Tetrahedron Letters 51 (2010) 3913–3917

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A modular approach to catalytic synthesis using a dual-functional linker for Click and Suzuki coupling reactions

James R. White [a], Gareth J. Price [a], Stefanie Schiffers [a], Paul R. Raithby [a], Pawel K. Plucinski [b], Christopher G. Frost [a,*]

[a] Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK
[b] Department of Chemical Engineering, University of Bath, Claverton Down, Bath BA2 7AY, UK

ARTICLE INFO

Article history:
Received 9 April 2010
Revised 4 May 2010
Accepted 21 May 2010
Available online 27 May 2010

ABSTRACT

The stable benzylazido-boronate ester **1** is presented as an example of a dual-functional linker that allows the synthetically valuable boronate motif to be *clicked* onto other molecules under mild conditions. The utility of the azido-boronate motif as a modular building block is demonstrated in the rapid synthesis of drug-like structures employing sequential catalytic azide–alkyne cycloaddition and Suzuki coupling reactions.

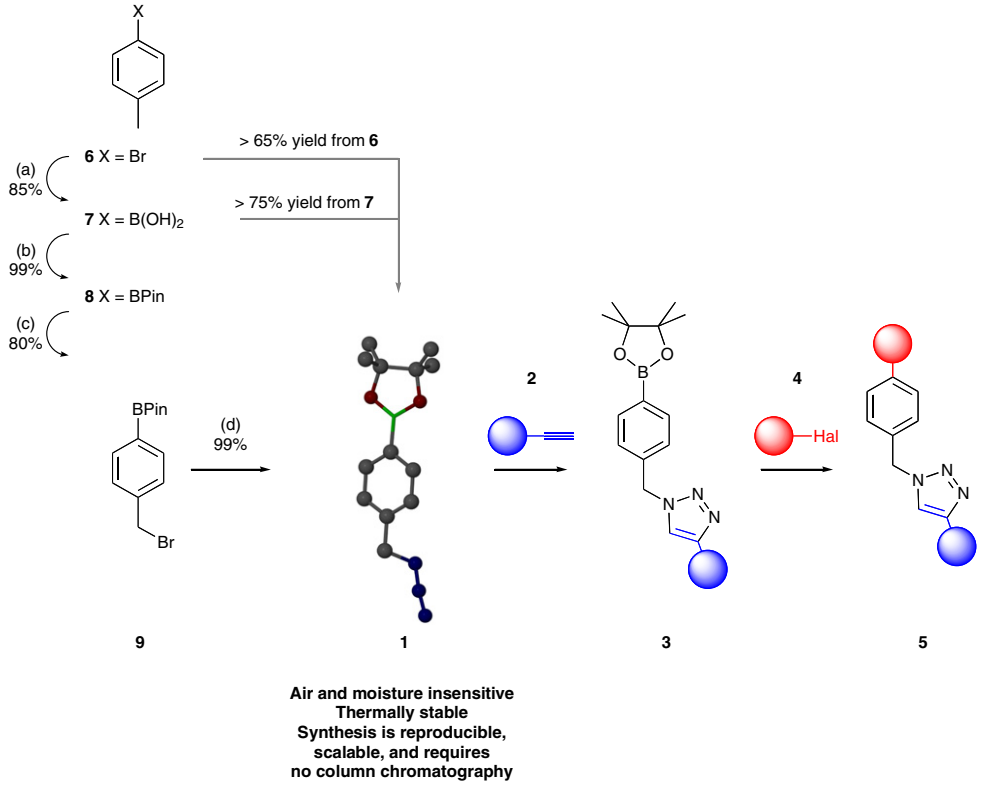
The construction of structures of increasing size and often corresponding complexity from modular components lies at the heart of not only synthetic chemistry but also the basis of many biological processes essential to life.[1] With this in mind, it is easy to see why robust synthetic manipulations, which allow chemospecific coupling of compounds containing other diverse motifs, attract such interest.[1b,c,2] An excellent example of this is the click-chemistry philosophy proposed by Sharpless et al., based on 'highly specific and reliable reactions' and a modular approach to tackling the synthesis of drug-like molecules.[1b] The reactions are typically air and water tolerant, high yielding and are straightforward in their execution. The significant growth of click-chemistry and in particular the copper-catalysed azide–alkyne cycloaddition reaction[3] (CuAAC) into the fields of macromolecular and surface science highlights the fundamental necessity for a core group of reproducible and broadly applicable reactions which may be employed across diverse disciplines of the physical sciences.[4] Many of the key features that make the CuAAC so popular are in fact shared with the Suzuki–Miyaura coupling. The organoboron derivatives employed frequently exhibit air and water stability at ambient temperature, show little toxicity when compared to other ubiquitous organometallics and allow a range of other synthetic manipulations to be performed in their presence.[5]

