Supplementary Information for

Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles

Christopher D. Smith and Michael F. Greaney*

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

michael.greaney@manchester.ac.uk

www.greaney.chemistry.manchester.ac.uk

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Experimental

$^1$H-NMR spectra were recorded on 500, 400 or 300 Bruker spectrometers with residual chloroform or DMSO as the internal reference (CHCl$_3$, $\delta_H = 7.26$ ppm; DMSO, $\delta_H = 2.50$ ppm). $^{13}$C-NMR spectra used the central resonance of CDCl$_3$ or DMSO as the internal reference (CDCl$_3$, $\delta_C = 77.0$ ppm; DMSO, $\delta_C = 39.5$ ppm). $^{19}$F-NMR spectra are measured relative to CFCl$_3$ $\delta_F = 0.0$ (external reference). Assignments were made using a range of NMR experiments (DEPT135, COSY, HMQC and HMBC). All chemical shifts are quoted in parts per million (ppm) down field from tetramethylsilane, measured from the centre of the signal except in the case of multiplets of more than one proton which are quoted as a range. Coupling constants are quoted to the nearest 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), sextet (sex.), septet (sept.), multiplet (m), apparent (ap.), broad (br.) and combinations thereof.

Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer as a thin film and are reported in cm$^{-1}$. Letters in parentheses refer to the relative absorbency of the main peak: w, weak, < 40%; m, medium, 41-74%; s, strong >75%; and br, broad.

Melting points were determined using a Büchi M-565 melting point apparatus.

High Resolution Mass Spectrometry (HRMS) were recorded on one of the following: Waters QTOF (ES, HRMS) or Thermo Finnigan MAT95XP (GC/MS, EI, HRMS).

LCMS analysis was performed on an Agilent HP 1100 chromatograph (Atlantis RP column) attached to an HPLC/MSD mass spectrometer (API-ES). Elution was carried out using a reversed-phase gradient of MeOH:i-PrOH (9:1) / water, with both solvents containing 0.2% formic acid. The gradient of the 6.0 min run is described in Table 1.

| Time (min) | MeOH:i-PrOH (9:1) (%) | Total flow rate (mL/min) |
|-----------|-----------------------|-------------------------|
| 0.00      | 2                     | 0.9                     |
| 3.50      | 98                    | 0.9                     |
| 4.50      | 98                    | 0.9                     |
| 4.60      | 2                     | 0.9                     |

All THF was distilled under N$_2$ over sodium wire and benzophenone. Toluene and dichloromethane were distilled under N$_2$ and over calcium hydride. All reagents were used as obtained from commercial sources.
Starting Materials

Azides

CAUTION: Azides are both shock sensitive and toxic. The use of acids in the presence of the azide ion is advised against due to the possible release of hydrazoic acid gas, a known poison. Furthermore, the use of CH₂Cl₂ in the presence of the azide ion may lead to the formation of diazidomethane (N₂H₂) which is known to self detonate. No incidents occurred during the synthesis or use of azides but for these reasons the reactions were not performed on scales greater than 5 g.

Benzyl azide was synthesised using known procedures.¹

General procedure for the synthesis of aromatic azides from their corresponding anilines.² A solution of the aniline (5 mmol) was dissolved in MeCN (25 mL), azidotrimethylsilane (6 mmol) was added before cooling to 0 °C. tert-Butyl nitrite (5.5 mmol) was added portion wise over 15 minutes to the solution. The reaction was allowed to warm to ambient temperature and stirred until complete by HPLC, typically 2 hours. The solvent was removed in vacuo and the crude material was purified by passing through a plug of silica and eluted with CH₂Cl₂.

The following known azides were synthesised using the above procedure 4-azidobenzonitrile,³ 2-azido-1,3-dichlorobenzene,⁴ 1-azido-3-bromobenzene,⁵ 1-azido-4-chlorobenzene,⁴ 1-azido-4-nitrobenzene,⁴ ethyl 4-azidobenzoate,⁶ N-(4-azidophenyl)acetamide,⁷ 1-azido-4-iodobenzene,² 5-azido-1,2,3-trimethoxybenzene.⁸

Novel Starting Materials

![FBrN₃](image)

Azide precursor to 3c

1-Azido-2-bromo-4-fluorobenzene – novel

Orange solid (5 mmol scale, 94%, 1015 mg); R₁ = 3.37 min, no mass observed; νmax (thin film) 2122s, 2079m, 1598w, 1590w, 1481s, 1308m, 1267m, 1205s, 1032w, 891w, 864w, 805m, 781m, 636m; δH (400 MHz; CDCl₃) 7.31 (1H, dd, J = 8.0, 2.5 Hz, Ar-H), 7.16-7.05 (2H, m, CH); δC (101 MHz; CDCl₃) 159.2 (d, J = 248.9 Hz, CF), 134.9 (d, J = 3.3 Hz, C), 121.0 (d, J = 25.5 Hz, CH), 120.0 (d, J = 8.7 Hz, CH), 115.7 (d, J = 23.0 Hz, CH), 114.0 (d, J = 9.8 Hz, C); δF (376 MHz; CDCl₃) -115.67; Mp = < 50 °C; Elemental calculated C 33.36, H 1.40, N 19.45, found C 33.56, H 1.61, N 19.33.

¹ D.-R. Hou, T.-C. Kuan, Y.-K. Li, R. Lee, K.-W. Huang, Tetrahedron, 2010, 66, 9415–9420
² K. Barral, A. D. Moorhouse and J. E. Moses, Org. Lett. 2007, 9, 1809.
³ K. D. Grimes, A. Gupte, C. C. Aldrich, Synthesis 2010, 9, 1441–1448
⁴ M. Kitamura, M. Yano, N. Tashiro, S. Miyagawa, M. Sando, T. Okauchi, Eur. J. Org. Chem. 2011, 458–462.
⁵ K. Knepper, S. Vanderheiden, S. Bräse, Eur. J. Org. Chem., 2006, 1886–1898.
⁶ F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, Org. Lett., 2008, 10, 2409–2412.
⁷ M. Novak, M. J. Kahley, Jing Lin, S. A. Kennedy, T. G. James, J. Org. Chem., 1995, 60, 8294–8304.
⁸ F. Kloss, U. Köhn, B. O. Jahn, M. D. Hager, H. Görils, U. S. Schubert. Chem. Asian J., 2011, 6, 2816–2824
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Azide precursor to 3n

1-(3-azidophenyl)ethanone – only ¹H-NMR reported previously⁹

Orange oil (5 mmol scale, 94%, 757 mg); Rₜ = 2.20 min, no mass observed; νmax (thin film) 2099s, 1683s, 1582m, 1481w, 1435m, 1357m, 1286s, 1247s, 1230w, 884w, 870w, 787m, 683; δH (300 MHz; CDCl₃) 7.64 (1H, ddd, J = 8.0, 1.5, 1.0 Hz, Ar-H), 7.54 (1H, t, J = 1.5 Hz, Ar-H), 7.39 (1H, t, J = 8.0 Hz, Ar-H), 7.14 (1H, ddd, J = 8.0, 2.0, 1.0 Hz, Ar-H), 2.53 (3H, s, CH₃); δC (75 MHz; CDCl₃) 197.0 (CO), 140.9 (C), 138.6 (C), 130.0 (CH), 124.8 (CH), 123.5 (CH), 118.4 (CH), 26.7 (CH₃); Elemental calculated C 59.62, H 4.38, N 26.07, found C 59.55, H 4.41, N 25.93.

