Supplementary Information

Synthesis of Multi-substituted 1,2,4-triazoles Utilising the Ambiphilic Reactivity of Hydrazones

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1. General Information

Flash column chromatography were performed using Silicycle silica gel (SiliaFlash® F60, 40-63 μm) or performed on Yamazen Automated Liquid Chromatography System Smart Flash EPCLC-AI-580S using ULTRAPACK SI-40B or Biotage Automated Liquid Chromatography System Isolera One using Biotage SNAP KP-Sil 25g or 50g or 100g silica gel cartridges. NMR spectra were recorded at 300 MHz/75 MHz (1H NMR/13C NMR), 500 MHz/125 MHz (1H NMR/13C NMR) or 600 MHz/150 MHz (1H NMR/13C NMR) using Varian MERCURY plus 300 (300 MHz), Varian NMR system AS-500 (500 MHz), or Bruker Avance III HD 600 (600 MHz) spectrometers. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, td = triplet of doublets, m = multiplet), coupling constants, and integration. Infrared (IR) spectra were recorded on a Perkin-Elmer SpectrumOne A spectrometer. The high-resolution mass spectra (HRMS) were obtained using Thermo Fischer Scientific Exactive Orbitrap mass spectrometer by ESI technique. Melting points (uncorrected) were determined on BÜCHI M-565 apparatus. Preparative TLC separations (PTLC) were carried out on precoated silica gel plates (E. Merck 60F254). N-Chlorosuccinimide (NCS), BF₃·OEt₂ were purchased from Nacalai Tesque, Inc. Hydrazones 1a, 1b, 1c, 1d, 1e, 1f, 1h, 1i, 1j, 1k, 1l, 1m, 1n, 1o, 1p, 1q, 1u, 1v were prepared according to literatures¹, respectively. The spectra data of these known compounds were identical with those reported in the literatures, respectively.

2. Experimental Section

2.1 Experimental procedure for the preparation of hydrazone (1d)

![Synthesis of 1d](image)

To a solution of 4-hydroxybenzaldehyde (S1) (733 mg, 6.0 mmol) in CH₂Cl₂ (7.3 mL) were added pyridine (823 μL, 10.2 mmol), DMAP (73 mg, 0.60 mmol) at 0 °C and then slowly added pivaloyl chloride (1.1 mL, 9.0 mmol) at the same temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with H₂O (10 mL) and extracted with CHCl₃ (10 mL × 3). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 5/1) to afford pivalate S2 as a colorless oil (1.40 g, 2
quant.). The spectra data matched those previously reported in the literature².

(E)-2,2-Dimethylpropionic acid 4-[(2,2-dimethylhydrazinylidene)methyl]phenyl ester (1d)

To a solution of S2 (1.4 g, 6.0 mmol) in MeOH (12 mL) was added N,N-dimethylhydrazine (486 μL, 7.2 mmol) at room temperature. After being stirred for 1.5 h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 10/1) to afford hydrazone 1d (1.33 g, 89%) as white crystals; Mp: 72-74 °C (Hexane); IR (KBr): 1744, 1563 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.56 (d, J = 8.7 Hz, 2H), 7.21 (s, 1H), 7.01 (d, J = 8.7 Hz, 2H), 2.95 (s, 6H), 1.35 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ: 176.9, 150.2, 134.4, 131.8, 126.3, 121.4, 42.8, 39.0, 27.1; HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₄H₂₁O₂N₂ 249.1598; Found 249.1596.

2.2 Experimental procedure for the preparation of hydrazone (1r)

2-(2,2-Diethoxyethoxy)benzaldehyde (S4)

To a solution of salicylaldehyde (S3) (5.2 mL, 50 mmol) in DMF (50 mL) were added bromoacetaldehyde diethyl acetal (8.1 mL, 52.5 mmol), K₂CO₃ (1.4 g, 100 mmol) at room temperature. The reaction mixture was stirred at 100 °C. After being stirred for 23 h, the reaction mixture was diluted with EtOAc (30 mL) and then filtered through celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in Et₂O (30 mL) and H₂O (20 mL) and extracted with Et₂O (30 mL × 3). The organic phase was washed with H₂O (20 mL × 3), brine (20 mL) and dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 10/1) to give 2-(2,2-diethoxyethoxy)benzaldehyde (S4) (10.6 g, 89%) as a yellow oil. The spectra data matched those previously reported in the literature³.
2-Benzofurancarboxaldehyde (S5)

A solution of aldehyde S4 (11 g, 44 mmol) in AcOH (18 mL) and H2O (2.4 mL) was stirred at reflux. After being stirred for 48 h at the same temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in Et2O (120 mL) and washed with sat. NaHCO3 aq. (24 mL × 3). The organic phase was dried over MgSO4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 20/1 to 10/1) to give 2-benzofurancarboxaldehyde (S5) (1.04 g, 16%) as a pale yellow oil. The spectra data matched those previously reported in the literature3.

(E)-2-Benzofurancarboxaldehyde dimethyl hydrazone (1r)

To a solution of 2-benzofurancarboxaldehyde (S5) (1.0 g, 7.1 mmol) in MeOH (14 mL) was added N,N-dimethylhydrazine (648 μL, 8.5 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (1.0 mL) and then added sat. NaHSO3 aq. (5.0 mL) and shaken for approximately 30 sec and extracted with hexanes (20 mL). The organic phase was dried over MgSO4 and concentrated under reduced pressure to give the hydrazones 1r (997.5 mg, 75%) as a yellow oil; IR (neat): 1595 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.50 (d, J = 9.0 Hz, 2H), 7.23 (m, 2H), 7.14 (s, 1H), 6.64 (s, 1H), 3.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ: 154.6, 154.0, 128.8, 124.1, 122.8, 121.3, 120.5, 111.2, 103.2, 42.6; HRMS (ESI) m/z: [M + H]+ Calcd for C₁₁H₁₃ON₂ 189.1022; Found 189.1022. The crude product 1r was used without the further purification.

2.3 General procedure for the preparation of hydrazones (1s, 1t)

To a solution of corresponding aldehydes S6 (10 mmol) in MeOH (20 mL) was added N,N-dimethylhydrazine (1.1 mL, 15 mmol) at room temperature. After being stirred for several hours, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography to give the corresponding hydrazones 1s and 1t.

(E)-Cyclohexanecarboxaldehyde 2,2-dimethylhydrazone (1s)

1.47 g, 96% yield; Reaction time: 3 h; Purification by flash column chromatography (Yamazen Smart Flash EPCLC-AI-580S using ULTRAPACK SI-40B) (Hexane/EtOAc = 19/1 to 47/13);
colorless oil; IR (neat): 1607 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 6.51 (d, \(J = 6.0\) Hz, 1H), 2.70 (s, 6H), 2.23-2.14 (m, 1H), 1.79-1.64 (m, 5H), 1.34-1.16 (m, 5H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 144.0, 43.2, 41.2, 31.3, 25.9, 25.6; HRMS (ESI) m/z: [M + H]\(^+\) Calcd for C\(_9\)H\(_{19}\)N\(_2\) 155.1543; Found 155.1542.

