A New Method for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles via Triazolium Salt Intermediates

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This work is dedicated on the occasion of the birth of my son. His name is Shigemasa.

Abstract: A new transition metal free procedure for the synthesis of 1,5-disubstituted 1,2,3-triazoles, which proceeds via a triazolium salt intermediate is described.

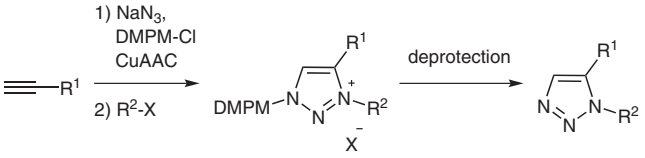
Key words: triazoles, triazolium salts, azides, alkynes, regioselective

Substituted 1,2,3,-triazoles are important structural components of a variety of biologically active compounds. They possess antibacterial,[1] anti-allergic,[2] anti-HIV,[3] and antineoplastic activities.[4] Additionally, they have been widely used in various research fields, including materials science[5] and synthetic organic chemistry.[6]

Many procedures have been developed for the synthesis of 1,4-disubstituted 1,2,3-triazoles, with the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) between organic azides and terminal alkynes representing a useful and extensively applied method.[7]

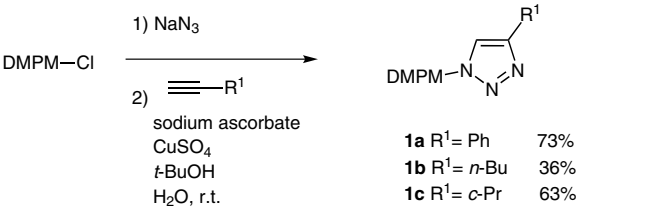
However, there are only a few reported methods describing the synthesis of 1,5-disubstituted 1,2,3-triazoles from organic azides and terminal alkynes. Fokin and co-workers have described the ruthenium(II)-catalyzed [CpRuCl(PPh_3)$_2$] regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles from azides and alkynes.[8] Chuprakov and co-workers reported the synthesis of 1,5-disubstituted 1,2,3-triazoles via direct palladium-catalyzed C-5 arylation from 4,5-unsubstituted 1,2,3-triazoles.[9] Both methods are disadvantaged by their use of expensive transition metals. In contrast, transition metal free click reactions using a silyl acetylene or a bromomagnesium acetylide have been reported for the synthesis of 1,5-disubstituted 1,2,3-triazoles.[10,11] However, these methods need an expensive silyl reagent or anhydrous reaction conditions. 1,5-Disubstituted 1,2,3-triazoles have also been prepared in the presence of hydroxide bases, but the substituent on the triazole ring was limited to an aryl group.[12]

In this paper, we describe the catalytic formation of 1,5-disubstituted 1,2,3,-triazoles via a 1-protected-3,4-disubstituted 1,2,3-triazolium salt intermediate without the requirement of a transition-metal catalyst (Scheme 1).



Scheme 1 The synthesis of 1,5-disubstituted 1,2,3-triazoles

Initially, we investigated the copper-catalyzed regioselective Huisgen cycloaddition of an alkyne and an azide (the so-called click reaction). The substrates, 1-(3,4-dimethoxybenzyl)-4-substituted 1,2,3-triazoles **1a**–**c**, were synthesized in good yields as white solids, via one-pot reactions of 4-(chloromethyl)-1,2-dimethoxybenzene, sodium azide and the appropriate alkyne under the Sharpless protocol[13] (Scheme 2). The obtained products were purified by recrystallization.



Scheme 2 Synthesis of 1-(3,4-dimethoxybenzyl)-4-substituted 1,2,3-triazoles **1a**–**c**

We prepared the 3,4-disubstituted-1,2,3-triazolium salt intermediates from 1,4-disubstituted-1,2,3-triazoles **1a**–**c** in the following manner. A mixture of triazole **1a**–**c** (3.5 mmol), alkyl halide (7.0 mmol), and acetonitrile (2.0 mL) was sealed in a glass vial and warmed to 80 °C overnight. The solvent was then removed under reduced pressure and the products were obtained by silica gel column chromatography using chloroform–methanol as the eluent. A variety of functional groups could be incorporated into the triazolium salt (Table 1).

Next, the effect of varying the halogen component on the synthesis of the triazolium salt was investigated. The reactivity of benzyl chloride was found to be the same as that of benzyl bromide (Table 1, entry 4). Also, the length of the alkyl chain was found to influence the reactivity of triazolium salt formation. Alkyl halides possessing longer carbon chains (ethyl iodide or *n*-butyl iodide) led to lower yields of the corresponding salts (Table 1, entries 1, 5 and

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6). However, the synthesis of 1-(3,4-dimethoxybenzyl)-3-(2-hydroxyethyl)-4-phenyl-1*H*-1,2,3-triazolium bromide (**2g**) using 2-bromoethanol only proceeded in 35% yield (Table 1, entry 7).

We have developed two methods for the deprotection (methods A and B) of triazolium salts **2**. Ammonium nitrate (NH_4NO_3) proved to be an efficient reagent for cleavage of the 3,4-dimethoxybenzyl group. Thus, treatment of salts **2a**–**c** with ammonium nitrate (2 equiv) in *N*,*N*-dimethylformamide at 120 °C gave the expected 1,5-disubstituted 1,2,3-triazoles in good to excellent yields (Table 1, entries 1–3, method A). However, this method only gave a poor yield (6%) of the corresponding benzyl-substituted product **3d** (Table 1, entry 4). The alternative developed procedure (method B) involved deprotection of the triazolium salt using ceric ammonium nitrate (CAN) in *N*,*N*-dimethylformamide. The deprotection of 3-benzyl-1-(3,4-dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazolium bromide (**2d**) using method B gave 1-benzyl-5-phenyl-1*H*-1,2,3-triazole (**3d**) in 72% yield (Table 1, entry 4). However, removal of the protecting group did not progress smoothly with compounds containing a non-aromatic group (*n*-butyl and cyclopropyl) at C-4 of the triazolium salt (**2b** and **2c**) under the conditions of method B (Table 1, entries 2 and 3). Hence, the synthesis of 1,2,3-triazoles **3** with aliphatic substituents at C-5 was possible using method A. Finally, we examined the deprotection of the 3,4-dimethoxybenzyl-1,2,3-triazolium salts using palladium on carbon (Pd/C) in the presence of hydrogen gas, or with trifluoroacetic acid, albeit without success.