Azide precursor to 3p

5-Azido-2-bromopyridine – novel

Brown solid (5 mmol scale, 93%, 925 mg); Rₜ = 2.30 min, no mass observed; ESI+ 201, 199, 173, 171, 92; νmax (thin film) 2129m, 2098s, 1453s, 1377w, 1298m, 1232w, 1134w, 1087m, 1015w, 826w; δH (400 MHz; CDCl₃) 8.13 (1H, dd, J = 3.0, 0.5 Hz, Ar-H), 7.46 (1H, dd, J = 8.5, 0.5 Hz, Ar-H), 7.23 (1H, dd, J = 8.5, 3.0 Hz, Ar-H); δC (101 MHz; CDCl₃) 141.3 (CH), 136.9 (C), 136.9 (C), 128.7 (CH), 128.6 (CH); Mp = < 50 °C; HRMS (+ESI) calculated for C₅H₄N₄Br [M + H]⁺ calculated 198.9614, found 198.9614

Alkynees

4-Phenyl-1-butyne, phenylacetylene, 1-hexyne, ethynyltrimethylsilane, 1,8-nonadiyne and 3-butyln-1-ol were purchased from Aldrich. Mestranol was purchased from TCI-UK,

But-3-ynyl benzoate¹⁰ and 2-(prop-2-ynylthio)benzo[d]thiazole¹¹ were synthesised using known procedures.

Alkyne precursor to 3g

⁹ Y. Ohba, S. Kubo, M. Nakai, A. Nagai, M. Yoshimoto, Bull. Chem. Soc. Jpn., 1986, 59, 2317–2320.
¹⁰ M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi, R. Terlizzi, Eur. J. Org. Chem., 2004, 3447-3458.
¹¹ R. Abele, E. Abele, K. Rubina, O. Dzenitis, P. Arsenyan, I. Shestakova, A. Nesterova, I. Domracheva, J. Popelis, S. Grinberga, E. Lukevics, Chem. Heterocycl. Compd., 2002, 38, 867-872.
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1-Chloro-2-(prop-2-yn-1-yl)oxy)benzene – $^1$H-NMR only

2-Chlorophenol (10 mmol, 1.28 g) was dissolved in THF (40 mL) and cooled to 0 °C. KOH pellets (11 mmol, 620 mmol) were added and after 30 min propargyl bromide (80% in toluene; 12 mmol, 1.34 mL) was added. The reaction allowed to warm to ambient temperature and stirred overnight (~24 hours). The reaction was partitioned between EtOAc (50 mL) and sat. NH$_4$Cl (aq) (100 mL). The organic phase was washed with water (100 mL). The mixture was passed through a plug of silica gel (eluted with CH$_2$Cl$_2$) to yield a clear oil. (74%, 1.23 g).

R$_f$ = 3.45 min, no mass observed; $\nu_{\text{max}}$ (thin film) 3294m, 1588m, 1482s, 1452m, 1295m, 1278m, 1230s, 1061s, 1042w, 928w, 747s, 684m; $\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 7.38 (1H, dd, $J = 8.0$, 1.5 Hz, Ar-H), 7.25-7.20 (1H, m, Ar-H), 7.09 (1H, dd, $J = 8.5$, 1.5 Hz, Ar-H), 6.95 (1H, td, $J = 7.5$, 1.5 Hz, Ar-H), 4.79 (2H, d, $J = 2.5$ Hz, CH$_2$), 2.54 (1H, t, $J = 2.5$ Hz, CCH); $\delta_c$ (75 MHz; CDCl$_3$) 153.1 (C), 130.5 (CH), 127.5 (CH), 123.3 (C), 122.4 (CH), 114.4 (CH), 77.20 (alkyne C-H), 76.11 (alkyne C), 56.79. (CH$_2$); Elemental calculated C 64.88, H 4.23, found C 65.10, H 4.20.

**Alkyne precursor to 3i**

**Prop-2-yn-1-yl 3,4-dichlorobenzoate – novel**

3,4-Dichlorobenzoic acid (10 mmol, 1.91 g) was suspended in CH$_2$Cl$_2$ (20 mL) and was cooled to 0 °C. An oxalyl chloride solution in CH$_2$Cl$_2$ (12 mmol, 6 mL, 2 M in CH$_2$Cl$_2$) was added in one portion followed by 3 drops of DMF which led to the formation of bubbles. The reaction was stirred for 3 hours until no further bubbles were observed. The reaction was then concentrated in vacuo before the crude was redissolved in CH$_2$Cl$_2$ (20 mL) and cooled to 0 °C. A CH$_2$Cl$_2$ solution (20 mL) containing propargylic alcohol (20 mmol, 1.12 g), triethylamine (20 mmol, 2.8 mL) and one crystal of 4-dimethylaminopyridine (~3 mg) was added dropwise to the crude reaction. The reaction was allowed to warm to ambient temperature and stirred overnight (~18 hours). The mixture was partitioned between sat. NH$_4$Cl (aq) (30 mL) and CH$_2$Cl$_2$ (10 mL). The organic phase was washed with sat. brine (20 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. The crude was passed through a plug of silica gel (eluted with CH$_2$Cl$_2$) to yield a white solid (86%, 3.94 g).

R$_f$ = 3.49 min, no mass observed; $\nu_{\text{max}}$ (thin film) 3300brw, 1727s, 1591w, 1564w, 1468w, 1434w, 1386w, 1369w, 1270s, 1234s, 1145w, 1106s, 1033m, 987w, 840v, 756v, 676w, 641v; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 8.14 (1H, d, $J = 2.0$ Hz, Ar-H), 7.89 (1H, dd, $J = 8.5$, 2.0 Hz, Ar-H), 7.53 (1H, d, $J = 8.5$ Hz, Ar-H), 4.92 (2H, d, $J = 2.5$ Hz, CH$_2$), 2.55 (1H, t, $J = 2.5$ Hz, C≡C-H); $\delta_c$ (101 MHz; CDCl$_3$) 163.9 (C=O), 138.1 (CH), 133.0 (C), 131.67 (C), 130.6 (CH), 129.1 (C), 128.8 (CH), 77.1 (C), 75.5 (CH), 53.0 (CH$_2$); Elemental calculated C 52.43, H 2.64, found C 52.69, H 3.02.

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$^{12}$ B. Li, S.-Q. Zang, C. Ji, T. C. W. Maka, J. Organomet. Chem., 2011, 696, 2820-2828
Synthesis of Final Products

**General Procedure for the Synthesis of 1,4-Substituted 1,2,3-Triazoles**

The azide (1 mmol), alkyne (1.2 mmol) and N-methylimidazole (0.1 mmol, 8 mg) were added to a glass vial or round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours) before quenching with sat. NH₄Cl (aq) (20 mL) – Caution – ethane gas is evolved at this stage. The mixture was partitioned between water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford the pure material.