Traditionally, high temperatures were required for Suzuki couplings,[5a,6] however, more recent reports have demonstrated viable couplings at lower temperatures, wide substrate scope and the catalytic ability of palladium at exceptionally low loadings.[7] In many respects this makes organoboronates ideal partners in the CuAAC reaction methodology. In this Letter we present the synthesis of bench-stable, dual-functional linkers that incorporate azido-boronate functionality amenable to both CuAAC and Suzuki couplings (Scheme 1).[8]

As illustrated in Figure 1, a number of azido-boronate compounds have been described in the literature, for example, the synthesis of regioisomers of **10** by Fedorov et al.[9] However, the true potential of these materials in catalysis is only just starting to emerge. Vasil'ev and co-workers have noted Suzuki couplings with compound **11**[10] and Molander and Ham initially reported CuAAC reactions on analogues of **12**.[11] In 2009, Harrity and co-workers detailed an innovative route to access another novel motif, typified by **14**, formed via thermal-Huisgen cycloaddition.[12] In this case the assembled triazole units bear two sites for subsequent derivatisation, namely the TMS-triazole and boronate centres, thus increasing their synthetic scope. Indeed, this group has more recently reported the use of their substrates in the synthesis of a small compound library, further supporting the potential that this class of materials possess.[13] Very recently, Fedorov and co-workers employed **10** (and related compounds) in an elegant approach towards the synthesis of coumarin-type compounds.[14] Molander and co-workers have utilised alternative azide-bearing organotrifluoroborates such as **13** in catalysis. This useful compound is formed in situ via nucleophilic aromatic substitution using the azide anion.[15] It should be noted however that many of these compounds also have issues associated with their synthesis, purification, handling or storage. From observations in the respective publications and our own experience with the synthesis and handling of boronate derivatives, we envisaged that these issues could be addressed by informed design choices. We therefore selected **1** as an ideal candidate which could be accessed using a modification of the synthetic route employed by James and co-workers for the synthesis of novel fluorescent saccharide sensor **15**.[16] The benzyl

* Corresponding author. Tel.: +44 (0) 1225 386142; fax: +44 (0) 1225 386231.
E-mail address: c.g.frost@bath.ac.uk (C.G. Frost).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.104



Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) $(i\text{-PrO})_3B$, −78 °C to rt; (iii) H_2O; (b) pinacol, CH_2Cl_2, $MgSO_4$, rt; (c) NBS, cat. AIBN, MeCN, 90 °C; (d) 1.1 equiv NaN_3, EtOH, rt.

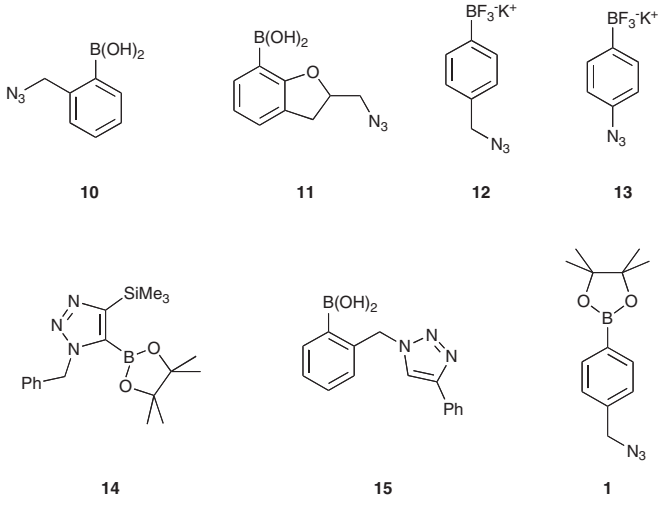


Figure 1. Representative examples of reported azido-boronates.