Table 1 Synthesis of 1,5-Disubstituted 1,2,3-Triazoles **3a**–**j**

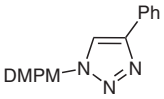
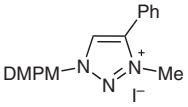
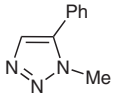
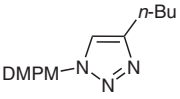
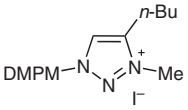
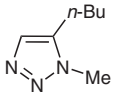
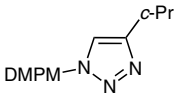
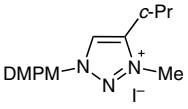
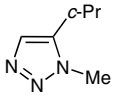
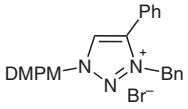
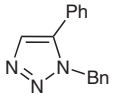
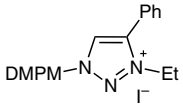
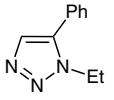
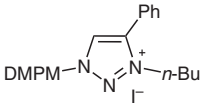
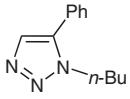
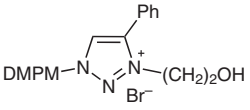
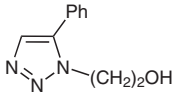
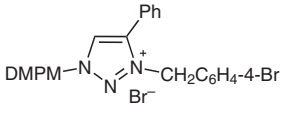
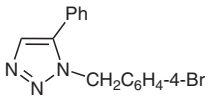
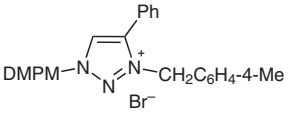
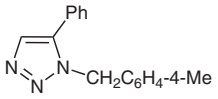
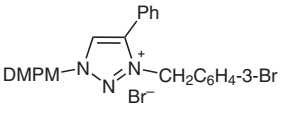
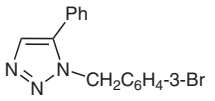
Entry	1,4-Disubstituted 1,2,3-triazole[a]	Alkyl halide	3,4-Disubstituted 1,2,3-triazolium salt[b]	Yield[c]	1,5-Disubstituted 1,2,3-triazole[d]	Yield[c]
1	 **1a**	MeI	 **2a**	quant.	 **3a**	method A: quant. method B: 99%
2	 **1b**	MeI	 **2b**	quant.	 **3b**	method A: 92% method B: trace
3	 **1c**	MeI	 **2c**	96%	 **3c**	method A: 80% method B: trace
4	**1a**	BnBr	 **2d**	90%	 **3d**	method A: 6% method B: 72%
5	**1a**	EtI	 **2e**	77%	 **3e**	method A: 71% method B: 72%
6	**1a**	*n*-BuI	 **2f**	50%	 **3f**	method A: 93% method B: 51%
7	**1a**	$HO(CH_2)_2Br$	 **2g**	35%	 **3g**	method A: 58% method B: 46%

Table 1 Synthesis of 1,5-Disubstituted 1,2,3-Triazoles **3a–j** (continued)

Entry	1,4-Disubstituted 1,2,3-triazole[a]	Alkyl halide	3,4-Disubstituted 1,2,3-triazolium salt[b]	Yield[c]	1,5-Disubstituted 1,2,3-triazole[d]	Yield[c]
8	**1a**	4-$BrC_6H_4CH_2Br$	 **2h**	84%	 **3h**	method A: 49% method B: 36%
9	**1a**	4-$MeC_6H_4CH_2Br$	 **2i**	66%	 **3i**	method A: 35% method B: 31%
10	**1a**	3-$BrC_6H_4CH_2Br$	 **2j**	68%	 **3j**	method A: 28% method B: 33%

[a] DMPM = 3,4-dimethoxybenzyl.
[b] *Reagents and conditions*: 1-(3,4-dimethoxybenzyl)-4-substituted-1,2,3-triazole **1a–c** (3.5 mmol), alkyl halide (7.0 mmol), MeCN (2.0 mL), 80 °C, 11 h.
[c] Yield of isolated product.
[d] *Reagents and conditions*: Method A: 3,4-disubstituted-1,2,3-triazolium salt **2a–j** (1.5 mmol), NH_4NO_3 (3.0 mmol), DMF (5 mL), 120 °C, 11 h. Method B: 3,4-disubstituted-1,2,3-triazolium salt **2a–j** (1.0 mmol), CAN (2.0 mmol), DMF (5 mL), 120 °C, 13 h.

In summary, we have demonstrated the synthesis of 1,5-disubstituted 1,2,3-triazoles via a triazolium salt intermediate. The reactions proceeded under cost-effective and environmentally benign conditions without using any toxic reagents or expensive transition metal catalysts. Further study of this chemistry is under way.

All chemicals (reagent grade) were obtained from commercial suppliers and were used as supplied. The progress of the reactions was monitored by TLC using aluminum sheets coated with silica gel 60 F_{254} (Merck). Column chromatography was performed using silica gel 60 (Kanto Chemical). Melting points were obtained with a Yamato MP-21 melting point apparatus. NMR spectra were recorded on a Bruker Avance DRX 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) spectrometer with $CDCl_3$ as the solvent. Chemical shifts (δ) are expressed in ppm and refer to the residual peak of the solvent or TMS as an internal standard; coupling constants (*J*) are in Hz. The mass analyses were obtained using a JEOL AccuTOF LC-plus JMS-T100LP spectrometer.

1-(3,4-Dimethoxybenzyl)-4-substituted-1*H*-1,2,3-triazoles 1a-c; General Procedure
A soln of 4-(chloromethyl)-1,2-dimethoxybenzene (40 mmol) and distilled H_2O (25 mL) in *t*-BuOH (75 mL) was added to NaN_3 (40 mmol). The resulting mixture was stirred at r.t. for 24 h and then added to a mixture of ethynylbenzene (40 mmol), $CuSO_4$ (8 mmol) in distilled H_2O (25 mL), and sodium ascorbate (16 mmol) in H_2O (25 mL). After stirring for 24 h at r.t., the solvent was removed under vacuum and the mixture extracted with $CHCl_3$, and the organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was purified by recrystallization from $CHCl_3$–Et_2O.

1-(3,4-Dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole (1a)
Yield: 4195 mg (14.20 mmol; 73%); white solid; mp 120–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 3.89 (s, 3 H), 5.51 (s, 2 H), 6.83 (d, *J* = 1.9 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.92 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.32 (t, *J* = 7.4 Hz, 1 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.64 (s, 1 H), 7.80 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1, 55.89, 55.92, 111.1, 111.2, 119.3, 120.8, 125.6, 126.9, 128.1, 128.7, 130.6, 149.4, 149.4.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1399; found: 296.1452.

4-Butyl-1-(3,4-dimethoxybenzyl)-1*H*-1,2,3-triazole (1b)
Yield: 791 mg (2.73 mmol; 36%); white solid; mp 86–87 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 1.36 (q, *J* = 7.4 Hz, 2 H), 1.60–1.64 (m, 2 H), 2.69 (t, *J* = 7.8 Hz, 2 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 5.42 (s, 2 H), 6.77 (s, 1 H), 6.85 (s, 2 H), 7.15 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 22.2, 25.4, 31.5, 53.8, 55.9, 111.0, 111.2, 120.2, 120.6, 127.4, 149.3, 149.4.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{22}N_3O_2$: 276.1712; found: 276.1765.

4-Cyclopropyl-1-(3,4-dimethoxybenzyl)-1*H*-1,2,3-triazole (1c)
Yield: 1272 mg (4.90 mmol; 63%); white solid; mp 74–75 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78–0.83 (m, 2 H), 0.89–0.94 (m, 2 H), 1.87–1.94 (m, 1 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 5.39 (s, 2 H), 6.78 (s, 1 H), 6.85 (s, 2 H), 7.11 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.7, 7.6, 53.8, 55.87, 55.89, 111.1, 111.2, 119.3, 120.7, 127.2, 149.3, 149.4.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}N_3O_2$: 260.1399; found: 260.1456.

1-(3,4-Dimethoxybenzyl)-3,4-disubstituted-1*H*-1,2,3-triazolium Salts 2a–j; General Procedure
A soln of 1-(3,4-dimethoxybenzyl)-4-substituted-1*H*-1,2,3-triazole **1a–c** (3.5 mmol) and an alkyl halide (7.0 mmol) in MeCN (2.0 mL) was stirred at 80 °C for 11 h. H_2O was added and the mixture extracted with $CHCl_3$. The organic layers were combined, washed with distilled H_2O and dried ($MgSO_4$). The solvent was removed

under vacuum and the product was isolated by silica gel column chromatography ($CHCl_3$–MeOH).

1-(3,4-Dimethoxybenzyl)-3-methyl-4-phenyl-1*H*-1,2,3-triazolium Iodide (2a)
Yield: 1404 mg (3.21 mmol; quant.); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 3.98 (s, 3 H), 4.29 (s, 3 H), 5.98 (s, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 7.23 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.49 (d, *J* = 1.9 Hz, 1 H), 7.54–7.62 (m, 3 H), 7.65–7.68 (m, 2 H), 9.37 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.1, 55.9, 56.9, 57.4, 111.4, 113.3, 121.7, 122.8, 123.4, 129.1, 129.5, 129.7, 132.0, 143.0, 149.5, 150.2.

HRMS (APCI): *m*/*z* [M – I]$^+$ calcd for $C_{18}H_{20}N_3O_2$: 310.1556; found: 310.1606.

4-Butyl-1-(3,4-dimethoxybenzyl)-3-methyl-1*H*-1,2,3-triazolium Iodide (2b)
Yield: 1106 mg (2.56 mmol; quant.); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H), 1.45 (q, *J* = 7.4 Hz, 2 H), 1.73–1.77 (m, 2 H), 2.84 (t, *J* = 8.0 Hz, 2 H), 3.87 (s, 3 H), 3.96 (s, 3 H), 4.23 (s, 3 H), 5.87 (s, 2 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 7.16 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.38 (d, *J* = 2.0 Hz, 1 H), 9.19 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 22.0, 23.6, 28.8, 38.6, 55.9, 56.7, 57.0, 111.3, 112.9, 122.5, 123.5, 128.6, 144.4, 149.4, 150.1.

HRMS (APCI): *m*/*z* [M – I]$^+$ calcd for $C_{16}H_{24}N_3O_2$: 290.1869; found: 290.1913.

4-Cyclopropyl-1-(3,4-dimethoxybenzyl)-3-methyl-1*H*-1,2,3-triazolium Iodide (2c)
Yield: 1175 mg (2.92 mmol; 96%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.16 (m, 2 H), 1.23–1.28 (m, 2 H), 1.90–1.97 (m, 1 H), 3.87 (s, 3 H), 3.96 (s, 3 H), 4.31 (s, 3 H), 5.81 (s, 2 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 7.16 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.38 (d, *J* = 2.1 Hz, 1 H), 9.21 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 4.4, 8.3, 38.3, 55.9, 56.8, 57.2, 111.4, 113.1, 122.6, 123.5, 128.0, 146.2, 149.5.

HRMS (APCI): *m*/*z* [M – I]$^+$ calcd for $C_{15}H_{20}N_3O_2$: 274.1556; found: 274.1620.

3-Benzyl-1-(3,4-dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazolium Bromide (2d)
Yield: 375 mg (0.79 mmol; 90%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.96 (s, 3 H), 5.66 (s, 2 H), 6.17 (s, 2 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 7.08 (d, *J* = 7.1 Hz, 2 H), 7.29 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.34–7.41 (m, 3 H), 7.46–7.54 (m, 5 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 10.10 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.2, 55.7, 56.3, 57.2, 111.1, 112.8, 121.6, 122.5, 123.9, 127.8, 129.1, 129.4, 129.5, 129.6, 131.2, 131.7, 142.6, 149.2, 149.9.

HRMS (APCI): *m*/*z* [M – Br]$^+$ calcd for $C_{24}H_{24}N_3O_2$: 386.1869; found: 386.1878.

1-(3,4-Dimethoxybenzyl)-3-ethyl-4-phenyl-1*H*-1,2,3-triazolium Iodide (2e)
Yield: 1181 mg (2.61 mmol; 77%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (t, *J* = 7.3 Hz, 3 H), 3.89 (s, 3 H), 3.99 (s, 3 H), 4.57 (q, *J* = 7.3 Hz, 2 H), 6.04 (s, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 7.23 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.54 (d, *J* = 2.1 Hz, 1 H), 7.56–7.64 (m, 5 H), 9.41 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 47.6, 55.9, 56.8, 57.5, 111.4, 113.3, 121.8, 122.8, 123.5, 129.3, 129.5, 129.7, 131.9, 142.4, 149.5, 150.2.

HRMS (APCI): *m*/*z* [M – I]$^+$ calcd for $C_{19}H_{22}N_3O_2$: 324.1712; found: 324.1760.

3-Butyl-1-(3,4-dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazolium Iodide (2f)
Yield: 476 mg (0.99 mmol; 50%); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 5.2 Hz, 3 H), 1.30–1.36 (m, 2 H), 1.90–1.93 (m, 2 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 4.54 (t, *J* = 6.2 Hz, 2 H), 6.03 (s, 2 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 7.26 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.52–7.56 (m, 5 H), 7.57–7.59 (m, 1 H), 9.46 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.0, 19.2, 30.7, 51.7, 55.6, 55.8, 56.7, 111.2, 113.1, 121.7, 122.6, 123.4, 129.3, 129.4, 129.5, 131.7, 142.3, 149.2, 150.0.

HRMS (APCI): *m*/*z* [M – I]$^+$ calcd for $C_{21}H_{26}N_3O_2$: 352.2025; found: 352.2038.

1-(3,4-Dimethoxybenzyl)-3-(2-hydroxyethyl)-4-phenyl-1*H*-1,2,3-triazolium Bromide (2g)
Yield: 742 mg (1.12 mmol; 35%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.94 (s, 3 H), 4.11–4.14 (m, 2 H), 4.52 (t, *J* = 4.5 Hz, 2 H), 5.87 (s, 2 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 7.20 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.38 (d, *J* = 1.5 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.69 (d, *J* = 7.4 Hz, 2 H), 8.74 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1, 55.8, 56.4, 57.4, 59.5, 111.3, 113.2, 123.0, 123.1, 128.4, 129.3, 130.0, 131.5, 143.8, 149.4, 150.1.

HRMS (APCI): *m*/*z* [M – Br]$^+$ calcd for $C_{19}H_{22}N_3O_3$: 340.1661; found: 340.1712.

3-(4-Bromobenzyl)-1-(3,4-dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazolium Bromide (2h)
Yield: 1427 mg (2.80 mmol; 84%); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.95 (s, 3 H), 5.63 (s, 2 H), 6.08 (s, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 8.2 Hz, 2 H), 7.48–7.57 (m, 8 H), 9.91 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.8, 55.8, 56.4, 57.3, 111.3, 113.0, 122.6, 124.1, 129.5, 129.6, 129.82, 129.84, 132.3, 142.7, 149.3, 150.0.

HRMS (APCI): *m*/*z* [M – Br]$^+$ calcd for $C_{24}H_{23}N_3O_2Br$: 464.0974 (^{79}Br), 466.0953 (^{81}Br); found: 464.0944 (^{79}Br), 466.0919 (^{81}Br).

1-(3,4-Dimethoxybenzyl)-3-(4-methylbenzyl)-4-phenyl-1*H*-1,2,3-triazolium Bromide (2i)
Yield: 1000 mg (2.08 mmol; 66%); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 5.59 (s, 2 H), 6.17 (s, 2 H), 7.12–7.30 (m, 4 H), 7.37–7.66 (m, 8 H), 10.10 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4, 54.7, 55.2, 55.7, 56.1, 121.0, 127.3, 127.5, 128.1, 128.7, 128.9, 129.0, 129.1, 138.65, 138.68, 141.9, 148.5, 149.2.

HRMS (APCI): *m*/*z* [M – Br]$^+$ calcd for $C_{25}H_{26}N_3O_2$: 400.2025; found: 400.2035.

3-(3-Bromobenzyl)-1-(3,4-dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazolium Bromide (2j)
Yield: 1216 mg (2.23 mmol; 68%); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 3.97 (s, 3 H), 5.63 (s, 2 H), 6.15 (s, 2 H), 7.20–7.62 (m, 12 H), 9.90 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.3, 55.4, 56.0, 56.8, 110.9, 121.1, 122.4, 126.6, 129.08, 129.16, 129.18, 130.3, 130.4, 142.3, 149.8, 150.0.

HRMS (APCI): *m*/*z* [M – Br]$^+$ calcd for $C_{24}H_{23}N_3O_2Br$: 464.0974 (^{79}Br), 466.0953 (^{81}Br); found: 464.0944 (^{79}Br), 466.0922 (^{81}Br).

1,5-Disubstituted 1*H*-1,2,3-triazoles 3a–j; General Procedure (Method A)

A soln of 1-(3,4-dimethoxybenzyl)-3,4-disubstituted-1*H*-1,2,3-triazolium salt **2a–j** (1.5 mmol) and NH_4NO_3 (3.0 mmol) in DMF (5 mL) was stirred at 120 °C for 11 h. The solvent was removed under vacuum and the mixture was extracted with $CHCl_3$ and washed with H_2O. The organic layers were combined, washed with H_2O, and dried ($MgSO_4$). The solvent was removed under vacuum and the product was isolated by silica gel column chromatography ($CHCl_3$–MeOH).

1,5-Disubstituted 1*H*-1,2,3-triazoles 3a–j; General Procedure (Method B)

A soln of 1-(3,4-dimethoxybenzyl)-3,4-disubstituted-1*H*-1,2,3-triazolium salt **2a–j** (1.0 mmol) and CAN (2.0 mmol) in DMF (5 mL) was stirred at 120 °C for 13 h. The solvent was removed under vacuum and the mixture was extracted with $CHCl_3$ and washed with H_2O. The organic layers were combined, washed with H_2O, and dried ($MgSO_4$). The solvent was removed under vacuum and the product was isolated by silica gel column chromatography ($CHCl_3$–MeOH).

1-Methyl-5-phenyl-1*H*-1,2,3-triazole (3a)

Yield: 263 mg (1.65 mmol; quant.) using method A, 176 mg (1.11 mmol; 99%) using method B; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (s, 3 H), 7.40–7.43 (m, 2 H), 7.47–7.51 (m, 3 H), 7.74 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.0, 127.3, 128.1, 128.3, 128.5, 128.6, 132.0, 137.4.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{10}N_3$: 160.0874; found: 160.0824.

5-Butyl-1-methyl-1*H*-1,2,3-triazole (3b)

Yield: 253 mg (1.82 mmol; 92%) using method A; trace using method B; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3 H), 1.39–1.45 (m, 2 H), 1.62–1.66 (m, 2 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 3.95 (s, 3 H), 7.45 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 21.9, 22.5, 29.7, 34.0, 131.7, 137.2.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_7H_{14}N_3$: 140.1187; found: 140.1154.

5-Cyclopropyl-1-methyl-1*H*-1,2,3-triazole (3c)

Yield: 211 mg (1.71 mmol; 80%) using method A; trace using method B; orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68–0.72 (m, 2 H), 1.03–1.08 (m, 2 H), 1.67–1.72 (m, 1 H), 4.05 (s, 3 H), 7.26 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 3.4, 6.3, 34.1, 130.3, 139.5.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_6H_{10}N_3$: 124.0874; found: 124.1042.

1-Benzyl-5-phenyl-1*H*-1,2,3-triazole (3d)

Yield: 11 mg (0.05 mmol; 6%) using method A; 213 mg (0.91 mmol; 72%) using method B; orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.55 (s, 2 H), 7.06–7.09 (m, 2 H), 7.24–7.29 (m, 5 H), 7.39–7.44 (m, 3 H), 7.75 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.8, 126.8, 127.1, 128.1, 128.77, 128.84, 128.9, 129.5, 133.2, 135.4.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3$: 236.1187; found: 236.1261.

1-Ethyl-5-phenyl-1*H*-1,2,3-triazole (3e)

Yield: 54 mg (0.31 mmol; 71%) using method A; 213 mg (1.23 mmol; 72%) using method B; orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.3 Hz, 3 H), 4.41 (q, *J* = 7.3 Hz, 2 H), 7.39 (m, 2 H), 7.47–7.51 (m, 3 H), 7.70 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 43.3, 127.1, 128.6, 129.0, 129.3, 133.0, 137.3.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{12}N_3$: 174.1031; found: 174.0943.

1-Butyl-5-phenyl-1*H*-1,2,3-triazole (3f)

Yield: 115 mg (0.57 mmol, 93%) using method A; 90 mg (0.45 mmol; 51%) using method B; orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.2 Hz, 3 H), 1.25–1.31 (m, 2 H), 1.80–1.84 (m, 2 H), 4.35 (t, *J* = 6.2 Hz, 2 H), 7.37–7.40 (m, 2 H), 7.47–7.51 (m, 3 H), 7.69 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2, 19.4, 31.9, 47.8, 125.4, 127.0, 128.50, 128.54, 128.9, 129.2, 132.7, 137.5.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}N_3$: 202.1344; found: 202.1448.

2-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)ethanol (3g)

Yield: 38 mg (0.20 mmol; 58%) using method A; 30 mg (0.16 mmol; 46%) using method B; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.14 (t, *J* = 5.0 Hz, 2 H), 4.42 (t, *J* = 5.0 Hz, 2 H), 7.42–7.46 (m, 2 H), 7.48–7.52 (m, 3 H), 7.72 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.4, 61.0, 126.6, 129.00, 129.04, 129.5, 132.6, 138.8.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{12}N_3O$: 190.0980; found: 190.1083.

1-(4-Bromobenzyl)-5-phenyl-1*H*-1,2,3-triazole (3h)

Yield: 191 mg (0.61 mmol; 49%) using method A; 142 mg (0.45 mmol; 36%) using method B; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.51 (s, 2 H), 7.50 (m, 1 H), 7.16 (m, 1 H), 7.21–7.28 (m, 3 H), 7.40–7.46 (m, 4 H), 7.74 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.4, 119.4, 122.8, 125.8, 128.2, 128.75, 128.83, 129.0, 129.6, 131.9, 132.2, 133.7, 148.3.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_3Br$: 314.0293 (^{79}Br), 316.0272 (^{81}Br); found: 314.0343 (^{79}Br), 316.0321 (^{81}Br).

1-(4-Methylbenzyl)-5-phenyl-1*H*-1,2,3-triazole (3i)

Yield: 90 mg (0.36 mmol; 35%) using method A; 80 mg (0.32 mmol; 31%) using method B; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 5.51 (s, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.25–7.28 (m, 2 H), 7.41–7.46 (m, 3 H), 7.74 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 51.4, 126.8, 127.0, 128.7, 128.8, 129.3, 129.6, 132.3, 133.0, 137.7, 137.9.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}N_3$: 250.1344; found: 250.1410.

1-(3-Bromobenzyl)-5-phenyl-1*H*-1,2,3-triazole (3j)

Yield: 100 mg (0.32 mmol; 28%) using method A; 115 mg (0.37 mmol; 33%) using method B; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.50 (s, 2 H), 6.98 (m, 1 H), 7.14–7.27 (m, 4 H), 7.37–7.50 (m, 4 H), 7.65 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.0, 125.7, 129.0, 129.6, 130.2, 130.3, 130.9, 131.3, 131.9, 133.3, 137.5, 138.1.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_3Br$: 314.0292 (^{79}Br), 316.0272 (^{81}Br); found: 314.0336 (^{79}Br), 316.0320 (^{81}Br).

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