![Chemical Structure](image)

**(3a)**

**4-(5-Phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel**

White solid (1 mmol 75%; 10 mmol 76%); Rₜ = 2.90 min, M + H = 275.2; νₘₐₓ (thin film) 2227 m, 1602 m, 1508 m, 1455 m, 1418 w, 1252 m, 1117 m, 1082 m, 1073 m, 1014 w, 979 m, 855 s, 842 s, 833 s, 827 s, 752 m, 722 s, 699 s, 667 m, 577 s, 557 s; δₜ (300 MHz; CDCl₃) 7.79 (2H, d, J = 8.5 Hz, Ar-H), 7.65 (1H, s, Ar-H), 7.44 (2H, d, J = 8.5 Hz, Ar-H), 7.28-7.20 (3H, m, Ar-H), 7.03 (2H, dd, J = 7.5, 2.0 Hz, Ar-H), 3.03 (2H, m, CH₂), 2.94 (2H, m, CH₂); δₑ (75 MHz; CDCl₃) 139.7 (C), 139.1 (C), 137.3 (C), 133.4 (CH), 133.2 (CH), 128.7 (CH), 128.2 (CH), 126.8 (CH), 125.6 (CH), 117.5 (C), 113.3 (C), 34.8 (CH₂), 25.7 (CH₂); Mp = 118 °C; HRMS (+ESI) calculated for C₁₇H₁₅N₄ [M + H]⁺ calculated 275.1290, found 275.1290; Elemental calculated C 74.43, H 5.14, N 20.42, found C 74.61, H 5.14, N 20.55.
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CCDC Reference: 931414
Manchester reference number: s3793ma
Formula: C17 H14 N4
Thermal ellipsoids at 50%
Unit cell parameters:  
Cell lengths – a = 6.7136(5), b = 10.0540(7), c = 11.3384(8)
Cell angles – α = 90.113(4), β = 106.818(4), γ = 107.293(5)
Triclinic
Space Group – P-1

Pale yellow solid (72%); R, = 2.70 min, M + H = 247.2; ν\text{max} (thin film) 2234m, 1605m, 1509m, 1480m, 1416m, 1376m, 1359m, 1232m, 1159s, 1129s, 1118m, 1108m, 1046w, 1001m, 988m, 966m, 842s, 831m, 766s, 696s, 617s, 610s, 566s; δH (300 MHz; CDCl3) 7.86 (1H, s, Ar-H), 7.73 (2H, d, J = 8.5 Hz, Ar-H), 7.52 (2H, s, J = 8.5 Hz, Ar-H), 7.45-7.36 (3H, m, Ar-H), 7.23 (2H, dd, J = 7.5, 1.5 Hz, S7

4-(5-Phenyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

Ar-H; δ_C (75 MHz; CDCl₃) 139.9 (C), 137.9 (C), 134.1 (CH), 133.4 (CH), 129.9 (CH), 129.3 (CH),
128.7 (CH), 126.2 (C), 125.3 (CH), 117.7 (C), 113.0 (C); Mp = 116 °C; HRMS (M + H, +ESI)
C₁₃H₁₁N₄ calculated 247.0978, found 247.0972.

1-(2-Bromo-4-fluorophenyl)-5-butyl-1H-1,2,3-triazole – novel

Yellow oil (71%); Rₜ = 3.22 min, M + H = 298.2 and 300.2 [Br]; ν_{max} (thin film) 1598w, 1502s,
1467w, 1260s, 1236w, 1202m, 1177w, 1102m, 1073w, 1017w, 975m, 876m, 811m, 6776w, 617m,
587w; δ_H (400 MHz; CDCl₃) 7.57 (1H, s, Ar-H), 7.48 (1H, dd, J = 8.0, 3.0 Hz, Ar-H), 7.37 (1H, dd,
J = 9.0, 5.5 Hz, Ar-H), 7.20 (1H, m, Ar-H), 1.53 (2H, quin., J = 7.5 Hz, CH₂), 1.29 (2H, sex., J =
7.5 Hz, CH₂), 0.84 (3H, t, J = 7.5 Hz, CH₃); δ_C (101 MHz; CDCl₃) 162.9 (d, J = 255.5 Hz, C_F),
139.5 (C), 132.0 (d, J = 3.5 Hz, C), 131.6 (CH), 130.4 (d, J = 9.4 Hz, CH),
122.6 (d, J = 10.5 Hz, C), 120.9 (d, J = 25.5 Hz, CH), 115.6 (d, J = 22.6 Hz, CH), 29.9 (CH₂), 22.8
(CH₂), 22.0 (CH₂), 13.5 (CH₃); δ_F (376 MHz, CDCl₃) -107.2; HRMS (M + H, +ESI) C₁₂H₁₀N₁BrF
calculated 298.0350, found 298.0344.

(E)-1-(2,6-Dichlorophenyl)-5-(1-phenylprop-1-en-2-yl)-1H-1,2,3-triazole – novel

Yellow solid (55%); Rₜ = 3.48 min, M + H = 330.2 and 332.1 [Cl]; ν_{max} (thin film) 1568w, 1480m,
1438s, 1234m, 1199w, 1143w, 1076w, 1049w, 1014w, 976w, 962w, 929w, 886w, 834w, 792s, 786s,
761s, 711m, 699s, 556w; δ_H (300 MHz; CDCl₃) 7.88 (1H, s, Ar-H), 7.55-7.50 (2H, m, Ar-H),
7.48-7.43 (1H, m, Ar-H), 7.38-7.25 (3H, m, Ar-H), 7.15 (2H, d, J = 7.5 Hz, Ar-H), 6.46 (1H, br s,
viny-H), 2.14 (3H, d, J = 1.5 Hz, CH₃); δ_C (75 MHz; CDCl₃) 141.7 (C), 136.0 (C), 134.4 (C), 133.4
(C), 132.2 (CH), 131.8 (CH), 131.7 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.5 (CH), 123.0
(C), 17.4 (CH₃); Mp = 84 °C; HRMS (+ESI) calculated for C₁₇H₁₄N₃Cl₂ [M + H]^+ calculated
330.0565, found 330.0568.
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4-(5-(Triisopropylsilyl)-1H-1,2,3-triazol-1-yl)benzonitrile – novel

Yellow solid (67%); Rt = 3.70 min, M + H = 327.3; νmax (thin film) 2956w, 2943w, 2867w, 2226w, 1606m, 1508m, 1460w, 1384w, 1244w, 1174w, 1054m, 1021w, 1010w, 994w, 974w, 883m, 856s, 831m, 682s, 648m, 583m, 569m; δH (300 MHz; CDCl3) 7.88 (1H, s, Ar-H), 7.82 (2H, d, J = 8.5 Hz, Ar-H), 7.59 (2H, d, J = 8.5 Hz, Ar-H), 7.17-1.06 (3H, m, SiCHMe2), 0.98 (18H, d, J = 7.0 Hz, CH3); δC (75 MHz; CDCl3) 143.4 (CH), 142.6 (C), 133.2 (C), 133.0 (CH), 127.3 (CH), 117.5 (C), 114.0 (C), 18.5 (CH3), 12.0 (CH); Mp = 122 °C; HRMS (+ESI) calculated for C18H27N4Si [M + H]+ calculated 327.2005, found 327.2010.