\((E)\)-Pentanal 2,2-dimethylhydrazone (1t)
641 mg, 50% yield; Reaction time: 3.5 h; Purification by flash column chromatography (Hexane/EtOAc = 5/1); A pale yellow oil; IR (neat): 1620 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 6.66 (t, \(J = 5.6\) Hz, 1H), 2.72 (s, 6H), 2.23 (td, \(J = 7.8, 5.6, 2H\)), 1.46 (quint, \(J = 7.4\) Hz, 2H), 1.36 (sext, \(J = 7.4\) Hz, 2H), 0.92 (t, \(J = 7.4\) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 139.7, 43.3, 32.7, 29.8, 22.2, 13.8; HRMS (ESI) m/z: [M + H]\(^+\) Calcd for C\(_7\)H\(_{17}\)N\(_2\) 129.1386; Found 129.1388.

2.4 General procedure for the preparation of hydrazones (1w, 1x)

2,2-Diethyldihyrazinecarboxylic acid 1,1-dimethylethyl ester (S8a)
To a solution of tert-butyl carbazate (S7) (4.0 g, 30 mmol) in MeCN were added iodoethane (6.1 mL, 75 mmol), DIPEA (16 mL, 90 mmol) at room temperature. After being stirred at reflux for 6 h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 2/1) to give the 2,2-diethyldihyrazine S8a (4.60 g, 82%) as a white solid; Mp: 53-57 \(^\circ\)C (Hexane); IR (KBr) 3240, 1712 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 5.23 (br s, 1H), 2.72 (q, \(J = 7.2\) Hz, 4H), 1.46 (s, 9H), 1.09 (t, \(J = 7.2\) Hz, 6H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 155.2, 79.3, 51.9, 28.2, 11.8; HRMS (ESI) m/z: [M + Na]\(^+\) Calcd for C\(_{9}\)H\(_{20}\)O\(_2\)N\(_2\)Na 211.1417; Found 211.1416.

\((E)\)-Benzaldehyde 2,2-diethyldihyrazone (1w)
To a solution of 2,2-diethyldihyrazine S8a (1.9 g, 10 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was added trifluoroacetic acid (5.0 mL) at room temperature. After being stirred for 1.5 h, the reaction mixture was concentrated under reduced pressure. The crude product S9a dissolved in MeOH (20 mL) and then added benzaldehyde (1.0 mL, 10 mmol), pyridine (1.2 mL, 15 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with 1 M HCl aq. (10 mL), sat.
NaHCO₃ aq. (10 ml), brine (10 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 10/1) to give the hydrazone 1w (585 mg, 33%) as a yellow oil; IR (neat): 1559 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.54 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.28 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H) 3.35 (q, J = 7.2 Hz, 4H), 1.17 (t, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ: 137.4, 130.1, 128.3, 126.7, 125.2, 46.6, 11.7; HRMS (ESI) m/z: [M + H]^+ Caled for C₁₁H₁₇N₂ 177.1386; Found 177.1384.

2,2-Dihexylhydrazinecarboxylic acid 1,1-dimethylethyl ester (S8b)

To a solution of tert-butyl carbazate (S7) (4.0 g, 30 mmol) in MeCN (30 mL) were added 1-iodohexane (15 mL, 105 mmol), DIPEA (16 mL, 90 mmol) at room temperature. After being stirred for 6 h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 10/1) to give the 2,2-dihexylhydrazine S8b (7.96 g, 88%) as a white solid; Mp: 30-32 °C; IR (KBr): 3230, 1699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 5.22 (br s, 1H), 2.64 (br m, 4H), 1.48-1.22 (m, 25H), 0.88 (t, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ: 155.1, 79.4, 58.3, 31.7, 28.3, 26.9, 26.8, 22.6, 14.0; HRMS (ESI) m/z: [M + Na]^+ Caled for C₁₈H₃₆O₃N₄Na 323.2669; Found 323.2668.

(E)-Benzaldehyde 2,2-dihexyhydrazone (1x)

To a solution of 2,2-dihexylhydrazine S8b (3.0 g, 10 mmol) in CH₂Cl₂ (20 mL) was added trifluoroacetic acid (5.0 mL) at room temperature. After being stirred for 3 h, the reaction mixture was concentrated under reduced pressure. The crude product S9b dissolved in MeOH (20 mL) and then added benzaldehyde (683 µL, 6.7 mmol), pyridine (1.6 mL, 20 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with 1 M HCl aq. (10 mL), sat. NaHCO₃ aq. (10 ml), brine (10 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/Et₂O = 20/1) to give the hydrazone 1x (1.75 g, 90%) as a yellow oil; IR (neat): 1560 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.52 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.19 (s, 1H), 7.15 (t, J = 7.2 Hz, 1H), 3.26 (br m, 4H), 1.59 (br quint, J = 7.2 Hz, 4H), 1.35-1.30 (m, 12H), 0.90 (t, J = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ: 137.7, 128.5, 128.3, 126.4, 125.1, 53.5, 31.7, 26.9, 26.8, 22.6, 14.0; HRMS (ESI) m/z: [M + H]^+ Caled for C₁₉H₃₃N₂ 289.2638; Found 289.2636.
2.5 Experimental procedure for the preparation of hydrazone 1y

To a suspension of 2-hydrazinoethanol (S10) (850 μL, 10 mmol) in DCM (10 mL) was added ethylene oxide in DCM (1.0 M, 10 mL, 10 mmol) at room temperature. The reaction mixture was stirred at reflux. After being stirred for 15 h, the reaction mixture was concentrated under reduced pressure. The crude product S11 dissolved in MeOH (16 mL) and then added benzaldehyde (790 μL, 7.8 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was concentrated under reduced pressure. The crude product S12 was used without the further purification.

(E)-2,2-Dimethylpropanoic acid 1,1'-((2-benzylideneaminimino)bis(2,1-ethanediyl) ester (1y)

To a suspension of hydrazone S12 in DCM (18 mL) were slowly added pyridine (2.4 mL, 30 mmol), DMAP (220 mg, 1.8 mmol), pivaloyl chloride (3.2 mL, 26 mmol) at 0 ℃ and then stirred at the same temperature. After being stirred for 1 h, pivaloyl chloride (2.2 mL, 18 mmol) was slowly added to the reaction mixture. After additional 30 min, the reaction mixture was quenched with H₂O (10 mL) and extracted with CHCl₃ (20 mL × 3). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was dissolved in CHCl₃ (20 mL) and basified by 1.0 M NaOH aq. (20 mL) and then extracted with CHCl₃ (20 mL × 2). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 20/1) to afford hydrazone 1y (1.31 g, 44%, 3 steps) an yellow oil; IR (neat): 1744, 1563 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.54 (d, J = 7.2 Hz, 2H), 7.37 (s, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.23-7.18 (m, 1H), 4.28 (t, J = 6.0 Hz, 4H), 3.63 (t, J = 6.0 Hz, 4H), 1.20 (s, 18H); ¹³C NMR (75 MHz, CDCl₃) δ: 178.4, 136.6, 130.9, 128.4, 127.3, 125.5, 61.7, 52.6, 38.7, 27.2; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₁H₂₃O₄N₂Na 399.2254; Found 399.2248.
2.6 Experimental procedure for the preparation of hydrazone 1z

Diisopropylamine S13 (2.8 mL, 20 mmol) was added to conc. HCl (2.0 mL, 24 mmol) at 0 °C. Then, to the resulting mixture was added NaNO₂ (1.7 g, 25 mmol) in H₂O (4.0 mL) at the same temperature and stirred at room temperature. After being stirred for 30 min, the reaction mixture was diluted with Et₂O (20 mL) and extracted with Et₂O (20 mL × 3). The organic phase was washed with brine (10 mL) and dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in 4 M HCl aq. (59 mL) and Zn powder (1.6 g, 25 mmol) was added at room temperature. After being stirred at the same temperature for 4 h, Zn powder (8.0 g, 125 mmol) was added and then stirred for 30 min. The reaction mixture was filtered through celite. Then, the filtrate was basified with 4 M NaOH aq. (60 mL) and extracted with CHCl₃ (50 mL × 3). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product S15 was used without the further purification.

(E)-Benzaldehyde 2,2-di(1-methylethyl)hydrazone (1z)

To a solution of benzaldehyde (1.4 mL, 14 mmol) in MeOH (28 mL) was added 2,2-diisopropylhydrazine (S15) (2.0 g, 17 mmol) at room temperature. After being stirred for 1 h, AcOH (81 μL, 1.42 mmol) was added and then stirred for 2.5 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc = 40/1) to give the hydrazone 1z (1.77 g, 61%) as a yellow oil; IR (neat): 1558 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.54 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.23 (s, 1H), 7.13 (t, J = 7.2 Hz, 1H), 3.89 (sept, J = 6.4 Hz, 2H), 1.21 (d, J = 6.4 Hz, 12H); ¹³C NMR (100 MHz, CDCl₃) δ: 138.6, 128.3, 126.0, 125.9, 124.7, 47.4, 21.0; HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₃H₂₁N₂ 205.1699; Found 205.1700.

2.7 General procedure for synthesis of triazoles 2

To a solution of hydrazones 1 (0.20 mmol) in dry nitriles (4.0 mL) were added NCS (40 mg, 0.30
mmol) and BF$_3$•OEt$_2$ (76 μL, 0.6 mmol). The reaction mixture was stirred at reflux in the dark. After being stirred for several hours, the reaction mixture was basified with 1 M NaOH aq. (4.0 mL) and extracted with CHCl$_3$ (10 mL × 3). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by preparative TLC or flash column chromatography to afford the corresponding triazoles 2.

1,5-Dimethyl-3-phenyl-1H-1,2,4-triazole (2aa)

31.2 mg, 90% yield; **Reaction time:** 14 h; Purification by preparative TLC (CHCl$_3$/MeOH = 50/1); A white solid; **Mp:** 116-117 ℃ (EtOAc); **IR** (KBr): 1527 cm$^{-1}$; **$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$: 8.06 (d, $J$ = 8.1 Hz, 2H), 7.40-7.27 (m, 3H), 3.59 (s, 3H), 2.28 (s, 3H); **$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$: 159.5, 152.2, 130.6, 128.2, 127.9, 125.3, 34.4, 11.0; **HRMS (ESI)** m/z: [M + H]$^+$ Calcd for C$_{10}$H$_{12}$N$_3$ 174.1026; Found 174.1030.

1-[(5-Methyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl]-2,5-pyrrolidinedione (4)

8.6 mg, 9% yield; Purification by preparative TLC (CHCl$_3$/MeOH = 50/1); A colorless oil; **IR** (CHCl$_3$): 1723, 1524 cm$^{-1}$; **$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$: 8.06 (d, $J$ = 8.4 Hz, 2H), 7.41-7.35 (m, 3H), 5.72 (s, 2H), 2.80 (s, 4H), 2.72 (s, 3H); **$^{13}$C NMR** (150 MHz, CDCl$_3$) $\delta$: 175.6, 161.7, 154.7, 130.5, 129.3, 128.4, 126.4, 48.4, 28.1, 12.1; **HRMS (ESI)** m/z: [M + Na]$^+$ Calcd for C$_{14}$H$_{14}$O$_2$NaNa 293.1009; Found 293.1008.

**Scalable synthesis of triazole 2aa (6.8 mmol scale)**

![Reaction Scheme](image)

To a solution of hydrazones 1a (1.0 g, 6.8 mmol) in dry MeCN (68 mL) were added NCS (1.4 g, 10 mmol) and BF$_3$•OEt$_2$ (2.6 mL, 20 mmol) in the dark. The reaction mixture was stirred at reflux in the dark. After being stirred for 19 h, the reaction mixture was basified with 1 M NaOH aq. (25 mL) and extracted with CHCl$_3$ (50 mL × 3). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Yamazen Smart Flash EPCLC-AI-580S using ULTRAPACK SI-40B) (CHCl$_3$ to CHCl$_3$/MeOH = 97/3) to afford the triazole 2aa (993 mg, 80%) as a white solid.
1,5-Dimethyl-3-(4-methylphenyl)-1H-1,2,4-triazole (2ba)

Hydrazone 1b (37.4 mg, 0.23 mmol) was used. 42.4 mg, 98% yield; 

**Reaction time:** 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A white solid; **Mp:** 204-205 °C (Hexane/EtOAc); **IR (KBr):** 1536 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.93 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 3.82 (s, 3H), 2.47 (s, 3H), 2.37 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 160.6, 152.7, 138.8, 129.2, 128.2, 125.9, 35.1, 21.3, 11.9; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₁H₁₄N₃ 188.1182; Found 188.1184.

1,5-Dimethyl-3-(4-methoxyphenyl)-1H-1,2,4-triazole (2ca)

Hydrazone 1c (50.0 mg, 0.28 mmol) was used. 39.9 mg, 68% yield; 

**Reaction time:** 24 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A white solid; **Mp:** 117-119 °C (Hexane/EtOAc); **IR (KBr):** 1538 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.97 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.45 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 160.2, 160.1, 152.5, 127.3, 123.6, 113.7, 55.1, 35.0, 11.7; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₁H₁₄ON₃ 204.1131; Found 204.1135.

2,2-Dimethylpropionic acid 4-(1,5-dimethyl-1H-1,2,4-triazol-3-yl)phenyl ester (2da)

28.6 mg, 52% yield; **Reaction time:** 17.5 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A white solid; **Mp:** 184-185 °C (Hexane/EtOAc); **IR (KBr):** 1736 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.05 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 2.47 (s, 3H), 1.36 (s, 9H); **¹³C NMR** (75 MHz, CDCl₃) δ: 176.8, 159.8, 152.8, 151.6, 128.5, 127.0, 121.5, 39.0, 35.1, 27.0, 11.8; **HRMS (ESI)** m/z: [M + Na]⁺ Calcd for C₁₃H₁₀O₂N₃Na 296.1370; Found 296.1366.

3-(4-Chlorophenyl)-1,5-dimethyl-1H-1,2,4-triazole (2ea)

Hydrazone 1e (41.5 mg, 0.23 mmol) was used. 40.7 mg, 85% yield; 

**Reaction time:** 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A white solid; **Mp:** 176 °C (decomposed) (Hexane/EtOAc); **IR (KBr):** 1526 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.98 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H), 2.48 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 159.6, 153.0, 134.7, 129.6, 128.7, 127.3, 35.2, 11.8; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₉H₁₆N₃Cl 208.0636; Found 208.0636.
3-(4-Bromophenyl)-1,5-dimethyl-1H-1,2,4-triazole (2fa)

35.4 mg, 70% yield; **Reaction time:** 22 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow solid; **Mp:** 194-196 °C (Hexane/EtOAc); **IR** (KBr): 1524 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.92 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H), 2.48 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 159.6, 153.2, 131.6, 130.0, 127.5, 123.0, 35.2, 11.8; **HRMS (ESI) m/z:** [M + H]^+ Calcd for C₁₀H₁₁N₃Br 252.0131; Found 252.0129.

1,5-Dimethyl-3-[4-(trifluoromethyl)phenyl]-1H-1,2,4-triazole (2ga)

34.3 mg, 71% yield; **Reaction time:** 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow solid; **Mp:** 167-169 °C (EtOAc); **IR** (KBr): 1620 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.98 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H), 2.48 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 159.1, 153.2, 134.4, 131.2 (C-F, ²J_C-F = 32.2 Hz), 130.7 (C-F, ³J_C-F = 32.2 Hz), 130.3 (C-F, ³J_C-F = 32.2 Hz), 129.9 (C-F, ²J_C-F = 32.2 Hz), 129.5 (C-F, ¹J_C-F = 270.4 Hz), 126.2, 125.9 (C-F, ¹J_C-F = 270.4 Hz), 125.5 (C-F, ³J_C-F = 3.8 Hz), 125.42 (C-F, ³J_C-F = 3.8 Hz), 122.3 (C-F, ¹J_C-F = 270.4 Hz), 118.7 (C-F, ¹J_C-F = 270.4 Hz), 35.2, 11.7; **HRMS (ESI) m/z:** [M + H]^+ Calcd for C₁₁H₁₁N₃F₃ 242.0900; Found 242.0904.

1,5-Dimethyl-3-(4-nitrophenyl)-1H-1,2,4-triazole (2ha)

Hydrazone 1h (468 mg, 2.42 mmol) was used. 373.9 mg, 71% yield; **Reaction time:** 22 h; Purification by Biotage Isolera One using Biotage SNAP KP-Sil 50g (CHCl₃ to CHCl₃/MeOH = 24/1); A white solid; **Mp:** 286 °C (decomposed) (Hexane/EtOAc); **IR** (KBr): 1602, 1509 cm⁻¹; **¹H NMR** (300 MHz, THF-d₈) δ: 8.02 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 2.41 (s, 3H); **¹³C NMR** (75 MHz, THF-d₈) δ: 160.0, 154.1, 135.0, 132.0, 129.4, 128.3, 35.4, 11.8; **HRMS (ESI) m/z:** [M + H]^+ Calcd for C₁₀H₁₁O₂N₄ 219.0877; Found 219.0877.

4-(1,5-Dimethyl-1H-1,2,4-triazol-3-yl)benzoic acid methyl ester (2ia)

30.5 mg, 66% yield; **Reaction time:** 16.5 h; Purification by preparative TLC (CHCl₃/MeOH = 20/1); A yellow solid; **Mp:** 190-192 °C (Hexane/EtOAc); **IR** (KBr): 1728 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.13 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.7 Hz, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 2.50 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 166.8,
159.6, 153.2, 135.2, 130.2, 129.8, 125.8, 52.1, 35.3, 11.9; HRMS (ESI) m/z: [M + H]+ Calcd for C_{12}H_{14}O_{2}N_{3} 232.1081; Found 232.1081.

1,5-Dimethyl-3-(3-methylphenyl)-IH-1,2,4-triazole (2ja)

35.5 mg, 95% yield; Reaction time: 17.5 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A white solid; Mp: 110-112 °C (Hexane/EtOAc); IR (KBr): 1529 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ:

7.88 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 3.83 (s, 3H), 2.48 (s, 3H), 2.39 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 160.6, 152.7, 138.1, 130.8, 129.7, 128.4, 126.6, 123.1, 35.1, 21.3, 11.8; HRMS (ESI) m/z: [M + H]+ Calcd for C₁₁H₁₄N₂ 188.1182; Found 188.1182.

1,5-Dimethyl-3-(3-methoxyphenyl)-IH-1,2,4-triazole (2ka)

Hydrazone 1k (50.0 mg, 0.28 mmol) was used. 48.5 mg, 85% yield; Reaction time: 21 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A white solid; Mp: 104-105 °C (Hexane/EtOAc); IR (KBr): 1614 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ:

7.65 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 160.5, 159.8, 152.8, 132.4, 129.6, 118.6, 115.7, 110.5, 55.4, 35.2, 11.9; HRMS (ESI) m/z: [M + H]+ Calcd for C₁₁H₁₄O₂N₂ 204.1131; Found 204.1135.

3-(3-Bromophenyl)-1,5-dimethyl-1H-1,2,4-triazole (2la)

31.9 mg, 63% yield; Reaction time: 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow solid; Mp: 97-99 °C (Hexane/EtOAc); IR (KBr): 1601 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ:

8.22 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 8.1 Hz, 1H), 3.84 (s, 3H), 2.48 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 159.1, 153.0, 133.0, 131.8, 130.0, 129.0, 124.5, 122.7, 35.3, 11.9; HRMS (ESI) m/z: [M + H]+ Calcd for C₁₀H₁₁N₃Br 252.0131; Found 252.0131.

1,5-Dimethyl-3-(2-methylphenyl)-IH-1,2,4-triazole (2ma)

19.4 mg, 52% yield; Reaction time: 16 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; IR (neat): 1530 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ:

7.84 (d, J = 8.1 Hz, 1H), 7.26-7.22 (m, 3H), 3.83 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 161.2, 151.9, 136.7,
130.9, 130.4, 129.2, 128.4, 125.5, 35.1, 21.4, 11.8; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₁H₁₄N₃ 188.1182; Found 188.1180.

1,5-Dimethyl-3-(2-methoxyphenyl)-1H-1,2,4-triazole (2na)

Hydrazone 1n (50.0 mg, 0.28 mmol) was used. 31.4 mg, 55% yield; **Reaction time**: 19 h; Purification by preparative TLC (CHCl₃/MeOH = 10/1); A colorless oil; **IR** (neat): 1585 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.82 (d, J = 7.8 Hz, 1H), 7.33 (dd, J = 7.8, 5.1 Hz, 1H), 7.02-6.96 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 2.48 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 158.5, 156.8, 151.8, 130.3, 129.9, 120.3, 119.8, 111.2, 55.9, 35.3, 12.0; **HRMS (ESI)** m/z: [M + Na]⁺ Calcd for C₁₁H₁₃ON₃Na 226.0951; Found 226.0951.

3-(2-Bromophenyl)-1,5-dimethyl-1H-1,2,4-triazole (2oa)

30.4 mg, 60% yield; **Reaction time**: 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR** (neat): 1524 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.73 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 8.1 Hz, 1H), 3.87 (s, 3H), 2.51 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 159.9, 152.3, 133.6, 132.3, 131.4, 129.9, 127.1, 121.7, 35.3, 11.9; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₀H₁₁N₃Br 252.0131; Found 252.0131.

1,5-Dimethyl-3-(1-naphthalenyl)-1H-1,2,4-triazole (2pa)

Hydrazone 1p (50.0 mg, 0.25 mmol) was used. 45.8 mg, 81% yield; **Reaction time**: 14.5 h; Purification by preparative TLC (EtOAc); A white solid; **Mp**: 139-141 °C (Hexane/EtOAc); **IR** (KBr): 1530 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.99 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.59-7.47 (m, 3H), 3.91 (s, 3H), 2.55 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 160.9, 152.3, 133.9, 130.9, 129.5, 128.3, 128.2, 127.5, 126.6, 126.3, 125.7, 125.1, 35.3, 11.9; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₄H₁₄N₃ 224.1182; Found 224.1183.

1,5-Dimethyl-3-(2-naphthalenyl)-1H-1,2,4-triazole (2qa)

Hydrazone 1q (57.6 mg, 0.29 mmol) was used. 57.2 mg, 88% yield; **Reaction time**: 14.5 h; Purification by preparative TLC (EtOAc); A white solid; **Mp**: 140-142 °C (EtOAc); **IR** (KBr): 1530 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.56 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.93-7.83 (m, 3H), 7.50-7.47 (m, 2H), 3.89 (s, 3H), 2.54 (s, 3H); **¹³C NMR** (75
3-(3-Chlorobenzofuran-2-yl)-1,5-dimethyl-1H-1,2,4-triazole (2ra)

24.5 mg, 49% yield; Reaction time: 17.5 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A pale yellow solid; Mp: 159-161 °C (Hexane/EtOAc); IR (KBr): 1517 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.65 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.42-7.31 (m, 2H), 3.93 (s, 3H), 2.56 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 153.2, 153.1, 152.6, 142.5, 127.1, 126.2, 123.6, 119.3, 111.9, 110.6, 35.6, 11.9

3-Cyclohexyl-1,5-dimethyl-1H-1,2,4-triazole (2sa)

23.8 mg, 66% yield; Reaction time: 16.5 h; Purification by preparative TLC (CHCl₃/MeOH = 20/1); A colorless oil; IR (neat): 1509 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 3.75 (s, 3H), 2.66 (tt, J = 11.4, 3.3 Hz, 1H), 2.41 (s, 3H), 1.98 (d, J = 11.7 Hz, 2H), 1.81 (d, J = 12.3 Hz, 2H), 1.71, (d, J = 10.8 Hz, 1H), 1.54 (q, J = 12.6 Hz, 2H), 1.42-1.24 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 167.0, 151.8, 37.5, 34.8, 31.9, 26.1, 25.9, 11.8; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₁₀H₁₃N₃ClNa 270.0405; Found 270.0403.

3-Butyl-1,5-dimethyl-1H-1,2,4-triazole (2ta)

19.1 mg, 62% yield; Reaction time: 18 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; IR (neat): 1515 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 3.75 (s, 3H), 2.64 (t, J = 7.8 Hz, 2H), 2.41 (s, 3H), 1.70 (quint, J = 7.8 Hz, 2H), 1.39 (sext, J = 7.2 Hz, 2H), 0.93 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 163.1, 152.0, 34.7, 30.5, 27.8, 22.4, 13.7, 11.7; HRMS (ESI) m/z: [M + H]⁺ Calcd for C₇H₁₆N₃ 154.1339; Found 154.1341.

1,5-Dimethyl-3-(2-phenylethyl)-1H-1,2,4-triazole (2ua)

19.6 mg, 49% yield; Reaction time: 17.5 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; IR (neat): 1515 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.32-7.16 (m, 5H), 3.74 (s, 3H), 3.08-3.01 (m, 2H), 2.98-2.91 (m, 2H), 2.42 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 162.2, 152.2, 141.4, 128.3, 128.2, 125.9, 34.8, 34.6, 30.2, 11.7; HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₂H₁₄N₃ 202.1339; Found 202.1338.
1,5-Dimethyl-3-(1-phenylethyl)-1H-1,2,4-triazole (2va)

21.0 mg, 52% yield; **Reaction time:** 17.5 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR (neat):** 1508 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 7.37-7.26 (m, 4H), 7.18 (t, J = 7.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 2.38 (s, 3H), 1.67 (d, J = 7.5 Hz, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 165.6, 152.2, 144.3, 128.4, 127.4, 126.3, 39.4, 34.9, 20.7, 11.9; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₂H₁₂N₃ 202.1339; Found 202.1338.

1-Ethyl-5-methyl-3-phenyl-1H-1,2,4-triazole (2va)

24.0 mg, 64% yield; **Reaction time:** 15.5 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR (neat):** 1518 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ: 8.05 (d, J = 9.0 Hz, 2H), 7.43-7.34 (m, 3H), 4.14 (q, J = 9.0 Hz, 2H), 2.50 (s, 3H), 1.48 (t, J = 9.0 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ: 160.6, 151.9, 131.2, 128.8, 128.5, 126.1, 43.4, 15.1, 11.8; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₃H₁₄N₃ 188.1182; Found 188.1177.

1-Hexyl-5-methyl-3-phenyl-1H-1,2,4-triazole (2xa)

28.3 mg, 58% yield; **Reaction time:** 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR (neat):** 1518 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ: 8.06 (d, J = 8.0 Hz, 2H), 7.42-7.34 (m, 3H), 4.06 (t, J = 7.0 Hz, 2H), 2.49 (s, 3H), 1.87 (quint, J = 7.0 Hz, 2H), 1.33 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ: 160.5, 152.3, 131.2, 128.8, 128.4, 126.1, 48.5, 31.3, 29.8, 26.2, 22.4, 13.9, 11.9; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₅H₂₂N₃ 244.1808; Found 244.1812.

