Synthesis and cycloaddition reactions of strained alkynes derived from 2,2′-dihydroxy-1,1′-biaryls†

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A series of strained alkynes, based on the 2,2′-dihydroxy-1,1′-biaryl structure, were prepared in a short sequence from readily-available starting materials. These compounds can be readily converted into further derivatives including examples containing fluorescent groups with potential for use as labelling reagents. The alkynes are able to react in cycloadditions with a range of azides without the requirement for a copper catalyst, in clean reactions with no observable side reactions.

Introduction

The use of highly reactive strained alkynes, typically within eight-membered rings, in cycloaddition reactions with azides is now a well-established reaction with numerous applications in materials chemistry and in bioconjugation applications.2 Such reagents are ideal for these applications because the cycloaddition reactions take place spontaneously and without the need for a catalyst to be added – in contrast to the reactions of unstrained terminal alkynes with azides in which case a copper-based catalyst is generally required.3

Widely adopted cyclooctyne reagents such as 1–3 and their derivatives (Fig. 1)4–6 are highly reactive, and can be used at the low concentrations which are often required in bioconjugation applications, particularly for in vivo reactions.7 In applications where the concentration of reagents is more typical of synthetic reactions e.g. 0.01–0.5 M, and on larger scales, less reactive larger-ring molecules, which can be prepared through a short synthetic sequence, have also proven to be synthetically valuable reagents.8 Earlier and less reactive cyclooctynes remain synthetically important, for example (2-cyclooctyn-1-yloxy)acetic acid (a derivative of ‘OCT’*) was the subject of a successful multi-gram scale up optimisation study reported in 2018.5d Some highly strained derivatives are also prone to addition of thiols.5e

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†Electronic supplementary information (ESI) available: General experimental details, synthesis of intermediates 7,†† 11,12 14,15 19,34 and compounds 29–31 and 41–45, 1H and 13C NMR spectra, graphs of conversion/time, fluorescence spectra, functionalisation of amino-loaded beads and X-ray crystallographic data. CCDC 1852221, 1852223 and 1852224. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob01768a. The research data supporting this publication can be accessed at http://wrap.warwick.ac.uk/.

Fig. 1 Strained alkynes 1–3, dioxabiaryldecyne 4 and its derivatives 5 and 6.
conjugation through its attachment to a number of peptides and one protein in in vitro studies. Following our report, another group reported the preparation of some of the same derivatives, as well as N-containing heterocyclic variants, together with a comprehensive molecular modelling study to explain the enhanced reactivity of the reagents. This group also demonstrated that the dioxiabiaryldecynes do not rapidly undergo reactions with thiols.

In this paper we report the synthesis of a series of functionalised analogues of the strained alkyne structure 4, in as little as two steps, from readily available and inexpensive starting materials, their subsequent functionalisation and representative applications to a number of cycloaddition reactions with several azides.

Results and discussion

In order to develop an extended synthesis of dioxiabiaryldecyne reagents, we employed the reported coupling reactions of iodo-benzaldehyde reagents 7 and 8 (iodovanillin) and 4-hydroxy-3′-iodoacetophenone 9 with 2-(hydroxyphenyl)boronic acid 10, to give diols 11–13 respectively. This was followed by the cyclisation reactions with ditosylate 14 using our previously-reported procedure (Scheme 1). Strained alkynes 15, 16 and 17 were isolated respectively (Scheme 1). 3-Iodo-4-hydroxybenzaldehyde was prepared from 4-hydroxybenzaldehyde through careful iodination using ICl/acetic acid. Iodovanillin can be prepared by the same method but is readily commercially available.

Both the Pd-catalysed coupling and the cyclisation to form aldehydes 15 and 16 worked more efficiently for the product containing a methoxy group adjacent to the strained alkyne, giving a product in unoptimised but acceptable yield in each case. In the case of the transformation of aldehyde 12 to 16, we followed the reaction over time using chiral HPLC, which resolved the two non-interconverting enantiomers of product and allowed the conversion to be monitored over time (see ESI† for HPLC details and graph of conversion over time). The X-ray crystallographic structures of aldehyde 16 (Fig. 2) and ketone 17 (Fig. 3) revealed the strained nature of the alkyne within the constrained ring.