2-(1-(4-Cyanophenyl)-1H-1,2,3-triazol-5-yl)ethyl benzoate – novel

Orange solid (68%); Rt = 2.82 min, M + H = 319.3; νmax (thin film) 2228w, 1716s, 1601w, 1508m, 1454w, 1438w, 1391w, 1309m, 1281s, 1236m, 1173w, 1118s, 1086m, 1072m, 1012w, 971w, 852m, 835m, 824m, 807w, 709s, 689w, 678w, 635w, 619w, 561w; δH (300 MHz; CDCl3) 7.89 (2H, dd, J = 8.5, 1.5 Hz, Ar-H), 7.83-7.75 (3H, m, Ar-H), 7.67-7.53 (3H, m, Ar-H), 7.42 (2H, t, J = 8.0 Hz, Ar-H), 4.54 (2H, t, J = 6.5 Hz, CH2), 3.23 (2H, t, J = 6.5 Hz, CH2); δC (75 MHz; CDCl3) 166.0 (C=O), 139.5 (C), 134.4 (C), 133.7 (CH), 133.4 (CH), 129.5 (CH), 129.2 (C), 128.5 (CH), 125.6 (CH), 117.4 (C), 113.5 (C), 62.1 (CH2), 23.7 (CH3); Mp = 76 °C; HRMS (+ESI) calculated for C19H14N4O2 [M + H]+ calculated 319.1195, found 319.1210.
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4-(5-((2-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)benzonitrile – novel

White solid (59%); R_t = 3.08 min, M + H = 311.2 and 313.2 [Cl]; v_max (thin film) 2227m, 1606w, 1581w, 1515m, 1498s, 1464w, 1448w, 1432w, 1391w, 1292w, 1238s, 1180m, 1168w, 1135w, 1113w, 1086m, 1060m, 1039w, 1001s, 966m, 870w, 844s, 767w, 747s, 709w, 699w, 683m, 664m, 559w; δ_H (300 MHz; CDCl_3) 7.88-7.73 (5H, m, Ar-H), 7.16 (1H, td, J = 8.0, 1.5 Hz, Ar-H); 13C (75 MHz; CDCl_3) 152.6 (C), 139.2 (C), 136.0 (CH), 133.5 (CH), 132.2 (C), 130.7 (CH), 127.9 (CH), 125.1 (CH), 123.5 (CH), 123.3 (C), 117.5 (C), 114.6 (CH), 113.5 (C), 59.0 (CH_2); Mp = 136 °C; HRMS (M + H, +ESI) C_{16}H_{12}N_4OCl calculated 311.0694, found 311.0683.

1-(3-Bromophenyl)-5-phenethyl-1H-1,2,3-triazole – novel

Orange oil (76%); R_t = 3.40 min, M + H = 328.1 and 330.1 [Br]; v_max (thin film) 1591m, 1579m, 1485s, 1453w, 1250w, 1070m, 1043w, 999w, 977m, 874w, 824w, 786m, 750s, 712m, 698s, 686s, 643w; δ_H (300 MHz; CDCl_3) 7.66-7.59 (2H, m, Ar-H), 7.44 (1H, t, J = 2.0 Hz, Ar-H), 7.37 (1H, t, J = 8.0 Hz, Ar-H), 7.26-7.20 (4H, m, Ar-H), 7.04 (2H, dd, J = 7.5, 2.0 Hz, Ar-H), 2.99 (2H, m, CH_2), 2.91 (2H, m, CH_2); δ_C (75 MHz; CDCl_3) 139.3 (C), 137.3 (C), 137.2 (C), 132.7 (CH), 132.6 (CH), 130.6 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 126.7 (CH), 123.9 (CH), 122.9 (C), 34.8 (CH_2), 25.5 (CH_2); HRMS (M + H, +ESI) C_{16}H_{12}N_3Br calculated 328.0444, found 328.0455.
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

(3i)

1-(4-Cyanophenyl)-1H-1,2,3-triazol-5-yl)methyl 3,4-dichlorobenzoate – novel

Orange solid (73%); R_t = 3.38 min, M + H = 373.2 and 375.5 [Cl]; ν_{max} (thin film) 2237w, 1726s, 1606w, 1588w, 1509m, 1464w, 1442w, 1412w, 1387m, 1311w, 1272s, 1238s, 1170w, 1152w, 1143w, 1115m, 1091s, 1034m, 1013w, 991w, 971m, 900w, 884w, 848m, 841m, 833s, 824m, 794w, 772w, 753s, 709w, 692w, 678w, 660w, 565m; δ_H (300 MHz; CDCl_3) 7.99 (1H, s, Ar-H), 7.97 (1H, d, J = 2.0 Hz, Ar-H), 7.90 (2H, d, J = 8.5 Hz, Ar-H), 7.77 (1H, dd, J = 8.5, 2.0 Hz, CH), 7.76 (2H, d, J = 8.5 Hz, Ar-H), 7.55 (1H, d, J = 8.5 Hz, Ar-H), 5.45 (2H, s, CH_2); δ_C (75 MHz; CDCl_3) 163.7 (C=O), 139.2 (C), 138.7 (C), 136.2 (C_H), 133.8 (C), 133.4 (C), 132.0, 131.5 (CH), 130.9 (CH), 128.6 (CH), 128.4 (C), 125.2 (CH), 117.3 (C), 114.0 (C), 54.6 (CH_2); Mp = 134 °C; HRMS (M + H, +ESI) C_{17}H_{11}O_{2}N_{4}Cl_2 calculated 373.0254, found 373.0257.

(3j)

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

Yellow solid (57%); R_t = 3.32 min, M + H = 256.2 and 258.2 [Cl]; ν_{max} (thin film) 1622w, 1512m, 1495s, 1092m, 988w, 832m, 765m, 747w, 697m, 565m; δ_H (400 MHz; CDCl_3) 7.86 (1H, s, Ar-H), 7.44-7.35 (5H, m, Ar-H), 7.34-7.29 (2H, m, Ar-H), 7.19 (2H, dd, J = 8.0, 1.5 Hz, Ar-H); δ_C (101 MHz; CDCl_3) 137.7 (C), 135.2 (C), 135.0 (C), 133.5 (CH), 129.6 (CH), 129.4 (CH), 129.0 (CH), 128.6 (CH), 126.4 (C), 126.3 (CH); Mp = 87 °C; HRMS (M + H, +ESI) C_{14}H_{11}N_3Cl calculated 256.0636, found 256.0629.