2,2-Dimethylpropionic acid 2-(5-methyl-3-phenyl-1H-1,2,4-triazol-1-yl)ethyl ester (2ya)

34.7 mg, 58% yield; **Reaction time:** 17 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR (neat):** 1731, 1518 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.06 (d, J = 8.1 Hz, 2H), 7.45-7.37 (m, 3H), 4.47 (t, J = 5.4 Hz, 2H), 4.35 (t, J = 5.4 Hz, 2H), 2.53 (s, 3H), 1.14 (s, 9H); **¹³C NMR** (75 MHz, CDCl₃) δ: 178.1, 161.0, 153.2, 130.9, 129.0, 128.4, 126.0, 62.4, 47.0, 38.6, 27.0, 11.9; **HRMS (ESI)** m/z: [M + Na]⁺ Calcd for C₁₆H₂₁O₂N₃Na 310.1526; Found 310.1523.
5-Methyl-1-(1-methylethyl)-3-phenyl-1H-1,2,4-triazole (2a)

Isobutynitrile (4.0 mL) was used. 21.3 mg, 53% yield; **Reaction time**: 22 h; Purification by preparative TLC (CHCl<sub>3</sub>/MeOH = 50/1); A yellow oil; **IR** (neat): 1512 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ: 8.07 (d, J = 8.1 Hz, 2H), 7.44-7.33 (m, 3H), 3.84 (s, 3H), 2.80 (q, J = 7.5 Hz, 2H), 1.38 (t, J = 7.5 Hz, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ: 160.3, 151.1, 131.5, 128.6, 128.4, 126.0, 50.0, 22.3, 11.9; **HRMS (ESI)** m/z: [M + H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub> 202.1339; Found 202.1339.

5-Ethyl-1-methyl-3-phenyl-1H-1,2,4-triazole (2b)

Propionitrile (4.0 mL) was used. 28.6 mg, 76% yield; **Reaction time**: 21 h; Purification by preparative TLC (CHCl<sub>3</sub>/MeOH = 50/1); A yellow oil; **IR** (neat): 1518 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ: 8.0 (d, J = 8.1 Hz, 2H), 7.44-7.33 (m, 3H), 3.83 (s, 3H), 2.80 (q, J = 7.5 Hz, 2H), 1.38 (t, J = 7.5 Hz, 3H); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ: 160.5, 157.5, 131.2, 128.8, 128.4, 126.1, 35.0, 19.4, 12.0; **HRMS (ESI)** m/z: [M + H]<sup>+</sup> Calcd for C<sub>11</sub>H<sub>14</sub>N<sub>3</sub> 188.1182; Found 188.1185.

5-Butyl-1-methyl-3-phenyl-1H-1,2,4-triazole (2c)

Valeronitrile (4.0 mL) was used. 34.0 mg, 79% yield; **Reaction time**: 19.5 h; Purification by preparative TLC (CHCl<sub>3</sub>/MeOH = 50/1); A yellow oil; **IR** (neat): 1518 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ: 8.05 (d, J = 8.1 Hz, 2H), 7.44-7.35 (m, 3H), 3.83 (s, 3H), 2.76 (t, J = 7.5 Hz, 2H), 1.76 (quint, J = 7.8 Hz, 2H), 1.44 (sext, J = 7.5 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ: 160.5, 156.7, 131.1, 128.8, 128.4, 126.0, 35.0, 29.8, 25.7, 22.4, 13.7; **HRMS (ESI)** m/z: [M + H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>3</sub> 216.1495; Found 216.1495.

1-Methyl-5-(2-methylpropyl)-3-phenyl-1H-1,2,4-triazole (2d)

Isovaleronitrile (4.0 mL) was used. 31.7 mg, 74% yield; **Reaction time**: 18.5 h; Purification by preparative TLC (CHCl<sub>3</sub>/MeOH = 50/1); A yellow oil; **IR** (neat): 1518 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ: 8.06 (d, J = 7.8 Hz, 2H), 7.45-7.36 (m, 3H), 3.84 (s, 3H), 2.65 (d, J = 7.5 Hz, 2H), 2.19 (sept, J = 6.9 Hz, 1H), 1.00 (d, J = 6.9 Hz, 6H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ: 160.5, 156.0, 131.1, 128.8, 128.4, 126.0, 35.2, 34.7, 28.3, 22.3; **HRMS (ESI)** m/z: [M + H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>3</sub> 216.1495; Found 216.1495.

1-Methyl-5-(1-methylethyl)-3-phenyl-1H-1,2,4-triazole (2e)

Isobutyronitrile (4.0 mL) was used. 33.1 mg, 82% yield; **Reaction time**: 15.5 h; Purification by
Found 202.1339.

5-Cyclopropyl-1-methyl-3-phenyl-1H-1,2,4-triazole (2af)

Cyclopropyl cyanide (4.0 mL) was used. 29.5 mg, 74% yield; **Reaction time:** 16 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR** (neat): 1540 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.02 (d, J = 8.1 Hz, 2H), 7.42-7.34 (m, 3H), 3.92 (s, 3H), 1.89-1.80 (m, 1H), 1.18-1.04 (m, 4H); **¹³C NMR** (75 MHz, CDCl₃) δ: 160.3, 158.0, 131.2, 128.7, 128.4, 126.1, 34.8, 7.9, 6.2; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₂H₁₈N₃ 200.1182; Found 200.1184.

5-Cyclohexyl-1-methyl-3-phenyl-1H-1,2,4-triazole (2ag)

Cyclohexanecarbonitrile (4.0 mL) was used. 34.7 mg, 72% yield; **Reaction time:** 16 h; Purification by preparative TLC (CHCl₃/MeOH = 50/1); A yellow oil; **IR** (neat): 1540 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃) δ: 8.06 (d, J = 8.4 Hz, 2H), 7.43-7.32 (m, 3H), 3.85 (s, 3H), 2.78-2.68 (tt, J = 11.7, 3.3 Hz, 1H), 1.94-1.89 (m, 4H), 1.80-1.67 (m, 3H), 1.43-1.31 (m, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ: 160.5, 160.3, 131.0, 130.0, 129.0, 128.5, 128.0, 128.7, 128.4, 126.1, 35.4, 34.9, 31.0, 26.0, 25.5; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₅H₂₀N₃ 242.1652; Found 242.1651.

3,5-Diphenyl-1-methyl-1H-1,2,4-triazole (2ah)

Benzonitrile (4.0 mL) was used. 41.7 mg, 89% yield; **Reaction time:** 16 h; Purification by Biotage Isolera One using Biotage SNAP KP-Sil 25g (Hexane/EtOAc = 17/1 to 5/2); A white solid; **Mp:** 80-81 °C (Hexane/Et₂O); **IR** (KBr): 1473 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ: 8.15 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.51-7.50 (m, 3H), 7.45-7.38 (m, 3H), 3.99 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ: 161.1, 155.6, 131.0, 130.0, 129.0, 128.8, 128.7, 128.5, 128.0, 126.3, 36.9; **HRMS (ESI)** m/z: [M + H]⁺ Calcd for C₁₅H₁₄N₃ 236.1182; Found 236.1182.

5-(4-Fluorophenyl)-1-methyl-3-phenyl-1H-1,2,4-triazole (2ai)

4-Fluorobenzonitrile (4.0 mL) was used. 32.2 mg, 64% yield; **Reaction time:** 19.5 h; Purification by
Biotage Isolera One using Biotage SNAP KP-Sil 100g (Hexane/EtOAc = 17/1 to 3/2); A yellow solid; Mp: 107-111 °C (Hexane); IR (KBr): 1608 cm⁻¹; H NMR (300 MHz, CDCl₃) δ: 8.14 (d, J = 8.4 Hz, 2H), 7.72 (dd, J = 9.0, 5.4 Hz, 2H), 7.47-7.39 (m, 3H), 7.21 (t, J = 8.4 Hz, 2H), 3.99 (s, 3H); C NMR (75 MHz, CDCl₃) δ: 165.3 (C-F, ḳC-F = 249.5 Hz), 162.0 (C-F, ḳC-F = 249.5 Hz), 161.1, 154.7, 130.8 (C-F, ḳC-F = 8.6 Hz), 130.7 (C-F, ḳC-F = 8.6 Hz), 129.1, 128.5, 126.2, 124.2 (C-F, ḳC-F = 3.5 Hz), 124.1 (C-F, ḳC-F = 3.5 Hz), 116.2 (C-F, ḳC-F = 21.8 Hz), 115.9 (C-F, ḳC-F = 21.8 Hz), 36.9; HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₅H₁₃N₃F 254.1088; Found 254.1088.

2.8 Control experiments

\[
\begin{align*}
\text{NCS (1.5 equiv.)} & \quad \text{BF₃·OEt₂ (3.0 equiv.)} \\
\text{MeCN, reflux, dark} & \quad 1 \text{ h}
\end{align*}
\]

Eq. 1

\[
\begin{align*}
\text{H₂O} \quad \text{O} & \quad \text{MeCN, reflux, dark} \\
\text{5: 42%}
\end{align*}
\]

Eq. 2

\[
\begin{align*}
\text{NCS (1.5 equiv.)} & \quad \text{BF₃·OEt₂ (3.0 equiv.)} \\
\text{MeCN, reflux, dark} & \quad 1 \text{ h}
\end{align*}
\]

Eq. 3

\[
\begin{align*}
\text{H₂O} \quad \text{O} & \quad \text{MeCN, reflux, dark} \\
\text{7: 44%}
\end{align*}
\]
To a solution of hydrazone 1a (30 mg, 0.20 mmol) in dry CH$_3$CN (4.0 mL) were added NCS (40 mg, 0.30 mmol) and BF$_3$•OEt$_2$ (76 μL, 0.60 mmol) in the dark. The mixture was stirred at reflux for 1 h. The ESI (+) MS spectrum of reaction mixture showed a peak of m/z 147.09161 which indicated the Intermediate C. The reaction mixture was basified with 1 M NaOH aq. (4.0 mL) and extracted with CHCl$_3$ (10 mL × 3). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by preparative TLC (CHCl$_3$/MeOH = 49/1) or flash column chromatography to afford the hydrazide 5 (13.9 mg, 42%) as a pale yellow solid. The spectra data matched those previously reported in the literature$^4$.

Eq. 2

To a solution of hydrazonoyl chloride 3a$^5$ (37 mg, 0.20 mmol) in dry MeCN (4.0 mL) was added BF$_3$•OEt$_2$ (76 μL, 0.60 mmol) in the dark. The reaction mixture was stirred at reflux in the dark. After being stirred for 17 h, the reaction mixture was basified with 1 M NaOH aq. (4.0 mL) and extracted with CHCl$_3$ (10 mL × 3). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by preparative TLC (CHCl$_3$/MeOH = 50/1) to afford the triazole 2aa (28.3 mg, 82%).

Eq. 3; N-[4-(5-Methyl-3-phenyl-1H-1,2,4-triazol-1-yl)butyl]acetamide (7)

To a solution of hydrazone 6 (35 mg, 0.20 mmol) in dry MeCN (4.0 mL) were added NCS (40 mg, 0.30 mmol), BF$_3$•OEt$_2$ (76 μL, 0.60 mmol) in the dark. The reaction mixture was stirred at reflux in the dark. After being stirred for 18 h, the reaction mixture was
basified with 1 M NaOH aq. (4.0 mL) and extracted with CHCl₃ (10 mL x 3). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by preparative TLC (CHCl₃/MeOH = 50/1) to afford the triazole 7 (23.7 mg, 44%) as a yellow oil; IR (neat): 3287, 1655, 1553 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 8.04 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.37 (t, J = 8.0 Hz, 1H), 5.77 (br s, 1H), 4.12, (t, J = 7.0 Hz, 2H), 3.28 (q, J = 6.5 Hz, 2H), 2.50 (s, 3H), 1.96 (s, 3H), 1.92 (quint, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 170.2, 160.6, 152.5, 131.0, 129.0, 128.5, 126.0, 47.7, 38.9, 27.1, 26.4, 23.3, 12.0; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₁₅H₂₀N₄Na 295.1529; Found 295.1529.

2.9 Experimental procedure for the transformation of triazoles 2

α,3-Diphenyl-1-methyl-1H-1,2,4-triazole-5-ethanol (8)

![Diagram of 2aa to 8]

To a solution of triazole 2aa (35 mg, 0.20 mmol) in dry THF (2.0 mL) was slowly added n-BuLi in hexane (1.6 M, 188 μL, 0.30 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at the same temperature for 1 h. Subsequently, benzaldehyde (30 μL, 0.30 mmol) was slowly added at the same temperature. The reaction mixture was stirred for 2.5 h. The reaction mixture was quenched with sat. NH₄Cl aq. (4.0 mL) and extracted with Et₂O (10 mL x 3). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Biotage Isolera One using Biotage SNAP KP 25g) (Hexane/EtOAc = 7/1 to 1/19) to afford the alcohol 8 (31.8 mg, 57%) as a white solid; Mp: 161 °C (decomposed) (Hexane/EtOAc); IR (KBr): 3152, 1492 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.05 (d, J = 8.1 Hz, 2H), 7.45-7.27 (m, 8H), 5.23 (t, J = 6.6 Hz, 1H), 4.89 (br s, 1H), 3.64 (s, 3H), 3.06 (d, J = 6.6 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ: 160.4, 154.0, 142.8, 130.6, 129.1, 128.6, 128.5, 127.8, 126.1, 125.5, 71.6, 35.5, 35.0; HRMS (ESI) m/z: [M + H]⁺ Calcd for C₁₇H₁₈O₃N₂ 280.1444; Found 280.1444.

2-[5-(2-Acetoxyphenyl)-1-methyl-1H-1,2,4-triazol-3-yl]-1,3-benzenediol 1,3-diacetate (9)

![Diagram of 2ah to 9]

2-[5-(2-Acetoxyphenyl)-1-methyl-1H-1,2,4-triazol-3-yl]-1,3-benzenediol 1,3-diacetate (9)
To a solution of triazole 2ah (47 mg, 0.20 mmol) in AcOH (2.0 mL) and Ac₂O (2.0 mL) were added Pd(OAc)$_2$ (4.5 mg, 0.020 mmol), PIDA (644 mg, 2.0 mmol). The reaction mixture was stirred at 110 °C. After being stirred for 2 h, the reaction mixture was poured into sat. NaHCO$_3$ aq. (20 mL) and extracted with EtOAc (20 mL × 2). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Biotage Isolera One using Biotage SNAP KP-Sil 25g) (Hexane/EtOAc = 7/1 to 1/16) to afford the triacetoxylated triazole 9 (44.3 mg, 54%) as a yellow oil; IR (neat): 1769, 1462 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ: 7.56 (t, $J$ = 7.8 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.42 (t, $J$ = 7.8 Hz, 1H), 7.39 (t, $J$ = 7.8 Hz, 1H), 7.25 (d, $J$ = 8.4 Hz, 1H), 7.08 (t, $J$ = 8.4 Hz, 2H), 3.83 (s, 3H), 2.25 (s, 6H), 2.12 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 169.8, 169.1, 155.0, 151.0, 149.8, 149.0, 131.6, 130.7, 129.6, 126.1, 123.4, 121.8, 121.5, 118.2, 36.4, 21.1, 20.6; HRMS (ESI) m/z: [M + Na]$^+$ Calcd for C$_{21}$H$_{19}$O$_6$N$_3$Na 432.1166; Found 432.1162.

2.10 Unsuccess results utilizing NBS instead of NCS

The reaction of $N,N$-dimethylhydrazone 1t with NBS under optimized conditions gave triazole 2ta in 20% yield. The use of hydrazone 6 with NBS led to the formation of alkyl-tethered triazole S16 with bromo group in 20% yield.

2.11 Substituent effects on nitrogen atom
The reaction of N-monomethyl hydrazone S17 under optimized conditions gave triazole 2aa in 38% yield with no formation of 5-methyl-3-phenyl-1H-1,2,4-triazole S18. Additionally, the use of simple hydrazone S19 led to the complex mixture.

The reaction of N-methyl-N-tosyl hydrazone S20 under optimized conditions did not give triazole S21. Moreover, the use of N-(4-methoxyphenyl) hydrazone S22 led to the formation of triazole S23 in 3% yield.

3. References
1d
(300 MHz in CDCl₃)
1d
(75 MHz in CDCl₃)
1r
(300 MHz in CDCl$_3$)
1r
(75 MHz in CDCl₃)
1s
(400 MHz in CDCl₃)
$\text{N} - \text{N} \text{Me}$

1s

(100 MHz in CDCl$_3$)
1t
(400 MHz in CDCl₃)
1t
(100 MHz in CDCl₃)
S8a
(400 MHz in CDCl₃)
Boc\_N\_Me

S8a

(100 MHz in CDCl\_3)
$^{1}H$ NMR spectrum of compound 1w (400 MHz in CDCl$_3$)
$N\equiv N$-Me

$1w$

(100 MHz in CDCl$_3$)
S8b
(400 MHz in CDCl₃)
S8b
(100 MHz in CDCl₃)
$\text{Me}$

(400 MHz in CDCl$_3$)
$1x$

(100 MHz in CDCl$_3$)
$\text{OPiv}$

$\text{OPiv}$

$\text{1y}$

(300 MHz in CDCl$_3$)
$1y$

(75 MHz in CDCl$_3$)
$^{1}z$

(400 MHz in CDCl$_3$)
$^{1z}$

(100 MHz in CDCl$_3$)
2aa
(300 MHz in CDCl₃)
2aa
(75 MHz in CDCl₃)
(600 MHz in CDCl₃)
4
(150 MHz in CDCl₃)
2ba
(300 MHz in CDCl₃)
(75 MHz in CDCl₃)
2ca
(300 MHz in CDCl₃)
2ca
(75 MHz in CDCl₃)
2da
(75 MHz in CDCl₃)
2ea
(300 MHz in CDCl₃)
2ea
(75 MHz in CDCl₃)
2fa
(300 MHz in CDCl₃)
2fa
(75 MHz in CDCl$_3$)
2ga
(300 MHz in CDCl₃)
2ga
(75 MHz in CDCl₃)
2ha

(300 MHz in THF-d$_8$)
2ha
(75 MHz in THF-d$_6$)
2ia
(300 MHz in CDCl₃)
(75 MHz in CDCl$_3$)
2ja
(300 MHz in CDCl$_3$)
2ja
(75 MHz in CDCl$_3$)
MeO
\begin{center}
\textbf{2ka} \\
(300 MHz in CDCl$_3$)
\end{center}
2ka
(75 MHz in CDCl₃)
2la
(300 MHz in CDCl₃)
21a
(75 MHz in CDC₆)
2ma
(75 MHz in CDCl₃)
2na
(300 MHz in CDCl₃)
2na
(75 MHz in CDCl₃)
2oa
(300 MHz in CDCl₃)
2oa
(75 MHz in CDCl₃)
2pa
(300 MHz in CDCl₃)
2pa
(75 MHz in CDCl₃)
2qa
(300 MHz in CDCl₃)
2qa
(75 MHz in CDCl₃)
2ra
(75 MHz in CDCl₃)
2sa
(300 MHz in CDCl₃)
2sa
(75 MHz in CDCl₃)
2ta
(300 MHz in CDCl₃)
**2ta**

(75 MHz in CDCl₃)
2ua
(300 MHz in CDCl₃)
2ua
(75 MHz in CDCl₃)
2va
(300 MHz in CDCl₃)
2va
(75 MHz in CDCl₃)
2wa
(500 MHz in CDCl₃)
2wa
(125 MHz in CDCl₃)
2xa
(500 MHz in CDCl₃)
2ya
(300 MHz in CDCl₃)
2ya
(75 MHz in CDCl₃)
$^{2}za$

(300 MHz in CDCl$_3$)
2za
(75 MHz in CDCl₃)
2ab
(500 MHz in CDCl₃)
2ab
(125 MHz in CDCl₃)
2ac
(300 MHz in CDCl$_3$)
2ac
(75 MHz in CDCl₃)
2ad
(300 MHz in CDCl₃)
2ad
(75 MHz in CDCl₃)
2ae
(300 MHz in CDCl₃)
2ae
(75 MHz in CDCl₃)
$2af$

(300 MHz in CDCl$_3$)
2af
(75 MHz in CDCl₃)
2ag
(300 MHz in CDCl₃)
2ag
(75 MHz in CDCl₃)
2ah
(500 MHz in CDCl₃)
2ah
(125 MHz in CDCl₃)
2ai
(300 MHz in CDCl₃)
2ai
(75 MHz in CDCl$_3$)
7
(300 MHz in CDCl₃)
7
(75 MHz in CDCl₃)
8

(75 MHz in CDCl₃)
$\text{AcO} \quad \text{Me} \quad \text{AcO}$

9

(600 MHz in CDCl$_3$)
9 (150 MHz in CDCl₃)