Alkyne 16 could also be reduced to the alcohol 19 using sodium borohydride, which gave a clean product, however attempts to reduce substrate 15, lacking the methoxy group, to 18 gave a complex mixture of products, for reasons that are not clear.

The strained alkynes prepared in this project are stable solids at rt which can be stored for months without significant decomposition. However a thermal gravimetric analysis (TGA) was carried out in order to examine their stability at higher temperatures. Aldehyde 16 exhibited a drop of ca. 10% mass around 180 °C which may be associated with the loss of C=O from the aldehyde, followed by a gradual mass loss of just over 20% as the temperature was raised to 600 °C. The TGA analysis of the previously reported methyl ester of acid 5 was stable to ca. 300 °C then gradually lost ca. 40% of its mass as the temperature was increased to 600 °C (see ESI†).

Scheme 1 Synthesis of aldehyde-functionalised CBD strained alkynes 15–17 and alcohol 19.

Fig. 2 Single crystal X-ray crystallographic structure of 16 (two views; ellipsoids are plotted at the 50% probability level). The bond angles at the sp atoms are 165.2° and 165.3° and the biphenyl torsion angle is 72.2°.

Fig. 3 Single crystal X-ray crystallographic structure of 17 (two views; ellipsoids are plotted at the 50% probability level). The bond angles at the sp atoms are 165.1° and 168.6° and the biphenyl torsion angle is 66.4°.
Given the improved synthesis of the methoxy-substituted aldehyde 16 over 15, we focussed our studies on the former reagent. Its reaction with a range of functionalised azides was studied (Scheme 2) and in each case the reactions were followed over time, using $^1$H NMR to monitor the cyclisations of a 1 : 1 mixture of reagents in solution; the spectra are in the ESI.$^\dagger$ The reaction of 16 with benzylazide 20 was also carried out in MeCN, the product 21 being isolated in 84% yield. In all cases, the cycloadditions proceeded smoothly, with no obvious accompanying decomposition of reagents. Conversions (by NMR) and yields (isolated products) are given in Scheme 2. In all cases the products were formed as inseparable regiosymmetric mixtures in ca. 1 : 1 : 3 : 2 ratios. Benzylazide gave a clean product 21 of addition, in analogy with previous reactions.$^9,11$ An azide attached to a red dye, disperse red, 22$^{15}$ gave a red product 23 from the cycloaddition, which was carried out at 0.128 M, 9 days at rt (95% conversion, 76% isolated yield). An azide containing a PEG-2000 chain, 24, also added cleanly to the strained alkyne 16, and the product in this case (25) was characterised by GPC as well as by NMR, revealing the expected increase to the molar mass of the polymeric product (ESI†). This was gratifying as the reagent concentration (0.025 M) in this example was lower than for other cycloadditions. The cycloaddition of coumarin azide 26 gave a highly fluorescent product 27 (see ESI†) as has been reported previously for this class of reagent.$^{15,30}$ For improved solubility, deuterated acetonitrile was used as the solvent, and the reaction at 0.11 M proceeded to ca. 80% conversion to 27. Although long reaction times are required relative to the more reactive strained alkynes such as 1–3, the benefits of the catalyst-free conditions and clean cycloadditions make these reagents potentially valuable for the preparation of materials for biological applications.

The addition of benzyl azide to alcohol 19 to give adduct 28 as a 3 : 2 regiosymmetric mixture of products (Fig. 4) proceeded at a similar rate (0.17 M, 5 d at rt, 97% yield, ESI†) indicating that the functional group has minimal influence on the rate of the cycloaddition, probably because of the separation from the alkyne.