(3k)

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

13 L. K. Rasmussen, B. C. Boren and V. V. Fokin, Org. Lett. 2007, 9, 5337.
14 S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov and V. V. Fokin, Org. Lett. 2010, 12, 4217.
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

Orange solid (51%); R_t = 3.06 min, M + H = 267.2; ν_max (thin film) 1594m, 1520m, 1498m, 1453w, 1307s, 1269m, 1237m, 1173w, 1109s, 1076w, 1045w, 989w, 965w, 854s, 762s, 751s, 730m, 697s, 688s, 679m, 565m; δ_H (400 MHz; CDCl_3) 8.30 (2H, d, J = 9.0 Hz, Ar-H), 7.89 (1H, s, Ar-H), 7.59 (2H, d, J = 9.0 Hz, Ar-H), 7.50-7.39 (3H, m, Ar-H), 7.24 (2H, dd, J = 8.0, 2.0 Hz, Ar-H); δ_C (101 MHz; CDCl_3) 147.5 (C), 141.2 (C), 138.0 (C), 134.2 (CH), 129.9 (CH), 129.3 (CH), 128.7 (CH), 126.0 (C), 125.3 (CH), 124.9 (CH); Mp = 162 °C; HRMS (M + H, +ESI) C_{14}H_{11}N_4O_2 calculated 267.0877, found 267.0876.

![Image](image_url)

(3l)

Ethyl 4-(5-phenyl-1H-1,2,3-triazol-1-yl)benzoate – previous reports by other groups provided no experimental data

Orange solid (73%); R_t = 3.25 min, M + H = 294.3; ν_max (thin film) 1717s, 1605m, 1511w, 1479w, 1409w, 1367w, 1308w, 1271s, 1233m, 1173m, 1130m, 1111m, 1078w, 1019w, 1050w, 989m, 975w, 964w, 860m, 842m, 769s, 701s, 679m, 567m; δ_H (300 MHz; CDCl_3) 8.08 (2H, d, J = 8.5 Hz, Ar-H), 7.84 (1H, s, Ar-H), 7.42 (2H, s, J = 8.5 Hz, Ar-H), 7.39-7.30 (3H, m, Ar-H), 7.20 (2H, dd, J = 8.0, 1.5 Hz, CH), 4.37 (2H, q, J = 7.0 Hz, CH_2), 1.37 (2H, t, J = 7.0 Hz, CH_3); δ_C (75 MHz; CDCl_3) 165.3 (C=O), 139.8 (C), 137.7 (C), 133.6 (CH), 130.9 (C), 130.6 (CH), 129.4 (CH), 128.9 (CH), 128.5 (CH), 126.3 (C), 124.6 (CH), 61.3 (CH_2), 14.2 (CH_3); HRMS (M + H, +ESI) C_{17}H_{16}N_3O_2 calculated 294.1237, found 294.1238.

![Image](image_url)

(3m)

N-(4-(5-Phenethyl-1H-1,2,3-triazol-1-yl)phenyl)acetamide – novel

White solid (70%); R_t = 2.83 min, M + H = 307.3; ν_max (thin film) 1674m, 1604m, 1516s, 1454w, 1409m, 1369m, 1311m, 1253m, 978w, 839m, 750m, 698s, 580w; δ_H (300 MHz; CDCl_3) 9.09 (1H, br, NH), 7.72 (2H, d, J = 8.0 Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.27-7.15 (3H, m, Ar-H), 7.03 (2H, d, J = 7.5 Hz, Ar-H), 3.02-2.81 (4H, m, CH_2CH_2), 2.19 (3H, s, CH_3); δ_C (75 MHz; CDCl_3) 169.3 (C=O), 139.8 (C), 139.4 (C), 137.7 (C), 132.3 (CH), 131.1 (C), 128.5 (CH), 128.2 (CH), 126.5 (CH), 125.8 (CH),
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

120.3 (CH), 34.4 (CH₂), 25.4 (CH₂), 24.4 (CH₃); Mp 131 °C; HRMS (M + H, +ESI) C₁₈H₁₉N₄O calculated 307.1553, found 307.1557.

![Chemical Structure](image)

(3n)

1-(3-(5-Phenethyl-1H-1,2,3-triazol-1-yl)phenyl)ethanone – novel

Sticky orange solid (52%); Rₜ = 3.78 min, M + H = 292.1; νₑ₉ (thin film) 2108w, 1687s, 1588m, 1358m, 1255m, 978w; δH (300 MHz; CDCl₃) 8.07 (1H, dt, J = 8.0, 1.5 Hz, Ar-H), 7.92 (1H, t, J = 2.0 Hz, Ar-H), 7.65-7.57 (2H, m, Ar-H), 7.49 (1H, ddd, J = 8.0, 2.0, 1.0 Hz, Ar-H), 7.25-7.17 (3H, m, Ar-H), 7.03 (2H, dd, J = 8.0, 2.0 Hz, Ar-H), 3.02-2.89 (4H, m, CH₂CH₂), 2.53 (3H, s, CH₃); δC (75 MHz; CDCl₃) 196.4 (C=O), 139.4 (C), 138.3 (C), 137.4 (C), 136.7 (C), 132.8 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 126.6 (CH), 124.9 (CH), 34.7 (CH₂), 26.7 (CH₃), 25.5 (CH₂); HRMS (M + H, +ESI) C₁₈H₁₉N₃O calculated 292.1444, found 292.1437.

![Chemical Structure](image)

(3o)

5-Butyl-1-(4-iodophenyl)-1H-1,2,3-triazole – novel

Brown solid (69%); Rₜ = 3.40 min, M + H = 328.2; νₑ₉ (thin film) 5955w, 2869w, 1492s, 1466w, 1395w, 1248w, 1058m, 1006m, 975s, 825s; δH (300 MHz; CDCl₃) 7.88 (2H, d, J = 8.5 Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.20 (2H, d, J = 8.5 Hz, CH), 2.64 (2H, t, J = 7.5 Hz, CH₂), 1.57 (2H, quin, J = 7.9 Hz, CH₂), 1.33 (2H, sex., J = 7.5 Hz, CH₂), 0.88 (3H, t, J = 7.5 Hz, CH₃); δC (75 MHz; CDCl₃) 138.7 (CH), 138.1 (C), 137.9 (C), 136.2 (C), 132.6 (CH), 126.8 (CH), 117.2 (CH), 94.9 (Cl), 30.3 (CH₂), 23.4 (CH₂), 22.2 (CH₃), 13.6 (CH₃); Mp = < 50 °C; HRMS (+ESI) calculated for C₁₂H₁₅N₃I [M + H]^+ calculated 328.0305, found 328.0297.

![Chemical Structure](image)
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

(3p)

2-Bromo-5-(5-butyl-1H-1,2,3-triazol-1-yl)pyridine – novel

Orange solid (71%); R<sub>t</sub> = 2.85 min, M + H = 281.1 and 283.1 [Br]; ν<sub>max</sub> (thin film) 2957w, 2871w, 1541w, 1472s, 1373w, 1256w, 1126w, 1092m, 1072w, 1005w, 974m, 833m, 731w; δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 8.52 (1H, dd, J = 2.0, 1.0 Hz, Ar-H), 7.77-7.66 (2H, m, Ar-H), 7.62 (1H, s, Ar-H), 2.67 (2H, t, J = 7.5 Hz, CH<sub>2</sub>), 1.61 (2H, quin., J = 7.5 Hz, CH<sub>2</sub>), 1.35 (2H, sex., J = 7.5 Hz, CH<sub>2</sub>), 0.88 (3H, t, J = 7.5 Hz, CH<sub>3</sub>); δ<sub>C</sub> (75 MHz; CDCl<sub>3</sub>) 145.7 (CH), 142.6 (C), 138.5 (C), 134.8 (CH), 132.9 (CH), 132.7 (C), 128.9 (CH), 30.3 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 13.6 (CH<sub>3</sub>); Mp = 58 °C; HRMS (M + H, +ESI) C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>Br calculated 281.0396, found 281.0395.

