describe the chemistry for the selective addition reactions of difluoromethyltriazoles to ketones and aldehydes without the formation of difluorocarbene. Addition reactions of 1-(difluoromethyl)-1*H*-benzotriazole **1** to benzophenone **2** using potassium *t*-butoxide as a base were found to proceed smoothly at 0 °C for 5 min with high yields (80-88%). A plausible mechanism for the addition reactions of 1-(difluoromethyl)-1*H*-benzotriazole **1** and 1-difluoromethyl-4-phenyltriazole **5** to benzophenones and benzaldehydes is proposed based on deuterium-quenching experiments.

1. Introduction

The introduction of the difluoromethyl group into organic compounds has been achieved recently due to its many special and important effects [1]. Synthesis of the difluoromethyl moiety in heteroatoms [2] and derivatization of difluoromethyl heterocycles [3] have been of great interest. Transition-metal catalyzed difluoroalkylation strategies, including metal-difluorocarbene couplings, have been developed for the synthesis of difluoroalkylated arenes [4]. In addition, nucleophilic addition reactions of difluoromethyl anion which was generated after deprotonation of the acidic proton of CF_2H using the base such as *n*-BuLi or LDA have been studied [5].

As shown in Scheme 1a, when difluoromethanes substituted with fluoro [2a], chloro [2b,c], trifluoromethanesulfonate [2d], sulfoximine compound [2e], and tri(*n*-butyl)ammonium chloride [2f] are treated with a base and heteroatom nucleophile, the formation of difluoromethylated products has been reported via the difluorocarbene pathway. The characteristic of this method is the removal of protons with strong bases, such as KOH, NaOH, and NaH.

In 2000, Yagupolskii et al. reported the synthesis of heteroaryl-*N*-bromodifluoromethane and the formation of heteroaryl-*N*-difluoromethyl anions, followed by their reaction with carbonyl compounds as electrophiles, as shown in Scheme 1b [3a]. After debromination of heteroaryl-*N*-bromodifluoromethane produces a difluoromethyl anion, the anion reacts with benzaldehyde to provide addition products (34-55% yield) over 35 h with the temperature changing from -10 °C to 40 °C. Instead of debromination, Röschenthaler et al. used desilylation from heteroaryl-*N*-difluoromethyltrimethylsilane to produce versatile sources of heteroaryl-*N*-difluoromethyl anions for use in reactions with carbonyl compounds [3b]. The products were obtained after the deprotection of silyl ether.

Our work is based on the addition reaction of difluoromethyl anions, which are generated directly from difluoromethyl heterocycles to benzophenone and benzaldehyde, as shown in Scheme 1c. As heterocycles such as triazoles and benzotriazoles can act as leaving groups, we expect that there are two reaction pathways: either the desired reaction route - deprotonation (formation of difluoromethyl anion) or the unfavored reaction route – the formation of difluorocarbene. Herein, we describe the chemistry for the selective addition reactions of difluoromethyltriazoles to ketones and aldehydes without the formation of difluorocarbene.

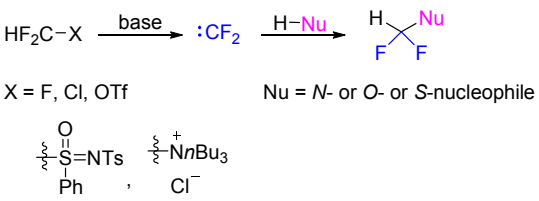
2. Results and discussion

Our plan for synthesis depends on whether the α-proton of difluoromethyl heterocycles is removed directly with the base to form difluoromethyl anions, which can lead to addition reactions. To determine the feasibility of this plan for synthesis, we carried out an addition reaction of 1-(difluoromethyl)-1*H*-benzo[*d*][1,2,3]triazole (**1**) to 4-bromobenzophenone **2a** using potassium *t*-butoxide (KO*t*Bu) as a base. After 5 min at 0 °C and

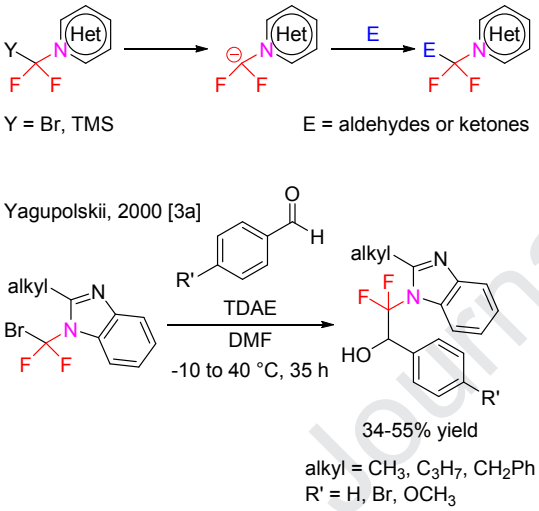
2 h at rt, the result was very successful, and we obtained the desired product **3a** with a yield of 78% (Table 1, entry 1). Then, when we reduced the reaction time from 2 h at rt to 10 min (entry 2) and 0 min (entry 3) after 5 min at 0 °C, the yields increased up to 82% and 87%, respectively. Although another base potassium bis(trimethylsilyl)amide (KHMDS) was used (entry 4), the yield was lowered to 53%. When LHMDS was used, a complex mixture containing the starting materials was obtained. When sodium methoxide was used, the reaction did not proceed at all. Sodium methoxide is not able to deprotonate the proton of the difluoromethyl group. The optimized condition for this addition reaction was considered as entry 3.

previous work

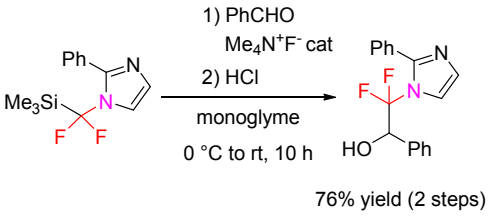
a) difluorocarbene pathway via deprotonation (difluoromethylation of heteroatom) [2]



b) heteroaryl-*N*-difluoromethyl anion pathway via debromination and desilylation

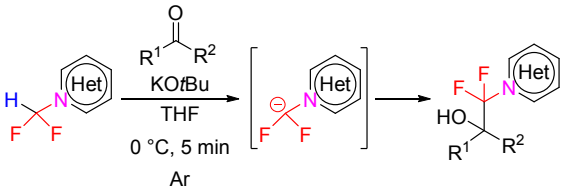


Roschenthaler, 2001 [3b]



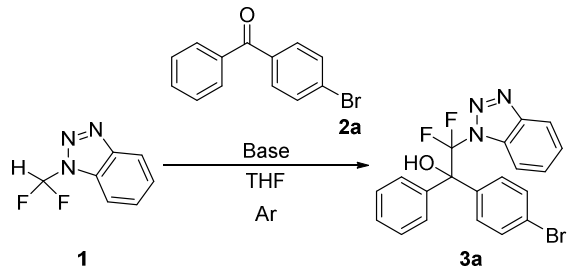
This work

c) heteroaryl-*N*-difluoromethyl anion pathway via deprotonation



Scheme 1. Previous work and this work.