The aldehyde group on 15 and 16 permits their functionalisation with other reagents. The reaction of 15 with benzylhydroxylamine in MeOH overnight at 45 °C gave oxime ether 29 in 66% isolated yield. The formation of oxime ethers represents a valuable method for functionalisation due to their high stability and ease of preparation.$^{16}$ Also, notably, reductive amination with benzylamine led to the synthesis of amine-containing derivatives 30 and 31. The reaction of methoxy-substituted 30 with benzylazide was found to proceed at a similar rate to aldehyde-containing reagents 16 (ESI†). It was gratifying that these functionalisations could be completed without damaging the strained alkyne group.

The treatment of amine-functionalised polystyrene beads with 16 and sodium cyanoborohydride was followed by reaction of the functionalised beads 32 with disperse red azide 22. After washing, the strong red colour of the dye remained on the beads 33 (Scheme 3). As a control reaction, stirring the solution of red dye-azide 22 with unfunctionalised beads gave only lightly coloured beads after washing, indicating that the cycloaddition had taken place on the dioxabiaryldicene reagent on the beads (ESI†).

Other reagents were prepared through reactions of the aldehyde, notably fluorescent groups. The reductive amination of 16 with the amine-functionalised dansyl reagent 34 resulted in formation of 35 (Scheme 4A), which showed strong fluorescent behaviour upon irradiation. A number of BoDIPY derivatives 36–38 were also prepared through the direct reaction of pyrroles with the aldehyde and BF$_3$ in good yield (Scheme 4B).$^{17}$ Again, the ability to functionalise aldehyde 16 with a variety of reagents, without damaging the strained alkyne, is noteworthy.
The X-ray crystallographic structure of 38 (Fig. 5) revealed the strained nature of the alkyne but also that the BoDIPY component was orientated almost perpendicular to the connected arenne ring, presumable with restricted rotation about the connecting C–C bond. This accounts for the observed differences in chemical shifts of the groups attached to the heterocyclic rings of the BoDIPY unit in each of 36–38, which will be in sharply different diastereotopic environments.

The fluorescence spectra for compounds 35–38 are given in the ESI†. However the strong and contrasting fluorescence behaviour of the BoDIPY dyes 36–38 is sharply illustrated by their response to UV irradiation. Compound 36 and 37 both show strong fluorescence upon irradiation whereas 38 gives a weaker response (ESI†).

The addition of benzylazide to BoDIPY derivative 36 was tested and worked efficiently to give two regiosiomers 39 and 40 in a 1:1 ratio (Fig. 6). In this case, we were able to separate the isomers by flash chromatography and independently characterise them. We have not unambiguously established which regiosiomer is which, of the two possibilities, however on the basis of the positions of the methylene groups in the $^{13}$C-NMR spectra compared to previous examples, we have tentatively assigned them as shown in Fig. 6 (see ESI†).

Further derivatives were also prepare from the corresponding alcohol 19 using a variety of coupling methods (Fig. 7). These included a biotin-containing reagent 41 which was formed through formation of an ester bond to biotin in one step.

It was also possible to attach a group through a carbamate i.e. 42, using $N,N'$-disuccinimidyl carbonate (DSC) as a coupling agent to attach alcohol 19 to form the dansyl amine derivative 34. 7d,18 Finally, from the alcohol, the direct reaction with an isocyanate could also be employed to create a derivative.
A series of strained alkyynes, based on the 2,2′-dihydroxy-1,1′-biaryl structure, were prepared in a short sequence from readily-available starting materials. This compound is novel.

Experimental section

General experimental details, synthesis of intermediates 7, 11, 12, 13, 19, 34 and compounds 29–31 and 41–45 are in the ESI.†

Alkyne 15

A series of strained alkyynes, based on the 2,2′-dihydroxy-1,1′-biaryl structure, were prepared in a short sequence from readily-available starting materials. This compound is novel.

Alkyne 16

This compound is novel.