(3q)

2-(((1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-5-yl)methyl)thio)benzo[d]thiazole - novel

Brown solid (69%); R<sub>t</sub> = 3.21 min, M + H = 414.9; ν<sub>max</sub> (thin film) 2938w, 1601m, 1508m, 1463m, 1427m, 1344w, 1232m, 1128s, 1084w, 1000m, 832w, 759w, 728w; δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 7.89 (1H, s, Ar-H), 7.87 (1H, d, J = 8.0 Hz, Ar-H), 7.77 (1H, d, J = 8.0 Hz, Ar-H), 7.46 (1H, td, J = 8.0, 1.0 Hz, Ar-H), 7.35 (1H, td, J = 8.0, 1.0 Hz, Ar-H), 6.81 (2H, s, Ar-H), 4.68 (2H, s, CH<sub>2</sub>), 3.89 (9H, s, 3 x OCH<sub>3</sub>); δ<sub>C</sub> (75 MHz; CDCl<sub>3</sub>) 163.4 (C), 153.8 (C), 152.7 (C), 139.1 (C), 135.4 (C), 134.6 (CH), 133.6 (C), 131.2 (C), 126.4 (CH), 124.9 (CH), 121.7 (CH), 121.2 (CH), 103.1 (CH), 61.0 (OCH<sub>3</sub>), 56.4 (OCH<sub>3</sub>), 25.0 (CH<sub>2</sub>); Mp = 102 °C; HRMS (M + Na, +ESI) C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>Na<sub>2</sub>S calculated 437.0713, found 437.0723.

(3r)

1,5-Bis(1-(4-chlorophenyl)-1H-1,2,3-triazol-5-yl)pentane – novel

S14
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

1-Azido-4-chlorobenzene (2.4 mmol, 367 mg), nona-1,8-diyne (1.0 mmol, 120 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (16 mL) was added to dissolve the starting materials before ZnEt₂ (3.0 mmol, 3.0 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours) before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL) and EtOAc (40 mL) to afford approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a brown oil (71%).

Rₜ = 3.39 min, M + H = 426.9 and 428.4 [Cl]; vₚₛ (thin film) 1497s, 1406w, 1252w, 1093m, 1012w, 976m, 833m, 560w; δ (300 MHz; CDCl₃) 7.55 (2H, s, Ar-H), 7.52 (4H, dt, J = 8.5, 2.0 Hz, Ar-H), 7.36 (4H, dt, J = 8.5, 2.0 Hz, Ar-H), 2.61 (4H, t, J = 7.5 Hz, CH₂), 1.56 (4H, quin., J = 7.5 Hz, CH₂), 1.31 (2H, quin., J = 7.5 Hz, CH₂); δc (75 MHz; CDCl₃) 137.6 (C), 135.7 (C), 134.8 (C), 132.5 (CH), 129.8 (CH), 126.4 (CH), 28.5 (CH₂), 27.8 (CH₂), 23.5 (CH₃); HRMS (M + Na, +ESI) C₂₁H₂₅N₅Cl₂Na calculated 449.1019, found 449.1020.

1-Benzyl-5-butyl-1H-1,2,3-triazole¹⁵

Benzyl azide (1 mmol, 133 mg), hexyne (1.2 mmol, 100 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature for approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a clear oil (65%).

Rₜ = 3.06 min, M + H = 216.2; vₚₛ (thin film) 2957w, 2931w, 1497w, 1456m, 1427w, 1260w, 1235m, 1126w, 1094w, 1073w, 1029w, 983m, 823m, 724s, 710s, 695s, 577m; δ (300 MHz; CDCl₃) 7.47 (1H, s, Ar-H), 7.37-7.27 (3H, m, Ar-H), 7.13 (2H, dd, J = 7.5, 2.0 Hz, Ar-H), 5.49 (2H, s, PhCH₂), 2.47 (2H, t, J = 7.5 Hz, CH₂), 1.49 (2H, quin., J = 7.5 Hz, CH₂), 1.29 (2H, sex., J = 7.5 Hz, CH₂), 0.85 (3H, t, J = 7.5 Hz, CH₃); δc (75 MHz; CDCl₃) 137.4 (C), 135.0 (C), 132.5 (CH), 128.9 (CH), 128.2 (CH), 127.0 (CH), 51.6 (PhCH₂), 29.9 (CH₂), 22.8 (CH₂), 22.1 (CH₂), 13.6 (CH₃); HRMS (M + Na, +ESI) C₁₃H₁₇N₅Na calculated 238.1315, found 238.1310.

¹⁵ Y.-H. Lo, T.-H. Wang, C.-Y. Lee, and Y.-H. Feng, Organometallics 2012, 31, 6887.

S15
4-Azidobenzonitrile (1.2 mmol, 173 mg), mestranol (1 mmol, 310 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (16 mL) was added to dissolve the starting materials before ZnEt₂ (2.5 mmol, 2.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature for approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL). The mixture was partitioned between water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (49%).

Rₚ = 3.67 min, M + H = 455.2; νₚₚ (thin film) 3461brs, 2924w, 2872w, 2240
νₚₚ (thin film) MHz; DMSO-d6) 8.00 (2H, d, J = 8.5 Hz, Ar-H, 22 or 23), 7.77 (2H, d, J = 8.5 Hz, Ar-H, 22 or 23), 7.15 (1H, s, Triazole-H, 20), 7.05 (1H, d, J = 8.5 Hz, Ar-H, 1), 6.63 (1H, dd, J = 8.5, 3.0 Hz, Ar-H, 2), 6.58 (1H, d, J = 3.0 Hz, Ar-H, 4), 5.61 (1H, s, OH), 3.66 (3H, s, OCH₂-26), 2.76 (2H, dd, J = 4.1, 3.6 Hz, CH₂=6), 2.32 (1H, ddd, J = 14.5, 10.0, 5.0 Hz, CH-16), 2.16-2.02 (2H, m, CH-11, CH-16), 1.95-1.80 (3H, m, CH-15, CH-19, CH-7), 1.44 (1H, qd, J = 12.0, 5.5 Hz, CH-15), 1.40-1.12 (5H, m, CH-14, CH-12, CH-11, CH-8, CH-7), 0.76 (3H, s, CH₃-18), 0.64 (1H, td, J = 13.5, 4.2 Hz, CH-12); δC (75 MHz; DMSO) 157.1 (C-3), 144.7 (C), 142.8 (C), 137.4 (C), 133.5 (CH-20), 132.2 (CH-27), 131.9 (C), 129.3 (CH-), 126.0 (CH-1), 118.2 (C), 113.5 (CH-4), 111.9 (C), 111.4 (CH-2), 81.9 (C-17), 54.9 (OCH₂-25), 48.1 (C-13), 47.8 (CH-14), 42.8 (CH-9), 39.0 (CH-8), 40.2 (CH₂-16), 33.8 (CH₂-12), 29.2 (CH₂-6), 27.0 (CH₃-7), 25.9 (CH₂-11), 22.8 (CH₂-15), 13.9 (CH₃-18); [α]D²⁷ = +140 (c = 0.25 in MeCN); Mp = 278 °C decomposition; HRMS (M + H, +ESI) C₂₆H₃₄N₄O₂ calculated 455.2442, found 455.2452.