Table 1
Optimization of the addition reactions of 1-(difluoromethyl)-1*H*-benzotriazole (**1**) to 4-bromobenzophenone (**2a**).[a]



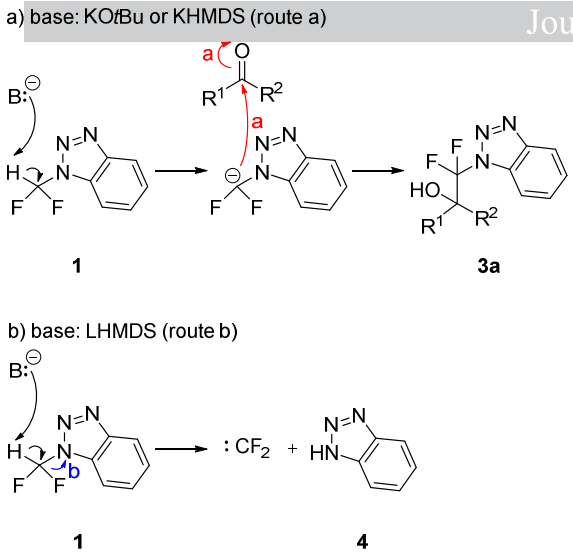
entry	base	temp	time	yield (%)[b]
1	KO*t*Bu	0 °C to rt	5 min + 2 h	78
2	KO*t*Bu	0 °C to rt	5 min + 10 min	82
3	KO*t*Bu	0 °C	5 min	87
4	KHMDS	0 °C	5 min	53

[a] Conditions: **1** (1.00 mmol), 4-bromobenzophenone (1.20 mmol) and base (2.00 mmol) in THF (3.0 mL).

[b] Isolated yield.

Scheme 2 shows two possible routes in this reaction: a) the desired addition route and b) the undesired side reaction route to form difluorocarbene. It is well known that triazole and benzotriazole act as leaving groups: 1) Triazole can act as a leaving group instead of cyanide in the Bruylants reaction [6]. Tertiary amine is synthesized using PhMgBr, CH_3MgCl, or CH_3MgBr from a compound that has triazole as a leaving group [6]; 2) nucleophilic aromatic substituted purines are obtained when an excessive amount of amine is reacted in purines with triazole [7]. 3) Benzotriazole also acts as a leaving group in insertion reaction and amidoalkylation reaction [8]. When benzotriazole acts as a leaving group, difluoromethylbenzotriazoles will decompose to difluorocarbene and benzotriazole (**4**), as shown in Scheme 2, route b. However, the triazole and benzotriazole groups did not act as leaving groups, and the reaction proceeded through the formation of *N*-difluoromethyl anions by deprotonation and the addition reaction to ketones or aldehydes (route a).

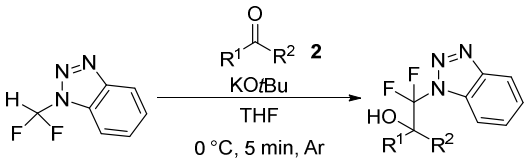
According to this plausible mechanism, the two routes a and b proceeded differently depending on the base. While benzotrialzole (**4**) was not formed when KO*t*Bu and KHMDS were used, **4** was formed using lithium bis(trimethylsilyl)amide (LHMDS). When we used KO*t*Bu as the base (Table 1, entry 3), **3a** was obtained via route a. The base removed the proton, and a difluoromethyl anion was formed. The difluoromethyl anion attacked the carbonyl carbon of 4-bromobenzophenone (**2a**), producing **3a** with a yield of 87%. On the other hand, when we used LHMDS as a base, benzotriazole (**4**, 65%) was obtained, presumably via route b, with **3a** (5%) via route a. We can explain this difference as arising from the cation of the base. A lithium cation is harder than a potassium cation. The difluoromethyl anion is considered to be a soft base, which can result in a stronger interaction with potassium, consequently leading to the formation of a stable difluoromethyl anion via a soft-soft interaction with the potassium cation. The stable difluoromethyl anion is able to attack the carbonyl of 4-bromobenzophenone (**2a**) due to its long retention period [9]. On the other hand, the interaction between the Li cation and difluoromethyl anion is less stable compared to that with the potassium cation, likely leading to decomposition to difluorocarbene.



Scheme 2. Mechanism of the addition reactions of difluoromethylbenzotriazoles to ketones and aldehydes and the formation of difluorocarbene.

Table 2

Addition reactions of difluoromethylbenzotriazole **1** to benzophenones and aldehydes.[a]



entry	R^1	R^2	product	yield (%)[b]
1[c]	C_6H_5	*p*-Br-C_6H_4	**3a**	87
2	C_6H_5	C_6H_5	**3b**	81
3	C_6H_5	*p*-NO_2-C_6H_4	**3c**	81
4	C_6H_5	*p*-CN-C_6H_4	**3d**	80
5	C_6H_5	*p*-Cl-C_6H_4	**3e**	86
6	C_6H_5	*p*-F-C_6H_4	**3f**	88
7	C_6H_5	*p*-MeO-C_6H_4	**3g**	85
8	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	**3h**	56
9	*p*-Cl-C_6H_4	H	**3i**	70
10	*p*-MeO-C_6H_4	H	**3j**	68
11	*o*-MeO-C_6H_4	H	**3k**	76
12	furan-3-yl	H	**3l**	62
13	6-chloro-pyridin-3-yl	H	**3m**	31

[a] Conditions: **1** (0.50 mmol), electrophile (0.60 mmol) and KO*t*Bu (1.00 mmol) in THF (1.5 mL).

[b] Isolated yield.

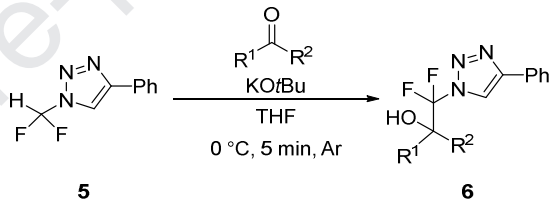
[c] The reaction was carried out at a 2-fold scale.

Under the optimized condition (Table 1, entry 3), the addition reaction of difluoromethylbenzotriazole **1** to 4-bromobenzophenone (**2a**) was rapidly completed over 5 min at 0 °C. Under this condition, we checked the scope for the benzophenones and aldehydes (Table 2). As results of experiments involving changing the substituent of one phenyl group of benzophenone, products were obtained with high yields, 80-88% yield (entries 1-7), regardless of the electron withdrawing and donating groups. In the case of two methoxy groups, the starting material remained and the product was obtained with a yield of only 56%.

To check the applicability to various carbonyl compounds, first, benzaldehydes were studied. Both the para and ortho substituents led to the generation of addition products with yields of 68-76% (entries 9-11). In the case of heteroaryl aldehydes, starting materials remained with lower yields (entries 12 and 13). However, 4'-bromoacetophenone and cyclohexanone, which have an α-proton, did not proceed at all. A mixture of side products was formed when *trans*-chalcone and *trans*-cinnamaldehyde were used as the starting ketones whether the 1,2- or 1,4-addition reaction occurred.

