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Synthesis, Structures and Reactions of Isolable Terminal Aryl/Biaryl-butadiynes (Ar–C≡C–C≡CH)

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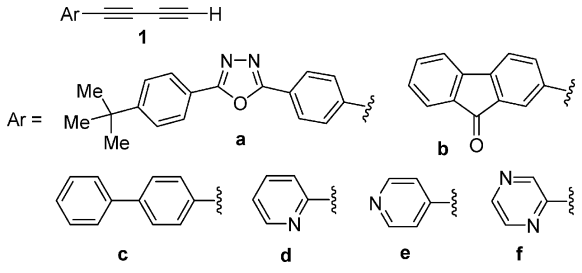
The synthesis and isolation is reported of five terminal aryl/biaryl-butadiynes, Ar–C≡C–C≡CH, (**5a**–**c**, **10a** and **10b**) from 2-methyl-6-aryl/biaryl-hexa-3,5-diyn-2-ol precursors [Ar–C≡C–C≡C–C(Me)$_2$OH; Ar = 2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-phenylpyridin-5-yl, 3-phenylpyridin-2-yl, respectively]. The X-ray crystal structures have been obtained for compounds **5c** and **10a**. Surprisingly, no ≡C–H···X (X = N or O) hydrogen bonds exist in the crystals of **5c** and **10a**. These structures illustrate the fact that ≡C–H···X hydrogen bonds are not always reliable tools for crystal engineering. Palladium-catalysed cross-coupling of **5c** with 2-iodopyrimidine gave the unsymmetrical 1,4-diarylbutadiyne derivative **12**; copper-catalysed reactions of **5c** and **10a** with benzyl azide proceeded regioselectively to give alkynyltriazoles **13** and **14**.

Introduction

The synthesis, isolation and properties of conjugated diyne molecules is a topic of great interest within contemporary acetylene chemistry.[1] In this context, simple terminal arylbutadiynes, Ar–C≡C–C≡CH, have generally been considered unsuitable for isolation and purification, due to their reported instability to decomposition or polymerisation.[2] They have usually been generated by desilylation of trialkylsilylated precursors (Ar–C≡C–C≡C–SiR$_3$)[3] or by dehydrohalogenation of haloene-yne (R–C≡C–CH=CHCl)[4] or ene-haloyne (R–CH=CH–C≡CCl) derivatives[5] and trapped in situ by reaction with aryl iodides to yield diarylbutadiyne derivatives, or homocoupled in situ to yield the symmetrical diaryloctatetrayne system. Lithiated phenylbutadiyne (Ph–C≡C–C≡C–Li) has been generated from a dibromoolefinic precursor [Ph–C(=CBr$_2$)–C≡CH] and efficiently trapped in situ with electrophiles.[6] However, some terminal arylbutadiyne derivatives have been isolated and spectroscopically characterised, for example, ferrocenylbutadiyne[2e] and 4-*t*BuC$_6$H$_4$–C≡C–C≡CH.[2f] Complementary studies have concerned oligoyne systems end-capped with organometallic groups where stability is enhanced by bulky ligands on the metal centre.[7]

Recently, we have developed the fragmentation of precursors Ar–C≡C–C≡C–C(Me)$_2$OH as an efficient route to Ar–C≡C–C≡CH species, and we have described the first X-ray crystal structures of compounds possessing the terminal arylbutadiyne structure, namely derivatives **1a**–**f** (Scheme 1).[8] In the crystal structures of **1a**,**b**,**d**–**f** the heteroatoms engage in weak intermolecular hydrogen bonding with a terminal alkyne proton (i.e. ≡C–H···X, where X = N or O) thereby stabilising the structures.[8]



Scheme 1. Arylbutadiyne derivatives previously characterised by X-ray crystallography.[8]

To probe further the stabilising effect of intermolecular hydrogen bonding in Ar–C≡C–C≡CH species, we reasoned that (methoxyphenyl)butadiyne derivatives might display ≡C–H···OMe hydrogen bonding, and phenylpyridinyl derivatives could engage in ≡C–H···N bonding. This paper extends our methodology for preparing Ar–C≡C–C≡CH derivatives and describes the characterisation of new species (Ar = methoxyphenyl and biaryl), including two X-ray crys-

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tal structures (compounds **5c** and **10a**). We also describe their reactions with benzyl azide to yield alkynyltriazoles in good yields.