(3t)

4-(5-{(8R,9S,13S,14S,17S)-17-hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl}-1H-1,2,3-triazol-1-yl)benzonitrile – novel
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

(3u)

4-(5-(2-Hydroxyethyl)-1H-1,2,3-triazol-1-yl)benzonitrile – novel

4-Azidobenzonitrile (1 mmol, 144 mg), but-3-yn-1-ol (1.2 mmol, 84 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (2.5 mmol, 2.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature for approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (71%).

Rₜ = 1.72 min, M + H = 215.2; νₚₑₚₑₑₑ (thin film) 3257w br, 2231m, 1607m, 1509s, 1413w, 1258m, 1236w, 1126w, 1089m, 1059s, 1015w, 983s, 854m, 837s, 823m, 704m, 561s; δₜ (400 MHz; CDCl₃) 7.85 (2H, dt, J = 8.5, 2.0 Hz, Ar-H), 7.72 (2H, dt, J = 8.5, 2.0 Hz, Ar-H), 7.67 (1H, s, Ar-H); δc (101 MHz; CDCl₃) 139.6 (C), 135.8 (C), 133.5 (CH), 133.3 (CH), 126.0 (CH), 117.6 (C), 113.4 (C), 60.8 (CH₂), 56.1 (CH₂); Mp = 121 °C; HRMS (M + H, +ESI) C₁₁H₁₁N₄O calculated 215.0927, found 215.0942.
**Synthesis of 1,4,5-Substituted 1,2,3-Triazoles**

(3v)

4-(4-$^{[2]H}$)-phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel

4-azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N$_2$ and kept under a N$_2$ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt$_2$ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). D$_2$O (1 mL) and D$_3$CCO$_2$D (1 mL) were added and the mixture was stirred vigorously for 30 minutes. The reaction was partitioned with sat. NH$_4$Cl (aq) (20 mL), water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, 4:6 EtOAc/hexane) to afford a pale yellow solid (71%).

R$_t$ = 2.91 min, M + H = 276.3; $\nu_{\text{max}}$ (thin film) 2238w, 1603w, 1509m, 1455w, 1409w, 1257w, 11073m, 990m, 854w, 837s, 755m, 724m, 717s, 709s, 698m, 569s, 557s; $\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 7.79 (2H, d, $J = 8.5$ Hz, Ar-H), 7.65 (0.11H, s, Ar-H), 7.44 (2H, d, $J = 8.5$ Hz, Ar-H), 7.28-7.20 (3H, m, Ar-H), 7.03 (2H, dd, $J = 7.5, 2.0$ Hz, Ar-H), 3.03 (2H, m, CH$_2$), 2.94 (2H, m, CH$_2$); $\delta_{\text{C}}$ (75 MHz; CDCl$_3$) 139.7 (C), 139.1 (C), 137.3 (C), 133.4 (CH), 133.2 (CH), 128.7 (CH), 128.2 (CH), 126.8 (CH), 125.6 (CH), 117.5 (C), 113.3 (C), 34.8 (CH$_2$), 25.7 (CH$_2$); Mp = 118 $^\circ$C; HRMS (M + H, +ESI) C$_{17}$H$_{14}$DN$_4$ calculated 276.1354, found 276.1352.

89% deuterium incorporation by $^1$H-NMR and LCMS.

(3w)

4-(4-Bromo-5-phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel

4-azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N$_2$ and kept under a N$_2$ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt$_2$ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was
stirred at ambient temperature overnight (approximately 18 hours). Bromine (2 mmol, 120 µL) was added and the mixture was stirred vigorously for 30 minutes. The reaction was partitioned with sat. NH₄Cl (aq) (20 mL), water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, 4:6 EtOAc/hexane) to afford a pale brown solid (76%).

R₂ = 3.20 min, M + H = 353.2 and 355.2 [Br]; νmax (thin film) 2226m, 1602m, 1536w, 1507m, 1451m, 1405w, 1303w, 1269m, 1242m, 1160w, 1100w, 1062m, 997m, 970m, 854s, 826m, 759s, 738m, 721m, 702s, 681w, 583s, 559s; δH (300 MHz; CDCl₃) 7.72 (2H, d, J = 8.6 Hz, Ar-H), 7.21-7.09 (5H, m, Ar-H), 6.86 (2H, dd, J = 6.4, 3.2 Hz, Ar-H), 3.04 (2H, t, J = 7.0 Hz, CH₂), 2.88 (2H, t, J = 7.0 Hz, CH₂); δC (75 MHz; CDCl₃) 139.2 (C), 138.7 (C), 135.3 (C), 133.4 (CH), 128.8 (CH), 128.4 (CH), 126.9 (CH), 125.9 (CH), 121.6 (C), 117.4 (C), 113.9 (C), 33.6 (CH₂), 25.1 (CH₂); Mp = 128 °C; HRMS (M + H, +ESI) C₁₇H₁₄N₄Br calculated 353.0396, found 353.0395.

4-(5-Phenyl-4-phenyl-1H-1,2,3-triazol-1-yl)benzonitrile - novel

4-azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyn e (1.2 mmol, 156 mg) and N-methylimidazole (0.1 mmol, 8 µg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). A THF solution (10 mL) containing Pd(PPh₃)₄ (0.02 mmol, 24 mg) and iodobenzene (2 mmol, 408 mg) was added to the reaction and the mixture was stirred at ambient temperature overnight (approximately 18 hours). The reaction was quenched with sat. NH₄Cl (aq) (20 mL) and partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (68%).

R₂ = 3.43 min, M + H = 351.3; νmax (thin film) 2229m, 1606m, 1511m, 1495m, 1448w, 1408w, 1369m, 1283m, 1265m, 1116w, 1091m, 1072m, 1002w, 980m, 917w, 848s, 829m, 777m, 755m, 738m, 723m, 696s, 679m, 571m, 559m; δH (300 MHz; CDCl₃) 7.77 (4H, d, J = 8.0 Hz, Ar-H), 7.51 (2H, t, J = 7.5 Hz, Ar-H), 7.44 (1H, t, J = 7.0 Hz, Ar-H), 7.31 (2H, d, J = 8.5 Hz, Ar-H), 7.15 (2H, dd, J = 5.0, 2.0 Hz, Ar-H), 7.13 (1H, m, Ar-H), 6.77 (2H, dd, J = 6.5, 3.0 Hz, Ar-H), 3.24 (2H, t, J = 7.5 Hz, CH₂), 2.72 (2H, t, J = 7.5 Hz, CH₂); δC (75 MHz; CDCl₃) 145.4 (C), 139.7 (C), 138.9 (C), 133.3 (CH), 133.1 (C), 130.9 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 126.7 (CH), 126.3 (CH), 117.6 (C), 113.4 (C), 34.0 (CH₂), 25.3 (CH₂); Mp = 165 °C; HRMS (M + H, +ESI) C₂₃H₁₉N₄ calculated 351.1604, found 351.1609.
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

