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# Palladium-Catalyzed Regioselective C-5 Arylation of 1,2,3-Triazoles with Diaryliodonium Salts

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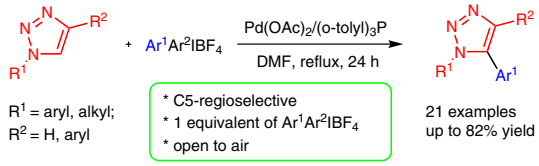


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**Abstract** An effective method for C-5 arylation of 1,4-disubstituted 1,2,3-triazoles and C-5 regioselective arylation of 1-substituted 1,2,3-triazoles via $sp^2$ C–H activation with palladium as a catalyst and diaryliodonium salts as arylating reagents is described. Various electron-rich and electron-deficient substituents attached to triazoles and diaryliodonium salts were tolerable to give the desired products with good isolated yields in 24 hours under air atmosphere.

**Key words** arylation, diaryliodonium salts, regioselectivity, 1,2,3-triazoles, C–H activation

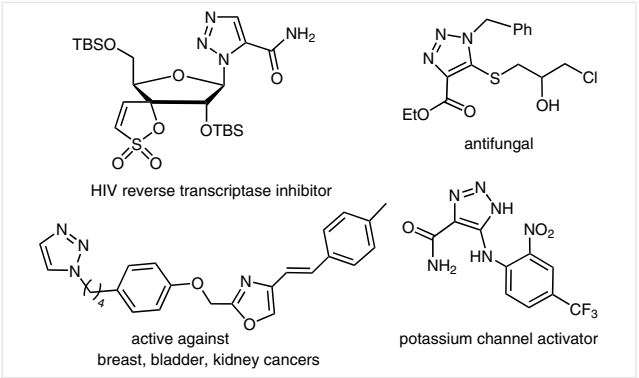
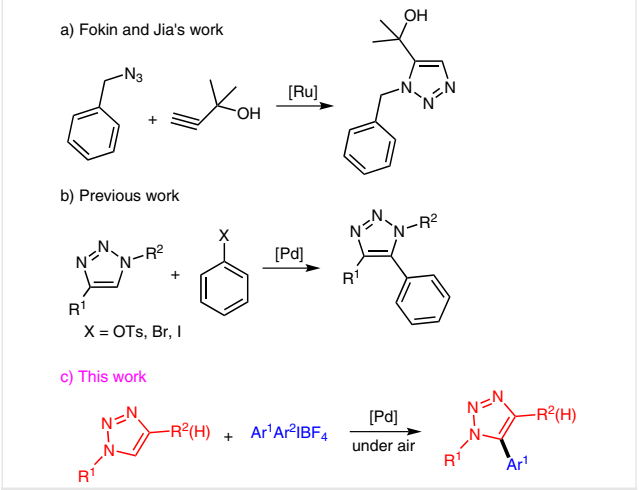



**Figure 1** Medical applications of 1,2,3-triazoles

1,2,3-Triazoles, as an important class of heterocyclic compounds, have received much attention over the past decades and have found wide applications in organocatalysis,[1] ionic liquids[2] and biological medicines (Figure 1).[3] There are two procedures available for the preparation of substituted 1,2,3-triazoles. One is the Cu-catalyzed azide-alkyne 1,3-dipolar [3+2] cycloaddition which has been fully developed.[4] The other is the transition-metal-catalyzed C–H functionalization of 1,2,3-triazoles which has gradually attracted lots of interest,[5] because azide-alkyne cycloaddition reaction, in most case, needs a strong electron-withdrawing group at the alkyne.[6]

As far as we know, transition-metal-catalyzed C–H functionalization of 1,2,3-triazoles mainly focused on the 2-substituted 1,2,3-triazoles in which triazole was always regarded as a directing group,[7] whereas the reaction of 1-substituted 1,2,3-triazoles reports were relatively few. In 2005, Jia and co-workers reported Cp*RuCl(PPh$_3$)$_2$-catalyzed regioselective click reaction of organic azides and terminal alkynes to produce 1,5-disubstituted 1,2,3-triazoles (Scheme 1, a).[8] Despite the remarkable progress, typically



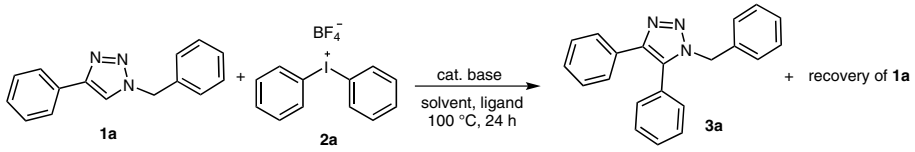

**Scheme 1** Synthesis of C-5 substituted triazoles

methods for the regioselective synthesis of substituted 1,2,3-triazoles are still desirable. Recently, Pd-catalyzed direct arylation and heteroarylation have emerged as a valuable alternative method used for the functionalization of heterocycle.[9] The direct arylation of 1,4-disubstituted 1,2,3-triazoles with aryl tosylates,[10] bromobenzene[11] or iodobenzene[12] as arylating reagents have also shown to be efficient for C-5 functionalization (Scheme 1, b). In some reactions, a solvent mixture and nitrogen atmosphere are needed. In recent years, diaryliodonium salts are receiving more and more attention as arylating reagents,[13] because they have remarkable advantages, such as high reactivity, low toxicity, easy preparation, and no need for additional oxidizing agent.[14] However, to the best of our knowledge, no literature was exposed for C–H arylation of triazoles with diaryliodonium salts as arylating reagents.

In this work, we studied the feasibility of a direct Pd-catalyzed C-5 arylation reaction of triazoles with diaryliodonium salt towards multisubstituted 1,2,3-triazoles. It is found that C-5 arylation of 1,4-disubstituted 1,2,3-triazoles and highly regioselective C-5 arylation of 1-substituted 1,2,3-triazoles proceeded smoothly in the presence of Pd catalyst in DMF under an air atmosphere (Scheme 1, c).[15]

The reaction of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**1a**, 0.2 mmol) with diphenyliodonium tetrafluoroborate (**2a**, 1 equiv) was conducted as a model reaction (Table 1).

**Table 1** Optimization of the Reaction Conditions[a]



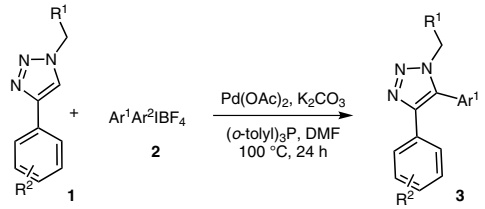

| Entry | Catalyst | Base | Ligand | Temp (°C) | Solvent | Conv. of **1a** (%) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | – | $K_2CO_3$ | – | 100 | DMF | 0 | 0 |
| 2 | $Pd(OAc)_2$ | $K_2CO_3$ | – | 100 | DMF | 58 | 56 |
| 3 | $PdCl_2(PPh_3)_2$ | $K_2CO_3$ | – | 100 | DMF | 55 | 50 |
| 4 | CuI | $K_2CO_3$ | – | 100 | DMF | 0 | 0 |
| 5 | Cu NPs | $K_2CO_3$ | – | 100 | DMF | 0 | 0 |
| 6 | $PdI_2$ | $K_2CO_3$ | – | 100 | DMF | 0 | 0 |
| 7 | $Pd(OAc)_2$ | *t*-BuOK | – | 100 | DMF | <2 | trace |
| 8 | $Pd(OAc)_2$ | $Cs_2CO_3$ | – | 100 | DMF | <2 | trace |
| 9 | $Pd(OAc)_2$ | pyridine | – | 100 | DMF | 17 | 15 |
| 10 | $Pd(OAc)_2$ | $Et_3N$ | – | 100 | DMF | 8 | 5 |
| 11 | $Pd(OAc)_2$ | $K_2CO_3$ | $PPh_3$ | 100 | DMF | 20 | 18 |
| 12 | $Pd(OAc)_2$ | $K_2CO_3$ | X-Phos | 100 | DMF | 59 | 55 |
| 13 | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 100 | DMF | 84 | 82 |
| 14 | $Pd(OAc)_2$ | $K_2CO_3$ | $PCy_3$ | 100 | DMF | 38 | 36 |
| 15 | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 80 | DMF | 59 | 55 |
| 16 | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 120 | DMF | 82 | 78 |
| 17 | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | reflux | $CH_2Cl_2$ | 55 | 52 |
| 18 | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | reflux | $H_2O$ | 38 | 35 |
| 19 | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 100 | PhMe | 27 | 25 |
| 20[c] | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 100 | DMF | 84 | 80 |
| 21[d] | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 100 | DMF | 85 | 82 |
| 22[e] | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 100 | DMF | 88 | 83 |
| 23[f] | $Pd(OAc)_2$ | $K_2CO_3$ | $(o\text{-tolyl})_3P$ | 100 | DMF | 0 | 0 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), base (2 equiv), catalyst (5 mol%), ligand (10 mol%), solvent (2 mL), 24 h.
[b] Isolated yield based on converted **1a**.
[c] The reaction was carried out under an Ar atmosphere.
[d] Amount of catalyst used was 10 mol%.
[e] Amount of **2a** used was 0.4 mmol.
[f] Diphenyliodonium triflate was instead of diphenyliodonium tetrafluoroborate.

Screening of the reaction was first performed in DMF at 100 °C for 24 hours under catalyst- and ligand-free conditions, but no reaction was observed when using only 2 equivalents of potassium carbonate under air atmosphere (Table 1, entry 1). Then, the reaction was explored in the presence of 5 mol% of palladium acetate under the abovementioned conditions. It was found that 56% yield of the targeted product 1-benzyl-4,5-diphenyl-1*H*-1,2,3-triazole (**3a**) was obtained with recovery of 42% **1a** (Table 1, entry 2). Based on this finding, the effect of different transition metal catalysts was further investigated. The use of $Pd(PPh_3)_2Cl_2$ as catalyst gave 50% of yield (Table 1, entry 3). However, when $Pd(OAc)_2$ was replaced by CuI, CuNPs and $PdI_2$, no reaction was observed and 100% of **1a** were recovered (Table 1, entries 4–6). Subsequently, various inorganic and organic bases were also examined and the results showed that potassium carbonate was the best base for this transformation (Table 1, entries 2 and 7–10). As we know, ligands always play an important role in the transition-metal-catalyzed organic reactions except for a few ligand-free literature reports.[16] So phosphorus ligands, such as $PPh_3$, 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl (X-Phos), tricyclohexylphosphine ($PCy_3$) and $(o\text{-tolyl})_3P$, were screened and it was found that $(o\text{-tolyl})_3P$ ligand could give a good yield (82%) of the product (Table 1, entry 13), whereas other ligands, such as $PPh_3$, $PCy_3$ and X-Phos were less effective, and the starting material **1a** was not consumed completely (Table 1, entries 11, 12 and 14). The temperature is another key factor for this reaction. When the temperature was decreased to 80 °C or increased to 120 °C, the yield decreased as expected (Table 1, entries 15 and 16). The reaction was also studied in other reaction media. The results manifested that $CH_2Cl_2$, water, and toluene were not the suitable solvents for this reaction as 25–52% yields were obtained even under reflux temperature in $CH_2Cl_2$ and in water (Table 1, entries 17–19). In order to explain the necessity of air atmosphere, the reaction was conducted under argon. It was found that 80% of the product yield was achieved and no significant decline was observed (Table 1, entry 20). Therefore we believe that oxygen is not necessary for this reaction. In addition, the amount of Pd catalyst could be increased to 10 mol% (Table 1, entry 21) or the amount of **2a** could be increased to 2 equivalents (Table 1, entry 22), with no significant change observed in the yield.

With these optimized conditions in hand (Table 1, entry 11), we explored the scope of this C–H bond functionalization protocol next. To our delight, several valuable functional groups were tolerated in this system, which enabled the preparation of a variety of trisubstituted triazoles in good yields (Table 2). It was observed that the electron-withdrawing or electron-donating groups on the benzene ring of triazoles could be applied to yield the desired products **3b–f**, and the electronic effect has little effect on the reaction (Table 2, entries 2–6). When $R^1$ was an alkyl group instead of an aryl group, this transformation was achieved in moderate yield. For example, 1-*n*-butyl, 1-*n*-hexyl and 1-*n*-octyl-substituted 4-phenyl-1*H*-1,2,3-triazoles were converted to the corresponding products **3g–i** in the yield of 66%, 64% and 53%, respectively (Table 2, entries 7–9). Subsequently, various symmetrical and unsymmetrical diaryliodonium salts were employed in the C-5 arylation of 1,4-substituted triazoles. For symmetrical di(2-fluorophenyl)iodonium tetrafluoroborate (Table 2, entry 10) and di(2-bromophenyl)iodonium tetrafluoroborate (Table 2, entry 11), the corresponding C-5 arylation products **3j** and **3k** of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole were obtained in the yield of 75% and 76%, respectively. For asymmetrical diaryliodonium salts, competitive arylation is possible, which is mainly determined by electronic and steric effect of the substituent on aryl group of diaryliodonium salts. When $Ar^1$ was phenyl and $Ar^2$ was $2\text{-}FC_6H_4$ and $4\text{-}NO_2C_6H_4$ in diaryliodonium salt, only C-5 phenylation products were obtained in 45–71% yield (Table 2, entries 12–15). However, when (phenyl)(2-tolyl)iodonium tetrafluoroborate as arylation reagent was treated with **1a** under the same condi-

**Table 2** C-5 Arylation of 1,4-Substituted 1,2,3-Triazoles[a]



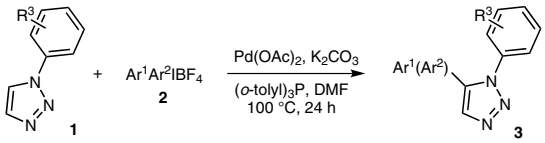

| Entry | $R^1$ | $R^2$ | $Ar^1$ | $Ar^2$ | Yield (%) |
|---|---|---|---|---|---|
| 1 | Ph | H | Ph | Ph | **3a**, 82 |
| 2 | 4-Tol | H | Ph | Ph | **3b**, 80 |
| 3 | Ph | 4-Me | Ph | Ph | **3c**, 78 |
| 4 | Ph | 4-F | Ph | Ph | **3d**, 74 |
| 5 | $4\text{-}FC_6H_4$ | 4-F | Ph | Ph | **3e**, 67 |
| 6 | $4\text{-}FC_6H_4$ | 4-Me | Ph | Ph | **3f**, 76 |
| 7 | Pr | H | Ph | Ph | **3g**, 66 |
| 8 | $C_5H_{11}$ | H | Ph | Ph | **3h**, 64 |
| 9 | $C_7H_{15}$ | H | Ph | Ph | **3i**, 53 |
| 10 | Ph | H | $2\text{-}FC_6H_4$ | $2\text{-}FC_6H_4$ | **3j**, 75 |
| 11 | Ph | H | $2\text{-}BrC_6H_4$ | $2\text{-}BrC_6H_4$ | **3k**, 76 |
| 12 | Ph | H | Ph | $2\text{-}FC_6H_4$ | **3a**, 71 |
| 13 | Ph | H | Ph | $4\text{-}O_2NC_6H_4$ | **3a**, 62 |
| 14 | $C_5H_{11}$ | H | Ph | $2\text{-}FC_6H_4$ | **3h**, 45 |
| 15 | $C_7H_{15}$ | H | Ph | $2\text{-}FC_6H_4$ | **3i**, 59 |
| 16[b] | Ph | H | Ph | 2-Tol | **3a**, 45 |

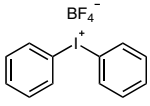
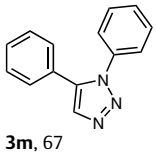
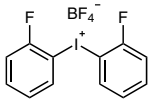
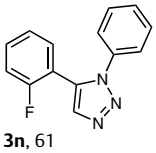
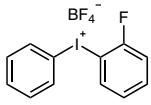
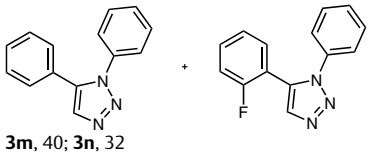
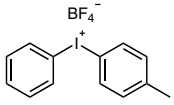
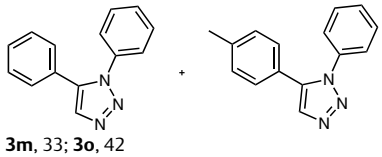
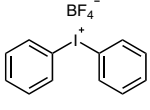
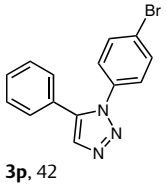
[a] Reaction condition: **1** (0.2 mmol), **2** (0.2 mmol), $K_2CO_3$ (2 equiv), $Pd(OAc)_2$ (5 mol%), $(o\text{-tolyl})_3P$ (10 mol%), DMF (2 mL), 24 h. Yield is the isolated yield.
[b] 5-Tolylation product **3l** (36%) was obtained simultaneously.

tions, phenylation product **3a** and 2-tolylation product **3l** were simultaneously obtained in 45% and 36% yield, respectively (Table 2, entry 16). This may be explained by the difference between removal capacity of the differently substituted aryl in diaryliodonium salt and the ability to generate aryl iodide.

Encouraged by these results, we further examined the arylation reaction of 4,5-unsubstituted triazoles with diaryliodonium salts under the above optimized conditions. We were pleased to find that palladium-catalyzed coupling reactions of various 1-substituted triazoles with diaryliodonium salts proceeded smoothly to afford the highly regioselective C-5 arylation products exclusively (Table 3). When 1-phenyl-1,2,3-triazole was allowed to interact with symmetrical diaryliodonium salt, the unique C-5 arylation product was obtained in moderate yield (Table 3, entries 1 and 2). However, when a bromo group was attached on the benzene ring of 1-phenyl-1,2,3-triazole, a manifest decrease of product yield was observed (Table 3, entry 5). Unsymmetrical diaryliodonium salts bearing functional group such as fluoro and methyl afforded a mixture of C-5 arylation triazoles regioselectively in good total yield of 72% and 75%, respectively (Table 3, entries 3 and 4). From these results we can see that the arylation reactivity of phenyl is close to the arylation reactivities of 2-fluorophenyl and 4-methylphenyl in this reaction to result in a mixture of C5-arylation products.

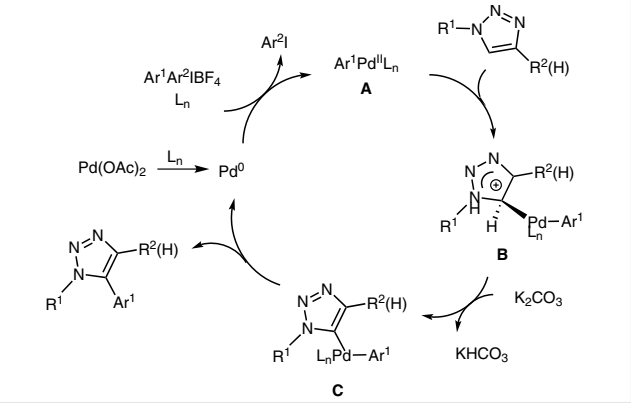
**Table 3** C-5 Regioselective Arylation of 1-Substituted Triazoles[a]




| Entry | $R^3$ | $Ar^1Ar^2IBF_4$ | Product yield (%) |
|---|---|---|---|
| 1 | H |  |  **3m**, 67 |
| 2 | H |  |  **3n**, 61 |
| 3 | H |  |  **3m**, 40; **3n**, 32 |
| 4 | H |  |  **3m**, 33; **3o**, 42 |
| 5 | 4-Br |  |  **3p**, 42 |

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $K_2CO_3$ (2 equiv), $Pd(OAc)_2$ (5 mol%), $(o\text{-tolyl})_3P$ (10 mol%), DMF (2 mL), 24 h. Isolated yields are reported.

According to a previous Gevorgyan's report, DFT calculations show negative charge at C-5 while positive charge at C-4 of *N*-methyl-1*H*-1,2,3-triazole.[11a] So we calculated charges at C-4 and C-5 of *N*-phenyl-1*H*-1,2,3-triazole using the same method. The results show substantial negative charge at C-5 while positive charge at C-4 position (for details, see the supporting information). Therefore we have the reason to believe that C-5 arylation of 1,4-disubstituted and 1-monosubstituted 1,2,3-triazoles is also based on negative charge of C-5 and is an electrophilic mechanism. Based on the above facts and previous literatures,[7c,11a,12a] a proposed mechanism to rationalize this transformation is shown in Scheme 2. First, Pd(0) is formed by the reduction of palladium acetate in the presence of phosphorus ligand, which is further transformed into aryl Pd(II) complex **A** by oxidative addition with diaryliodonium salt. Subsequently, electrophilic addition is initiated between complex **A** and substrate triazoles to generate C5-metalation transition state **B**, then hydrogen is removed under base to form C5-metalation triazole intermediate **C**. The reductive elimination of intermediate **C** gives the coupling product and regenerates $Pd^0$ which is further oxidized by diaryliodonium salts into Pd(II) complex **A** to participate in the next cycle.




**Scheme 2** Proposed mechanism [L = (*o*-tolyl)$_3$P]

In summary, we have successfully developed a Pd-catalyzed C-5 arylation of 1,2,3-triazoles via $sp^2$ C–H activation with diaryliodonium salts as arylating reagents. When 1-substituted 1,2,3-triazoles were used as substrates, the highly regioselective C-5 arylation to afford 1,5-disubstituted 1,2,3-triazoles was realized efficiently. This method shows good tolerance for various electron-rich and electron-deficient substitutions and moderate to good yields are obtained. Compared with the use of multiple equivalents of diaryliodonium salts in most of previous literatures, only one equivalent of diaryliodonium salt was needed in this reaction. The possible mechanism is also proposed.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588815.

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(15) **General Procedure for Regioselective C-5 Arylation of 1,2,3-Triazoles**: To a dried flask were added 1,2,3-triazoles (0.2 mmol), diaryliodonium salt (0.2 mmol), $K_2CO_3$ (2.0 equiv), $Pd(OAc)_2$ (5 mol %), tris(*o*-tolyl)phosphine (10 mol%), and DMF (2 mL). Then the reaction mixture was stirred in an oil bath and heated slowly to 100 °C for 24 h. The reaction was monitored by TLC until no change was observed. The solution was cooled to r.t., and then diluted with EtOAc (10 mL). The organic phase was washed with brine (3 × 10 mL), dried over anhyd $Na_2SO_4$ and concentrated under vacuum to get the crude product. The crude product was further purified by column chromatography with hexane–EtOAc as eluent and the pure product was obtained. Diaryliodonium salts were prepared in accordance with the method previously reported by Olofsson's group.[14a] 1,4-Disubstituted 1,2,3-triazoles were prepared according to our previous work.[16a] 1-Substituted 1,2,3-triazoles were prepared according to the previous literature.[17] The analytical data of new compounds are as follows.

**1-(4-Fluorobenzyl)-4-(4-fluorophenyl)-5-phenyl-1*H*-1,2,3-triazole** (**3e**): white solid; yield: 46.5 mg (67%); mp 112–115 °C. $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 13.8, 6.5 Hz, 3 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.19 (s, 1 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 6.90–6.97 (m, 2 H), 6.87 (q, *J* = 8.0 Hz, 3 H), 5.30 (s, 2 H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C-F}$ = 227.8 Hz), 143.8, 133.5, 130.9 (d, $J_{C-F}$ = 3.6 Hz), 129.9, 129.5, 129.4, 129.3, 128.4 (d, $J_{C-F}$ = 8.1 Hz), 127.6, 115.7 (d, $J_{C-F}$ = 21.6 Hz), 51.4. HRMS (ESI, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}F_2N_3$: 348.1307; found: 348.1315. IR (KBr): 3032, 2921, 2853, 1512, 1224, 843, 766, 705 cm$^{-1}$.

**1-(4-Fluorobenzyl)-5-phenyl-4-(4-tolyl)-1*H*-1,2,3-triazole** (**3f**): white solid; yield: 52.1 mg (76%); mp 147–150 °C. $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.48–7.53 (m, 3 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.15 (d, *J* = 7.3 Hz, 2 H), 7.06 (d, *J* = 7.8 Hz, 2 H), 6.92–6.99 (m, 4 H), 5.36 (s, 2 H), 2.30 (s, 3 H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ = 161.5 (d, $J_{C-F}$ = 247.1 Hz), 143.7, 137.9, 133.6, 132.3, 130.1, 129.7, 129.3, 129.2, 128.4 (d, $J_{C-F}$ = 8.1 Hz), 127.7, 127.5, 127.1 (d, $J_{C-F}$ = 3.1 Hz), 115.3 (d, $J_{C-F}$ = 21.5 Hz), 51.9, 21.1. HRMS (ESI, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}FN_3$: 344.1558; found: 344.1564. IR (KBr): 3034, 2924, 2854, 1514, 1354, 1216, 839, 746, 696 cm$^{-1}$.

**1-Benzyl-5-(2-bromophenyl)-4-phenyl-1*H*-1,2,3-triazole** (**3k**): pale yellow solid; yield: 59.3 mg (76%); mp 99–101 °C. $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.0 Hz, 2 H), 7.47 (d, *J* = 7.1 Hz, 1 H), 7.42 (t, *J* = 7.4 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 1 H), 7.24 (s, 3 H), 7.15 (d, *J* = 7.2 Hz, 2 H), 7.03 (d, *J* = 4.6 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 1 H), 5.41 (s, 2 H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ = 155.5, 144.5, 135.2, 133.9, 132.3, 130.7, 130.5, 130.1, 129.7, 129.2, 128.5, 128.2, 127.8, 127.5, 126.8, 117.4, 52.1. HRMS (ESI, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}BrN_3$: 390.0601; found: 390.0609. IR (KBr): 3061, 2925, 2855, 1344, 763, 734, 695, 601 cm$^{-1}$.

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