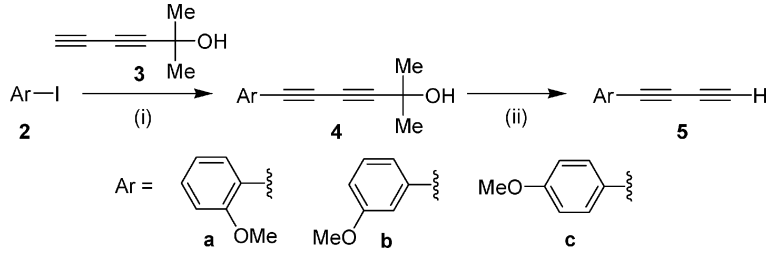
Results and Discussion

The reaction of 2-, 3- and 4-iodoanisole **2a**–**c**, with 2-methyl-3,5-hexadiyn-2-ol (**3**)[9] under standard Sonogashira conditions[10] [triethylamine, CuI, $PdCl_2(PPh_3)_2$, 20 °C] gave precursors **4a**–**c** (50–75% yields) (Scheme 2).[11] The deprotection of **4a**–**c** with loss of acetone was achieved by using a catalytic amount of NaOH in refluxing toluene.[12] The isomeric (methoxyphenyl)butadiyne derivatives **5a**–**c** were thereby obtained in 89, 65 and 84% yields, respectively, after column chromatography and were characterised by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Compounds **5a** and **5b** were isolated as oils which gradually darkened on storage within a few hours, whereas **5c** is a crystalline solid which is stable to storage for several days without any observable decomposition.[13] The X-ray crystal structure of **5c** is discussed below.

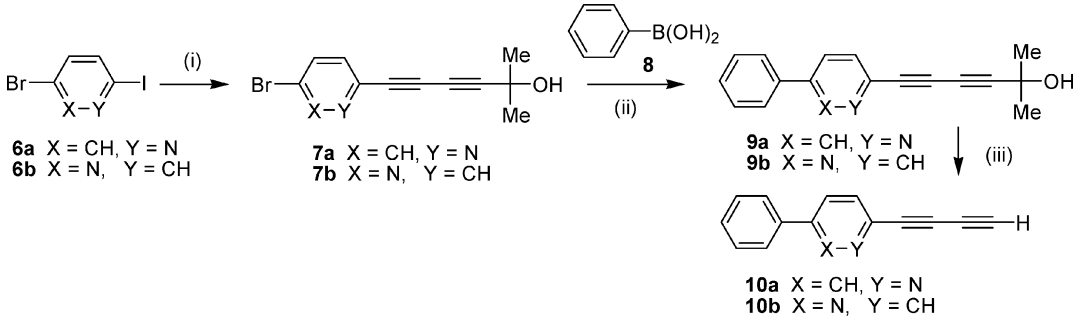
We next turned to new terminal biarylbutadiyne derivatives. The relative stability of **1c** is notable, as in contrast to **1a**,**b**,**d**–**f**, there is no heteroatom in structure **1c** to act as a hydrogen-bond acceptor. Instead, the herringbone layers of molecules in the crystal prevent close interactions of the butadiyne rods, thereby disfavouring polymerisation.[8b] Analogous phenylpyridinyl systems **10a** and **10b** were, therefore, interesting targets.

The syntheses of **10a** and **10b** are shown in Scheme 3. Selective displacement of the iodide substituent[14] of **6a** and **6b** gave the isomeric products **7a** and **7b**, functionalised with both a protected butadiyne group and a reactive bromo substituent for a subsequent Suzuki–Miyaura cross-coupling. The significant feature here is that the reactions of **7a** and **7b** with phenylboronic acid (**8**) proceeded cleanly to yield **9a** and **9b** (57 and 75% yields, respectively) under the basic conditions of the reaction [$PdCl_2(PPh_3)_2$, Na_2CO_3 (aq.), refluxing THF] without fragmentation of the 2-methylhexa-3,5-diyn-2-ol substituent. A directly analogous reaction of **7a** in refluxing dioxane (i.e. at higher temperature) gave only dark base-line material on TLC analysis, probably due to the formation and subsequent decomposition of **10a** under these conditions. Attempted reactions of **7a** with both 3- and 4-pyridylboronic acid were unsuccessful.[15] Deprotection of **9a** and **9b** gave compounds **10a** and **10b** which were isolated in high yields as white solids. Crystals of **10a** suitable for X-ray analysis were grown; however, crystals of **10b** could not be obtained.

The single-crystal X-ray structures of both **5c** and **10a** (Figures 1, 2, and 3) contain slanted arrays of diyne rods; in **5c** the adjacent rods are related by the *a* translation and hence are rigorously parallel, whereas in **10a** they are related by the *b* glide plane and are parallel within 5.6°. Such stacking, described by the length *d* of the vector connecting the diyne centres and the angle ϕ between this vector and the rod, is a well-known prerequisite for solid-state topochemical polymerisation of 1,3-diynes. Efficient reaction requires either $\phi \approx 45°$ and $d \approx 4.7$–5.2 Å (optimum 4.9 Å) or $\phi \approx 90°$ and $d \leq 4.0$ Å, to achieve close contact (R) between reactive carbon atoms.[16] As shown in Figure 3, **10a** adopts the former motif with $\phi = 43°$, $d = 5.20$ Å (half the crystallographic parameter *b*) and uniform intermolecular $C_\alpha \cdots C_\delta$ contacts $R = 3.57$ Å. The packing of **5c** is a slanted ($\phi = 75°$) version of the latter motif, where both *d* and *R* are



Scheme 2. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, CuI, triethylamine, 20 °C; (ii) NaOH, toluene, reflux.



Scheme 3. Reagents and conditions: (i) **3**, $PdCl_2(PPh_3)_2$, CuI, triethylamine, THF, 20 °C; (ii) **8**, $PdCl_2(PPh_3)_2$, Na_2CO_3 (aq.), THF, reflux; (iii) NaOH, toluene, reflux.

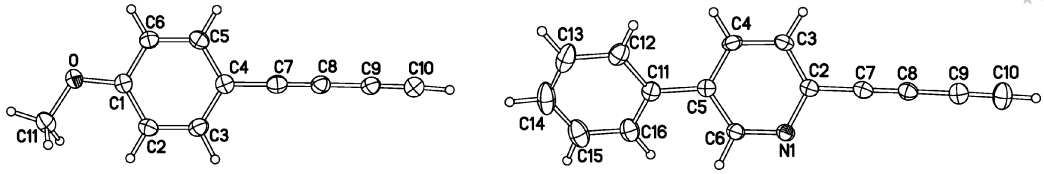


Figure 1. Molecular structures of **5c** (left) and **10a** (right) showing thermal ellipsoids at 50% probability level. Bond lengths [Å]: C(Ar)–C(7) 1.435(3) and 1.436(2), C(7)–C(8) 1.203(3) and 1.200(2), C(8)–C(9) 1.380(3) and 1.371(2), C(9)–C(10) 1.187(3) and 1.187(2), respectively. The angle between the aromatic ring planes in **10a** is 32°.

equal to the lattice parameter *a* (Figure 2). Thus, both structures are close to the upper limit of *d* suitable for polymerisation, which nevertheless does not occur readily. In fact, it does not occur even for **1b**,**d**–**f**,[8b] and HC_4PyC_4H (Py = pyridin-2,5-diyl),[17] all of which are arrayed in crystals similarly to **5c**, with even a shorter value of *d* (ca. 3.8 Å).[8b]

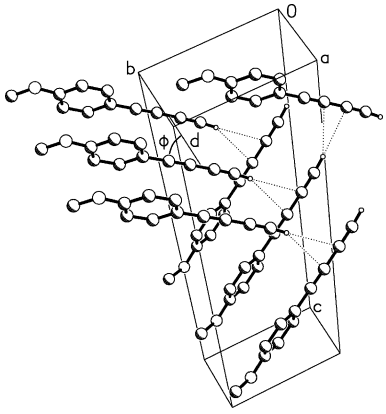


Figure 2. Crystal structure of **5c** (H atoms, except acetylene ones, are omitted).

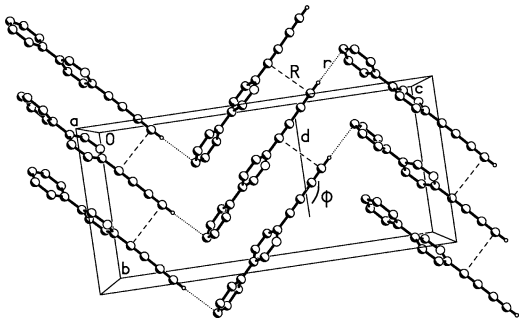


Figure 3. Crystal structure of **10a** (H atoms, except acetylene ones, are omitted).

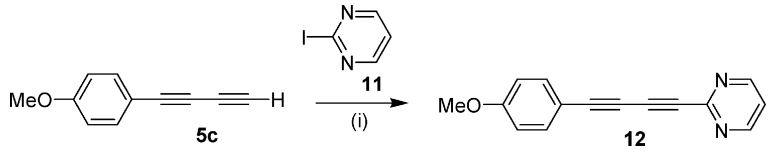
Molecules **1** (except **1c**) in crystals are linked by continuous networks of hydrogen bonds ≡C–H···X, where X = N or O. Due to the relatively high acidity of the acetylene hydrogen atom, they are stronger than most hydrogen bonds with a CH donor.[18] Thus, it came as a surprise that no such bonds exist in the crystals of **5c** and **10a**, which contain acetylene hydrogen atoms and electronegative atoms in a 1:1 ratio. Instead, C≡C–C≡CH groups in **5c** form a herringbone pattern with an inter-rod angle of 75° and shortest contacts ≡C(10)–H···C(8) and···C(9) of 2.71 and 2.73 Å, respectively,[19] which is rather awkward for a C–H···π(C≡C) interaction, the C(8)–C(9) bond being a single one. Even for an optimum geometry, the ≡C–H···π(C≡C) hydrogen bond is weaker than ≡C–H···O (1.2–1.4 kcal mol^{-1} vs. 2.2 kcal mol^{-1} from MO calculations),[18] yet the oxygen atom in **5c** contacts only with a methyl hydrogen atom, the energy estimates for such interactions vary from 0.3 to 0.8 kcal mol^{-1}. Similarly, in the structure of **10a** the ≡C–H bond points toward the pπ orbital of the phenyl C(14) atom (see Figure 3, $r_{H\cdots C}$ = 2.73 Å[19]), whereas the N atom contacts with two aryl hydrogen atoms.

To illustrate the synthetic potential of these terminal arylbutadiynes to yield diverse products we have performed: (i) a cross-coupling reaction (Scheme 4) and (ii) reactions with benzyl azide (Scheme 5).

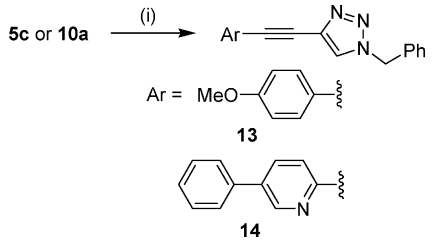
Unsymmetrical 1,4-biaryl/heteroaryl-butadiynes are fundamentally important targets for optoelectronic studies.[20] Terminal butadiynes are particularly attractive reagents in this regard as their cross-coupling reactions will not yield the symmetrical (self-coupled) 1,4-biaryl byproducts which are obtained as byproducts during the oxidative coupling of two different acetylene precursors.[21] Accordingly, as a prototype reaction, purified compound **5c** was treated with 2-iodopyrimidine (**11**) to cleanly yield the unsymmetrical push-pull system **12** in 62% yield.

At the outset of this work, we were aware of only two reports of cycloaddition reactions of terminal butadiynes; both described the Huisgen 1,3-dipolar cycloaddition reaction of benzyl azide at the terminal alkyne bond to yield an alkynyltriazole product.[22] While our work was in progress, Tykwinski et al. reported the in situ trapping of arylbutadiynes (Ar = Ph, 4-$OMeC_6H_4$, 4-FC_6H_4 and 4-$tBuC_6H_4$) generated by desilylation of Ar–C≡C–C≡C–SiR_3 precursors[23] with benzyl azide by using copper catalysis.[24] Our results with the isolated and purified aryl/biaryl-butadiynes **5c** and **10a** reported herein, complement these studies. In particular the regioselectivity of the reaction is the same in all cases.

Scheme 5 shows the formation of alkynyltriazole derivatives from **5c** and **10a**. The regiochemistry of **13** and **14** was established by NMR spectroscopic data, in agreement with the literature precedent that only one regioisomer is formed at 25 °C in the presence of a copper catalyst.



Scheme 4. Reagents and conditions: (i) **11**, $PdCl_2(PPh_3)_2$, CuI, triethylamine, 20 °C.



Scheme 5. (i) benzyl azide, DMF, water, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, 25 °C.

Conclusions

We have extended our methodology for the synthesis of terminal aryl/biaryl-butadiynes to yield a series of new isolable derivatives. It is now apparent that a wide range of simple terminal arylbutadiyne derivatives can be purified and thoroughly characterised by standard spectroscopic and X-ray crystallographic techniques. These structures illustrate the fact that ≡C–H···X hydrogen bonds are not always effective tools for crystal engineering, and can be easily overruled, e.g. by packing requirements. Arylbutadiynes should no longer be considered as unstable intermediates which require generation and trapping in situ, or need bulky substituents or heteroatoms on the aryl ring to provide steric hindrance to prevent polymerisation. The terminal alkyne bond of arylbutadiynes can be functionalised by efficient Sonogashira cross-coupling and cycloaddition reactions with benzyl azide. The clean Suzuki–Miyaura reactions of **7a** and **7b** [Scheme 3, step (ii)] clearly provide scope for the synthesis of new aryl/biaryl-butadiynes and their derived products – these reactions also illustrate the versatility of the 2-hydroxy-2-propyl protecting group in oligoyne chemistry.

Experimental Section

General Procedure for the Preparation of 4a–c and 7a,b: A mixture of the iodoarene **2a**–**c**, **6a**,**b**, and 2-methyl-3,5-hexadiyn-2-ol (**3**), $PdCl_2(PPh_3)_2$, CuI and triethylamine was stirred at 20 °C (18 h for **4a**–**c**; 3 h for **7a**, **b**) as detailed below. The volatile liquids were removed by vacuum evaporation, and the residue was chromatographed on a silica column and/or recrystallised to afford products **4a**–**c** and **7a**,**b**.

5-Bromo-2-(5-hydroxy-5-methyl-1,3-hexadiynyl)pyridine (7a): 5-Bromo-2-iodopyridine (**6a**) (700 mg, 2.46 mmol), 2-methyl-3,5-hexadiyn-2-ol (**3**) (534 mg, 4.94 mmol), $PdCl_2(PPh_3)_2$ (87 mg), CuI (24 mg) and triethylamine (100 mL) were stirred at 20 °C for 3 h. Column chromatography (silica, eluent DCM/Et_2O, 90:10 v/v) afforded **7a** as a white solid (552 mg, 85%); m.p. 128.3–128.8 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.62 (s, 1 H), 7.77 (dd, J = 8.4, 2.4 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 2.65 (s, 1 H), 1.52 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.5, 140.4, 138.9, 128.9, 121.0, 88.6, 76.9, 74.5, 66.5, 65.6, 40.0 ppm. MS (EI): m/z = 265.1 [M^+]. $C_{12}H_{10}BrNO$ (264.1): calcd. C 54.57, H 3.82, N 5.30; found C 54.57, H 3.93, N 4.98.

2-(5-Hydroxy-5-methyl-1,3-hexadiynyl)-5-phenylpyridine (9a): Compound **7a** (382 mg, 1.45 mmol), phenylboronic acid (**8**) (264 mg, 2.17 mmol) and $PdCl_2(PPh_3)_2$ (76 mg) were dissolved in degassed THF (40 mL), to which degassed Na_2CO_3 (aq.) (1 M, 4.24 mL) was added and the reaction refluxed under argon whilst being carefully monitored by TLC analysis. THF was removed and the remaining residue dissolved in diethyl ether. The organic layer was washed with brine (3 × 50 mL), dried with $MgSO_4$, filtered and the solvent removed. A white solid of **9a** (215 mg, 57% yield) was obtained after column chromatography (silica, eluent DCM changing to DCM/Et_2O, 90:10 v/v) and recrystallisation from cyclohexane; m.p. 122.1–122.6 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.82 (s, 1 H), 7.86–7.83 (dd, J = 8.4, 2.4 Hz, 1 H), 7.59–7.41 (m, 6 H), 2.48 (s, 1 H), 1.60 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 140.8, 137.1, 136.6, 134.5, 129.4, 128.8, 128.2, 127.2, 88.2, 73.9, 67.7, 65.8, 65.2, 31.2 ppm. MS (ES^+): m/z = 262.3 [M^+]. $C_{18}H_{15}NO$ (261.3): calcd. C 82.73, H 5.79, N 5.36; found C 82.44, H 5.72, N 5.41.

General Procedure for the Preparation of 5a–c, 10a,b: Compound **4a**–**c**, **9a**,**b** was dissolved in dry toluene. NaOH powder was added, and the mixture was stirred and heated with an oil-bath at 135 °C under Ar for ca. 10 min. TLC was used to monitor the end-point of the reaction. The reaction mixture was concentrated and the residue purified by column chromatography on silica. ***CAUTION:*** Care should be taken when handling solid samples of the terminal butadiynes. No problems were encountered in the present work, but there is a history of explosions with analogous compounds in other laboratories, e.g. terminal hexatriynes.[25]

2-(Buta-1,3-diynyl)-5-phenylpyridine (10a): Compound **9a** (136 mg, 0.524 mmol), NaOH (65 mg) and toluene (20 mL) afforded **10a** as a white solid (82 mg, 85%) after purification by column chromatography (silica, eluent DCM). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.83 (s, 1 H), 7.87–7.84 (dd, J = 7.6, 2.0 Hz, 1 H), 7.59–7.42 (m, 6 H), 2.53 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 140.1, 136.8, 136.7, 134.3, 129.2, 128.8, 128.7, 128.3, 127.1, 74.1, 73.7, 72.4, 67.8 ppm. MS: m/z = 204.1 [M^+]. Crystals for X-ray analysis were grown by slow concentration of a cyclohexane solution.

2-[4-(4-Methoxyphenyl)buta-1,3-diynyl]pyrimidine (12): 2-Iodopyrimidine (**11**) (229 mg, 1.12 mmol), compound **5c** (116 mg, 0.74 mmol), $PdCl_2(PPh_3)_2$ (20 mg) and CuI (3 mg) were stirred in anhydrous triethylamine (30 mL) at 20 °C for 18 h. Vacuum evaporation of volatiles followed by column chromatography (silica, eluent DCM/Et_2O, 90:10 v/v) afforded **12** as a pale yellow solid (107 mg, 62%); m.p. 164.6–165.9 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.72 (d, J = 4.8 Hz, 2 H), 7.50 (d, J = 8.0 Hz, 2 H), 7.25–7.24 (m, 1 H), 6.88–6.85 (m, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$,

100 MHz): δ = 168.2, 158.5, 152.7, 134.6, 120.1, 114.3, 112.8, 83.5, 78.9, 73.0, 72.3, 55.4 ppm. MS (EI): *m*/*z* = 234.0 [M$^+$]. $C_{15}H_{10}N_2O$ (234.3): calcd. C 76.91, H 4.30, N 11.96; found C 76.49, H 4.25, N 11.71.

2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethynyl]-5-phenylpyridine (14): $CuSO_4 \cdot 5H_2O$ (50 mg) and sodium ascorbate (50 mg) were added to a stirred mixture of benzyl azide (0.07 mL, 0.52 mmol), **10a** (105 mg, 0.52 mmol), DMF (7 mL) and water (2 mL). The mixture was then stirred at 25 °C for 18 h to afford a green solution. Ethyl acetate (30 mL) was added, and the organic layer was separated and washed with a saturated EDTA solution (3 × 30 mL), and the organic phase was dried with $MgSO_4$, filtered and the solvent removed. Purification by column chromatography (silica, DCM, followed by gradual addition of Et_2O) afforded **14** as a white solid (152 mg, 87%); m.p. 168.0–168.4 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.84 (d, *J* = 0.8 Hz, 1 H), 7.90–7.87 (m, 1 H), 7.42 (s, 1 H), 7.63–7.59 (m, 3 H), 7.51–7.47 (m, 2 H), 7.44–7.39 (m, 4 H), 7.31–7.28 (m, 2 H), 5.79 (s, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.6, 148.7, 141.4, 137.1, 136.1, 134.5, 134.1, 130.8, 129.32, 129.3, 129.1, 128.6, 128.2, 127.2, 127.1, 126.9, 91.9, 79.0, 77.3, 54.5 ppm. MS (ES$^+$): *m*/*z* = 337.2 [M$^+$]. $C_{22}H_{14}N_4$ (336.4): calcd. C 78.55, H 4.79, N 16.65; found C 78.37, H 4.71, N 16.91.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterisation data for compounds **4a**–**c**, **5a**–**c**, **7b**, **9b**, **10b** and **13**; X-ray crystallographic data for structures **5c** and **10a**.

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