2′,6-Dihydroxybiphenyl-3-carbaldehyde 11 (3.20 g, 14.9 mmol), potassium carbonate (10.22 g, 73.95 mmol) and but-2-yne-1,2-diyl bis(4-methylbenzenesulfonate) 14 (5.31 g, 13.5 mmol) were added to a clean dry schlenk. The schlenk was then put under nitrogen and purged, thereafter dry acetonitrile (747 mL) was added to the mixture and the reaction left to stir at rt for 10 days. The organics were removed under vacuum, water (500 mL) and DCM (500 mL) were added and the product extracted with DCM (3 × 300 mL). The organic extracts were washed with brine and dried over Na2SO4, filtered and concentrated under vacuum. The crude product was purified by column chromatography (8:2 hexane:ethyl acetate) to afford the product 15 as a white solid (1.50 g, 5.68 mmol, 38%). Mp 143–145 °C; (found [ESI-Q-TOF] [M + Na]+ 287.0675. C17H12O3Na requires 287.0679; νmax 2910, 2863, 1686, 1568, 1495, 1473, 1415, 1345, 1305, 1288, 1188 cm−1; δH (500 MHz, CDCl3) 9.98 (1H, s, CHO), 7.94 (1H, dd, J 8.4, 2.9, ArH), 7.75 (1H, d, J 2.0, ArH), 7.44–7.40 (1H, m, ArH), 7.32 (1H, d, J 8.3, ArH), 7.22–7.19 (3H, m, ArH), 4.63–4.61 (1H, m, CH3), 4.54–4.50 (m, 1H, CH2), 4.41–4.32 (m, 2H, CH3); δC (125 MHz, CDCl3) 191.2, 159.8, 154.4, 136.8, 134.9, 134.6, 132.6, 131.7, 129.7, 129.6, 124.3, 123.6, 122.6, 87.3, 86.0, 63.8, 63.5; m/z (ESI) 287.1 [M + Na]+).
1 ml min⁻¹, IB column. Full details are in the ESI.† The X-ray crystallographic structure of this compound was obtained and is described in the ESI.†

**Alkyne alcohol 19**

This compound is novel.

NaBH₄ (15 mg, 0.41 mmol, 1.0 eq.) was added carefully at 0 °C to a stirring solution of 16 (0.12 g, 0.41 mmol, 1.0 eq.) in methanol (10 mL) under a nitrogen atmosphere and the reaction was left for 1 hour to react at rt. The methanol was removed under vacuum and the residue was redissolved in ethyl acetate (15 mL). The organic extracts were washed with sat. NH₄Cl (15 mL) and then brine (15 mL). The organics collected, dried over Na₂SO₄, filtered and solvent removed under vacuum to afford a white solid. This was purified by column chromatography (1:1 hexane:ethyl acetate) to afford the product 19 as a white solid (0.12 g, 0.40 mmol, 99%). Mp 165–168 °C; (found (ESI-Q-TOF) [M + Na]⁺ 319.0940. This compound is novel.

**Cycloadduct 21**

This compound is novel.

Alkyne 16 (30 mg, 0.102 mmol) and benzyl azide 20 (13.8 mg, 0.18 μL, 0.102 mmol) were stirred in MeCN (0.6 mL) for 6 days at rt (ca. 0.17 M), monitoring each day by TLC. At the end of this time the solvent was removed under vacuum and the product purified by flash chromatography on silica gel (hexane:EtOAc: 7:3) to yield the product 21 as a white solid (40 mg, 0.94 mmol, 84%). TLC (hexane:EtOAc: 7:3), silica, Rf 0.15; M.p. 181–183 °C; (found (ESI+): [M + Na]⁺ 450.1426. C₂₅H₂₁N₃NaO₄ requires 450.0861); δH (1H NMR, 400 MHz, CDCl₃) 8.00 (1H, d, J 7.9, ArH, major regiosomer), 7.82 (0.2H, s, CHO, minor regiosomer), 7.70 (0.8H, t, J 7.5, CH, minor regiosomer), 7.10 (1H, t, J 7.9, ArH, major regiosomer), 6.90 (0.4H, d, J 15.0, CH, major regiosomer), 5.04 (0.4H, d, J 14.0, CH, minor regiosomer), 4.96 (0.4H, d, J 11.0, CH, minor regiosomer), 4.83 (0.6H, d, J 13.0, CH, major regiosomer), 4.02 (3H, s, OCH₃), 3.95 (3H, s, OCH₂); δC (125 MHz, CDCl₃) 191.0 (CH), 191.0 (CH), 153.8 (C), 153.6 (C), 152.7 (C), 152.6 (C), 151.7 (C), 145.0 (C), 144.2 (C), 134.9 (C), 134.1 (C), 133.6 (C), 133.1 (C), 133.0 (C), 132.6 (C), 132.4 (C), 131.4 (CH), 130.7 (CH), 129.5 (CH), 129.3 (CH), 129.0 (CH), 128.5 (C), 128.0 (C), 127.7 (CH), 127.1 (CH), 126.7 (CH), 122.3 (CH), 121.9 (CH), 113.2 (CH), 111.2 (CH), 110.6 (CH), 109.9 (CH), 67.5 (CH₂), 62.6 (CH₂), 61.0 (CH₂), 57.7 (CH₃), 56.2 (CH₁), 56.1 (CH₃), 53.0 (CH₂), 52.0 (CH₃), m/z (ES-API⁺) 450.0 ([M + Na]⁺). The reaction was also followed over time by ¹H NMR and full details are in the ESI.† Alkyne 16 (15 mg, 0.051 μmol) and benzyl azide 20 (6.4 mg, 51.0 μmol) were added together in deuterated chloroform (0.4 mL) (0.128 M in both reagents) and the reaction was followed at rt by ¹H NMR.
This compound is novel.

Aldehyde 16 (15 mg, 51.0 µmol) and azide 22 (19 mg, 51.0 µmol) were combined in deuterated chloroform (0.4 mL) and the reaction (ca. 0.128 M in both reagents) was left at rt. The progression of the reaction was monitored daily. The progression of the reaction was monitored daily by 1H NMR (ESI†). Upon completion, the reaction was worked up and the product purified by column chromatography (DCM → EtOAc in hexane (14 mg, 28 µmol, 64%). TLC hexane : EtOAc 3:2 gave 23 as a red solid (26 mg, 0.039 mmol, 76%).

Fluorescent coumarin dye cycloadduct 27

This compound is novel.

Compound 16 (13 mg, 44.2 µmol) and coumarin azide 26 (9.0 mg, 44.2 µmol) were added together in deuterated acetonitrile (0.4 mL) and the reaction left at r.t. (ca. 0.11 M in both reagents). The progression of the reaction was monitored daily. Stacked NMR spectra and the conversion/time graph are in the ESI†. At the end of this time (80% conversion after 12 d) the solvent was removed and the product 27 was purified by column chromatography using a gradient of EtOAc in hexane (14 mg, 28 µmol, 64%). TLC hexane : EtOAc 3:7, silica, Rf 0.60; M.p. 222–228 °C; (found (ESI+): [M + Na]+ 520.1119. C27H24N6NaO5 requires 520.1115; δmax 1725, 1688, 1605, 1574, 1223, 1133, 966, 684 cm⁻¹; δH (500 MHz, CDCl3) (two regioisomers 1:1) 9.89 (1H, s, CHO), 8.30–8.25 (0.4H, brs, NH or OH; by HSQC, minor regioisomer), 8.10–8.05 (0.6H, brs, NH or OH; by HSQC, major regioisomer), 7.95 (0.6H, s, CH, major regioisomer), 7.50–7.45 (1H, m, ArH), 7.42 (0.6H, s, ArH, major regioisomer), 7.35–7.30 (1H, m, ArH), 7.25–7.15 (2H, m, ArH), 6.95–6.85 (2H, m, ArH), 6.82–6.80 (1.8H, m, ArH, 1 × major, 3 × minor regioisomer), 6.65 (0.6H, d, J 10.0, ArH, major regioisomer), 5.88 (0.4H, d, J 13.0, OCH, minor regioisomer), 5.75 (0.6H, d, J 13.0, OCH, major regioisomer), 5.52 (0.4H, d, J 12.0, OCH, minor regioisomer), 5.35–5.25 (1H, m, OCH), 5.25 (0.6H, d, J 13.0, OCH, major regioisomer), 5.05–4.95 (1H, m, 0.4 OCH, minor regioisomer + 0.6 OCH, major regioisomer), 3.98 (1.2H, s, OCH3 minor regioisomer), 3.88 (1.8H, s, OCH3 major regioisomer), 1.65 (1H, brs, OH); δC (125 MHz, CDCl3) 191.3 (CH), 191.2 (CH), 162.6 (C), 157.7 (C), 157.5 (C), 155.9 (C), 153.8 (C), 152.7 (C), 152.5 (C), 151.4 (C), 147.5 (C), 142.5 (CH), 141.1 (CH), 136.0 (C), 134.9 (C), 132.7 (C), 132.5 (C), 131.6 (CH), 130.9 (CH), 130.8 (CH), 129.4 (C), 128.9 (C), 128.5 (CH), 128.1 (CH), 127.2 (C), 126.7 (C), 122.5 (CH), 122.1 (CH), 118.9 (C), 118.5 (C), 115.2 (CH), 114.9 (CH), 113.0 (CH), 111.1 (C), 1110.0 (C), 110.9 (CH), 110.7 (CH), 110.1 (CH), 103.6 (CH), 103.5 (CH), 67.1 (CH2), 63.2 (CH2), 60.7 (CH3), 58.4 (CH2), 56.2 (CH3), 56.1 (CH3); m/z (ES-API+) 520.0 ([M + Na]+).
Alcohol 19/benzyl azide Cycloadduct 28

This compound is novel.

Alcohol 19 (30 mg, 0.096 mmol) and benzyl azide 20 (13 mg, 12 μL, 0.096 mmol) were stirred in MeCN (0.6 mL) for 5 days, monitoring each day by TLC (0.16 M in each reagent). At the end of this time the solvent was removed under vacuum and the product purified by flash chromatography on silica gel (hexane : EtOAc, 7 : 3) to yield the product 28 as a white solid (40 mg, 0.093 mmol, 97%). TLC hexane : EtOAc, 7 : 3, silica, Rf 0.1; M.p. 126–129 °C; [found (ESI+): [M + Na] + 452.1579; C23H23N3NaO4 requires 452.1581; ʋmax (500 MHz, CDCl3) 8.52 (1H, d, J 5.6, NCH2), 2.85 (6H, s, N(CH3)2), 5.43 (2H, t, J 5.6, NCH3), 2.95 (2H, t, J 5.6, NCH3), 5.6, NCH2), 2.85 (6H, s, N(CH3)2). ʋc (126 MHz, CDCl3) 154.5, 153.3, 152.1, 141.5, 136.9, 136.1, 135.9, 134.7, 132.1, 130.5, 130.0, 129.9, 129.7, 129.3, 128.6, 124.3, 123.3, 122.7, 118.8, 115.3, 110.9, 87.7, 86.2, 63.7, 60.4, 55.9, 53.0, 47.3, 45.5, 42.6. m/z (ES-API+) 452.0 ([M + Na]+). The reaction was followed over time in a separate run using alcohol 19 (0.050 mmol) and benzyl azide (0.050 mmol) in CDCl3 (0.05 mL) ([(CH3), 54.8 (CH3), 51.9 (CH2), 50.9 (CH2). This compound is novel.

N-(2-Aminoethyl)-5-(dimethylamino)naphthalene-1-sulfonamide 34 (100 mg, 0.34 mmol) was added to aldehyde strained alkyne 35 (128 mg, 0.22 mmol, 66%). Mp 67–73 °C. [found (ESI) [M + H]+ 591.2609; C34H34N3O3S requires 591.2610; ʋmax 2962, 2928, 2868, 1536, 1454, 1315, 1182, 972 and 960 cm−1; ʋH (500 MHz, CDCl3) 7.38 (1H, t, J 7.5, ArH), washed with sat. aq. NaHCO3 (3 × 5 mL), and dried over MgSO4. Purification by column chromatography (silica; EtOAc/Hex: 20:80 → 50:50) afforded 35 as a waxy green solid (128 mg, 0.22 mmol, 66%).
This compound is novel.

To a solution of aldehyde 16 (100 mg, 0.340 mmol, 1.0 eq.) in DCM (22 mL) pyrrole (47 mg, 0.71 mmol, 2.1 eq.), TFA (3.8 mg, 34 µmol, 0.1 eq.) was added and the solution was stirred for 3 h. The solution was then washed with a saturated solution of NaHCO3 (20 mL) and brine (20 mL). The organic layer was then dried over MgSO4, which was subsequently removed by filtration, and the solvent evaporated. The residue was then dissolved in toluene (12.3 mL) and a suspension of DDQ (84 mg, 0.37 mmol, 1.1 eq.) in toluene (6 mL) was added. The mixture was then stirred for 1 h before TEA (141 mg, 1.4 mmol, 4.1 eq.) was added along with BF3·Et2O (290 mg, 2.04 mmol, 6.0 eq.) and the mixture was refluxed at 80 °C for 45 min. The mixture was then cooled to rt, before being filtered through a silica plug eluted with DCM. The resulting solution was then concentrated under vacuum to afford the crude product. The crude product was purified by flash column chromatography to afford the pure product 37 as an orange/green metallic solid (38 mg, 0.074 mmol, 22%). $R_f = 0.44$ (Hexane–EtOAc 3:1); (found [ESI]) [M + Na]+ 535.1354 $C_{26}H_{19}BF_2N_2NaO_3$ requires 535.1351; $\lambda_{\text{ex}}$ (CDCl3) 299 nm; $\lambda_{\text{em}}$ (CDCl3) 303 nm; $\epsilon$ (CDCl3) = 497 (58 563) nm.

### 2.4-Dimethyl BoDIPY Strained alkyne 37

This compound is novel.

To a solution of aldehyde 16 (100 mg, 0.340 mmol, 1.0 eq.) in DCM (22 mL), 2,4-dimethylpyrrole (67 mg, 0.71 mmol, 2.1 eq.), TFA (3.8 mg, 34 µmol, 0.1 eq.) was added and the solution was stirred for 3 h. The solution was then washed with a saturated solution of NaHCO3 (20 mL) and brine (20 mL). The organic layer was then dried over MgSO4, which was subsequently removed by filtration, and the solvent evaporated. The residue was then dissolved in toluene (12.3 mL) and a suspension of DDQ (84 mg, 0.37 mmol, 1.1 eq.) in toluene (6 mL) was added. The mixture was then stirred for 1 h before TEA (141 mg, 1.4 mmol, 4.1 eq.) was added along with BF3·Et2O (290 mg, 2.04 mmol, 6.0 eq.) and the mixture was refluxed at 80 °C for 45 min. The mixture was then cooled to rt, before being filtered through a silica plug eluted with DCM. The resulting solution was then concentrated under vacuum to afford the crude product. The crude product was purified by flash column chromatography to afford the pure product 38 as an orange/green metallic solid (42 mg, 0.089 mmol, 26%). $R_f = 0.55$ (DCM); (found [ESI]) [M + Na]+ 479.1351 $C_{25}H_{17}BF_2N_2NaO_3$ requires 479.1354; $\lambda_{\text{ex}}$ (CDCl3) 299 nm; $\lambda_{\text{em}}$ (CDCl3) 303 nm; $\epsilon$ (CDCl3) = 497 (58 563) nm.

### (Me, Et, Me) BoDIPY clicked product 39 and 40

These compounds are novel. We have not confirmed which regioisomer is which, however tentative assignments have been made; full details are in the ESI.†

To a solution of (Me, Et, Me) BoDIPY alkylne (28.4 mg, 0.05 mmol, 1 eq.) in CDCl3 (0.5 mL), benzylazide (0.56 mg, 5.2 µL, 0.05 mmol, 1 eq.) was added. The reaction was followed...
by $^1$H NMR. The solvent was then removed under vacuum to give the crude product. This was then purified by flash column chromatography (eluent EtOAc–Hexane gradient 1:1–4:1), to give the pure products 39 and 40 in a 1:1 ratio as two isomeric regioisomers A (first to elute) and B (second to elute).

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**Conflicts of interest**

There are no conflicts to declare.

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