CCDC Reference: 931415
Manchester reference number: s3790ma
Formula: C23 H18 N4
Thermal ellipsoids at 50%
Unit cell parameters:
  Cell lengths – a = 10.5311(2), b = 11.4207(3), c = 15.0422(4)
  Cell angles – α = 90.00, β = 95.3710(10), γ = 90.00
Monoclinic
Space Group - P2(1)/c

(3y)
(1-(4-Chlorophenyl)-5-phenethyl-1H-1,2,3-triazol-4-yl)(3,4-dichlorophenyl)methanone – novel

1-Azido-4-chlorobenzene (1 mmol, 154 mg), 4-phenyl-1-butyn (1.2 mmol, 156 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). A THF solution S20
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

(10 mL) containing Ni(acac)$_2$ (0.05 mmol, 13 mg) and 3,4-dichlorobenzoyl chloride (2 mmol, 420 mg) was added to the reaction and the mixture was stirred at ambient temperature overnight (approximately 18 hours). The reaction was quenched with sat. NH$_4$Cl (aq) (20 mL) and partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a pale orange solid (66%).

R$_f$ = 4.26 min, M + H = 456.1 and 458.1 [Cl]; $\nu_{max}$ (thin film) 1647m, 1583w, 1497s, 1453w, 1242m, 1168w, 1095m, 958m, 938m, 832m, 776m, 700m; $\delta_{HI}$ (300 MHz; CDCl$_3$) 8.55 (1H, d, $J$ = 2.0 Hz, Ar-H), 8.32 (1H, dd, $J$ = 8.5, 2.0 Hz, Ar-H), 7.62 (1H, d, $J$ = 8.5 Hz, Ar-H), 7.46 (2H, d, $J$ = 8.5 Hz, Ar-H), 7.20-7.15 (3H, m, Ar-H), 7.03 (2H, d, $J$ = 8.5 Hz, Ar-H), 6.92 (2H, dd, $J$ = 6.5, 3.0 Hz, Ar-H), 3.32 (2H, t, $J$ = 7.5 Hz, CH$_2$), 2.94 (2H, t, $J$ = 7.5 Hz, CH$_2$); $\delta_C$ (75 MHz; CDCl$_3$) 184.5 (C=O), 143.9 (C), 142.8 (C), 139.3 (C), 137.6 (C), 136.7 (C), 136.5 (C), 133.5 (C), 132.9 (C), 132.6 (CH), 130.4 (CH), 129.8 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 126.6 (CH), 34.2 (CH$_2$), 26.1 (CH$_2$); Mp = 136 °C; HRMS (M + H, +ESI) C$_2$H$_7$N$_3$OCl$_3$ calculated 456.0432, found 456.0443.

4-(4-((4-Chlorophenyl)(hydroxy)methyl)-5-phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel

4-Azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butynyl (1.2 mmol, 156 mg) and N-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N$_2$ and kept under a N$_2$ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt$_2$ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). Magnesium turnings (4 mmol, 96 mg) were added to a second round bottomed flask and the vessel was purged with N$_2$ and kept under a N$_2$ balloon. Dry THF 10 mL was added and the flask was put in an ambient temperature water bath. 1,2-dichloroethane (2 mmol, 160 $\mu$L) was added to the magnesium suspension and the reaction was vigorously stirred for 1 hour. Some white precipitate, in addition to the excess magnesium, was observed and was dissolved with a further 5 mL of dry THF. The decanted solution of MgCl$_2$ (~2 mmol) was added to a third N$_2$ purged round bottom flask containing 4-chlorobenzaldehyde (2 mmol, 280 mg). The aryl zinc solution was then added to the MgCl$_2$/aldehyde solution and the reaction was stirred overnight (approximately 18 hours) at ambient temperature. The reaction was quenched with sat. NH$_4$Cl (aq) (20 mL) and partitioned between water (20 mL) and EtOAc (40 mL), the organic layer was washed with water (20 mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (52%).

R$_f$ = 4.24 min, M + H = 424.1 and 426.1 [Cl]; $\nu_{max}$ (thin film) 3360br w, 2232m, 1607s, 1511s, 1490s, 1454m, 1409w, 1254m, 1089s, 1013s, 910w, 844s, 795m, 751s, 700s; $\delta_{HI}$ (300 MHz; CDCl$_3$) 7.73 (2H, d, $J$ = 8.5 Hz, Ar-H), 7.44 (2H, d, $J$ = 8.5 Hz, Ar-H), 7.35 (2H, d, $J$ = 8.5 Hz, CH), 7.25 (2H, d, $J$ = 8.5 Hz, CH), 7.15 (2H, m, Ar-H), 7.03 (2H, d, $J$ = 8.5 Hz, Ar-H), 6.92 (2H, dd, $J$ = 6.5, 3.0 Hz, Ar-H), 3.32 (2H, t, $J$ = 7.5 Hz, CH$_2$), 2.94 (2H, t, $J$ = 7.5 Hz, CH$_2$); $\delta_C$ (75 MHz; CDCl$_3$) 184.5 (C=O), 143.9 (C), 142.8 (C), 139.3 (C), 137.6 (C), 136.7 (C), 136.5 (C), 133.5 (C), 132.9 (C), 132.6 (CH), 130.4 (CH), 129.8 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 126.6 (CH), 34.2 (CH$_2$), 26.1 (CH$_2$); Mp = 136 °C; HRMS (M + H, +ESI) C$_2$H$_7$N$_3$OCl$_3$ calculated 456.0432, found 456.0443.
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

8.5 Hz, Ar-H), 7.19-7.10 (3H, m, Ar-H), 6.70 (2H, dd, J = 7.5, 2.1 Hz, Ar-H), 6.06 (1H, s, Ar$_2$CHOH), 3.7-3.3 (1H, br s, OH), 2.88 (2H, m, CH$_2$), 2.54 (2H, t, J = 7.5 Hz, CH$_2$); $\delta_\mathrm{C}$ (75 MHz; CDCl$_3$) 147.2 (C), 140.0 (C), 139.4 (C), 138.9 (C), 134.3 (C), 133.7 (C), 133.4 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 126.8 (CH), 126.1 (CH), 117.4 (C), 113.5 (C), 68.3 (Ar$_2$CHOH), 34.7 (CH$_2$), 24.8 (CH$_2$); $\text{Mp} = 152 ^\circ \text{C}$; HRMS (M + H, +ESI) $\text{C}_{24}\text{H}_{20}\text{N}_4\text{OCl}$ calculated 415.1320, found 4151322.
NMR Spectra

$^1$H- and $^{13}$C-NMR Spectra of Novel Starting Materials

Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

S23
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

$^1$H- and $^{13}$C-NMR Spectra of 1,5-Substituted Triazoles
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

S32
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

| Zn | Proton | 500 MHz DMSO |
|----|--------|--------------|
|    | ![Proton Spectrum](image) |

| Zn | Carbon | 75 MHz, DMSO |
|----|--------|--------------|
|    | ![Carbon Spectrum](image) |
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

$^1$H- and $^{13}$C-NMR Spectra of 1,4,5-Substituted Triazoles

![NMR Spectra](image-url)
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI