有机化学 DOI: 10.6023/cjoc202204024 研究论文
Chinese Journal of Organic Chemistry ARTICLE

# 碱催化下单-1-取代-1,2,3-三唑选择性氢-氘交换反应研究

李冬英 邱闪光 陈昱学 赵艳梅 魏云龙
吴禄勇* 陈文豪
(海南师范大学化学与化工学院 热带药用资源化学教育部重点实验室 海口 571158)

**摘要** 探索了一种碱催化下单-1-取代的 1,2,3-三唑的选择性氢-氘交换反应. 以 *t*-BuOK, *t*-BuONa 或 $Cs_2CO_3$ 作为碱, 单-1-取代的 1,2,3-三唑在二甲基亚砜(DMSO)-$d_6$ 溶液中可以选择性地实现 C5 位置的氘代. 在相应的反应条件下, 4,5-双氘代 1,2,3-三唑在相应的反应条件下进行氘-氢交换, 可以选择性地实现 C5 位置的去氘代过程, 从而实现 C4 氘代的 1,2,3-三唑化合物的合成. 同时, 三唑环辅助下的苯环上的氢-氘交换过程也被观察到.
**关键词** 氢-氘交换; 标记化合物; 单-1-取代-1,2,3-三唑; 碱催化

# Research for the Reaction of Base-Catalyzed Selective Hydrogen-Deuterium Exchange in Mono-1-substituted 1,2,3-Triazoles

Li, Dongying Qiu, Shanguang Chen, Yuxue Zhao, Yanmei Wei, Yunlong
Wu, Luyong* Chen, Wenhao
(*Key Laboratory of Tropical Medicinal Resources Chemistry of Ministry of Education, College of Chemistry and Chemical Engineering, Hainan Normal University, Haikou 571158*)

**Abstract** An effective and selective deuteration of mono-1-substituted 1,2,3-triazoles using base-catalyzed hydrogen-deuterium exchange is proposed. The H/D exchange was selectively conducted at C5 position of 1,2,3-triazoles with catalytic amount of *t*-BuOK, *t*-BuONa or $Cs_2CO_3$ in dimethyl sulfoxide DMSO-$d_6$. From corresponding 1,2,3-triazoles via H/D exchange process, 5-deutero and 4-deutero mono-1-substituted 1,2,3-triazoles were given from corresponding 1,2,3-triazoles respectively. In addition, the triazole-induced deuteration on phenyl ring was observed.
**Keywords** H/D exchange; labeling compounds; mono-1-substituted 1,2,3-triazoles; base-catalysis

## 1 Introduction

Deuteration, as an important labeling strategy for inorganic molecules, has received long-term significant attention, and has been widely used in the synthesis of deuterium-labeled compounds, which were widely applied to the organic reaction mechanism investigation, drug metabolism, and analysis fields.[1] As a result, the synthesis of deuterium compounds has become an important technology in organic chemistry and pharmaceutical chemistry with wide and increasing interest,[2] especially since the deutetrabenazine (Austedo) was approved by the U. S. Food and Drug Administration (FDA) in 2017.[3-4] Among these deuterium-labeled approaches, hydrogen-deuterium (H/D) exchange reactions have been exploited as a direct and popular strategy.[5] Up to now, many methods have been extremely developed in H/D exchange reactions, including base-,[6] Brønsted acid-,[7] organocatalyst-,[8] transition metal-catalyzed[9] and photoredox[10]-catalyzed H/D exchanges.

Because of bearing abundant C—H bonds in deuterium-labeled compounds, the selective H/D exchanges were highly important in the deuteration. Generally, because of the reactivity and the significance, selective H/D exchanges of C($sp^2$)—H bonds in (hetero)aromatic rings were highly desired. In the past decade, many aromatic moieties have been investigated to produce corresponding regioselective deuterium-labelling compounds, including phenols,[10-11] fluoroarenes,[12] anilines,[9e,13] indoles,[14] aro-

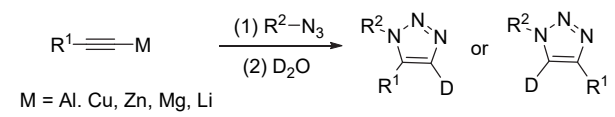
* Corresponding author. E-mail: wuluyong@hainnu.edu.cn
Received April 10, 2022; revised May 18, 2022; published online June 8, 2022.
Project supported by the Hainan Provincial Natural Science Foundation (No. 219MS044), the National Natural Science Foundation of China (No. 22167013) and the Graduate Student Innovation Research Project of College of Chemistry and Chemical Engineering, Hainan Normal University (No. Hgs202006).
海南省自然科学基金(No. 219MS044)、国家自然科学基金(No. 22167013)和海南师范大学化学与化工学院研究生创新基金(No. Hgs202006)资助项目.

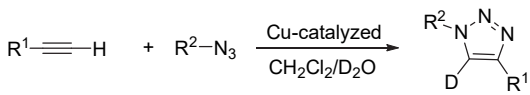
matic carboxyl compounds,[15] five-membered aromatic heterocycles,[16] and so on.[17]

1,2,3-Triazole, as a special five-membered heterocycle, has received increasing attention in recent years, due to its unique properties in medicinal and material chemistry.[18] In deuterium-labeled 1,2,3-triazoles, early researchers have developed the deuteration of aluminum-,[19] copper-,[20] magnesium-[21] or lithium-[22] 1,2,3-triaozle intermediates to synthesize C4 or C5 deuterated 1,2,3-triaozle (Scheme 1a). These metallic-triazole intermediates were generated from the cycloaddition of stoichiometric metallic alkynes with azides. Meanwhile, Lakshman group[23] has described a hydrogen-deuterium exchange protocol of C5 deuterated 1,4-disubsituted 1,2,3-triazoles via copper-catalyzed azide-alkyne cycloaddition (CuAAC) in $CH_2Cl_2/D_2O$ biphasic medium (Scheme 1b). In fact, the electron density distributions of 1,2,3-triazoles caused the different reactivity of C4 and C5 positions of 1,2,3-triazoles in lithiation or arylation process.[24-25] And in 2016, Chen group[26] has described this difference between C4 and C5 positions of 1,2,3-triazole in 1,4- or 1,5-disubsituted 1,2,3-triazoles in $Cs_2CO_3$-catalyzed C5 hydrogen-deuterium exchanges (Scheme 1c).

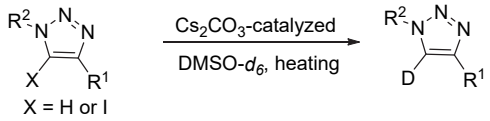
(a) Deuteration of metal-1,2,3-triaozle intermediates



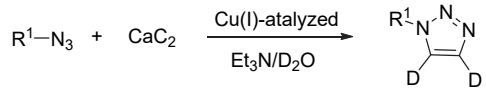

(b) Synthesis of deuterated 1,2,3-triazoles from CuAAC reaction in $CH_2Cl_2/D_2O$ by Lakshman group in 2012



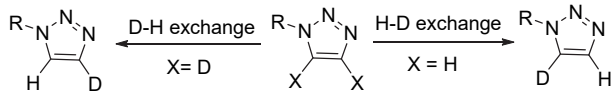

(c) Base-catalyzed deuteration of 1,4-disubstitued 1,2,3-triazoles by Chen group in 2016




(d) Dideuterated mono-1-substituted 1,2,3-triazoles from azides with $CaC_2$ and $D_2O$ by Novak group in 2010 and Ananikov group in 2021




(e) This work: selective deuteration of mono-1-substituted 1,2,3-triazoles




**Scheme 1** Deuteration of 1,2,3-triazoles

Mono-1-substituted 1,2,3-triazoles were a special class of 1,2,3-triazoles which have important application in pharmaceutical chemistry.[27] Recently, Novák group[28a] and Ananikov group[28b] developed the synthetic procedures for mono-1-substituted 4,5-dideutero triazoles from organic azides using *in situ* generated deuterated acetylene (Scheme 1d). However, it is still desiring to afford regioselective labeling 4,5-unsubstituted 1,2,3-triazoles using convenient method. Considering the electron density distributions of 1,2,3-triazoles, base-mediated H/D exchange would provide a practical opportunity to selectively deuterated mono-1-substituted 1,2,3-triazoles. Because of our interest in 1,2,3-triazole chemistry, we demonstrate a base-catalyzed selective and efficient deuteration of mono-1-substituted 1,2,3-triazoles (Scheme 1e).

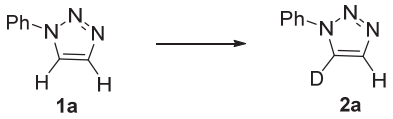
## 2 Results and discussion

Initially, the deuteration of mono-1-phenyl 1,2,3-triazoles was implemented in deuterated solvents in the presence of bases. To our delight, mono C5-deuterated product was produced in DMSO-$d_6$ in the presence of a series of chosen base, and this position selectivity is coinciding with the acidity of $sp^2$-C—H bond in 1,2,3-triazoel ring (Table 1). When the reaction was carried out with 0.2 equiv. of $Cs_2CO_3$ at 80 ℃ for 6 h, excellent deuteration incorporation (97%) on C5 was given (Entry 1, Table 1). Considering the acidity of the C—H bond in C5 position, different bases have been used to test this H/D exchange reaction. When $K_2CO_3$ was also examined at 80 ℃, the deuteration incorporation was only 7% (Entry 2, Table 1). To avoid heating and lessen energy consumption in this progress, the reaction temperature was decreased to 40 ℃ using $Cs_2CO_3$ as base, and the deuteration incorporation was disappointedly reduced to 71% (Entry 3, Table 1). Commercially available alkali *tert*-butoxides were applied in this deuteration progress in DMSO-$d_6$ at room temperature. When 10 mol% *t*-BuOLi was used, the deuteration incorporation at C5 was 60% (Entry 4, Table 1). Relatively, the strong bases, *t*-BuONa and *t*-BuOK, were applied into the H/D exchanges and gave better results at room temperature (Entry 5 and 7, Table 1). Probably, the strong base gave the higher deuteration incorporation at ambient temperature. However, when elevating the temperature to 80 ℃ using *t*-BuOK as base, the H/D exchange was implemented not only at C5 positions (100% deuteration incorporation) but also at C4 positions (31% deuteration incorporation). Obviously, the H/D exchanges were directly influenced by the different acidities at C4 and C5 positions of mono-1-substituted 1,2,3-triazole. In H/D exchange at C5 of 1,2,3-triazole, $Cs_2CO_3$, *t*-BuONa and *t*-BuOK could also gave the excellent conversion, good selectivity and high deuteration incorporation.

With these efficient protocols for base-catalyzed selective H/D exchange of mono-1-substituted 1,2,3-tirazoles in hand, its application for the synthesis of other mono-C5-deuterated-1,2,3-triazoles was tested, and the results were shown in Table 2. With $Cs_2CO_3$, *t*-BuONa or *t*-BuOK as catalyst in random, 1,2,3-triazoles **1** bearing electron-donating or electron-withdrawing phenyl rings were efficiently deuterated with excellent deuteration incorporation. The H/D exchanges were regioselectively proceeded at C5-position of triazoles with high isotopic enrichment, and C4-position has not participated in these H/D exchange

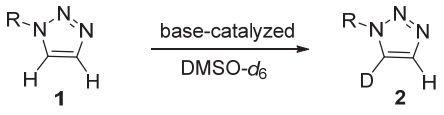
**Table 1** Optimization of the reaction conditions for selective deuteration of 4,5-unsubstituted 1,2,3-triazoles[a]




| Entry | Solvent | Base ($x$ equiv.) | Temperature | Time/h | Yield[b]/% | D content[c]/% |
|---|---|---|---|---|---|---|
| 1 | DMSO-$d_6$ | $Cs_2CO_3$ (0.2 equiv.) | 80 ℃ | 6 | 98 | 98 |
| 2 | DMSO-$d_6$ | $K_2CO_3$ (0.2 equiv.) | 80 ℃ | 6 | 99 | 7 |
| 3 | DMSO-$d_6$ | $Cs_2CO_3$ (0.2 equiv.) | 40 ℃ | 6 | 98 | 71 |
| 4 | DMSO-$d_6$ | LiO$^t$Bu (0.2 equiv.) | r.t. | 6 | 97 | 60 |
| 5 | DMSO-$d_6$ | NaO$^t$Bu (0.2 equiv.) | r.t. | 6 | 99 | 89 |
| 6 | DMSO-$d_6$ | NaO$^t$Bu (0.1 equiv.) | r.t. | 6 | 97 | 97 |
| 7 | DMSO-$d_6$ | KO$^t$Bu (0.2 equiv.) | r.t. | 6 | 98 | 98 |
| 8 | DMSO-$d_6$ | KO$^t$Bu (0.1 equiv.) | r.t. | 6 | 98 | 97 |
| 9 | Acetone-$d_6$ | KO$^t$Bu (0.1 equiv.) | r.t. | 6 | 98 | 0 |
| 10 | $D_2O$ | KO$^t$Bu (0.1 equiv.) | r.t. | 6 | 99 | 0 |
| 11 | $CDCl_3$ | KO$^t$Bu (0.1 equiv.) | r.t. | 6 | 97 | 0 |
| 12 | DMSO-$d_6$ | Without | r.t. | 6 | 98 | 0 |

[a] Reaction conditions: all reactions were performed with **1a** (30 mg, 0.2 mmol), base, solvent (0.5 mL) in enclosed dry vial. [b] Isolated yield. [c] Deuterium incorporation was determined by $^1$H NMR spectroscopy.

**Table 2** Synthesis of various C5-deutero 1,2,3-triazoles[a]




| Entry | R | Product | Method | Yield[b]/% | D content[c]/% |
|---|---|---|---|---|---|
| 1 | Ph | **2a** | A, 6 h | 96 | 97 |
| 2 | $p$-$CH_3C_6H_4$ | **2b** | B, 6 h | 96 | 93 |
| 3 | $m$-$CH_3C_6H_4$ | **2c** | A, 6 h | 98 | 96 |
| 4 | $p$-$CH_3OC_6H_4$ | **2d** | B, 12 h | 97 | 98 |
| 5 | $o$-$CH_3OC_6H_4$ | **2e** | B, 8 h | 95 | 100 |
| 6 | $o$-$EtOC_6H_4$ | **2f** | A, 6 h | 93 | 96 |
| 7 | $p$-$EtOC_6H_4$ | **2g** | C, 6 h | 95 | 96 |
| 8 | $p$-$CNC_6H_4$ | **2h** | C, 6 h | 95 | 96 |
| 9 | $m$-$CNC_6H_4$ | **2i** | B, 2.5 h | 96 | 93 |
| 10 | $p$-$ClC_6H_4$ | **2j** | B, 3.5 h | 97 | 99 |
| 11 | $o$-$ClC_6H_4$ | **2k** | A, 6 h | 97 | 70 |
| 12 | $p$-$BrC_6H_4$ | **2l** | C, 6 h | 96 | 96 |
| 13 | $m$-$BrC_6H_4$ | **2m** | B, 4 h | 98 | 99 |
| 14 | $m$-$CF_3C_6H_4$ | **2n** | B, 2.5 h | 98 | 97 |
| 15 | $n$-$C_9H_{19}$ | **2o** | B, 6 h | 95 | 96 |
| 16 | $PhCH_2$ | **2p** | B, 6 h | 93 | 100 ($\alpha$-D: 98) |

[a] Reactions were performed using 0.2 mmol of **1** with 0.5 mL of DMSO-$d_6$ in the presence of base in enclosed dry vial: method A: $Cs_2CO_3$ (0.2 equiv.) under 80 ℃; method B: $t$-BuONa (0.1 equiv.) under ambient temperature; method C: $t$-BuOK (0.1 equiv.) under ambient temperature. [b] Isolated yield. [c] Deuterium incorporation was determined by $^1$H NMR spectroscopy.

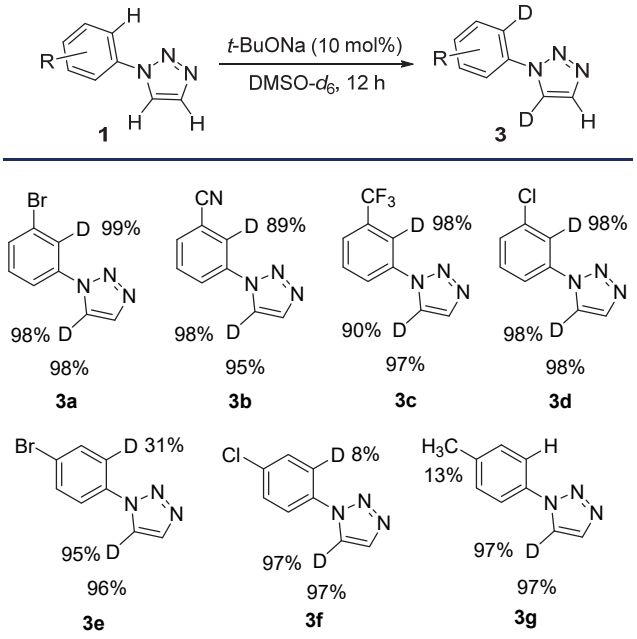
processes. For 1,2,3-triazoles **1b** and **1c**, the deuteration of $CH_3$ group has not been observed in current conditions. When Cl, $CF_3$ and CN were present on triazoles (**1i**, **1j** and **1n**), the H/D exchanges need shorter reaction time. In 1-$n$-$C_9H_{19}$ 1,2,3-triazole **1o**, H/D exchange with high selectivity was also observed at C5 of triazole ring, and $\alpha$-H of alkyl group did not anticipate this process. Relatively, in the reaction of 1-benzyl 1,2,3-triazole **1p**, both C5-H of triazole ring and $CH_2$ position were deuterated with 10 mol% $t$-BuONa.

Interestingly, when accidentally prolonged the reaction of **1m** to 12 h with $t$-BuONa (10 mol%), the novel and efficient deuteration of phenyl ring was observed to give the product **3a** (shown in Table 3). This result promoted us to apply this novel labeling process to other mono-1-substituted 1,2,3-tirazoles. As shown in Table 3, several electron-deficient triazoles with *meta*-substituents transformed smoothly to dideutero triazoles (**3a**～**3d**). When $Cs_2CO_3$ was used as the catalyst, the deuteration of phenyl ring was also observed but obviously with lower deuterium incorporation. In addition, when Br or Cl group was on *para*-position of phenyl ring, the deuteration incorporation was obviously lower than that with Br or Cl group on *meta*-position (**3e** and **3f**). Substituent Cl on *para*-position **3f** of phenyl ring could give lower deuteration incorporation than **3e** with Br on *para*-position. Relatively, electron-rich 1,2,3-triazole was deuterated not at phenyl ring but at $CH_3$ group on *pata*-position with 13% deuteration incorporation (**3g**). The deuteration of phenyl ring could be facilitated by the coordination of N(2)-atom of triazoles[25] and the electron-deficient property of *meta*-substituted group. Obviously, there was a significant difference in H/D exchange rate of C—H bonds between phenyl ring and triazole ring, and the reaction time was important factor to influence the deuteration process.

C4-deutero 1,2,3-triazoles, as a special class of triazoles, could be provided from metal-alkylides with azides and

**Table 3** Base-catalyzed multi-position deuteration of aryl-substituted 1,2,3-triazoles[a]




[a] Reaction conditions: all reactions were performed with **1** (0.2 mmol), *t*-BuONa (10 mol%), 0.5 mL of solvent in enclosed dry vial under ambient temperature for 12 h; Isolated yield was given; Deuterium incorporation was determined by $^1$H NMR spectroscopy.

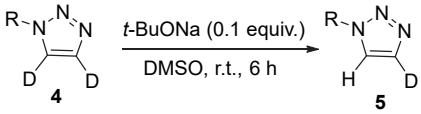
then quenching by $D_2O$. In mono-1-substituted 1,2,3-triazoles, the method for preparation of C4-deutero structures is still lacking. In 2010, Novák group[25] reported the convenient and efficient synthesis of 4,5-dideutero triazoles from copper-catalyzed click reaction between azides and calcium carbide (as an acetylene surrogate) with the addition of $D_2O$. To expand the application of selectivity of H/D exchange, 4,5-dideutero triazoles were used to synthesize C4-deuterated 1,2,3-triazoles via dedeuteration process. Comparing with the NMR spectrum of 4,5-dideutero triazoles and C4-deuterated 1,2,3-triazoles, D atom on C4 did not participate in the dedeuteration process (see Supporting Information). As shown in Table 4, 4,5-dideutero triazoles could efficiently and selectively remove C5 deuterium atom to give C4-deutero 1,2,3-triazoles in DMSO with 10 mol% *t*-BuONa. Substituted groups on phenyl rings could be RO (**5b**～**5d**), $CH_3$ (**5e**), halo (**5f**～**5j**), CN (**5k**), and $CF_3$ (**5l**). And in the identical reaction condition and time, electron-deficient triazoles afforded higher dedeuteration rate (**5f**～**5l**).

According to references, a plausible reaction mechanism for base-catalyzed H-D exchange is proposed in Scheme 2. Initially, the base catches a proton from triazole **1** to produce the intermediate **A**. Subsequently, the intermediate **A** accepts a deuterium from DMSO-$d_6$ to give deuteron 1,2,3-triazole **2**. In a dedeuteration progress, D-H exchange takes place in a similar procedure.

## 3 Conclusions

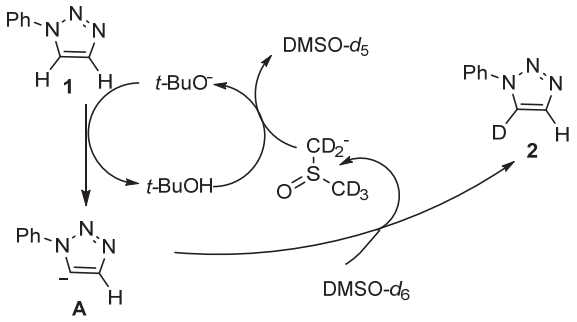
In conclusion, base-catalyzed hydrogen-deuterium exchange in mono-1-substituted 1,2,3-triazoles has been investigated, and this reaction is regioselectively occurring in C-5 position of 1,2,3-triazoles in DMSO-$d_6$ or DMSO. From this hydrogen-deuterium exchange process, C5 deutero 1,2,3-triazoles were provided from mono-1-substituted 1,2,3-triazoles in DMSO-$d_6$ with highly selective deuterium incorporation, and C4 deutero 1,2,3-triazoles could be provided from 4,5-dideutero 1,2,3-triazoles in DMSO, respectively. Additionally, triazoles-introduced H/D exchanges on N(1) aryl rings were observed to provide multi-position deuterated compounds.

**Table 4** Base-catalyzed selective dedeuteration of 4,5-dideutero 1,2,3-triazoles to synthesize 4-deutero 1,2,3-triazoles[a]




| Entry | R | Product | Yield[b]/% | D-4[c]/% | D-5[c]/% |
|---|---|---|---|---|---|
| 1 | Ph | **5a** | 93 | 96 | 6 |
| 2 | *p*-$CH_3OC_6H_4$ | **5b** | 95 | 87 | 5 |
| 3 | *o*-$CH_3OC_6H_4$ | **5c** | 92 | 92 | 3 |
| 4 | *p*-$EtOC_6H_4$ | **5d** | 95 | 92 | 4 |
| 5 | *m*-$CH_3C_6H_4$ | **5e** | 91 | 91 | 11 |
| 6 | *p*-$ClC_6H_4$ | **5f** | 96 | 97 | 3 |
| 7 | *m*-$ClC_6H_4$ | **5g** | 95 | 92 | 0 |
| 8 | *p*-$BrC_6H_4$ | **5h** | 97 | 96 | 3 |
| 9 | *m*-$BrC_6H_4$ | **5i** | 96 | 95 | 0 |
| 10 | *o*-$BrC_6H_4$ | **5j** | 95 | 95 | 5 |
| 11 | *p*-$CNC_6H_4$ | **5k** | 97 | 91 | 0 |
| 12 | *m*-$CF_3C_6H_4$ | **5l** | 89 | 95 | 0 |

[a] Reactions were performed using 0.2 mmol of **4** with 0.5 mL of DMSO in the presence of *t*-BuONa (10 mol%) in enclosed dry vial. [b] Isolated yield. [c] Deuterium incorporation was determined by $^1$H NMR spectroscopy.




**Scheme 2** Proposed mechanism

## 4 Experimental section

### 4.1 Instruments and reagents

Melting points were measured with a Beijing-Taike X-4 apparatus without corrected. NMR spectra were recorded on a Brucker 400 MHz spectrometer ($^1$H NMR) and 100 MHz ($^{13}$C NMR) using $CDCl_3$ as solvent unless noted otherwise. Chemical shifts are reported with TMS as an internal standard. Column chromatography was carried out on silica gel (200～300 mesh). All chemicals used were of reagent grade and all reactions carried out under argon. All

solvents were commercial and dried using standard procedures. To allow full relaxation of all hydrogen environments for accurate integration, all quantitative $^1$H NMR spectra on isotopic exchange reactions were acquired using 32 scans with a 30 s relaxation delay time. Deuterium incorporation was determined by $^1$H NMR against the integral value of the peak in the corresponding $^1$H NMR spectra of known undeuterated compounds.

### 4.2 General procedure for the synthesis of mono-1-substituted 1,2,3-triazoles **1**

To a solution of organic azide (1.0 mmol), $Et_3N$ (0.4 mmol) in DMSO (2.0 mL), CuI (0.1 mmol) was added into the mixture under $N_2$ atmosphere. Then, the flask was purged by acetylene for several times with an acetylene gas balloon. The mixture was stirred at room temperature for 24 h. Then, the mixture was diluted with EtOAc (30 mL), and washed by $H_2O$ (10 mL×4) and brine. The organic phase was dried over $Na_2SO_4$ (anhyd.). After removal of the solvent, the residue was purified on silica-gel with petroleum ether (PE)/EtOAc ($V$∶$V$=4∶1 to 1∶2) as the eluent to give mono-1-substituted 1,2,3-triazoles **1**.[29] Caution: Azides are potentially explosive compounds and should be handled with great care.

### 4.3 General procedure for the synthesis of 4,5-dideutero 1,2,3-triazoles **4**[28]

To a 10 mL flask equipped balloon, azides (1.0 mmol) 0.55～0.57 g calcium carbide (techn. grade, ⩾75%), CuI (0.05 mmol), and $Et_3N$ (1.0 mL) was added under $N_2$ atmosphere. The mixture was stirred, and $D_2O$ (0.5 mL) was added to each part. The mixture was stirred at 50 ℃ for 3 d. The mixture was diluted with EtOAc (30 mL), and washed by $H_2O$ (10 mL×4) and brine. The organic phase was dried over $Na_2SO_4$ (anhyd.). After removal of the solvent, the residue was purified on silica-gel with PE/EtOAc ($V$∶$V$=4∶1 to 1∶2) as the eluent to give 4,5-dideutero mono-1-substituted 1,2,3-triazoles **4**.

### 4.4 General procedure for the synthesis of 5-deutero 1,2,3-triazoles **2**

To a solution of mono-substituted 1,2,3-triazole (**1**, 0.2 mmol) in the dry DMSO-$d_6$ (0.5 mL) was added corresponding base in (0.02 mmol) a dry vial. After enclosing the cap, the reaction mixture was stirred at room temperature. After the given reaction time, the reaction mixture was quenched by 1 mL of $NH_4Cl$ solution, diluted with 20 mL of ethylacetate, washed with water (10 mL×3) and brine, dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give product **2a**～**2p**.

1-Phenyl-1*H*-1,2,3-triazole-5-*d* (**2a**): White solid, m.p. 52～53 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.00 (d, $J$=1.1 Hz, 0.02H), 7.84 (s, 1H), 7.77～7.70 (m, 2H), 7.55～7.49 (m, 2H), 7.47～7.40 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.15, 134.46, 129.89, 128.90, 120.79. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.00 (d, $J$=1.1 Hz, 1H).

1-(*p*-Tolyl)-1*H*-1,2,3-triazole-5-*d* (**2b**): White solid, m.p. 78～79 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.96 (s, 0.07H), 7.82 (s, 1H), 7.60 (d, $J$=8.2 Hz, 2H), 7.31 (d, $J$=8.1 Hz, 2H), 2.41 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 139.00, 134.82, 134.34, 130.35, 120.67, 21.20. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.96 (s, 0.07H).

1-(*m*-Tolyl)-1*H*-1,2,3-triazole-5-*d* (**2c**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.98 (d, $J$=1.1 Hz, 0.04H), 7.82 (s, 1H), 7.56 (s, 1H), 7.50 (d, $J$=8.1 Hz, 1H), 7.38 (t, $J$=7.8 Hz, 1H), 7.23 (d, $J$=7.6 Hz, 1H), 2.43 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 140.11, 137.06, 129.63, 121.44, 117.81, 21.48. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.98 (d, $J$=1.1 Hz, 0.04H).

1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole-5-*d* (**2d**): White solid, m.p. 77～79 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.91 (s, 0.03H), 7.80 (s, 1H), 7.61 (d, $J$=9.0 Hz, 2H), 6.99 (d, $J$=9.0 Hz, 2H), 3.84 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 159.90, 130.54, 122.36, 114.86, 55.70. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.91 (s, 1H).

1-(2-Methoxyphenyl)-1*H*-1,2,3-triazole-5-*d* (**2e**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.11 (d, $J$=0.9 Hz, 0.02H), 7.83～7.72 (m, 2H), 7.42 (td, $J$=8.0, 1.7 Hz, 1H), 7.13～7.04 (m, 2H), 3.87 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 151.30, 133.22, 130.19, 126.41, 125.66, 121.34, 112.41, 56.09. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.11 (d, $J$=0.9 Hz, 1H).

1-(2-Ethoxyphenyl)-1*H*-1,2,3-triazole-5-*d* (**2f**): Yellow solid, m.p. 74～76 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.17 (d, $J$=1.1 Hz, 0.01H), 7.80 (d, $J$=6.8 Hz, 2H), 7.38 (ddd, $J$=8.3, 7.5, 1.7 Hz, 1H), 7.12～7.03 (m, 2H), 4.11 (q, $J$=7.0 Hz, 2H), 1.38 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 150.47, 133.16, 130.02, 126.54, 125.47, 121.25, 113.38, 64.80, 14.73. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.17 (d, $J$=1.1 Hz, 1H).

1-(4-Ethoxyphenyl)-1*H*-1,2,3-triazole-5-*d* (**2g**): White solid, m.p. 74～75 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.90 (s, 0.04H), 7.80 (s, 1H), 7.65～7.55 (m, 2H), 7.03～6.95 (m, 2H), 4.06 (q, $J$=7.0 Hz, 2H), 1.43 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 159.30, 134.25, 130.38, 122.37, 115.35, 64.00, 14.82. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.90 (s, 1H).

4-(1*H*-1,2,3-triazol-1-yl-5-*d*)benzonitrile (**2h**): Yellow solid, m.p. 149～152 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.93 (d, $J$=8.7 Hz, 2H), 7.88 (s, 1H), 7.84 (d, $J$=8.6 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 139.86, 135.09, 134.06, 120.79, 117.79, 112.51. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.08 (d, $J$=1.2 Hz, 1H).

3-(1*H*-1,2,3-triazol-1-yl-5-*d*)benzonitrile (**2i**): Pale yellow solid, m.p. 130.5～132 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.075 (t, $J$=2.2 Hz, 1H), 8.05 (dt, $J$=7.9, 1.2

Hz, 1H), 7.88 (s, 1H), 7.73 (dt, $J$=7.8, 1.4 Hz, 1H), 7.68 (t, $J$=7.9 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.65, 135.03, 132.21, 131.06, 124.72, 123.84, 117.47, 114.29. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.09～8.02 (m, 1H).

1-(4-Chlorophenyl)-1*H*-1,2,3-triazole-5-*d* (**2j**): Pale yellow solid, m.p. 111～113 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.98 (s, 0.01H), 7.83 (s, 1H), 7.72～7.63 (m, 2H), 7.52～7.45 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 135.61, 134.67, 130.05, 121.91, 121.59. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.98 (s, 0.01H).

1-(2-Chlorophenyl)-1*H*-1,2,3-triazole-5-*d* (**2k**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.99 (d, $J$=1.1 Hz, 0.30H), 7.83 (s, 1H), 7.61～7.52 (m, 2H), 7.45～7.40 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 134.91, 133.47, 130.82, 128.73, 127.99, 127.88, 127.71, 125.75. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.99 (d, $J$=1.1 Hz, 1H).

1-(4-Bromophenyl)-1*H*-1,2,3-triazole-5-*d* (**2l**): White solid, m.p. 145～146 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.99 (s, 0.04H), 7.86 (s, 1H), 7.71～7.60 (m, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 134.63, 132.97, 126.24, 122.47, 122.07. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.99 (s, 1H).

1-(3-Bromophenyl)-1*H*-1,2,3-triazole-5-*d* (**2m**): White solid, m.p. 100～101 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.99 (s, 0.01H), 7.94 (t, $J$=2.0 Hz, 1H), 7.84 (s, 1H), 7.74～7.66 (m, 1H), 7.57 (ddd, $J$=8.0, 1.9, 1.0 Hz, 1H), 7.40 (t, $J$=8.1 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 138.06, 134.68, 131.92, 131.22, 123.87, 123.45, 119.24. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.99 (s, 0.01H).

1-(3-(Trifluoromethyl)phenyl)-1*H*-1,2,3-triazole-5-*d* (**2n**): Yellow solid, m.p. 58～60 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.03 (s, 0.02H), 8.00～7.95 (m, 1H), 7.88 (s, 1H), 7.75～7.64 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.44, 134.91, 132.58 (q, $J$=32.6, 31.7 Hz), 130.73, 126.14 (q, $J$=273.7 Hz), 125.55 (q, $J$=3.7 Hz), 123.81, 122.07, 117.68 (q, $J$=3.9 Hz); $^{19}$F NMR (377 MHz, $CDCl_3$) $\delta$: −62.85. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.03 (s, 1H).

1-Nonyl-1*H*-1,2,3-triazole-5-*d* (**2o**): White solid, m.p. 30～32 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.66 (s, 0.91H), 7.52 (d, $J$=1.0 Hz, 0.04H), 4.35 (t, $J$=7.2 Hz, 2H), 1.87 (q, $J$=7.3 Hz, 2H), 1.61～1.13 (m, 12H), 0.83 (d, $J$=7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 133.66, 123.01, 50.23, 31.85, 30.38, 29.38, 29.20, 29.04, 26.52, 22.68, 14.12. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.52 (d, $J$=1.0 Hz, 1H).

1-(Phenylmethyl-$d_2$)-1*H*-1,2,3-triazole-5-*d* (**2p**): White solid, m.p. 51～53 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.70 (s, 1H), 7.42～7.32 (m, 3H), 7.26 (dd, $J$=7.4, 2.2 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 134.65, 134.16, 129.18, 128.82, 128.10. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.60 (s, 2H), 5.45 (s, 2H).

### 4.5 General procedure for the synthesis of multi-position deuteration of aryl-substituted 1,2,3-triazoles **3**

To a solution of mono-substitued 1,2,3-triazole (**1**, 0.2 mmol) in the dry DMSO-$d_6$ (0.5 mL) was added NaO$^t$Bu in (0.02 mmol) a dry vial. After enclosing the cap, the reaction mixture was stirred at room temperature. After the given reaction time, the reaction mixture was quenched by 1 mL of $NH_4Cl$ solution, diluted with 20 mL of ethyl acetate, washed with water (10 mL×3) and brine, dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give product **3a**～**3d**.

1-(3-Bromophenyl-2-*d*)-1*H*-1,2,3-triazole-5-*d* (**3a**): White solid, m.p. 100～101 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.00 (d, $J$=1.2 Hz, 0.02H), 7.92 (t, $J$=2.0 Hz, 0.01H), 7.83 (s, 1H), 7.68 (dd, $J$=8.1, 1.0 Hz, 1H), 7.55 (dd, $J$=8.0, 1.0 Hz, 1H), 7.38 (t, $J$=8.1 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.91, 134.65, 131.85, 131.17, 123.28, 119.15. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.00 (d, $J$=1.2 Hz, 1H), 7.92 (t, $J$=2.0 Hz, 1H).

3-(1*H*-1,2,3-triazol-1-yl-5-*d*)benzonitrile-2-*d* (**3b**): Pale yellow solid, m.p. 130.5～132 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.14 (d, $J$=2.1 Hz, 0.11H), 8.09～8.02 (m, 1H), 7.89 (s, 1H), 7.76～7.64 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.50, 134.95, 132.11, 130.96, 124.61, 123.74, 121.68, 117.36, 114.11. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.14 (d, $J$=2.1 Hz, 1H), 8.09～8.02 (m, 2H).

1-(3-(Trifluoromethyl)phenyl-2-*d*)-1*H*-1,2,3-triazole-5-*d* (**3c**): Yellow solid, m.p. 58～60 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.08 (d, $J$=1.2 Hz, 0.10H), 8.03 (s, 0.02H), 7.97 (dd, $J$=7.2, 1.9 Hz, 1H), 7.88 (s, 1H), 7.73～7.63 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.39, 134.89, 132.52 (q, $J$=33.4 Hz), 130.72, 130.62, 125.53 (q, $J$=34.3 Hz), 123.80, 123.5 (q, $J$=279.7 Hz), 121.87; $^{19}$F NMR (377 MHz, $CDCl_3$) $\delta$: −62.85. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.08 (d, $J$=1.2 Hz, 1H), 8.03 (s, 1H).

1-(3-Chlorophenyl-2-*d*)-1*H*-1,2,3-triazole-5-*d* (**3d**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.01 (d, $J$=1.1 Hz, 0.02H), 7.84 (s, 1H), 7.78 (t, $J$=2.0 Hz, 0.02H), 7.64 (dd, $J$=7.8, 1.2 Hz, 1H), 7.49～7.37 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.81, 135.54, 134.60, 130.86, 128.86, 120.91, 120.65, 118.60. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.01 (d, $J$=1.1 Hz, 1H), 7.78 (t, $J$=2.0 Hz, 1H).

### 4.6 General procedure for the synthesis of 4-deutero 1,2,3-triazoles **5**

To a solution of 4,5-dideutero 12,3-triazole (**4**, 0.2 mmol) in the dry DMSO (0.5 mL) was added correspond-

ing base in a dry vial. After enclosing the cap, the reaction mixture was stirred at room temperature. After the given reaction time, the reaction mixture was quenched by 1 mL of $NH_4Cl$ solution, diluted with 20 mL of ethylacetate, washed with water (10 mL×3) and brine, dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure and the residue were purified by flash chromatography to give product **5a**～**5l**.

1-Phenyl-1*H*-1,2,3-triazole-4-*d* (**5a**): White solid, m.p. 52～53 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.00 (s, 0.94H), 7.83 (s, 0.04H), 7.73 (d, $J$=9.5 Hz, 2H), 7.51 (t, $J$=7.7 Hz, 2H), 7.47～7.38 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.04, 129.79, 128.81, 124.64, 122.17, 120.69. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.00 (s, 1H), 7.83 (s, 1H).

1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole-4-*d* (**5b**): White solid, m.p. 77～79 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.90 (s, 0.95H), 7.80 (s, 0.13H), 7.62 (d, $J$=9.0 Hz, 2H), 7.01 (d, $J$=9.0 Hz, 2H), 3.85 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 159.93, 134.37, 130.59, 122.41, 121.91, 114.88, 55.73. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.90 (s, 1H), 7.80 (s, 1H).

1-(2-Methoxyphenyl)-1*H*-1,2,3-triazole-4-*d* (**5c**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.10 (s, 0.96H), 7.77 (d, $J$=1.1 Hz, 0.08H), 7.73 (dd, $J$=8.1, 1.8 Hz, 1H), 7.39 (td, $J$=8.1, 1.7 Hz, 1H), 7.09～7.04 (m, 2H), 3.84 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 151.20, 133.03, 130.15, 126.26, 125.67, 125.54, 121.20, 112.31, 55.98. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 8.10 (s, 1H), 7.77 (d, $J$=1.1 Hz, 1H).

1-(4-Ethoxyphenyl)-1*H*-1,2,3-triazole-4-*d* (**5d**): White solid, m.p. 74～75 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.90 (s, 0.96H), 7.80 (s, 0.08H), 7.62～7.58 (m, 2H), 7.02～6.96 (m, 2H), 4.07 (q, $J$=7.0 Hz, 2H), 1.43 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 159.23, 130.34, 122.30, 115.28, 63.93, 14.73. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.90 (s, 1H), 7.80 (s, 1H).

1-(*m*-Tolyl)-1*H*-1,2,3-triazole-4-*d* (**5e**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.88 (s, 0.89H), 7.72 (d, $J$=1.1 Hz, 0.09H), 7.47 (s, 1H), 7.40 (d, $J$=8.1 Hz, 1H), 7.29 (t, $J$=7.8 Hz, 1H), 7.14 (d, $J$=7.6 Hz, 1H), 2.34 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 140.11, 137.08, 134.44, 129.62, 121.87, 121.78, 121.45, 117.82, 21.49. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.88 (s, 1H), 7.72 (d, $J$=1.1 Hz, 1H).

1-(4-Chlorophenyl)-1*H*-1,2,3-triazole-4-*d* (**5f**): Pale yellow solid, m.p. 107～110 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.98 (s, 0.97H), 7.84 (s, 0.03H), 7.73～7.67 (m, 2H), 7.53～7.46 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 135.53, 134.59, 129.97, 121.84, 121.60; Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.98 (s, 1H), 7.84 (s, 1H).

1-(3-Chlorophenyl)-1*H*-1,2,3-triazole-4-*d* (**5g**): Yellow solid, m.p. 86～87 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.01 (s, 1H), 7.85 (s, 0.08H), 7.78 (t, $J$=2.0 Hz, 1H), 7.64 (ddd, $J$=7.8, 2.1, 1.2 Hz, 1H), 7.46 (t, $J$=8.0 Hz, 1H), 7.42 (dd, $J$=1.9, 1.2 Hz, 1H), 7.40 (dd, $J$=1.9, 1.2 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.95, 135.69, 130.97, 128.95, 121.73, 121.01, 118.72. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at 7.85 (s, 1H).

1-(4-Bromophenyl)-1*H*-1,2,3-triazole-4-*d* (**5h**): White solid, m.p. 145～146 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.98 (s, 0.97H), 7.84 (s, 0.04H), 7.72～7.57 (m, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 136.09, 134.89, 133.03, 122.55, 122.16, 121.64. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.98 (s, 1H), 7.84 (s, 1H).

1-(3-Bromophenyl)-1*H*-1,2,3-triazole-4-*d* (**5i**): White solid, m.p. 100～101 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.02 (s, 1H), 7.95 (t, $J$=1.9 Hz, 1H), 7.86 (s, 0.05H), 7.71 (d, $J$=8.1 Hz, 1H), 7.58 (d, $J$=7.3 Hz, 1H), 7.41 (t, $J$=8.0 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.95, 131.81, 131.12, 123.76, 123.33, 121.63, 119.13. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.86 (s, 1H).

1-(2-Bromophenyl)-1*H*-1,2,3-triazole-4-*d* (**5j**): Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.95 (s, 0.95H), 7.83 (s, 0.05H), 7.73 (dd, $J$=8.0, 1.4 Hz, 1H), 7.55～7.43 (m, 2H), 7.37 (td, $J$=7.7, 1.9 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 136.58, 133.96, 133.31, 131.26, 128.57, 128.31, 125.71, 118.73. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.95 (s, 1H), 7.83 (s, 1H).

4-(1*H*-1,2,3-triazol-1-yl-4-*d*)benzonitrile (**5k**): Yellow solid, m.p. 149～152 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.10 (s, 1H), 7.94 (d, $J$=8.7 Hz, 2H), 7.89 (s, 0.09H), 7.84 (d, $J$=8.7 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 139.84, 133.99, 121.50, 120.75, 117.71, 112.48. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.89 (s, 1H).

1-(3-(Trifluoromethyl)phenyl)-1*H*-1,2,3-triazole-4-*d* (**5l**): White solid, m.p. 58～60 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.10 (s, 1H), 8.05 (s, 1H), 7.90 (s, 0.05H), 7.70 (q, $J$=8.5, 7.8 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$: 137.37, 134.68, 132.46 (q, $J$=33.5 Hz), 130.61, 125.43 (q, $J$=3.7 Hz), 123.71, 123.32 (q, $J$=270.9 Hz), 121.66, 117.58 (q, $J$=4.0 Hz); $^{19}$F NMR (377 MHz, $CDCl_3$) $\delta$: −62.86. Deuterium incorporation was determined by $^1$H NMR against the integral value of a peak at $\delta$: 7.90 (s, 0.05H).

**Supporting Information** The spectra of $^1$H NMR of compounds of **1a**～**1p**, the $^1$H NMR and $^{13}$C NMR of **2a**～**2p**, **3a**～**3d**, **4a**～**4l**, **5a**～**5l**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

## References


[1] (a) Yang, J. *Deuterium*: *Discovery and Applications in Organic Chemistry*, Elsevier, Amsterdam, **2016**, pp. 1～116.
(b) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev*. **2011**, *111*, 4857.
(c) Hesk, D. J. *Labelled Compd. Radiopharm*. **2020**, *63*, 247.
(d) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem.*, *Int. Ed*. **2018**, *57*, 1758.
(e) Helfenbein, J.; Lartigue, C.; Noirault, E.; Azim, E.; Legailliard, J.; Galmier, M. J.; Madelmont, J. C. *J. Med. Chem*. **2002**, *45*, 5806.
(f) Gardner, K. H.; Kay, L. E. *J. Am. Chem. Soc*. **1997**, *119*, 7599.
(g) Yang, X.; Ben, H.; Ragauskas, A. J. *Asian J. Org. Chem*. **2021**, *10*, 2473.

[2] (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett*. **2007**, *9*, 2333.
(b) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem.*, *Int. Ed*. **2018**, *57*, 3022.
(c) Zhou, R.; Ma, L.; Yang, X.; Cao, J. *Org. Chem. Front*. **2021**, *8*, 426.
(d) Gant, T. G. *J. Med. Chem*. **2014**, *57*, 3595.

[3] Frank, S.; Stamler, D.; Kayson, E.; Claassen, D. O.; Colcher, A. *JAMA Neurol*. **2017**, *74*, 977.

[4] Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. *J. Med. Chem*. **2019**, *62*, 5276.

[5] (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem.*, *Int. Ed*. **2007**, *46*, 7744.
(b) Hu, G.-Q.; Bai, J.-W.; Li, E.-C.; Liu, K.-H.; Sheng, F.-F.; Zhang, H.-H. *Org. Lett*. **2021**, *23*, 1554.
(c) Lepron, M.; Daniel-Bertrand, M.; Mencia, G.; Chaudret, B.; Feuillastre, S.; Pieters, G. *Acc. Chem. Res.* **2021**, *54*, 1465.
(d) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem.*, *Int. Ed*. **2018**, *57*, 3022.
(e) Junk, T.; Catallo, W. J. *Chem. Soc. Rev*. **1997**, *26*, 401.
(f) Wu, D.-C.; Bai, J.-W.; Guo, L.; Hu, G.-Q.; Liu, K.-H.; Sheng, F.-F.; Zhang, H.-H.; Sun, Z.-Y.; Shen, K.; Liu, X. *Tetrahedron Lett.* **2021**, *66*, 152807.

[6] (a) Tie, L.; Shan, X.-H.; Qu, J.-P.; Kang, Y.-B. *Org. Chem. Front.* **2021**, *8*, 2981.
(b) Greene, A. K.; Scott, L. T. *J. Org. Chem*. **2013**, *78*, 2139.
(c) Martin, J.; Eyselein, J.; Grams, S.; Harder, S. *ACS Catal.* **2020**, *10*, 7792.
(d) Alburquerque, P. R.; Ramachandran, B. R.; Junk, T.; Karsili, T. N. V. *J. Phys. Chem. A* **2020**, *124*, 2530.

[7] (a) Bamford, K. L.; Qu, Z.-W.; Stephan, D. W. *J. Am. Chem. Soc*. **2019**, *141*, 6180.
(b) Liang, X.; Duttwyler, S. *Asian J. Org. Chem*. **2017**, *6*, 1063.
(c) Duttwyle, S.; Butterfiel, A. M.; Siegel, J. S. *J. Org. Chem*. **2013**, *78*, 2134.

[8] (a) Anthony, S. M.; Kelleghan, A. V.; Mehta, M. M.; Garg, N. K. *Nat. Catal*. **2019**, *2*, 1058.
(b) Geng, H.; Chen, X.; Gui, J.; Zhang, Y.; Shen, Z.; Qian, P.; Chen, J.; Zhang, S.; Wang, W. *Nat. Catal*. **2019**, *2*, 1071.
(c) Zhang, X.; Chen, Q.; Song, R.; Xu, J.; Tian, W.; Li, S.; Jin, Z.; Chi, Y. R. *ACS Catal*. **2020**, *10*, 5475.
(d) Landge, V. G.; Shrestha, K. K.; Grant, A. J.; Young, M. C. *Org. Lett*. **2020**, *22*, 9745.

[9] (a) Kerr, W. J.; Knox, G. J.; Paterson, L. C. *J. Labelled Comp. Radiopharm*. **2020**, *63*, 281.
(b) Koneczny, M.; Ho, L. P.; Nasr, A.; Freytag, M.; Jones, P. G.; Tamm, M. *Adv. Synth. Catal*. **2020**, *362*, 3857.
(c) Dong, B.; Cong, X.; Hao, N. *RSC Adv*. **2020**, *10*, 25475.
(d) Valero, M.; Kruissink, T.; Blass, J.; Weck, R.; Güssregen, S.; Plowright, A. T.; Derdau, V. *Angew. Chem.* **2020**, *59*, 5626.
(e) Valero, M.; Bouzouita, D.; Palazzolo, A.; Atzrodt, J.; Dugave, C.; Tricard, S.; Feuillastre, S.; Pieters, G.; Chaudret, B.; Derdau, V. *Angew. Chem.*, *Int. Ed*. **2020**, *59*, 3517.
(f) Giles, R.; Kyung, G. A.; Jung, W. *Tetrahedron Lett*. **2015**, *56*, 6231.

[10] Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; Macmillan, D. W. C. *Science* **2017**, *358*, 1182.

[11] (a) Randolph, C.; Lahive, C. W.; Sami, S.; Havenith, R. W. A.; Heeres, H. J.; Deuss, P. J. *Org. Process Res. Dev*. **2018**, *22*, 1663.
(b) Fischer, O.; Hubert, A.; Heinrich, M. R. *J. Org. Chem*. **2020**, *85*, 11856.
(c) Zhan, M.; Xu, R.; Tian, Y.; Jiang, H.; Zhao, L.; Xie, Y.; Chen, Y. *Eur. J. Org. Chem*. **2015**, 3370.

[12] (a) Hu, G.-Q.; Li, E.-C.; Zhang, H.-H.; Huang, W. *Org. Biomol. Chem*. **2020**, *18*, 6627.
(b) Salamanca, V.; Albéniz, A. C. *Eur. J. Org. Chem*. **2020**, 3206.

[13] Liu, W.; Cao, L.; Zhang, Z.; Zhang, G.; Huang, S.; Huang, L.; Zhao, P.; Yan, X. *Org. Lett*. **2020**, *22*, 2210.

[14] (a) Zhang, J.; Zhang, S.; Gogula, T.; Zou, H. *ACS Catal*. **2020**, *10*, 7486.
(b) Wu, J.; Qian, B.; Lu, L.; Yang, H.; Shang, Y.; Zhang, J. *Org. Chem. Front.* **2021**, *8*, 3032.

[15] (a) Kopf, S.; Ye, F.; Neumann, H.; Beller, M. *Chem.-Eur. J*. **2021**, *27*, 9768.
(b) Kopf, S.; Neumann, H.; Beller, M. *Chem. Commun*. **2021**, *57*, 1137.

[16] (a) Tlahuext-Aca, A.; Hartwig, J. F. *ACS Catal*. **2021**, *11*, 1119.
(b) Ahmed, B. M.; Mezei, G. *J. Org. Chem*. **2018**, *83*, 1649.

[17] Koniarczyk, J. L.; Hesk, D.; Overgard, A.; Davies, I. W.; McNally, A. *J. Am. Chem. Soc.* **2018**, *140*, 1990.

[18] (a) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J*. **2011**, *6*, 2696.
(b) Rani, A.; Singh, G.; Singh, A.; Maqbool, U.; Kaur, G.; Singh, J. *RSC Adv*. **2020**, *10*, 5610.
(c) Dheer, D.; Singh, V.; Shankar, R. *Bioorg. Chem*. **2017**, *71*, 30.
(d) Bonandi, E.; Christodoulou, M. S.; Fumagalli, G.; Perdicchia, D.; Rastelli, G.; Passarella, D. *Drug Discovery Today* **2017**, *22*, 1572.
(e) Suazo, K. F.; Park, K.-Y.; Distefano, M. D. *Chem. Rev*. **2021**, *121*, 7178.
(f) Aromí, G.; Barrios, L. A.; Roubeau, O.; Gamez, P. *Coord. Chem. Rev*. **2011**, *255*, 485.

[19] Zhou, Y.; Lecourt, T.; Micouin, L. *Angew Chem.*, *Int. Ed*. **2010**, *49*, 2607.

[20] Shao, C.; Wang, X.; Xu, J.; Zhao, J.; Zhang, Q.; Hu, Y. *J. Org. Chem*. **2010**, *75*, 7002.

[21] Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett*. **2004**, *6*, 1237.

[22] Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett*. **2007**, *9*, 2333.

[23] Akula, H. K.; Lakshman, M. K. *J. Org. Chem*. **2012**, *77*, 8896.

[24] Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.

[25] Lutter, F. H.; Grokenberger, L.; Perego, L. A.; Broggini, D.; Lemaire, S.; Wagschal, S.; Knochel, P. *Nat Commun*. **2020**, *11*, 4443.

[26] Wang, D.; Chen, S.; Wang, J.; Astruc, D.; Chen, B. *Tetrahedron* **2016**, *72*, 6375.

[27] (a) Yang, Y.; Rasmussen, B. A.; Shlaes, D. M. *Pharmacol. Ther*. **1999**, *83*, 141.
(b) Fan, H.; Xu, G.; Chen, Y.; Jiang, Z.; Zhang, S.; Yang, Y.; Ji, R. *Eur. J. Med. Chem*. **2007**, *42*, 1137.

[28] (a) Gonda, Z.; Lőrincz, K.; Novák, Z. *Tetrahedron Lett.* **2010**, *51*, 6275.
(b) Voronin, V. V.; Ledovskaya, M. S.; Rodygin, K. S.; Ananikov, V. P. *Eur. J. Org. Chem*. **2021**, 5640.

[29] Wu, L.-Y.; Xie, Y.-X.; Chen, Z.-S.; Niu, Y.-N.; Liang, Y.-M. *Synlett* **2009**, 1453.


(Cheng, F.)