Table 3

Addition reactions of 1-difluoromethyl-4-phenyltriazole **5** to benzophenones.[a]



entry	R^1	R^2	product	yield (%)[b]
1	C_6H_5	*p*-Br-C_6H_4	**6a**	87
2	C_6H_5	C_6H_5	**6b**	88
3	C_6H_5	*p*-CN-C_6H_4	**6d**	85
4	C_6H_5	*p*-MeO-C_6H_4	**6g**	81
5	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	**6h**	53

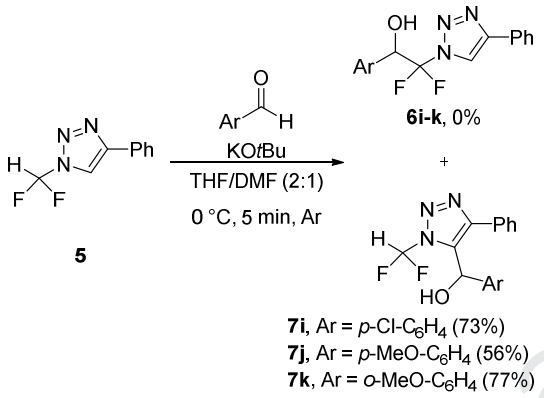
[a] Conditions: **5** (0.50 mmol), an electrophile (0.60 mmol) and KO*t*Bu (1.00 mmol) in THF (1.5 mL).

[b] Isolated yield.

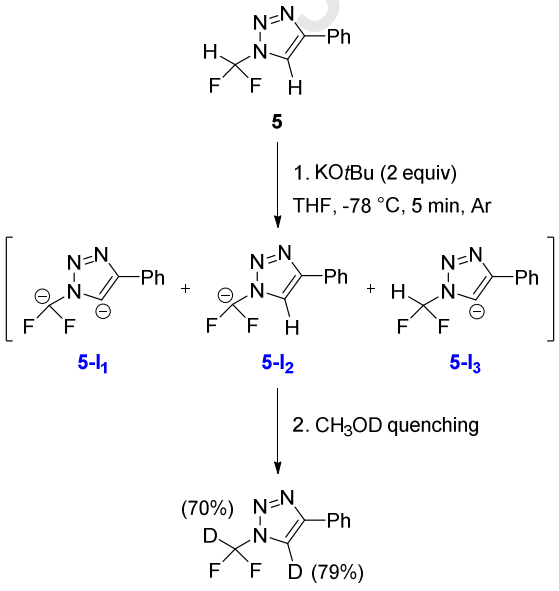
When the starting triazole was changed to triazole **5**, which has a C5-proton, instead of benzotriazole **1**, the α-protons of difluoromethyl were removed by treatment with KO*t*Bu, providing selective addition products with yields of 81-88% from benzophenone with one substituent (Table 3, entries 1-4). In the case of benzophenone with two methoxy groups, the yield of the addition product was lower, at 53%, with the unreacted starting material **5**.

Triazole **5** has two acidic protons: the α-proton in difluoromethyl and the C5 proton. When triazole **5** reacted with benzaldehyde under the same conditions in THF, a mixture of **6** and **7** was formed. We examined this reaction by changing the solvent. When we used the solvent as a mixture of THF:DMF (2:1), the addition product **7** was selectively synthesized with yields ranging from 56-77%. Two anions as nucleophiles

(difluoromethyl anion and anion at C5 position) and two different electrophiles (benzophenone and benzaldehyde) were formed. The difluoromethyl anion is a less sterically hindered nucleophile than the anion at the C5 position. Benzophenone is a more sterically hindered electrophile than benzaldehyde. In addition, a mixed solvent system of THF and DMF increases the reactivity compared to pure THF. Two anions, the difluoromethyl anion and the anion at the C5 position, are in equilibrium. In the reaction in THF and the benzophenone electrophile, only product **6** is formed, although two anions are formed. We can explain these results by the fact that the anion at the C5 position undergoes almost no attack due to the steric hindrance of both the anion at the C5 position and benzophenone, consequently leading to an attack of the difluoromethyl anion (Table 3). In the reaction in the mixture of THF and DMF and the benzaldehyde electrophile, the increasing reactivity in the mixture of THF and DMF and the less sterically hindered benzaldehyde helped with the selective formation of **7** (Scheme 3).

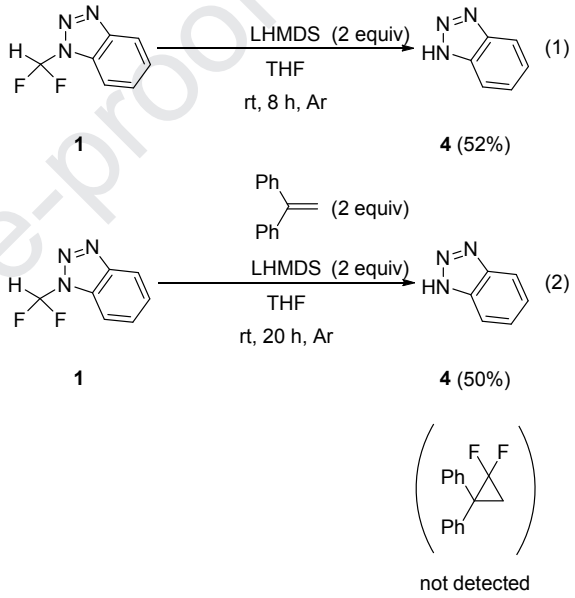


Scheme 3. Addition Reactions of 1-Difluoromethyl-4-phenyltriazole **5** to Aldehydes. Conditions: **5** (0.50 mmol), an electrophile (0.60 mmol) and KO*t*Bu (1.00 mmol) in THF/DMF (2:1, 1.5 mL). The yields are given for the isolated products.



Scheme 4. Deuterium Exchange Experiment. Deuteration ratio was indicated by ^{1}H NMR spectra.

To confirm the formation of a difluoromethyl anion and a C5-position anion, a deuterium exchange experiment using triazole **5** was performed. KO*t*Bu was added to a solution of **5** at -78 °C, and after 5 min, the reaction was quenched by adding cooled CH_3OD at -78 °C. After the workup reaction mixture was confirmed by ^{1}H NMR, the proton of difluorocarbon was replaced by D with a 70% yield, and the C5-proton was replaced by D with a 79% yield, as shown in Scheme 4 (See Supporting Information (SI), Figure S1–S3). The formation of a dianion from **5** was confirmed by using ESI-MS (See SI, Figure S4 and S5). Thus, both the difluoromethyl anion (**5-I$_2$**) and difluoromethyl anions in the dianion (**5-I$_1$**) rapidly attack benzophenone. Additionally, the difluoromethyl anion and the anion in the C5 position are in equilibrium.



Scheme 5. Experimental Evidence.

Another reaction using the LHMDS base without an electrophile, as shown in Scheme 5, was carried out to understand the reaction mechanism shown in Scheme 2b. Only dedifluoromethylated benzotriazole **4** was obtained. To check the formation of difluorocarbene, 1,1-diphenylethylene was added to trap the difluorocarbene (Scheme 5, eq 2). While benzotriazole **4** could be obtained in 50% of yield, 2,2-difluoro-1,1-diphenylcyclopropane was not identified in ^{1}H NMR spectrum of workup reaction mixture (see Supplementary data). When **1** was broken-down, further study is needed for the formation of benzotriazole **4** and difluorocarbene.

3. Conclusion

We studied the addition reaction for the difluoromethyl anion of difluoromethyl heterocycles to benzophenone and benzaldehyde. The addition reaction of *N*^{1}-difluoromethylbenzotriazole to benzophenones and benzaldehydes proceeded well and rapidly at 0 °C for 5 min. While *N*^{1}-difluoromethylbenzotriazole has only one acidic proton, *N*^{1}-difluoromethyl-4-phenyltriazole has two acidic

protons – the α-proton in the difluoromethyl and the C5 proton. We determined the optimized condition for selective addition reactions to benzophenone and benzaldehyde for the reaction mechanism using deuterium-labeling studies. This chemistry and mechanism for the addition reactions of N^1-difluoromethylbenzotriazole and N^1-difluoromethyl-4-phenyltriazole will be useful to understand the reactivity of difluoromethyl heterocycles.

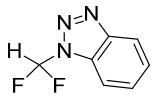
4. Experimental section

4.1. General information.

All the chemicals were purchased from commercial sources and used without further purification. All reactions were monitored by TLC using Merck silica gel 60 F_{254} plates and the plates were visualized with UV light. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Melting points were determined on a Kruss melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz NMR spectrometer. The High resolution mass spectra were obtained from Bruker Compact Ultra High Resolution ESI Q-TOF mass spectrometer or Thermo Scientific LTQ Orbitrap XL high resolution mass spectrometer at Organic Chemistry Research Center of Sogang University. The elemental analysis was performed on Thermo Scientific FLASH 2000 elemental analyzer at Organic Chemistry Research Center of Sogang University.

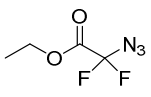
*4.2. Synthesis of Substrates **1** and **5**.*

*4.2.1. 1-(Difluoromethyl)-1H-benzo[d][1,2,3]triazole (**1**) [10].*



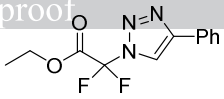
To an oven dried pressure tube containing a stirring bar was added benzotriazole (625 mg, 5.25 mmol), sodium chlorodifluoroacetate (1.60 g, 10.5 mmol) and K_2CO_3 (1.09 g, 7.88 mmol). The pressure tube was fitted with a rubber septum, kept under vacuum, and purged with Ar. Anhydrous DMF (21 mL) was added via syringe under Ar and the pressure tube was tightly capped with a plug. The reaction mixture was stirred at 95 °C for 14 h. The mixture was added into water (400 mL) and extracted with EtOAc (2 x 400 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography (hexane/EtOAc = 95/5) to afford the product **1** as a white solid (468 mg, 53%): mp 42.3–42.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.86 (t, *J* = 58.6 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 130.1 (t, *J* = 1.9 Hz), 129.6, 125.7, 120.6, 111.4 (t, *J* = 249.9 Hz), 110.9 (t, *J* = 1.6 Hz). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_7H_5F_2N_3Na$ 192.0344; Found 192.0346. (CAS 149243-57-2)

*4.2.2. Ethyl 2-azido-2,2-difluoroacetate (**8**).*



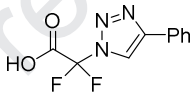
Prepared by modification of a literature procedure [11]. To NaN_3 (1.92 g, 29.6 mmol) dissolved in CH_3CN (21 mL) in a pressure tube was added ethyl bromodifluoroacetate (1.90 mL, 14.8 mmol) and the pressure tube was tightly capped. The reaction mixture was stirred at 110 °C for 48 h. The mixture was cooled in a refrigerator. After further 2 h, the mixture was placed at rt for the next step. (CAS 153755-61-4)

*4.2.3. Ethyl 2,2-difluoro-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetate (**9**).*



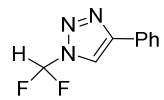
Prepared by modification of a literature procedure [11]. To a solution of ethyl 2-azido-2,2-difluoroacetate (**8**) in CH_3CN (21 mL) was added phenylacetylene (1.78 mL, 16.3 mmol) and CuI (281 mg, 1.48 mmol). *N*,*N*-Diisopropylethylamine (DIPEA, 0.515 mL, 2.96 mmol) was slowly dropped to the solution at 0 °C. The pressure tube was tightly capped. After 5 min, the reaction mixture was stirred at rt for 6 h. The mixture was transferred to a 500 mL round-bottom flask and concentrated in vacuo. Hexane (400 mL) was added to the 500 mL round-bottom flask and the hexane solution was transferred to a 1000 mL round-bottom flask and the solution was concentrated in vacuo (3 times). The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 90/10) to afford the product **9** as a white solid (1.62 g, 41%): mp 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 4.51 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (t, *J* = 34.3 Hz), 148.6, 129.2, 129.1, 129.0, 126.2, 117.1, 109.5 (t, *J* = 265.6 Hz), 65.2, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{11}F_2N_3O_2Na$ 290.0712; Found: 290.0715. (CAS 1355965-07-9) Note: When the residue was purified, slight decomposition of **9** to **10** occurred. When the compound **9** was left at rt for long periods of time, it slowly decomposed to **10**.

*4.2.4. 2,2-Difluoro-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetic acid (**10**).*



To ethyl 2,2-difluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (**9**, 1.00 g, 3.74 mmol) in a pressure tube was added solution of THF and water (v/v= 1:1, 7.5 mL) and the pressure tube was tightly capped. The reaction mixture was stirred at 80 °C for 12 h. The mixture was concentrated and transferred to a freeze dry flask. The mixture in the flask was cooled at -78 °C and dried by freeze dryer for 6 h. The product **10** was obtained as a white solid (848 mg, 95%): mp 116.5–116.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7 (t, *J* = 32.2 Hz), 147.4, 129.2, 129.1, 128.9, 125.8, 119.9, 109.8 (t, *J* = 266.0 Hz). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_7F_2N_3O_2Na$ 262.0399; Found: 262.0396. (CAS 1989672-28-7)

*4.2.5. 1-(Difluoromethyl)-4-phenyl-1H-1,2,3-triazole (**5**) [12].*



To 2,2-difluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetic acid (**10**, 718 mg, 3.00 mmol) and CsF (501 mg, 3.30 mmol) in a round-bottom flask was added DMF (4.1 mL). The reaction mixture was stirred at 120 °C for 10 h. The mixture was added into water (200 mL) and extracted with CH_2Cl_2 (5 x 200 mL). The combined organic layer was dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography on silica gel (hexane/EtOAc = 90/10) to afford the product **5** as a white solid (517 mg, 88%): mp 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 59.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 129.21, 129.16, 129.1, 126.2, 115.8, 110.0 (t, *J* = 253.3 Hz). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_9H_7F_2N_3Na$ 218.0500; Found 218.0498. Anal. Calcd for $C_9H_7F_2N_3$: C, 55.39; H, 3.62; N, 21.53. Found: C, 55.44; H, 3.72; N, 21.52. (CAS 2242477-65-0)

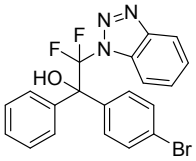
4.3. General procedure for addition reactions.

4.3.1. Method A (for solid ketones and aldehydes).

To an oven dried 2-necked 10 mL round bottom flask containing a stirring bar was added substrate (0.50 mmol, 1.0 equiv) and the carbonyl compound (0.60 mmol, 1.2 equiv). The flask was capped with two rubber septa, purged with Ar for 10 min, and left under Ar atmosphere. To the reaction mixture was added anhydrous THF (0.5 mL) via a syringe at 0 °C. KO*t*Bu (1.0 M in THF, 1.0 mL) was slowly dropped to the solution at 0 °C. After stirring under Ar at 0 °C for 5 min, the reaction was quenched by an ice-cold water (1.5 mL). The mixture was added into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography on silica gel to afford the product.

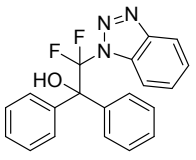
4.3.2. Method B (for Liquid Aldehydes). To an oven dried 2-necked 10 mL round bottom flask containing a stirring bar was added substrate (0.50 mmol, 1.0 equiv). The flask was capped with two rubber septa, purged with Ar for 10 min, and left under Ar atmosphere. To a 4 mL vial was added the aromatic aldehyde (2 mL). The vial was purged with Ar and left under Ar atmosphere. To the reaction flask was added anhydrous THF (0.5 mL) via a syringe at 0 °C. To the reaction mixture was added the aromatic aldehyde (0.60 mmol, 1.2 equiv) via a microsyringe at 0 °C. KO*t*Bu (1.0 M in THF, 1.0 mL) was slowly dropped to the solution at 0 °C. After stirring under Ar at 0 °C for 5 min, the reaction was quenched by an ice-cold water (1.5 mL). The mixture was added into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography on silica gel to afford the product.

*4.3.3. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-1-(4-bromophenyl)-2,2-difluoro-1-phenylethan-1-ol (**3a**).*



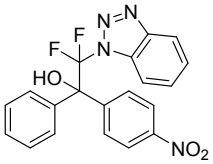
Method A (1.0 mmol scale). An oven dried 2-necked 25 mL round bottom flask was used. Compound **1** (169 mg, 1.00 mmol) and 4-bromobenzophenone (**2a**, 313 mg, 1.20 mmol) were used. The flask was purged with Ar for 20 min. Anhydrous THF (1.0 mL) and KO*t*Bu (1.0 M in THF, 2.0 mL) were used. The product was purified by flash column chromatography on silica gel (hexane/EtOAc = 85/15) to give a white solid (372 mg, 87%): mp 148–149 °C; R_f 0.29 (hexane/EtOAc = 85/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.50-7.37 (m, 7H), 7.30-7.29 (m, 3H), 5.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 139.6, 139.0, 131.9, 131.3, 129.8, 129.5, 128.7, 128.3, 127.4, 125.6, 122.9, 120.5, 120.1 (t, *J* = 265.1 Hz), 111.6 (t, *J* = 3.6 Hz), 81.4 (t, *J* = 25.4 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}BrF_2N_3O$ 430.0361; Found 430.0362. Anal. Calcd for $C_{20}H_{14}BrF_2N_3O$: C, 55.83; H, 3.28; N, 9.77. Found: C, 55.80; H, 3.34; N, 9.70.

*4.3.4. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1,1-diphenylethan-1-ol (**3b**).*



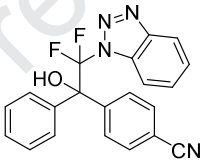
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and benzophenone (**2b**, 109 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 85/15) to give a white solid (143 mg, 81%): mp 168–169 °C; R_f 0.27 (hexane/EtOAc = 85/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.51-7.49 (m, 4H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.30-7.28 (m, 6H), 4.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 140.0, 132.0, 129.7, 128.5, 128.2, 127.7 (t, *J* = 1.9 Hz), 125.4, 120.5, 120.4 (t, *J* = 265.3 Hz), 111.7 (t, *J* = 3.7 Hz), 81.7 (t, *J* = 25.4 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{20}H_{16}F_2N_3O$ 352.1256; Found 352.1257. Anal. Calcd for $C_{20}H_{15}F_2N_3O$: C, 68.37; H, 4.30; N, 11.96. Found: C, 68.39; H, 4.11; N, 11.89.

*4.3.5. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-(4-nitrophenyl)-1-phenylethan-1-ol (**3c**).*



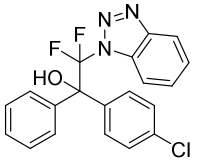
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4-nitrobenzophenone (**2c**, 136 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 75/25) to give a pale-yellow solid (161 mg, 81%): mp 66–71 °C; R_f 0.24 (hexane/EtOAc = 75/25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.53-7.47 (m, 3H), 7.34-7.30 (m, 3H), 5.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 146.7, 145.1, 139.1, 131.8, 130.1, 129.01, 128.97, 128.6, 127.3, 125.8, 123.3, 120.6, 119.9 (t, *J* = 264.7 Hz), 111.6 (t, *J* = 3.6 Hz), 81.4 (t, *J* = 25.5 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{14}F_2N_4O_3Na$ 419.0926; Found 419.0926.

*4.3.6. 4-(2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-hydroxy-1-phenylethyl)benzonitrile (**3d**).*



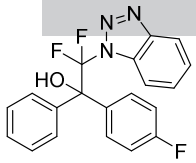
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4-cyanobenzophenone (**2d**, 124 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (150 mg, 80%): mp 136.5–137.3 ° C; R_f 0.32 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68–7.59 (m, 5H), 7.52-7.45 (m, 3H), 7.33-7.29 (m, 3H), 5.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 144.9, 139.1, 131.9, 131.8, 130.0, 128.9, 128.7, 128.6, 127.3, 125.7, 120.6, 120.0 (t, *J* = 264.8 Hz), 118.4, 112.5, 111.6 (t, *J* = 3.5 Hz), 81.4 (t, *J* = 25.5 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{21}H_{15}F_2N_4O$ 377.1208; Found 377.1209.

*4.3.7. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-1-(4-chlorophenyl)-2,2-difluoro-1-phenylethan-1-ol (**3e**).*



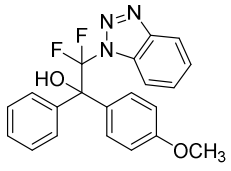
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4-chlorobenzophenone (**2e**, 130 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 85/15) to give a white solid (166 mg, 86%): mp 137–138 °C; R_f 0.27 (hexane/EtOAc = 85/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.50-7.44 (m, 5H), 7.30-7.28 (m, 5H), 5.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 139.7, 138.5, 134.6, 131.9, 129.8, 129.2, 128.7, 128.4, 128.3, 127.4, 125.5, 120.5, 120.2 (t, *J* = 265.1 Hz), 111.6 (t, *J* = 3.4 Hz), 81.4 (t, *J* = 25.4 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}ClF_2N_3O$ 386.0866; Found 386.0867. Anal. Calcd for $C_{20}H_{14}ClF_2N_3O$: C, 62.27; H, 3.66; N, 10.89. Found: C, 62.24; H, 3.67; N, 10.85.

*4.3.8. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-(4-fluorophenyl)-1-phenylethan-1-ol (**3f**).*



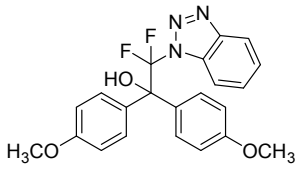
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4-fluorobenzophenone (**2f**, 120 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 80/20) to give a white solid (162 mg, 88%): mp 154–155 °C; R_f 0.38 (hexane/EtOAc = 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.49-7.45 (m, 5H), 7.30-7.28 (m, 3H), 6.98 (t, *J* = 8.8 Hz, 2H), 5.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.5, 145.0, 140.0, 135.7 (d, *J* = 3.3 Hz), 132.0, 129.9 (t, *J* = 1.8 Hz), 129.8, 128.6, 128.3, 127.5 (t, *J* = 1.9 Hz), 125.5, 120.5, 120.3 (t, *J* = 265.2 Hz), 115.1 (d, *J* = 21.4 Hz), 111.7 (t, *J* = 3.7 Hz), 81.4 (t, *J* = 25.5 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}F_3N_3O$ 370.1162; Found 370.1162. Anal. Calcd for $C_{20}H_{14}F_3N_3O$: C, 65.04; H, 3.82; N, 11.38. Found: C, 65.11; H, 3.76; N, 11.21.

*4.3.9. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-(4-methoxyphenyl)-1-phenylethan-1-ol (**3g**).*



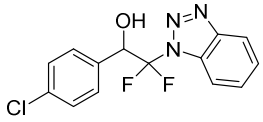
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4-methoxybenzophenone (**2g**, 127 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 80/20) to give a white solid (162 mg, 85%): mp 121–124 °C; R_f 0.29 (hexane/EtOAc = 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.49-7.43 (m, 3H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.29-7.27 (m, 3H), 6.81 (d, *J* = 9.2 Hz, 2H), 4.91 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.0, 140.3, 132.04, 132.01, 129.6, 129.1, 128.4, 128.2, 127.6, 125.3, 120.5 (t, *J* = 265.6 Hz), 120.3, 113.5, 111.8 (t, *J* = 3.7 Hz), 81.5 (t, *J* = 25.6 Hz), 55.3. HRMS (ESI/LTQ Orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{17}F_2N_3O_2Na$ 404.1181; Found 404.1180. Anal. Calcd for $C_{21}H_{17}F_2N_3O_2$: C, 66.14; H, 4.49; N, 11.02. Found: C, 66.06; H, 4.51; N, 10.89.

*4.3.10. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1,1-bis(4-methoxyphenyl)ethan-1-ol (**3h**).*



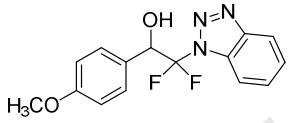
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4,4'-dimethoxybenzophenone (**2h**, 145 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (115 mg, 56%): mp 116–117 °C; R_f 0.32 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 4H), 6.80 (d, *J* = 8.8 Hz, 4H), 4.86 (s, 1H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.0, 132.3, 132.1, 129.5, 129.0, 125.3, 120.6 (t, *J* = 265.3 Hz), 120.4, 113.5, 111.8 (t, *J* = 3.7 Hz), 81.3 (t, *J* = 25.6 Hz), 55.3. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{22}H_{20}F_2N_3O_3$ 412.1467; Found 412.1469. Anal. Calcd for $C_{22}H_{19}F_2N_3O_3$: C, 64.23; H, 4.66; N, 10.21. Found: C, 64.21; H, 4.71; N, 10.26.

*4.3.11. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-1-(4-chlorophenyl)-2,2-difluoroethan-1-ol (**3i**).*



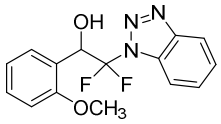
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 4-chlorobenzaldehyde (**2i**, 84.3 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 75/25) to give a white solid (109 mg, 70%): mp 135.6–136.1 °C; R_f 0.36 (hexane/EtOAc = 75/25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 5.99 (d, *J* = 17.2 Hz, 1H), 4.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 135.4, 132.6, 131.8, 129.73, 129.71, 128.7, 125.7, 120.0, 119.5 (t, *J* = 260.3 Hz), 111.7 (dd, *J* = 5.1, 2.3 Hz), 73.1 (dd, *J* = 31.8, 23.9 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{10}ClF_2N_3ONa$ 332.0373; Found 332.0375. Anal. Calcd for $C_{14}H_{10}ClF_2N_3O$: C, 54.30; H, 3.25; N, 13.57. Found: C, 54.25; H, 3.29; N, 13.56.

*4.3.12. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-ol (**3j**).*



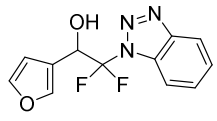
Method B. The product was obtained from **1** (84.6 mg, 0.50 mmol) and *p*-anisaldehyde (**2j**, 73.0 µL, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a beige solid (104 mg, 68%): mp 94.7–95.2 °C; R_f 0.23 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.93 (dd, *J* = 16.8, 3.2 Hz, 1H), 3.86 (br, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 145.5, 131.9, 129.54, 129.49, 126.2, 125.4, 120.0, 119.8 (t, *J* = 260.0 Hz), 113.9, 111.7 (dd, *J* = 4.9, 2.5 Hz), 73.5 (dd, *J* = 31.6, 24.2 Hz), 55.4. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}F_2N_3O_2$ 306.1049; Found 306.1050. Anal. Calcd for $C_{15}H_{13}F_2N_3O_2$: C, 59.02; H, 4.29; N, 13.76. Found: C, 59.07; H, 4.34; N, 13.80.

*4.3.13. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-(2-methoxyphenyl)ethan-1-ol (**3k**).*



Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and *o*-anisaldehyde (**2k**, 81.7 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (116 mg, 76%): mp 164–166 °C; R_f 0.30 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.60-7.57 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.22 (dd, *J* = 15.2, 4.8 Hz, 1H), 4.00 (br, 1H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 145.8, 132.0, 130.6, 129.7, 129.2, 125.2, 122.0, 121.0, 120.1, 119.9 (t, *J* = 262.0 Hz), 111.6 (dd, *J* = 4.1, 3.1 Hz), 110.8, 70.0 (dd, *J* = 31.6, 26.1 Hz), 55.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}F_2N_3O_2$ 306.1049; Found 306.1049. Anal. Calcd for $C_{15}H_{13}F_2N_3O_2$: C, 59.02; H, 4.29; N, 13.76. Found: C, 59.04; H, 4.32; N, 13.74.

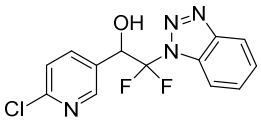
*4.3.14. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,2-difluoro-1-(furan-3-yl)ethan-1-ol (**3l**).*



Method B. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 3-furancarboxaldehyde (**2l**, 45.7 µL, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give as a beige solid (82 mg, 62%): mp 65–66 °C; R_f 0.33 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.64-7.60 (m, 2H), 7.50-7.45 (m, 2H), 6.58 (s, 1H), 6.01 (d, *J* = 15.2 Hz, 1H), 3.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 143.6, 142.1, 131.8, 129.7, 125.6, 120.2, 119.60, 119.55 (t, *J* = 259.5 Hz), 111.7 (dd, *J* = 4.8, 2.5 Hz), 109.6, 68.1 (dd, *J* =

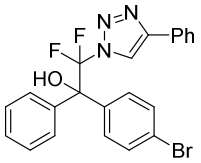
32.2, 25.4 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{12}H_{10}F_2N_3O_2$ 266.0736; Found 266.0736. Anal. Calcd for $C_{12}H_9F_2N_3O_2$: C, 54.34; H, 3.42; N, 15.84. Found: C, 54.29; H, 3.39; N, 15.78.

*4.3.15. 2-(1H-Benzo[d][1,2,3]triazol-1-yl)-1-(6-chloropyridin-3-yl)-2,2-difluoroethan-1-ol (**3m**).*



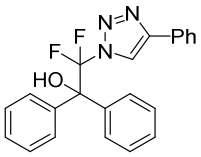
Method A. The product was obtained from **1** (84.6 mg, 0.50 mmol) and 6-chloropyridine-3-carboxaldehyde (**2m**, 84.9 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 65/35) to give a white solid (48 mg, 31%): mp 118–119 °C; R_f 0.25 (hexane/EtOAc = 65/35); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 6.10 (d, *J* = 17.6 Hz, 1H), 4.52 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.5, 145.4, 138.9, 131.8, 129.9, 129.6, 125.8, 124.4, 120.0, 119.4 (t, *J* = 260.1 Hz), 111.7 (dd, *J* = 5.3, 1.9 Hz), 71.2 (dd, *J* = 32.7, 24.1 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}ClF_2N_4O$ 311.0506; Found 311.0507.

*4.3.16. 1-(4-Bromophenyl)-2,2-difluoro-1-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethan-1-ol (**6a**).*



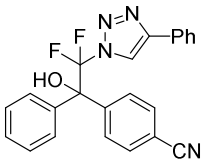
Method A. The product was obtained from **5** (97.6 mg, 0.50 mmol) and 4-bromobenzophenone (**2a**, 157 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 85/15) to give a white solid **6a** (199 mg, 87%): mp 182–183 °C; R_f 0.30 (hexane/EtOAc = 85/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.48-7.43 (m, 6H), 7.40-7.37 (m, 3H), 7.33-7.31 (m, 3H), 5.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.9, 139.5, 139.4, 130.9, 129.6, 129.5, 129.0, 128.5, 128.4, 128.1, 127.3, 125.5, 121.8, 121.3, 120.0 (t, *J* = 272.7 Hz), 79.6 (t, *J* = 27.6 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}BrF_2N_3O$ 456.0518; Found 456.0516. Anal. Calcd for $C_{22}H_{16}BrF_2N_3O$: C, 57.91; H, 3.53; N, 9.21. Found: C, 57.95; H, 3.55; N, 9.18.

*4.3.17. 2,2-Difluoro-1,1-diphenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethan-1-ol (**6b**).*



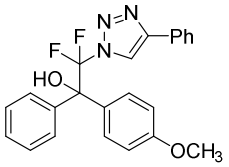
Method A. The product was obtained from **5** (97.6 mg, 0.50 mmol) and benzophenone (**2b**, 109 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 80/20) to give a white solid **6b** (166 mg, 88%): mp 171–173 °C; R_f 0.26 (hexane/EtOAc = 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.52-7.50 (m, 4H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.33-7.31 (m, 6H), 4.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 139.4, 129.2, 129.1, 129.0, 128.7, 128.3, 127.5, 126.1, 119.0 (t, *J* = 270.0 Hz), 118.7, 81.2 (t, *J* = 25.4 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}F_2N_3O$ 378.1412; Found 378.1412. Anal. Calcd for $C_{22}H_{17}F_2N_3O$: C, 70.02; H, 4.54; N, 11.13. Found: C, 70.04; H, 4.63; N, 11.08.

*4.3.18. 4-(2,2-Difluoro-1-hydroxy-1-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl)benzonitrile (**6d**).*



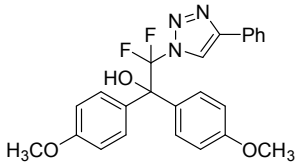
Method A. The product was obtained from **5** (97.6 mg, 0.50 mmol) and 4-cyanobenzophenone (**2d**, 124 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (171 mg, 85%): mp 165–169 °C; R_f 0.31 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.47-7.43 (m, 4H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.34-7.33 (m, 3H), 5.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 144.3, 138.6, 132.1, 129.3, 129.2, 128.8, 128.7, 128.5, 127.1, 126.1, 118.52, 118.48, 118.43 (t, *J* = 269.1 Hz), 118.41, 112.6, 80.9 (t, *J* = 25.3 Hz). HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}F_2N_4O$ 403.1365; Found 403.1364.

*4.3.19. 2,2-Difluoro-1-(4-methoxyphenyl)-1-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethan-1-ol (**6g**).*



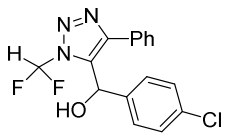
Method A. The product was obtained from **5** (97.6 mg, 0.50 mmol) and 4-methoxybenzophenone (**2g**, 127 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 80/20) to give a white solid (165 mg, 81%): mp 204–205 °C; R_f 0.28 (hexane/EtOAc = 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.50–7.35 (m, 7H), 7.32-7.30 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.77 (s, 1H). 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.9, 145.8, 140.3, 131.9, 129.6, 129.0, 128.8, 128.5, 128.1, 128.0, 127.4, 125.5, 121.3, 120.3 (t, *J* = 272.3 Hz), 113.3, 79.6 (t, *J* = 27.4 Hz), 55.1. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}F_2N_3O_2$ 408.1518; Found 408.1520. Anal. Calcd for $C_{23}H_{19}F_2N_3O_2$: C, 67.81; H, 4.70; N, 10.31. Found: C, 67.85; H, 4.76; N, 10.24.

*4.3.20. 2,2-Difluoro-1,1-bis(4-methoxyphenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethan-1-ol (**6h**).*



Method A. The product was obtained from **5** (97.6 mg, 0.50 mmol) and 4,4'-dimethoxybenzophenone (**2h**, 145 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (117 mg, 53%): mp 180–181 °C; R_f 0.37 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.45-7.35 (m, 7H), 6.83 (d, *J* = 8.8 Hz, 4H), 4.68 (s, 1H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.9, 145.8, 132.1, 129.6, 129.0, 128.7, 128.5, 125.5, 121.3, 120.3 (t, *J* = 271.8 Hz), 113.2, 79.4 (t, *J* = 27.4 Hz), 55.1. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}F_2N_3O_3$ 438.1624; Found 438.1625. Anal. Calcd for $C_{24}H_{21}F_2N_3O_3$: C, 65.90; H, 4.84; N, 9.61. Found: C, 65.92; H, 4.97; N, 9.51.

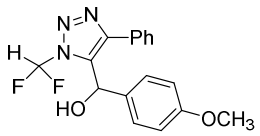
*4.3.21. (4-Chlorophenyl)(1-(difluoromethyl)-4-phenyl-1H-1,2,3-triazol-5-yl)methanol (**7i**).*



Method A. Anhydrous THF (0.5 mL) was replaced by anhydrous DMF (0.5 mL). The product was obtained from **5** (97.6 mg, 0.50 mmol) and 4-chlorobenzaldehyde (**2i,** 84.3 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 75/25) to give a white solid (122 mg, 73%): mp 125–127 °C; R_f 0.30 (hexane/EtOAc = 75/25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 57.8 Hz, 1H), 7.46-7.44 (m, 2H), 7.38-7.32 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.42 (s, 1H), 4.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 137.6, 134.6, 134.4, 129.3, 129.1, 128.99, 128.95, 128.3, 127.4, 109.1 (t, *J* = 255.1 Hz), 65.0. HRMS (ESI/LTQ Orbitrap)

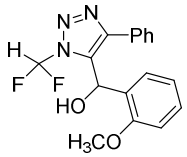
m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}ClF_2N_3O$ 336.0710; Found 336.0710.

4.3.22. (1-(Difluoromethyl)-4-phenyl-1H-1,2,3-triazol-5-yl)(4-methoxyphenyl)methanol (7j).



Method B. Anhydrous THF (0.5 mL) was replaced by anhydrous DMF (0.5 mL). The product was obtained from **5** (97.6 mg, 0.50 mmol) and *p*-anisaldehyde (**2j**, 73.0 μ L, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (93 mg, 56%): mp 113–116 °C; R_f 0.29 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 58.0 Hz, 1H), 7.56-7.53 (m, 2H), 7.40-7.38 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.41 (s, 1H), 3.80 (s, 3H), 3.15 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 154.9, 134.8, 131.2, 129.3, 129.1, 128.9, 128.3, 127.5, 114.4, 108.8 (t, *J* = 254.4 Hz), 65.7, 55.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}F_2N_3O_2$ 332.1205; Found 332.1206.

4.3.23. (1-(Difluoromethyl)-4-phenyl-1H-1,2,3-triazol-5-yl)(2-methoxyphenyl)methanol (7k).



Method A. Anhydrous THF (0.5 mL) was replaced by anhydrous DMF (0.5 mL). The product was obtained from **5** (97.6 mg, 0.50 mmol) and *o*-anisaldehyde (**2k**, 81.7 mg, 0.60 mmol) and purified by flash column chromatography on silica gel (hexane/EtOAc = 70/30) to give a white solid (128 mg, 77%): mp 101–102 °C; R_f 0.25 (hexane/EtOAc = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, *J* = 58.2 Hz, 1H), 7.50-7.47 (m, 2H), 7.39-7.34 (m, 4H), 6.97-6.91 (m, 2H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 3.85 (s, 3H), 3.83 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 145.7, 133.0, 130.5, 129.7, 128.71, 128.69, 128.3, 127.5, 127.0, 121.2, 111.0, 108.7 (t, *J* = 254.2 Hz), 64.2, 55.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}F_2N_3O_2$ 332.1205; Found 332.1207.

4.4. Procedure for Scheme 2 (Base: LHMDS)

Method A. KO*t*Bu (1.0 M in THF, 1.0 mL) was replaced by LHMDS (1.0 M in THF, 1.0 mL). Compound **1** (84.6 mg, 0.50 mmol) and 4-bromobenzophenone (**2a**, 157 mg, 0.60 mmol) were used. The organic layer was concentrated and purified by flash column chromatography on silica gel (hexane/EtOAc = 85/15) to afford benzotriazole **4** (39 mg, 65%) and **3a** (11 mg, 5%). Note: Benzotriazole **4** was identified by comparison with a commercially available reagent (Aldrich).

4.5. Procedure for deuterium exchange experiment (Scheme 4).

To an oven dried 8 mL vial containing a stirring bar was added 1-(difluoromethyl)-4-phenyl-1*H*-1,2,3-triazole (**5**, 97.6 mg, 0.50 mmol). The vial was capped with a rubber septum, purged with Ar for 25 min, and left under Ar atmosphere. To the vial was added anhydrous THF (0.4 mL) via a syringe at -78 °C. KO*t*Bu (0.9 M in THF, 1.1 mL) was slowly dropped to the solution at -78 °C. After stirring under Ar at -78 °C for 5 min, the reaction was quenched by -78 °C CH_3OD (1.5 mL). Half of the reaction mixture was concentrated in vacuo and analyzed by ^{1}H NMR (in DMSO-d_6). The mixture in DMSO-d_6 was added into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na_2SO_4. The organic layer was concentrated and analyzed by ^{1}H NMR (in $CDCl_3$) and ESI-MS. The residue was purified by column (pipet) chromatography on silica gel (hexane/EtOAc = 90/10) and analyzed by ^{1}H NMR (in $CDCl_3$).

4.6. Procedure for experimental evidence (Scheme 5, eq 1).

To an oven dried 2-necked 10 mL round bottom flask containing a stirring bar was added 1-(difluoromethyl)-1*H*-benzo[*d*][1,2,3]triazole (**1**, 84.6 mg, 0.50 mmol). The flask was capped with two rubber septa, purged with Ar for 10 min, and left under Ar atmosphere. To the reaction mixture was added anhydrous THF (0.5 mL) via a syringe at rt. LHMDS (1.0 M in THF, 1.0 mL) was slowly dropped to the solution at rt. After stirring under Ar at rt for 8 h, the reaction was quenched by water (1.5 mL). The mixture was added into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography on silica gel (hexane/EtOAc = 50/50) to afford benzotriazole **4** (31 mg, 52%).

4.7. Procedure for Scheme 5, eq 2.

To an oven dried 2-necked 10 mL round bottom flask containing a stirring bar was added 1-(difluoromethyl)-1*H*-benzo[*d*][1,2,3]triazole (**1**, 84.6 mg, 0.50 mmol). The flask was capped with two rubber septa, purged with Ar for 10 min, and left under Ar atmosphere. To a 4 mL vial was added 1,1-diphenylethylene (0.35 mL). The vial was purged with Ar and left under Ar atmosphere. To the reaction flask was added anhydrous THF (0.5 mL) via a syringe at rt. To the reaction mixture was added 1,1-diphenylethylene (0.18 mL, 1.02 mmol) via a syringe at rt. LHMDS (1.0 M in THF, 1.0 mL) was slowly dropped to the solution at rt. After stirring under Ar at rt for 20 h, the reaction was quenched by water (1.5 mL). The mixture was added into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4. The organic layer was concentrated and purified by flash column chromatography on silica gel (hexane/EtOAc = 50/50) to afford benzotriazole **4** (30 mg, 50%). Note: The ^{1}H NMR spectrum of an authentic sample of (2,2-difluorocyclopropane-1,1-diyl)dibenzene was consistent with the previous report [13].

Declaration of competing interest

We have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org

Highlights

Formation of difluoromethyl anion generated directly from difluoromethyl heterocyles

Addition reaction of difluoromethyl anion to benzophenone and benzaldehyde

Strategy to figure out plausible mechanism using deuterium labeling experiments

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: