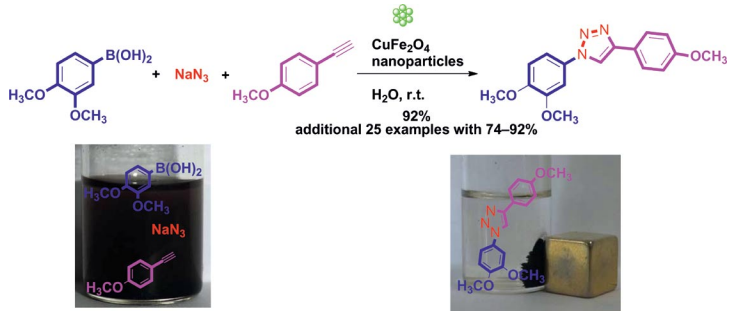
EurJOC European Journal of Organic Chemistry

Magnetic Nanoparticles



Magnetic and catalytically competent $CuFe_2O_4$ nanoparticles proved to be highly efficient in the three-component synthesis of 1,4-diaryl-1,2,3-triazoles, a class of compounds that has been recognized for its anticancer activity.

Keywords: Synthetic methods / Nanoparticles / Magnetic properties / Azides / Iron

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Magnetically Recoverable $CuFe_2O_4$ Nanoparticles: Catalyzed Synthesis of Aryl Azides and 1,4-Diaryl-1,2,3-triazoles from Boronic Acids in Water

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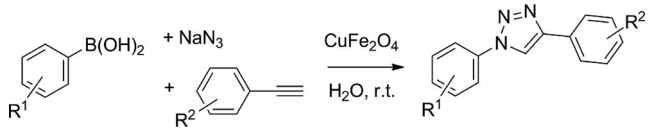
Keywords: Synthetic methods / Nanoparticles / Magnetic properties / Azides / Iron

Magnetically recoverable and reusable $CuFe_2O_4$ nanoparticles are shown to be highly efficient catalysts for the one-pot synthesis of biologically important 1,4-diaryl-1,2,3-triazoles starting from boronic acids, sodium azide, and acetylenes. The use of aqueous reaction medium at room temperature, the low cost and facile recovery of the catalyst by application of an external magnetic field, and consistently high catalytic efficiency for at least three consecutive cycles renders the protocol operationally attractive.

Introduction

The use of more environmentally benign catalysts coupled with practical and efficient processes for catalyst separation and reuse provides both economical and ecological benefits.[1] Therefore, the use of catalysts supported on heterogeneous materials such as organic polymers, silica or graphene, to enable facile recovery by filtration, is an actively pursued strategy to improve catalytic processes. Quite recently, nanoparticles have emerged as viable alternatives to traditional supports, being robust with a high surface area, inexpensive, and readily available.[2] Among them, magnetic nanoparticles are especially attractive because they offer a simple and economical alternative to filtration or centrifugation by retention through the application of an external magnetic field, thus efficiently preventing loss of catalyst and enhancing reusability.[3]

In addition to using nanoparticles as supports, such particles might also serve directly as catalysts. To render them magnetic, they must contain an appropriate metal, such as rare earth, cobalt or iron metal; the latter appears to be especially attractive for reasons of cost, low toxicity, and the ability to form hybrids with other metals. Nanoparticles of spinel type $CuFe_2O_4$ have been recognized as a magnetic material with catalytically active copper centers, which has resulted in a number of applications[4] including very recently reported azide-alkyne cycloadditions,[4a,4b] epoxide openings,[4c] and Ullmann-type couplings.[4d,4e] In a continuation of our efforts towards the development of anticancer agents and the use of magnetic catalysts,[5,6] we demonstrate in this study that $CuFe_2O_4$ nanoparticles also efficiently catalyze the formation of aryl azides[7] from boronic acids or esters in water at room temperature, which can be extended to a one-pot protocol for the synthesis of medicinally relevant triazols[8] by adding alkynes as a third component (Scheme 1).



Scheme 1. Magnetically separable $CuFe_2O_4$-catalyzed one-pot synthesis of 1,4-aryl-1,2,3-triazoles.

The conventional synthesis of aryl azides include diazotization of the corresponding amines[9] or the reactions of organometallic aryls with *p*-tosyl azide.[10] Furthermore, copper-catalyzed protocols towards aryl azides have been developed from the corresponding aryl halides.[11]

As a synthetic application of aryl azides, copper-catalyzed [3+2] cycloaddition with alkynes has attracted much attention because it yields 1,4-disubstituted 1,2,3-triazoles as the sole regioisomer.[12] In view of the diverse biological, medicinal, and chemical properties of 1,4-disubstituted 1,2,3-triazoles,[13–15] several environmentally friendly strategies have been reported to carry out this process, including performing the reaction without the use of solvent,[16] replacing the use of stoichiometric amounts of reagents with catalysts,[17] and performing the reactions in aqueous media or other nonclassical reaction solvents.[18] There are only a few reports on the direct synthesis of 1,4-diaryl-1,2,3-triazoles using aryl halides, sodium azide and terminal alkynes because these protocols suffer from longer reaction times

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even at elevated temperature and require inert gas atmosphere because of the slow azidonation of aryl halides.[19] To overcome these limitations, copper-catalyzed protocols for the synthesis of aryl azides and 1,4-diaryl-1,2,3-triazoles from boronic acids as alternative substrates to aryl halides have been developed.[20]

Results and Discussion

$CuFe_2O_4$ nanoparticles were synthesized according to literature procedures[21] and were characterized by atomic absorption spectroscopy (AAS), X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), and transmission electron microscopy (TEM). In particular, the copper content of the nanoparticles, was determined to be 27.3% by AAS. Furthermore, the XRD spectra of fresh and used $CuFe_2O_4$ nanoparticles (Figure 1) are characteristic of tetragonal $CuFe_2O_4$ (JCPDS card No. 34-0425) with good crystallinity. XRD analysis indicates that the metal oxides are in the form of the spinel structure of $CuFe_2O_4$ (d = 2.53, 2.98, 1.49, 1.61 Å). The size of the particles was calculated by means of the Debye–Scherrer formula based on the full-width at half-maximum of the high intensity diffraction peak at 2θ = 35.6° and was found to be approximately 18 nm, which is in agreement with TEM analysis (Figure 2), which shows mainly spherical nanoparticles with particle size in the range 10–30 nm. Notably, the morphology and size of the particles were unaltered even after three cycles, which correlates well with retention of catalytic activity after recycling.

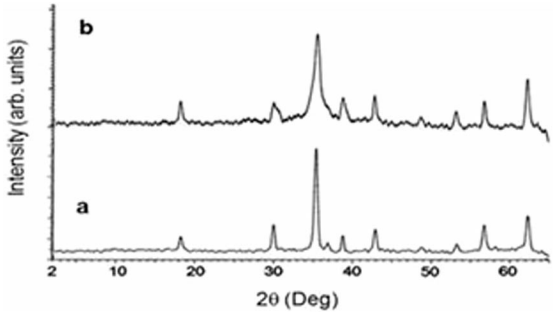


Figure 1. XRD patterns of $CuFe_2O_4$ nanoparticles (a) fresh and (b) after 1st catalytic cycle.

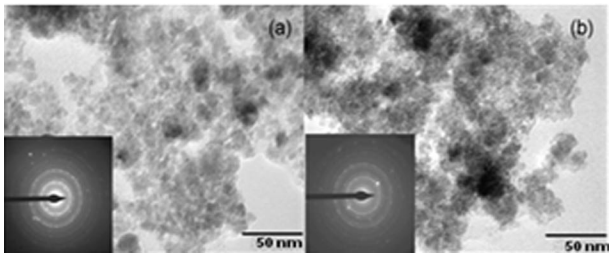


Figure 2. TEM and SAED images of $CuFe_2O_4$ nanoparticles (a) before and (b) after use.

Selected-area electron diffraction (SAED) images also confirm the crystalline nature of both the fresh and used magnetic nanoparticles. The chemical composition of the $CuFe_2O_4$ nanoparticles were characterized by XPS analysis (Figure 3), which revealed the characteristic peaks for C 1s (285 eV), O 1s (535 eV), Fe 2p (710 eV), and Cu 2p (935 eV) (Figure 3, A). The high-resolution narrow scan for Fe 2p in $CuFe_2O_4$ revealed Fe $2p_{3/2}$ and Fe $2p_{1/2}$ binding energy peaks at 710.0 and 723.7 eV, and at 710.7 and 723.4 eV, respectively, for the fresh and used catalyst (Figure 3, B). The observed binding energy values are characteristic of iron in its +3 oxidation state. Likewise, the high-resolution narrow scan for Cu 2p in $CuFe_2O_4$ displays energy peaks of $2p_{2/3}$ and $2p_{1/2}$ at 933.2 and 953.3 eV (freshly prepared catalyst) and 933.3 and 953.5 eV (recycled catalyst, Figure 3, C), clearly indicating that copper is in its +2 oxidation state.[22] The XPS analysis also corroborated the XRD, TEM analyses, and corresponded to the retention of catalytic activity, which confirmed that the catalyst is fundamentally unaltered after the reaction.

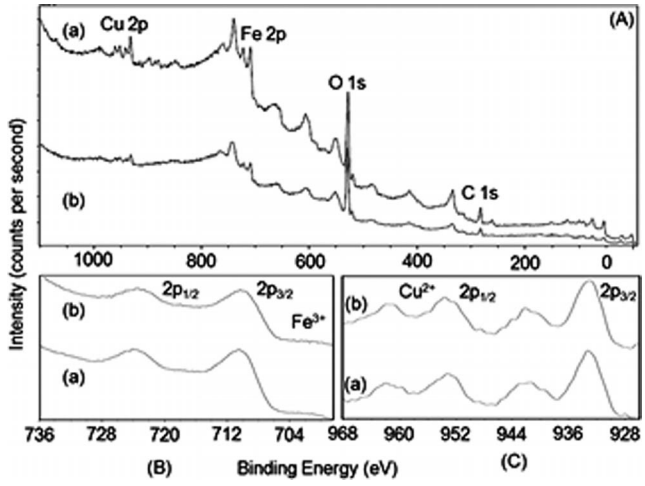
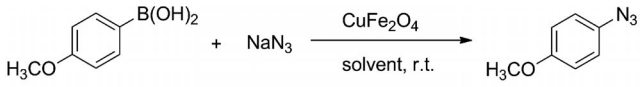


Figure 3. XPS spectra of (a) fresh and (b) used $CuFe_2O_4$ nanoparticles. (A) XPS survey of spectra. (B) High-resolution spectrum for the Fe^{3+} 2p region. (C) High-resolution spectrum for the Cu^{2+} 2p region.

To evaluate the so prepared nanoparticles in the synthesis of aryl azides, we selected 4-methoxyphenylboronic acid and sodium azide as model substrates in a range of solvents. Employing $CuFe_2O_4$ nanoparticles (10 mol-%) in water or methanol was found to be the most promising conditions, giving the desired 1-(4-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole in 88 and 85% yield, respectively (Table 1, entries 1 and 3). A control reaction conducted in water in the absence of catalyst under otherwise identical conditions gave no product, despite prolonged reaction time (Table 1, entry 2). Ethanol proved to be less suitable for the reaction (entry 4), whereas organic solvents such as CH_2Cl_2, tetrahydrofuran (THF) or dioxane (entries 5–7) resulted in the formation of only trace amounts of product.

By exploring the scope of the reaction under the optimized conditions (Table 2) we were pleased to find that boronic acids with either electron-donating or electron-withdrawing substituents efficiently underwent the title transformation to give the corresponding azides in 76–90% yield.

Table 1. Screening solvents for coupling between 4-methoxyphenylboronic acid and sodium azide.[a]



Entry	Solvent	Yield [%][b]
1	water	88
2	water	0[c]
3	methanol	85
4	ethanol	48
5	DCM	trace
6	THF	trace
7	dioxane	trace

[a] Reaction conditions: 4-methoxylphenylboronic acid (1 mmol), NaN_3 (1.2 mmol), $CuFe_2O_4$ (10 mol-%), solvent (3 mL), r.t., 7 h. [b] Isolated yield. [c] Reaction without catalyst.

Encouraged by these results, we investigated the use of $CuFe_2O_4$ nanoparticles for the one-pot synthesis of 1,4-diaryl-1,2,3-triazoles; a class of compounds that has been recognized for its anticancer activity.[8] Initially, we added a terminal alkyne to the same reaction mixture after aryl azide formation was complete (reaction followed by TLC analysis) (Table 3). Indeed, it was found that this protocol produced the corresponding triazoles in high yields (74–89%) without the need to isolate and purify the intermediate azides (entries 1–11). We further investigated this method with the use of boronic esters instead of acids. Whereas hydrolytically labile dimethyl and diethyl boronates both gave rise to the corresponding triazoles in comparable yields with respect to the boronic acids (entries 12 and 13), the hydrolytically more stable pinacol and catechol boronates gave very low yields under the same reaction conditions (entries 14 and 15).

With the aim of avoiding the build-up of azide in the reaction mixture, considering potential large-scale applications, several structurally and electronically diverse terminal alkynes were reacted directly with boronic acids and sodium azides, thus generating the aryl azides in situ in a true three-component reaction, yielding the desired triazoles again in high yields (75–92%; Table 4).[23]

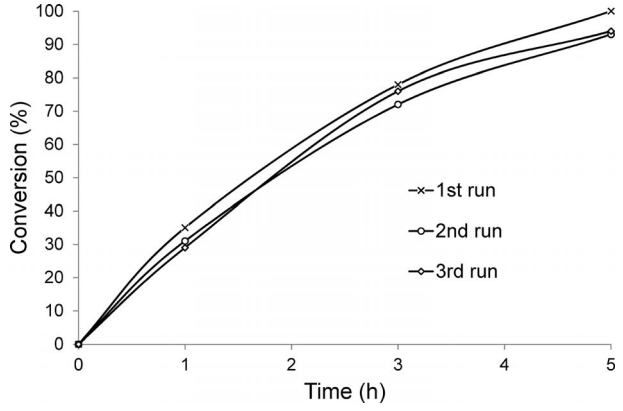
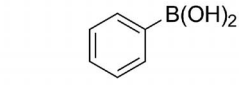
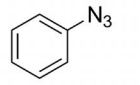
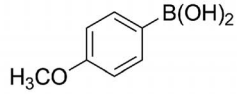
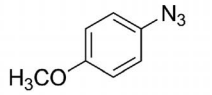
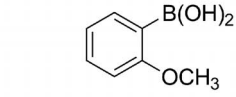
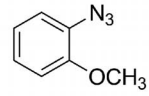
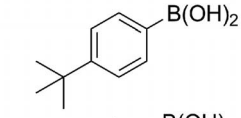
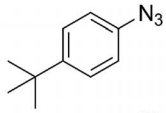
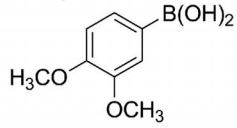
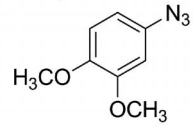
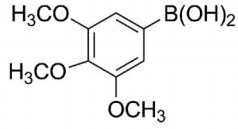
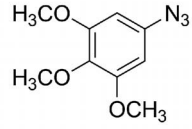
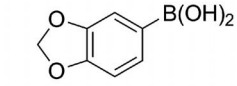
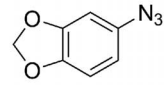
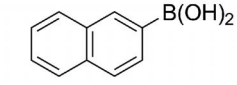
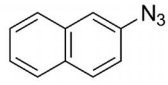
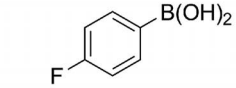
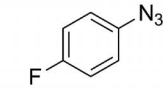
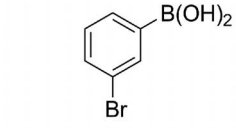
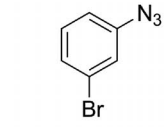
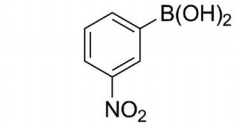
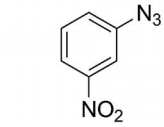


Figure 4. Recyclability and kinetic study of $CuFe_2O_4$-catalyzed azide formation with 4-methoxyphenylboronic acid (1.0 mmol), NaN_3 (1.2 mmol), $CuFe_2O_4$ (10 mol-%) in water (3 mL) at room temperature. Conversion determined by ^1H NMR spectroscopic analysis with diphenyl methane as internal standard.

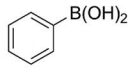
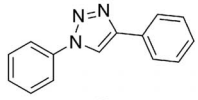
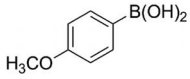
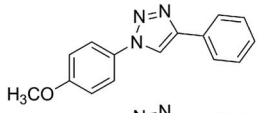
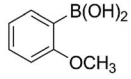
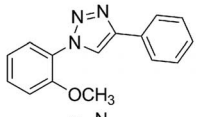
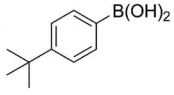
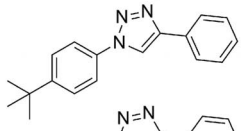
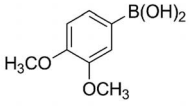
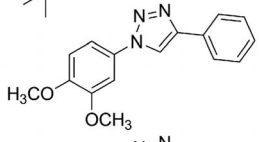
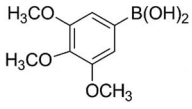
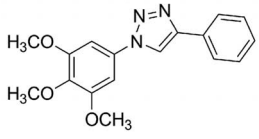
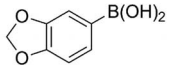
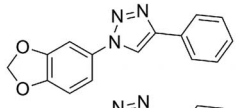
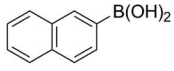
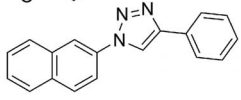
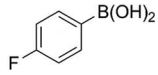
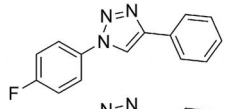
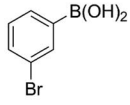
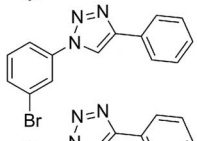
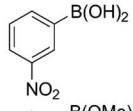
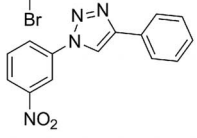
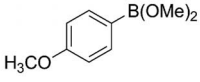
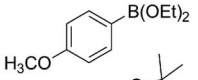
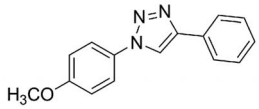
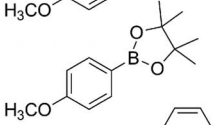
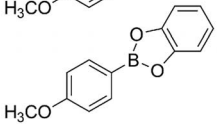
Table 2. Magnetically separable $CuFe_2O_4$-catalyzed synthesis of aryl azides from boronic acids.[a]

Entry	Boronic acid	Product	Yield [%][b]
1			**2a** 86
2			**2b** 88
3			**2c** 85
4			**2d** 87
5			**2e** 88
6			**2f** 90
7			**2g** 85
8			**2h** 88
9			**2i** 78
10			**2j** 80
11			**2k** 76

[a] Reaction conditions: boronic acid (1.0 mmol), NaN_3 (1.2 mmol), $CuFe_2O_4$ (10 mol-%), H_2O (3 mL), r.t., 7 h. [b] Isolated yield.

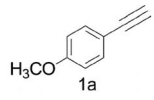
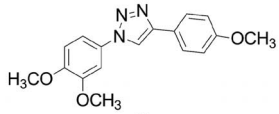
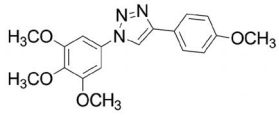
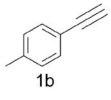
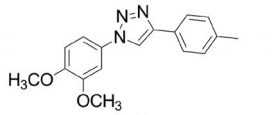
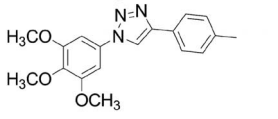
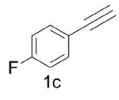
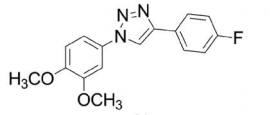
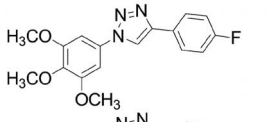
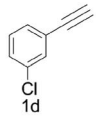
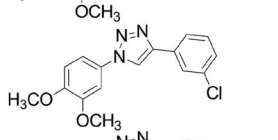
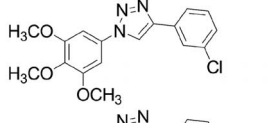
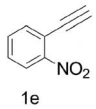
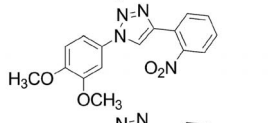
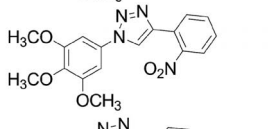
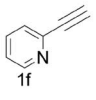
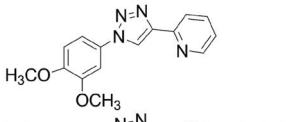
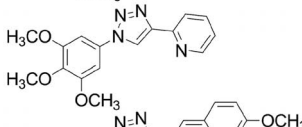
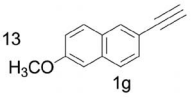
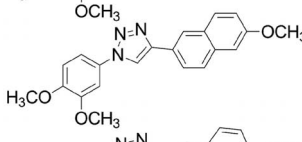
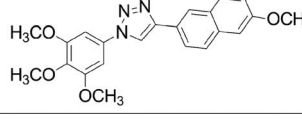
The recyclability of the catalyst was investigated in combination with a kinetic study (Figure 4). The conversion of 4-methoxyphenylboronic acid in the rate-limiting azide formation step was determined. After each run, the catalyst

Table 3. Magnetically separable $CuFe_2O_4$-catalyzed one-pot synthesis of 1,4-diaryl-1,2,3-triazoles from boronic acids/boronates with sodium azide and phenylacetylene.[a]

Entry	Boronic acid/boronate	Product	Yield [%][b]
1		 **3a**	85
2		 **3b**	89
3		 **3c**	86
4		 **3d**	84
5		 **3e**	89
6		 **3f**	82
7		 **3g**	86
8		 **3h**	85
9		 **3i**	75
10		 **3j**	76
11		 **3k**	74
12			85
13		 **3b**	83
14			2
15			0

[a] Reaction conditions: boronic acid/boronate (1.0 mmol), NaN_3 (1.2 mmol), phenylacetylene (1.1 mmol), $CuFe_2O_4$ (10 mol-%), H_2O (3 mL), r.t., 12 h. [b] Isolated yield.

Table 4. Magnetically separable $CuFe_2O_4$-catalyzed one-pot synthesis of 1,4-diaryl-1,2,3-triazoles from alkynes with 3,4-dimethoxy phenyl and 3,4,5-trimethoxy phenyl boronic acids and sodium azide.[a]

Entry	Alkyne	Product	Yield [%][a]
1	 1a		**4a** 92
2	1a		**4b** 81
3	 1b		**4c** 90
4	1b		**4d** 80
5	 1c		**4e** 85
6	1c		**4f** 83
7	 1d		**4g** 83
8	1d		**4h** 80
9	 1e		**4i** 77
10	1e		**4j** 75
11	 1f		**4k** 79
12	1f		**4l** 80
13	 1g		**4m** 78
14	1g		**4n** 75

[a] Reaction conditions: boronic acid (1.0 mmol), NaN_3 (1.2 mmol), alkyne (1.1 mmol), $CuFe_2O_4$ (10 mol-%), H_2O (3 mL), r.t., 12 h. [b] Isolated yield.

was separated from the reaction mixture by applying an external magnet, washed with methanol, dried, and used directly for the next cycle without further purification. It was observed that the catalyst could be reused for at least three cycles without significant loss of catalytic activity.

Conclusion

A simple and efficient green procedure using water as solvent for the synthesis of aryl azides and biologically important 1,4-diaryl-1,2,3-triazoles in good to excellent yields in a three-component approach, avoiding the isolation of unstable aryl azides, has been developed by using a magnetically separable and easily recyclable heterogeneous copper catalyst. The structural class of triazole compounds may be amenable for lead optimization in anticancer activity studies.

Experimental Section

General Experimental Procedure for the Synthesis of Aryl Azides from Boronic Acids: Boronic acid (1.0 mmol), NaN_3 (1.2 mmol) and $CuFe_2O_4$ (10 mol-%) in water (3 mL) was stirred at room temperature for 7 h. After completion of the reaction the catalyst was separated from the reaction mixture with an external magnet and the reaction mixture was extracted with ethyl acetate, dried with sodium sulfate, and the solvents were evaporated under vacuum to give the crude product, which was purified by column chromatography on silica.

General Experimental Procedure for the One-Pot Synthesis of 1-Aryl-1,2,3-triazoles: Boronic acid (1.0 mmol), NaN_3 (1.2 mmol) and $CuFe_2O_4$ (10 mol-%) catalyst were stirred in water (3 mL) in a 25 mL round-bottom flask at room temperature. After the formation of aryl azide (reaction monitored by TLC), alkyne (1.1 mmol) was added into the reaction mixture and stirring was continued for 5 h. The catalyst was separated with an external magnet after completion of the reaction. The reaction mixture was extracted with ethyl acetate, dried with sodium sulfate, and the solvents were evaporated under vacuum to give the crude product, which was purified by column chromatography on silica.

4-Phenyl-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (3f): Table 3, entry 6. Pale-yellow solid; m.p. 110–112 °C. IR (KBr): $\tilde{\nu}$ = 2924, 2855, 1602, 1507, 1463, 1237, 1127, 1031, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 3.93 (s, 6 H), 6.99 (s, 2 H), 7.32–7.50 (m, 3 H), 7.89 (d, J = 8.1 Hz, 2 H), 8.17 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1, 60.7, 98.2, 117.9, 125.5, 128.1, 128.6, 129.9, 132.6, 138.0, 148.0, 153.6 ppm. MS (ESI): m/z = 312 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{17}H_{18}O_3N_3$ 312.13427; found 312.13454.

4-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (4b): Table 4, entry 2. Pale-yellow solid; m.p. 180–182 °C. IR (KBr): $\tilde{\nu}$ = 2929, 1604, 1503, 1462, 1245, 1127, 1029, 830 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.72 (s, 3 H), 3.81 (s, 3 H), 3.90 (s, 6 H), 7.07 (d, J = 8.9 Hz, 2 H), 7.26 (s, 2 H), 7.86 (d, J = 8.9 Hz, 2 H), 9.18 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 55.1, 56.2, 60.1, 97.7, 114.3, 118.7, 122.7, 126.5, 132.5, 137.1, 147.0, 153.4, 159.2 ppm. MS (ESI): m/z = 342 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{18}H_{20}O_4N_3$ 342.14483; found 342.14516.

1-(3,4-Dimethoxyphenyl)-4-*p*-tolyl-1*H*-1,2,3-triazole (4c): Table 4, entry 3. White solid; m.p. 130–132 °C. IR (KBr): $\tilde{\nu}$ = 2927, 2849, 1601, 1518, 1465, 1261, 1170, 1019, 812 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 3.90 (s, 3 H), 3.95 (s, 3 H), 6.89 (d, J = 9.0 Hz, 1 H), 7.11–7.15 (m, 1 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.37 (s, 1 H), 7.73 (d, J = 8.0 Hz, 2 H), 8.02 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 55.9 (2 C), 104.7, 111.0, 111.9, 117.1, 125.6, 127.4, 129.4, 129.5, 130.6, 148.1, 149.1, 149.6 ppm. MS (ESI): m/z = 296 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{17}H_{18}O_2N_3$ 296.13935; found 296.13930.

4-*p*-Tolyl-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (4d): Table 4, entry 4. Pale-yellow solid; m.p. 103–105 °C. IR (KBr): $\tilde{\nu}$ = 2924, 2855, 1602, 1507, 1463, 1237, 1127, 1031, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.86 (s, 3 H), 3.94 (s, 6 H), 6.96 (s, 2 H), 7.22 (d, J = 7.5 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H), 8.05 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 56.2, 60.8, 98.1, 117.2, 125.6, 127.3, 129.4, 129.5, 132.8, 137.9, 148.2, 153.8 ppm. MS (ESI): m/z = 326 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{18}H_{20}O_3N_3$ 326.14992; found 326.15033.

1-(3,4-Dimethoxyphenyl)-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (4e): Table 4, entry 5. White solid; m.p. 138–140 °C. IR (KBr): $\tilde{\nu}$ = 2930, 2846, 1602, 1518, 1446, 1236, 1163, 1022, 836 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 3.84 (s, 3 H), 3.88 (s, 3 H), 7.17 (d, J = 8.5 Hz, 1 H), 7.31–7.39 (m, 2 H), 7.43–7.52 (m, 2 H), 7.93–8.00 (m, 2 H), 9.22 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.7, 55.8, 104.4, 111.9 (d, J = 5.1 Hz), 115.7, 116.0, 119.5, 126.9, 127.2 (d, J = 8.1 Hz), 129.9 (d, J = 2.9 Hz), 146.1, 148.8, 149.2, 161.8 (d, J = 244.7 Hz) ppm. MS (ESI): m/z = 300 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{16}H_{15}O_2N_3F$ 300.11428; found 300.11490.

4-(4-Fluorophenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (4f): Table 4, entry 6. Pale-yellow solid; m.p. 143–145 °C. IR (KBr): $\tilde{\nu}$ = 2930, 1601, 1506, 1458, 1231, 1127, 1032, 829 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 3.73 (s, 3 H), 3.90 (s, 6 H), 7.26 (s, 2 H), 7.31–7.41 (m, 2 H), 7.91–8.02 (m, 2 H), 9.28 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 56.1, 60.1, 97.7, 115.8 (d, J = 22.1 Hz), 119.6, 126.7 (d, J = 2.9 Hz), 127.2 (d, J = 8.1 Hz), 132.3, 137.2, 146.2, 153.4, 161.8 (d, J = 244.7 Hz) ppm. MS (ESI): m/z = 330 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{17}H_{17}O_3N_3F$ 330.12485; found 330.12549.

4-(3-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-1*H*-1,2,3-triazole (4g): Table 4, entry 7. Pale-yellow solid; m.p. 133–136 °C. IR (KBr): $\tilde{\nu}$ = 2930, 2831, 1599, 1515, 1466, 1229, 1167, 1019, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 3.97 (s, 3 H), 6.92 (d, J = 9.0 Hz, 1 H), 7.13–7.20 (m, 1 H), 7.28–7.41 (m, 3 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.84 (s, 1 H), 8.10 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.0, 56.1, 104.8, 111.2, 112.2, 118.0, 123.7, 125.7, 128.2, 130.0, 130.4, 132.0, 134.8, 146.8, 149.5, 149.8 ppm. MS (ESI): m/z = 316 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{16}H_{15}O_2N_3Cl$ 316.08473; found 316.08484.

4-(3-Chlorophenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (4h): Table 4, entry 8. Pale-yellow solid; m.p. 152–154 °C. IR (KBr): $\tilde{\nu}$ = 2928, 1602, 1510, 1464, 1241, 1121, 1036, 828 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.92 (s, 6 H), 6.93 (s, 2 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.77 (d, J = 7.8 Hz, 1 H), 7.82 (s, 1 H), 8.09 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.3, 60.8, 98.3, 117.9, 123.7, 125.7, 128.2, 130.0, 132.0, 132.6, 134.8, 138.5, 146.8, 153.9 ppm. MS (ESI): m/z = 346 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{17}H_{17}O_3N_3Cl$ 346.09530; found 346.09569.

1-(3,4-Dimethoxyphenyl)-4-(2-nitrophenyl)-1*H*-1,2,3-triazole (4i): Table 4, entry 9. Pale-yellow solid; m.p. 132–134 °C. IR (KBr): $\tilde{\nu}$ = 2925, 2856, 1605, 1521, 1452, 1243, 1166, 1028, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.96 (s, 3 H), 3.98 (s, 3 H), 6.98 (d, J = 9.0 Hz, 1 H), 7.17–7.25 (m, 1 H), 7.39 (s, 1 H), 7.50–7.60 (m, 1 H), 7.67–7.75 (m, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 8.13 (d, J = 9.0 Hz, 1 H), 8.17 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.0, 56.1, 104.7, 111.0, 112.1, 121.0, 123.9, 128.9, 129.4, 130.0, 130.9, 132.3, 142.4, 148.0, 149.3, 149.5 ppm. MS (ESI): m/z = 327 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{16}H_{15}O_4N_4$ 327.10878; found 327.10868.

4-(2-Nitrophenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (4j): (Table 4, entry 10). Pale-yellow solid; m.p. 163–165 °C. IR (KBr): $\tilde{\nu}$ = 2925, 2856, 1603, 1511, 1464, 1233, 1123, 825 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.93 (s, 6 H), 6.95 (s, 2 H), 7.52 (t, J = 7.0 Hz, 1 H), 7.68 (t, J = 7.0 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H), 8.16 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.3, 60.9, 98.5, 121.2, 124.1, 124.2, 129.0, 131.0, 132.4, 132.5, 138.3, 142.5, 148.0, 153.8 ppm. MS (ESI): m/z = 357 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{17}H_{17}O_5N_4$ 357.11935; found 357.11963.

2-[1-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl]pyridine (4k): Table 4, entry 11. Pale-brown solid; m.p. 73–75 °C. IR (KBr): $\tilde{\nu}$ = 2925, 2855, 1604, 1517, 1461, 1252, 1168, 1036, 832 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 3.83 (s, 3 H), 3.89 (s, 3 H), 7.15 (d, J = 8.5 Hz, 1 H), 7.35–7.44 (m, 1 H), 7.53–7.61 (m, 2 H), 7.89–7.98 (m, 1 H), 8.11 (d, J = 7.9 Hz, 1 H), 8.65 (d, J = 4.3 Hz, 1 H), 9.32 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.7, 55.8, 104.4, 111.8, 112.0, 119.6, 121.1, 123.1, 129.8, 137.2, 147.9, 148.8, 149.2, 149.5 (2 C) ppm. MS (ESI): m/z = 305 $[M + Na]^+$. HRMS (EI, 70 eV): calcd. for $C_{15}H_{14}O_2N_4Na$ 305.10090; found 305.10029.

2-[1-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl]pyridine (4l): Table 4, entry 12. Pale-brown solid; m.p. 80–82 °C. IR (KBr): $\tilde{\nu}$ = 2927, 2858, 1604, 1511, 1468, 1250, 1123, 1035, 829 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 3.72 (s, 3 H), 3.91 (s, 6 H), 7.30–7.45 (m, 3 H), 7.95 (td, J = 1.6, 7.6 Hz, 1 H), 8.12 (d, J = 7.9 Hz, 1 H), 8.65 (d, J = 3.2 Hz, 1 H), 9.42 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 56.2, 60.1, 97.8, 119.6, 121.4, 123.2, 132.3, 137.2 (2 C), 148.0, 149.4, 149.5, 153.4 ppm. MS (ESI): m/z = 335 $[M + Na]^+$. HRMS (EI, 70 eV): calcd. for $C_{16}H_{16}O_3N_4Na$ 335.11146; found 335.11080.

1-(3,4-Dimethoxyphenyl)-4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazole (4m): Table 4, entry 13. White solid; m.p. 176–178 °C. IR (KBr): $\tilde{\nu}$ = 2828, 2845, 1604, 1516, 1471, 1236, 1165, 1025, 818 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 3.96 (s, 3 H), 4.00 (s, 3 H), 6.98 (d, J = 8.3 Hz, 1 H), 7.14–7.26 (m, 3 H), 7.40–7.48 (m, 1 H), 7.76–7.48 (m, 2 H), 7.97 (d, J = 8.3 Hz, 1 H), 8.20 (s, 1 H), 8.34 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 56.0, 56.1, 104.7, 105.6, 111.1, 112.2, 115.6, 117.6, 119.2, 124.3, 127.3, 128.8, 129.6, 130.5, 131.9, 134.4, 148.2, 149.2, 149.6, 157.8 ppm. MS (ESI): m/z = 362 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{21}H_{20}O_3N_3$ 362.14992; found 362.15022.

4-(6-Methoxynaphthalen-2-yl)-1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (4n): Table 4, entry 14. Pale-yellow solid; m.p. 148–150 °C. IR (KBr): $\tilde{\nu}$ = 2928, 2845, 1604, 1516, 1471, 1236, 1165, 1025, 818 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 6 H), 6.96 (s, 2 H), 7.04–7.16 (m, 2 H), 7.73 (d, J = 8.3 Hz, 2 H), 7.90 (d, J = 8.3 Hz, 1 H), 8.13 (s, 1 H), 8.25 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 56.3, 60.9, 98.3, 105.7, 114.1, 117.6, 119.2, 124.3, 125.2, 127.3, 128.8, 129.5, 132.8, 134.3, 138.2, 148.3, 153.8, 157.9 ppm. MS (ESI): m/z = 392 $[M + H]^+$. HRMS (EI, 70 eV): calcd. for $C_{22}H_{22}O_4N_3$ 392.16048; found 392.16079.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of the compounds, copies of the NMR spectra.

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