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COPPER/HP20: NOVEL AND POLYMER-SUPPORTED COPPER CATALYST FOR HUISGEN CYCLOADDITION

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Abstract – A polymer-supported copper catalyst (Cu/HP20) is easily prepared in water and effectively catalyzed the Huisgen cycloaddition between azides and terminal alkynes.

This paper is dedicated to Dr. Keiichiro Fukumoto, Professor Emeritus at Tohoku University and editor of Heterocycles for the occasion of his 75th birthday.

INTRODUCTION

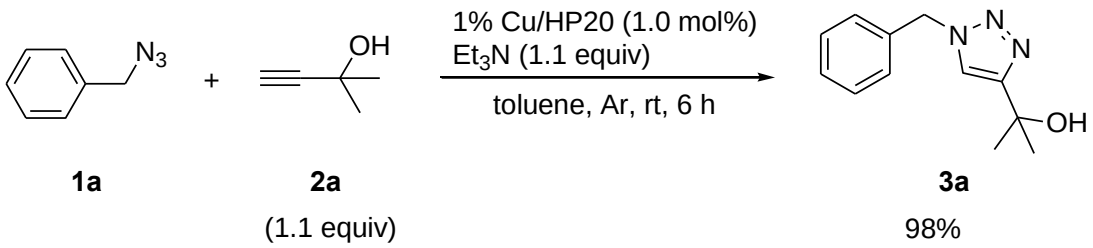
Recently, heterogeneous catalysts have attracted much attention due to the increasing global momentum for the development of environmentally-friendly reactions in terms of green chemistry. Activated carbon, polymers, alumina, silica-gel, zeolites and clay are usually used as the support of a heterogeneous catalyst. Activated carbon is a useful and versatile support, although the catalyst activity of activated carbon-supported catalysts is often and subtly different depending on the production lot because it is a natural material. Therefore, various catalysts supported by synthetic polymers have been investigated.[1] Copper plays a remarkable role as a catalyst in various reactions, and many homogeneous copper catalysts are well known,[2] while quite a few heterogeneous catalysts are reported in the literature.[3,4] For example, Girard *et al*. recently developed a heterogeneous catalyst that relies on chelation to potentially

labile copper using a polystyryl-based benzylic amine polymer,[3] and Lipshutz *et al*. reported an activated carbon-supported copper catalyst (Cu/C).[4] In this article, we report the preparation of a polystyrene polymer supported novel copper catalyst (Diaion HP20: commercially available from Mitsubishi Chemical Corporation), Cu/HP20, and its evaluation as a catalyst for the Huisgen cycloaddition reaction between azides and terminal alkynes.

RESULTS AND DISCUSSION

Preparation of 1% Cu/HP20: We followed the preparation method of Cu/C developed by Lipshutz *et al*.[4] A suspension of Diaion HP20 in a $Cu(NO_3)_2$ aqueous solution was sonicated for 2 h and then filtered. Subsequently, the resulting Cu/HP20 was washed with toluene and dried under vacuum to produce approximately 1% Cu/HP20 (See Experimental for the determination of the Cu content in the Cu/HP20).

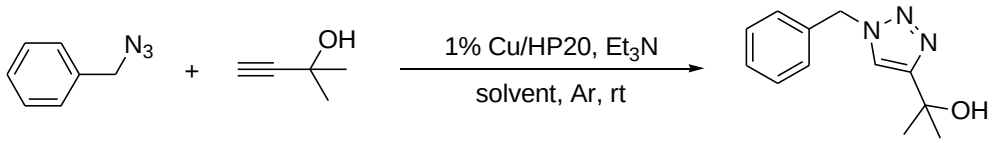
To investigate the catalyst activity of the 1% Cu/HP20, the Huisgen cycloaddition reaction was carried out. It is well known that the reaction rate of the Huisgen cycloaddition was dramatically accelerated in the presence of a copper catalyst and stoichiometric amount of Et_3N.[4] Thus we examined the cycloaddition of benzylazide (**1a**) and 1.1 equiv. of 3-methyl-1-butyn-3-ol (**2a**) in the presence of 1.0 mol% Cu/HP20 and 1.1 equiv. of Et_3N at room temperature. The cycloaddition was completed in toluene within 6 h and provided [2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propane-2-ol] (**3a**) in 98% yield as the sole product (Scheme 1).



Scheme 1. Huisgen's cycloaddition catalyzed by Cu/HP20

To optimize the reaction conditions, several reaction parameters were surveyed (Table 1). The reduction of the Cu/HP20 dose caused an extended reaction time (Entry 2), and no product was obtained in the absence of Cu/HP20 (Entry 1). Among the tested solvents (Entries 4-7), hexane and H_2O appeared to be of equal potential to toluene (Entries 4 and 5), while EtOAc and MeOH were found to be less efficient (Entries 6 and 7). In the absence of Et_3N, the Huigen cycloaddition reaction never proceeded (Entry 8).

Table 1. Optimization of the reaction conditions



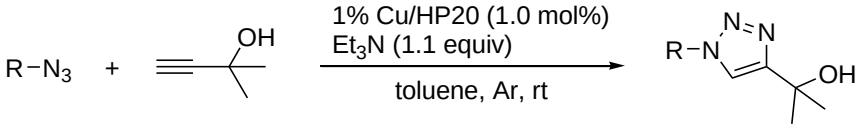
1a **2a** (1.1 equiv) **3a**

Entry	1% Cu/HP20 (mol %)	solvent	Time (h)	Yield (%)[a]
1	0	toluene	24	—[b]
2	0.1	toluene	24	100
3	1.0	toluene	6	100
4	1.0	hexane	6	100
5	1.0	H_2O	6	100
6	1.0	AcOEt	24	100
7	1.0	MeOH	24	100
8[c]	1.0	toluene	24	—[b]

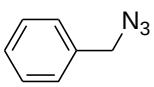
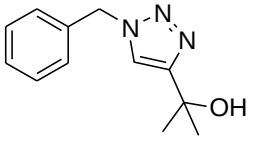
[a] The yield was determined based on the ^{1}H NMR analysis. [b] No reaction. [c] The reaction was carried out without Et_3N.

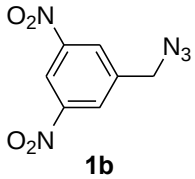
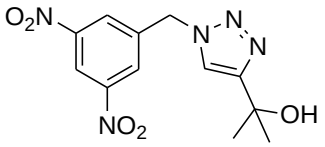
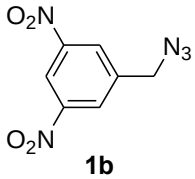
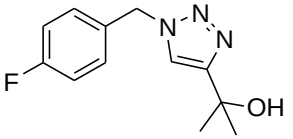
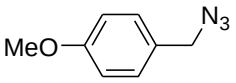
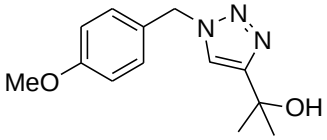
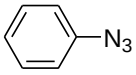
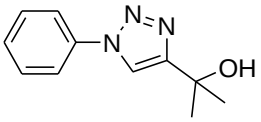
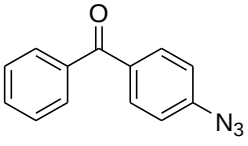
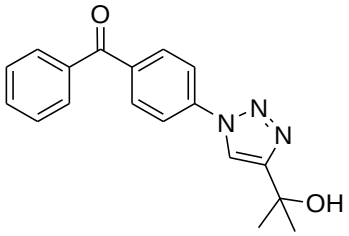
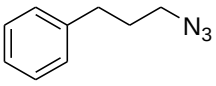
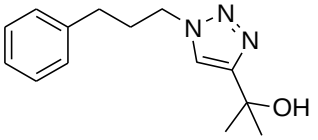
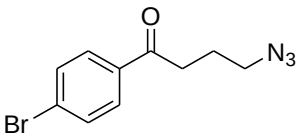
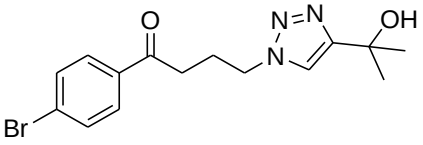
We explored the scope and limitations of substrates for the Huisgen cycloaddition reaction under the optimal conditions (1.0 mol% Cu/HP20 and 1.1 equiv. of Et_3N in toluene at room temperature, Tables 2 and 3). As shown in Table 2, a wide range of azide derivatives smoothly reacted with **2a** within 24 h except for Entry 2. In the case of 3,5-dinitrobenzylazide (**1b**), the reaction could be successfully achieved by applying heat (60 ˚C) (Entry 2), since the low solubility of **1b** in toluene might be the cause of the difficult cycloaddition reaction at room temperature in this unusual case.

Table 2. Cu/HP20-catalyzed the Huisgen cycloaddition of various azides with 3-methyl-1-butyn-3-ol (**2a**)



1a-h **2a** (1.1 equiv) **3a-h**

Entry	Azide	Time (h)	Product	Yield (%)[a]
1	 **1a**	6	 **3a**	98

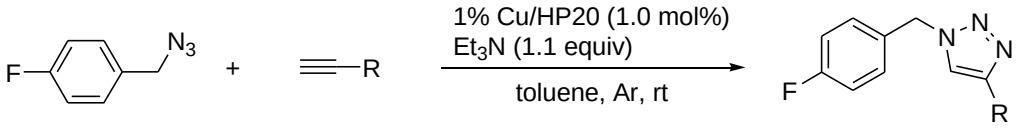
2	 **1b**	24 (5)[b]	 **3b**	—[c] (100)[b]
3	 **1b**	5	 **3c**	100
4	 **1d**	24	 **3d**	97
5	 **1e**	24	 **3e**	90
6	 **1f**	24	 **3f**	98
7	 **1g**	24	 **3g**	98
8	 **1h**	24	 **3h**	99

[a] Isolated yield. [b] The reaction was carried out at 60 °C. [c] No reaction.

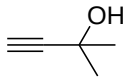
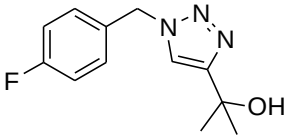
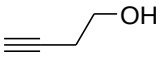
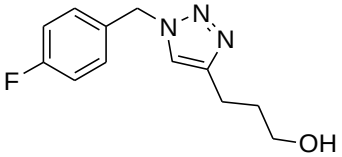
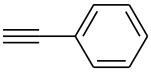
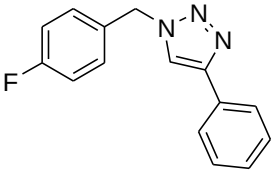
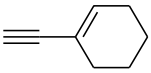
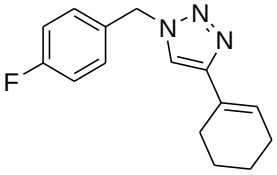
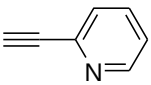
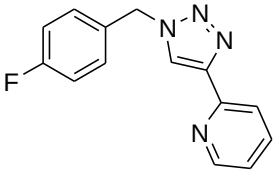
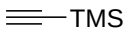
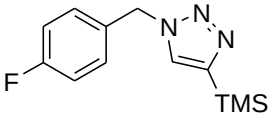
We next attempted to apply the coupling of 4-fluorobenzylazide (**1c**) with various terminal alkynes (Table 3). A wide range of terminal alkynes smoothly reacted with **1c** within 24 h. Remarkably, the coupling with 3-methyl-1-butyn-3-ol (**2a**) and 2-ethynylpyridine (**2e**) were completed within 5 h and 3 h, respectively (Entries 1 and 5). In the case of **2a** or 2-ethynylpyridine (**2e**), the coordination of the oxygen or nitrogen atom of the alkyne to the Cu metal facilitated the approach of Cu species to the adjacent C-C

triple bond. In addition, the cycloaddition of **2a** was completed within 0.5 h by applying heat (60 ˚C), while the same reaction could be completed within 5 h at room temperature (Entry 1).

Table 3. Cu/HP20-catalyzed Huisgen's cycloaddition of 4-fluorobenzylazide (**1c**) with various alkynes



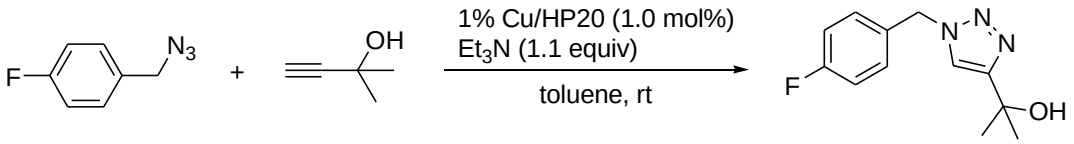
1c **2a-f** (1.1 equiv) **3c, 3i-m**

Entry	Alkyne	Time (h)	Product	Yield (%)[a]
1	 **2a**	5 (0.5)[b]	 **3c**	100 (100)[b]
2	 **2b**	24	 **3i**	79
3	 **2c**	10	 **3j**	99
4	 **2d**	24	 **3k**	99
5	 **2e**	3	 **3l**	100
6	 **2f**	24	 **3m**	90

[a] Isolated yield. [b] The reaction was carried out at 60 ˚C.

The reusability of the heterogeneous catalyst could offer significant advantages by association with the cost reduction and the concept of green chemistry. Cu/HP20 could be recovered by only simple filtration and reused at least two additional reaction cycles without any loss of activity in the present Huisgen cycloaddition reaction between 4-fluorobenzylazide (**1c**) and 3-methyl-1-butyn-3-ol (**2a**) (Table 4).

Table 4. Investigation in the reuse of Cu/HP20



1c **2a** (1.1 equiv) **3c**

Entry	Catalyst	Time (h)	Yield (%)[a]
1	Cu/HP20	5	100
2	Recycled Cu/HP20 (1 st)	5	99
3	Recycled Cu/HP20 (2 nd)	5	99

[a] Isolated yield.

CONCLUSION

In conclusion, we have developed a novel polystyrene polymer-supported catalyst (Cu/HP20) for the Huisgen cycloaddition. Aliphatic and aromatic azides underwent the Huisgen cycloaddition reaction with various terminal alkynes in good-to-excellent yields under mild reaction conditions.

EXPERIMENTAL

General Methods. All reactions were carried out under argon unless otherwise noted. Unless otherwise stated, the commercially obtained materials were used without further purification. Deionized water was purchased from Wako Pure Chemical Industries, Ltd. HP20 was gifted from the Mitsubishi Chemical Co. The azides were prepared according to the known procedure. The terminal alkynes were purchased from Tokyo Chemical Industry Co., Ltd. Et_3N and the solvents were purchased from Nacalai Tasque, Inc. or Wako Pure Chemical Industries, Ltd. The ^1H and ^{13}C NMR spectra were recorded by a JEOL JNM EX-400 or JEOL JNM AL-400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are expressed in ppm and internally referenced (0.00 ppm for tetramethylsilane (TMS)-$CDCl_3$ and 2.49 ppm for DMSO-d_6 for ^1H NMR and 77.0 ppm for $CDCl_3$, 39.5 ppm for DMSO-d_6 for ^{13}C NMR). The EI mass spectra were obtained using a JEOL JMS-SX102A instrument. The elemental analyses were performed by a YANACO MT-5 instrument. The flash column chromatography was

performed using Kanto Chemical Co., Inc. silica gel 60N, spherical neutral (63-210 μm).

Preparation of 1% Cu/HP20: Diaion HP20 (10.0 g) was suspended in an aqueous solution of $Cu(NO_3)_2 \cdot 3H_2O$ (Wako Pure Chemical Industries, Ltd., 1.91 g, 7.9 mmol) in deionized water (40 mL) at rt. The mixture was sonicated [Honda Electronics W-240R (Honda Electronics Co., Ltd., Aichi, Japan)] for 2 h and the resulting Cu/HP20 was filtered, washed with toluene (20 mL) and dried under vacuum at rt for 12 h to give approximately 1% Cu/HP20 (4.47 g). Commercially available Diaion HP20 contains around 50% water and the resulting Cu/HP20 is nearly anhydrous. Therefore, the copper contents of HP20 was calculated on the basis of the measurement of the copper absorbance of the aqueous filtrate using an atomic absorption photometer [Shimadzu AA-6500 (Shimadzu, Kyoto, Japan)].

Synthesis of substrate:

Preparation of aliphatic azides. Under an argon atmosphere, a mixture of an alkylchloride or alkylbromide (10.0 mmol), sodium azide (30.0 mmol), and DMF (10 mL) was stirred overnight at rt. The mixture was extracted with AcOEt (50 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the corresponding azide.

Benzylazide (1a)[5]: Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.41–7.31 (m, 5H), 4.34 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 135.3, 128.8, 128.3, 128.2, 54.8; HRMS (EI) Calcd for $C_7H_7N_3$ (M^+) 133.0640. Found 133.0649.

3,5-Dinitrobenzylazide (1b): Pale yellow solid; mp 50–52 °C. ^{1}H NMR (DMSO-d_6) δ 8.76 (s, 1H), 8.65 (s, 2H), 4.82 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 148.1, 140.6, 128.5, 117.9, 51.6; HRMS (EI) Calcd for $C_7H_5N_5O_4$ (M^+) 223.0342. Found 223.0348. Anal. Calcd for $C_7H_5N_5O_4$: C, 37.68; H, 2.26; N, 31.38. Found: C, 37.65; H, 2.41; N, 31.40.

4-Fluorobenzylazide (1c)[6]: Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.31–7.27 (m, 2H), 7.09–7.04 (m, 2H), 4.31 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.6 (d, J = 247.7 Hz), 131.2 (d, J = 3.3 Hz), 130.0 (d, J = 8.2 Hz), 115.7 (d, J = 21.4 Hz), 54.0; HRMS (EI) Calcd for $C_7H_6N_3F$ (M^+) 151.0546. Found 151.0540.

4-Methoxybenzylazide (1d)[7]: Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.27 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 129.7, 127.4, 114.2, 55.2, 54.3; HRMS (EI) Calcd for $C_8H_9N_3O$ (M^+) 163.0746. Found 163.0750.

Phenylpropylazide (1g)[8]: Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32–7.28 (m, 2H), 7.22–7.18 (m, 2H), 3.29 (t, J = 6.8 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 1.92 (quint, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 140.8, 128.5, 128.4, 126.1, 50.6, 32.7, 30.4

4-Azido-4'-bromobutylphenone (1h)[9]: Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 3.42 (t, J = 6.4 Hz, 2H), 3.05 (t, J = 7.0 Hz, 2H), 2.07-2.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ

197.8, 135.4, 131.9, 129.5, 128.3, 50.7, 35.1, 25.3; HRMS (EI) Calcd for $C_{10}H_{10}BrN_3O$ (M^+) 267.0007. Found 267.0019

Preparation of aromatic azides. To a solution of an arylamine (10.0 mmol) in 10% HCl (15 mL) was added a solution of sodium nitrite (0.690 g, 10.0 mmol) in water (3 mL) at 0–5°C with vigorous stirring. The mixture was kept below 5 °C for 30 min and then a solution of sodium azide (0.72 g, 11.0 mmol) in water (15 mL) was dropwise added while the temperature was kept below 5 °C. After being stirred for 1 h, the mixture was warmed to rt and extracted with AcOEt (50 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the corresponding azide.

Phenylazide (1e)[10]**:** Colorless oil; ^{1}H NMR ($CDCl_3$) δ7.35 (t, J = 7.6 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 140.0, 129.7, 124.8, 119.0; HRMS (EI) Calcd for $C_6H_5N_3$ (M^+) 119.0484. Found 119.0487.

4-Benzyoylphenylazide (1f)[11]**:** Pale yellow solid; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 195.0, 144.3, 137.4, 133.9, 132.2, 131.9, 129.7, 128.2, 118.6; HRMS (EI) Calcd for $C_{13}H_9N_3O$ (M^+) 223.0746. Found 223.0751.

Experiment for the determination of the regiochemistry. Under an argon atmosphere, a mixture of a benzylazide (650 mg, 5 mmol) and 3-methyl-1-butyn-3-ol (**2a**, 540 μL, 5.5 mmol) in DMF (5 mL) was stirred at 80 °C. After being stirred for 72 h, the mixture was extracted with AcOEt (50 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 20:1) to give 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (467 mg, 43%) and 2-(1-benzyl-1*H*-1,2,3-triazol-5-yl)-propan-2-ol (445 mg, 41%).

2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (3a)[12]**:** Colorless solid; ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H), 7.35-7.33 (m, 3H), 7.29-7.27 (m, 2H), 5.46 (s, 2H), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 156.0, 134.6, 129.0, 128.6, 128.0, 119.1, 68.4, 54.0, 30.3; HRMS (EI) Calcd for $C_{12}H_{15}N_3O$ (M^+) 217.1215. Found 217.1221.

2-(1-benzyl-1*H*-1,2,3-triazol-5-yl)propan-2-ol[13]**:** Colorless solid; ^{1}H NMR ($CDCl_3$) δ 7.27-7.21 (m, 3H), 7.20-7.17 (m, 3H), 5.88 (s, 2H), 1.58 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.6, 136.4,130.6, 128.7, 128.2, 128.0, 127.6, 67.6, 52.8, 30.7; HRMS (EI) Calcd for $C_{12}H_{15}N_3O$ (M^+) 217.1215. Found 217.1221.

General procedure for Huisgen cycloaddition in a solvent system. To a test tube with a stir bar were added the azide (1.0 mmol), terminal alkyne (1.1 mmol), Et_3N (152 μL, 1.1 mmol), 1% Cu/HP20 (63.5

mg, 10 μmol), and toluene (1 mL), and then the system was sealed with a septum. The air inside was replaced with argon (balloon) by three vacuum/argon cycles and the mixture was stirred at rt. After a certain period, the mixture was diluted with H_2O (10 mL) and EtOAc (10 mL), and passed through a filter paper. The filtrate was separated into two layers and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the corresponding 1,4-triazole.

2-[1-(3,5-Dinitrobenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-ol (3b): Pale yellow solid; mp 117–119 °C. ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H), 8.65 (s, 2H), 8.09 (s, 1H), 5.86 (s, 2H), 5.16 (s, 1H), 1.44 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 156.4, 148.2, 140.1, 128.9, 121.2, 118.4, 67.1, 50.9, 30.7; HRMS (EI) Calcd for $C_{12}H_{13}N_5O_5$ (M^+) 307.0917. Found 307.0910. Anal. Calcd for $C_{12}H_{13}N_5O_5$: C, 46.91; H, 4.26; N, 22.79. Found: C, 46.33; H, 4.04; N, 22.20.

2-[1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-ol (3c): Pale brown solid; mp 74–76 °C. ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H), 7.27 (dd, *J* = 8.6 Hz, 5.4 Hz, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 5.46 (s, 2H), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 162.8 (d, *J* = 247.0 Hz), 156.1, 130.5, 130.0 (d, *J* = 8.2 Hz), 118.9, 116.0 (d, *J* = 21.4 Hz), 68.5, 53.3, 30.4; HRMS (EI) Calcd for $C_{12}H_{15}N_3OF$ (M^+) 236.1199. Found 236.1205. Anal. Calcd for $C_{12}H_{15}N_3OF$: C, 61.26; H, 6.00; N, 17.86. Found: C, 61.11; H, 5.90; N, 17.63.

2-[1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-ol (3d): Yellow solid; mp 86–88 °C. ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.43 (s, 2H), 3.81 (s, 3H), 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.9, 155.9, 129.7, 126.5, 118.7, 114.4, 68.4, 55.3, 53.6, 30.4; HRMS (EI) Calcd for $C_{13}H_{17}N_3O_2$ (M^+) 247.1321. Found 247.1313. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.81; H, 7.00; N, 16.83.

2-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (3e): Yellow solid; mp 69–71 °C. ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 1.72 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 156.5, 136.8, 129.4, 128.4, 120.2, 117.8, 68.3, 30.3; HRMS (EI) Calcd for $C_{11}H_{13}N_3O$ (M^+) 203.1059. Found 203.1063. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.03; H, 6.47; N, 20.30.

{4-[4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]phenyl}phenylmethanone (3f): Pale brown solid; mp 142–144 °C. ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 195.2, 139.7, 137.3, 137.0, 132.8, 131.7, 129.9, 128.5, 119.8, 117.4, 68.7, 30.4; HRMS (EI) Calcd for $C_{18}H_{17}N_3O_2$ (M^+) 307.1321. Found 307.1317. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 69.27; H, 5.42; N, 13.30.

2-[1-(3-Phenylpropyl)-1*H*-1,2,3-triazol-4-yl]propan-2-ol (3g): Yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1H), 7.28 (t, *J* = 8.2 Hz, 2H), 7.19 (t, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 4.29 (t, *J* = 8.2 Hz, 2H), 2.64 (t, *J* = 8.2 Hz, 2H), 2.21 (quint, *J* = 8.2 Hz, 2H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.8, 140.1, 128.5, 128.3, 126.2, 119.1, 68.3, 49.4, 32.4, 31.5, 30.4; HRMS (EI) Calcd for $C_{14}H_{19}N_3O$ (M^+) 245.1528. Found 245.1524. Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.01; H, 8.03; N, 16.91.

1-(4-Bromophenyl)-4-[4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]butan-1-one (3h): Colorless solid; mp 126–128 °C. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.49 (s, 1H), 4.46 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.34 (t, *J* = 6.8 Hz, 2H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 197.5, 155.8, 135.1, 132.0, 129.5, 128.6, 119.2, 100.5, 68.4, 49.2, 34.7, 30.4, 24.4; HRMS (EI) Calcd for $C_{15}H_{18}N_3O_2Br$ (M^+) 351.0582. Found 351.0575. Anal. Calcd for $C_{15}H_{18}N_3O_2Br$: C, 51.15; H, 5.15; N, 11.93. Found: C, 51.27; H, 5.11; N, 11.77.

3-[1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]propan-1-ol (3i): Pale yellow solid; mp 45–47 °C. ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H), 7.25 (dd, *J* = 8.7 Hz, 5.2 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 5.43 (s, 2H), 3.97 (s, 1H), 3.85 (t, *J* = 6.0 Hz, 1H), 2.89 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 163.2 (d, *J* = 248.6 Hz), 146.4, 131.1 (d, *J* = 3.3 Hz), 130.4 (d, *J* = 8.2 Hz), 122.2, 116.4 (d, *J* = 22.2 Hz), 61.6, 53.7, 29.3; HRMS (EI) Calcd for $C_{11}H_{12}N_3OF$ (M^+) 221.0964. Found 221.0973. Anal. Calcd for $C_{11}H_{12}N_3OF$: C, 59.72; H, 5.47; N, 18.99. Found: C, 59.13; H, 5.49; N, 18.63.

1-(4-Fluorobenzyl)-4-phenyl-1H-1,2,3-triazole (3j): Colorless solid; mp 125–127 °C. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, *J* = 7.4 Hz, 2H), 7.67, 7.40 (t, *J* = 7.4 Hz, 2H), 7.33-7.26 (m, 3H), 7.07 (t, *J* = 8.4 Hz, 2H), 5.54 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.6 (d, *J* = 246.2 Hz), 148.1, 130.5 (d, *J* = 3.3 Hz), 130.3, 129.8 (d, *J* = 8.2 Hz), 128.7, 128.1, 125.5, 119.4, 115.9 (d, *J* = 21.2 Hz), 53.2; HRMS (EI) Calcd for $C_{15}H_{12}N_3F$ (M^+) 253.1015. Found 253.1009. Anal. Calcd for $C_{15}H_{12}N_3F$: C, 71.13; H, 4.78; N, 16.59. Found: C, 71.15; H, 4.82; N, 16.46.

4-Cyclohexenyl-1-(4-fluorobenzyl)-1*H*-1,2,3-triazole (3k): Colorless solid; mp 97–99 °C. ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.25 (dd, *J* = 8.5 Hz, 5.2 Hz, 2H), 7.05 (t, *J* = 8.5 Hz, 2H), 6.50 (t, *J* = 1.9 Hz, 1H), 5.47 (s, 2H), 2.35–2.33 (m, 2H), 2.19–2.17 (m, 2H), 1.75–1.71 (m, 2H), 1.68–1.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.7 (d, *J* = 247.0 Hz), 150.0, 130.8 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 8.2 Hz), 127.1, 125.2, 118.0, 116.0 (d, *J* = 22.2 Hz), 53.2, 26.3, 25.2, 22.4, 22.1; HRMS (EI) Calcd for $C_{15}H_{16}N_3F$ (M^+) 257.1328. Found 257.1321. Anal. Calcd for $C_{15}H_{16}N_3F$: C, 70.02; H, 6.27; N, 16.33. Found: C, 70.01; H, 6.23; N, 16.17.

2-[1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]pyridine (3l): Pale brown solid; mp 104–106 °C. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, *J* = 5.0 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.08 (s, 1H), 7.74 (dd, *J* = 7.8 Hz, 6.3 Hz, 1H), 7.31 (dd, *J* = 8.7 Hz, 5.2 Hz, 2H), 7.19 (dd, *J* = 6.3 Hz, 5.0 Hz, 1H), 7.04 (t, *J* = 8.7 Hz, 2H), 5.54 (s,

2H); ^{13}C NMR ($CDCl_3$) δ 162.7 (d, J = 247.0 Hz), 149.9, 149.2, 148.6, 136.7, 130.2 (d, J = 3.3 Hz), 130.0 (d, J = 8.2 Hz), 122.7, 121.7, 120.0, 115.9 (d, J = 21.4 Hz), 53.3; HRMS (EI) Calcd for $C_{14}H_{11}N_4F$ (M^+) 254.0968. Found 254.0962. Anal. Calcd for $C_{14}H_{11}N_4F$: C, 66.13; H, 4.36; N, 22.04. Found: C, 65.96; H, 4.46; N, 21.80.

1-(4-Fluorobenzyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (3m): Pale yellow solid; mp 59–61 °C. ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1H), 6.98 (dd, J = 8.6 Hz, 4.8 Hz, 2H), 6.75 (t, J = 8.8 Hz, 2H), 5.24 (s, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.6 (d, J = 248.6 Hz), 147.1, 130.8 (d, J = 3.3 Hz), 129.8 (d, J = 8.1 Hz), 128.6, 115.8 (d, J = 22.2 Hz), 60.2, 52.5; HRMS (EI) Calcd for $C_{12}H_{16}N_3FSi$ (M^+) 249.1098. Found 249.1093. Anal. Calcd for $C_{12}H_{16}N_3FSi$: C, 57.80; H, 6.47; N, 16.85. Found: C, 57.75; H, 6.32; N, 16.90.

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