azide of **1**, easily formed from precursor **9**, would, after both coupling reactions, ultimately produce an inert benzyl-triazole core.[17] As it would be desirable to use a slight excess of azide to drive the substitution reaction, a pinacolboronate ester would be an ideal partner due to the high lipophilicity and inhibition of azide coordination at the boron centre it imparts.[5b,18] This combination should ensure high yields, with correspondingly simple removal of hazardous azide salts. After optimisation, we secured a route to **1** in over 75% isolated yield from commercially available boronic acid **7**.[19] The synthesis also proved robust and scalable, allowing multigram quantities of **1** to be produced, without the requirement for purification by column chromatography (Scheme 1). Most pleasingly of all, we found that **1** crystallised as a high-purity solid, ideal for easy handling and also allowing us to obtain a crystal structure (Fig. 2). Organoazides have been known to exhibit photolytic behaviour;[20] however, we were surprised to find that deliberate attempts at inducing photodegradation of **1**, using high intensity UV-light and monitoring the process in situ by single crystal X-ray diffraction, were totally unsuccessful.[21] Indeed, samples of **1** remained unchanged over periods of greater than nine months, even when stored open to the air; demonstrating a level of stability beyond what we expected. Though a *top-to-tail* arrangement of azide groups in the unit cell of the crystal was observed, the intermolecular azide–azide distance was not atypical,[22] suggesting that no abnormal stabilising interactions are responsible for this behaviour. The solubility profile of **1** is also impressive, being readily soluble in solvents with such diverse polarities as methanol and petroleum ether. This wide compatibility is particularly important due to the significant increases in polarity when converting parent azides into the corresponding triazoles.[1c] This allows **1** to be employed across a much broader polarity range than, for example, quaternised borates.[23]

We then proceeded with initial attempts at forming **3a** via the CuAAC of **1** and phenylacetylene (**2a**). At both ambient and subsequently elevated temperatures, low conversions were observed (Table 1, entries 1–3). These initial reactions did, however, demonstrate that exposure to reasonably high copper loadings, without attempts to preclude oxygen, had no detrimental effects on the boronate group of **1**. Whereas boronic acids could be anticipated to undergo side reactions,[18a] **1** only reacted at the azide substituent as desired. Consistent with the literature precedent an amine additive, in particular DIPEA, gave a significant improvement in reactivity (Table 1, entries 4–6).[4c]

The low excess of alkyne and short reaction times prompted us not to optimise the reaction conditions further, but to proceed with

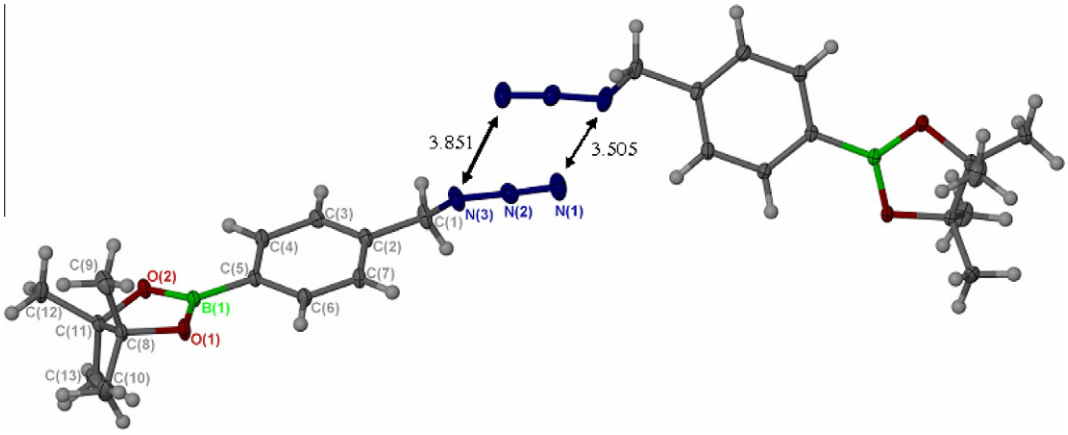
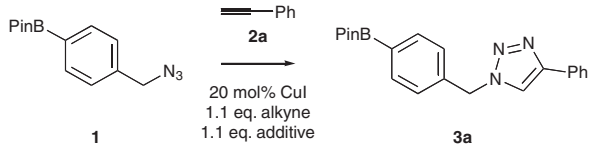


Figure 2. Crystal structure diagram of **1** showing intermolecular azide–azide configuration (distances in Å). The thermal ellipsoids are drawn at 50% probability. Structure deposited with the CCDC; entry number 747986.

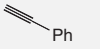
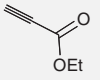
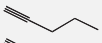
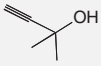
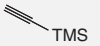
Table 1
Initial CuAAC reactivity of **1** with phenylacetylene (**2a**)[a]



Entry	Solvent	Additive	% Conversion[b]
1	H_2O	—	20[c]
2	1,4-Dioxane	—	20[c]
3	EtOH	—	12[c]
4	H_2O	Et_3N	56[d]
5	H_2O	DIPEA	93[d]
6	1:1 *t*-BuOH/H_2O[e]	DIPEA	93[d]

[a] All reactions performed in sealed tubes under air atmosphere using 0.50 mmol of **1** in 1.0 ml of solvent.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Reaction run at rt for 18 h, then at 60 °C for 6 h.
[d] Reaction run at 60 °C for 1 h.
[e] Used to aid mixing.

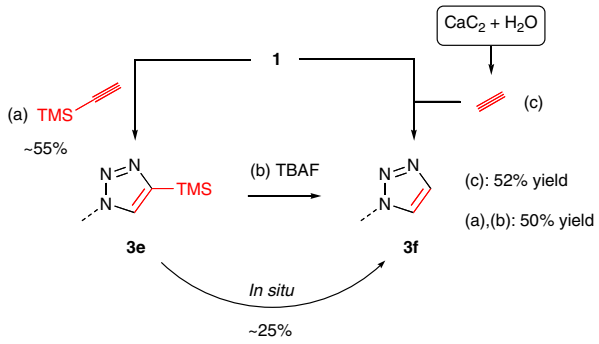
Table 2
CuAAC reactivity of **1** with selected terminal alkynes[a]

Entry	Alkyne		Product	% Yield[b]
1		**2a**	**3a**	72
2		**2a**	**3a**	95[c]
3		**2b**	**3b**	78
4		**2c**	**3c**	92
5		**2d**	**3d**	90
6		**2e**	**3e**	(30)[d]
7		**2f**	**3f**	52[e]

[a] All reactions performed in sealed tubes under air atmosphere using 1.0 mmol of **1** in 2.0 ml of 1:1 *t*-BuOH/H_2O as solvent.
[b] Isolated yields after purification.
[c] Performed on 3.0 mmol of **1** using 20 mol % $CuSO_4$/40 mol % sodium ascorbate, 24 h, rt, see Supplementary data for details.
[d] Using 2.0 equiv of **2e**, 2 h, 60 °C. ^{1}H NMR spectroscopic analysis revealed a mixture containing unreacted **1** (45%), **3e** (30%) and **3f** (25%).
[e] See Scheme 2.

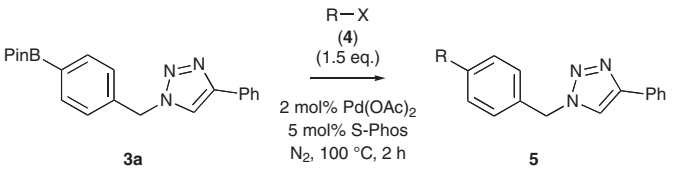
the reaction of **1** with a selection of representative terminal alkynes (Table 2). The only alkyne which exhibited particularly low reactivity was trimethylsilyl acetylene (**2e**) (Table 2, entry 6), which gave incomplete conversion into a mixture of **3e** and in situ-de-silylated **3f**.[24] Furthermore, **3e** exhibited lower crystallinity when compared with other 1,2,3-triazoles, such that it was not possible to separate from **1** by recrystallisation. Given these factors, we realised the potential that acetylene gas would have in giving direct access to mono-substituted 1,2,3-triazoles such as **3f**, which could otherwise be produced via uneconomic silyl deprotection of **3e** (Scheme 2).[25] Indeed Liang and co-workers reported the use of acetylene gas (**2f**) sourced from pressured cyclinders.[26] However, our approach was to generate discrete amounts of acetylene, formed upon contact of water with calcium carbide and introduced into the reaction solution via a cannula.[27] This route to 4*H*-1,2,3-triazoles proved more than competitive with that using trimethylsilyl acetylene (Table 2, entries 6 and 7; Scheme 2).

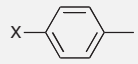
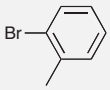
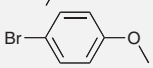
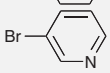
Subsequent Suzuki couplings using **3a** as a model substrate under typical conditions for the coupling of boronate esters were then investigated.[28] Pleasingly, a range of aryl and heteroaryl bromides all gave complete conversion into the corresponding products (Table 3, entries 3–7); the variations in yield being due principally to differences in the ease of purification.



Scheme 2. Alternative routes to mono-substituted triazole **3f**. Reagents and conditions: (a) (see Table 2, entry 6); (b) TBAF, THF, rt; (c) twice reacted for 1 h at 60 °C, after purging with acetylene; conditions otherwise as (a).[29]

Table 3
Suzuki coupling reactivity of **3a** with aryl- and heteroaryl halides[a]



Entry	Aryl halide		Product	% Yield
1		**4a**′ (X = Cl)	**5a**	54[b]
2		**4a**′	**5a**	81[c,d]
3		**4a** (X = Br)	**5a**	89[d]
4		**4b**	**5b**	99
5		**4c**	**5c**	99
6		**4d**	**5d**	82[d]
7		**4e**	**5e**	74[d]

[a] All reactions performed using 0.5 mmol of **3a**, 3.0 equiv of K_3PO_4 and 2.0 ml of 9:1 DMF/H_2O.
[b] 32% of unchanged **1** was also recovered.
[c] Reaction run at 100 °C for 5 h.
[d] Purification resulted in disproportionate attrition of the yield, though conversions were complete by ^1H NMR spectroscopy; see Supplementary data for details.

The use of the appropriate aryl chloride (Table 3, entry 1) in the synthesis of **5a** under the standard Suzuki coupling conditions gave a lower yield than the corresponding aryl bromide (Table 3, entry 3), though the majority of the unreacted boronate was recovered intact, exhibiting remarkable stability. Consequently, by extending the reaction time to five hours, a comparable yield to the aryl bromide was achieved (Table 3, entry 2).

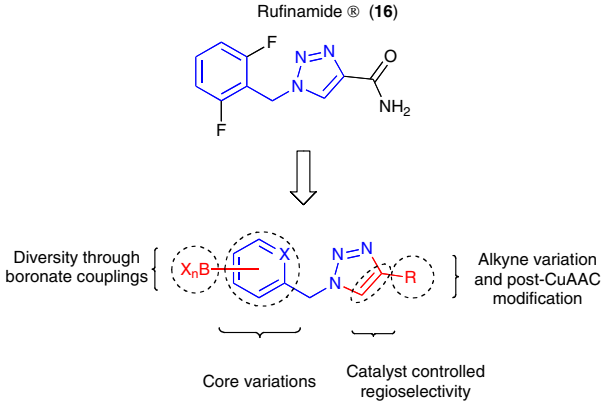
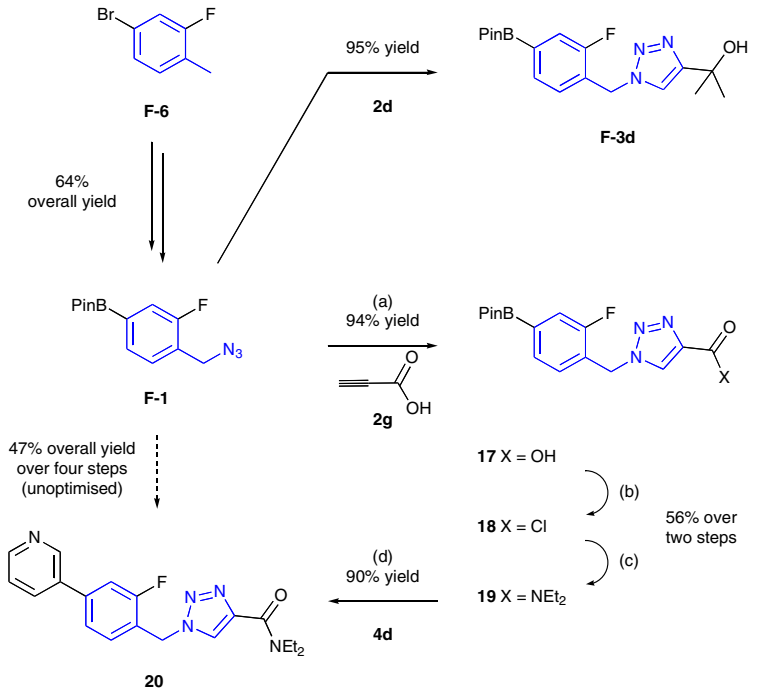


Figure 3. Analogues of **1** provide multiple points of synthetic divergence for building pharmacologically active compounds such as rufinamide® (**16**).

The rapid and divergent nature of this protocol suggests significant potential for use in drug discovery.[30] Here the wide availability of aryl and heteroaryl halides in particular allows a large number of products to be obtained from a single stable dual-functional starting material.[31] This is particularly relevant given the recent approval of rufinamide® (**16**) as an anti-epilepsy agent, which critically shares its benzyl-triazole core with **1** (Fig. 3).[32]

It can be envisaged that a small selection of varied cores could be employed to build large compound libraries, using a selection of robust and cost-attractive transformations (Fig. 3).

To demonstrate this we synthesised **F-1** (Scheme 3), which bears a single aryl-fluoro substituent. Compound **F-1** was prepared in a manner analogous to **1**, in 64% overall yield from **F-6** (see Supplementary data for details). To ascertain the CuAAC reactivity of **F-1** we subjected it to reaction with **2d** and with a 95% yield



Scheme 3. Proof-of-concept use of **F-1** as a synthetic building block for the preparation of 5*H*-rufinamide derivative **20**. Reagents and conditions: (a) 1.2 equiv **2g**, 1:1 *t*-BuOH/H_2O (2.0 ml), 10 mol % $Cu(OAc)_2$, 20 mol % sodium ascorbate, 18 h, rt; (b) oxalyl chloride, cat. DMF, CH_2Cl_2, 0 °C to rt, 18 h; then: (c) Et_2NH, CH_2Cl_2, 0–10 °C; (d) **19** (0.44 mmol scale), otherwise as Table 3, entry 6. Compound **F-3d** was synthesised in an analogous manner to **3d** (Table 2, entry 5).

obtained of **F-3d** found it to be equally amenable to this type of chemistry (compared with **3d**; Table 2, entry 5). We therefore set out to synthesise a proof-of-concept target, starting with the coupling of **F-1** with propiolic acid (**2g**), which gave the triazole-4-carboxylic acid **17** in 94% yield. Although we ideally aimed for a protected secondary amide synthesised in parallel to **F-1**, our initial attempts, though not exhaustive, were problematic and we therefore opted in this instance to incorporate a tertiary amide after the CuAAC. Pleasingly, *N,N*-diethylamide **19** was obtained in 56% yield in an unoptimised one-pot procedure from **17**. With this final intermediate in hand we subjected it to reaction with **4d** under the same Suzuki coupling conditions as used previously for **3a**; obtaining our target compound **20**, bearing a 3-pyridyl motif, in a respectable 90% yield. 5*H*-rufinamide derivative **20** was thus synthesised in a 47% overall yield in *four unoptimised* steps, starting from 1.0 mmol of azido-boronate **F-1**.

In conclusion, we have demonstrated that azido-boronate esters such as **1** have the potential to undergo sequential coupling reactions in high overall yield. The isolation and storage of **1** makes positive improvements to process safety by eliminating contamination from the azide anion, which is dangerously incompatible with a wide range of common solvents, metal salts and acids.[8] Finally, the successful synthesis of **20** demonstrates the potential these substrates possess for diversity-oriented synthesis of drug-like molecules. We are currently investigating alternative cores and further applications of these privileged structures.

Acknowledgements

We are grateful to the EPSRC for funding. Dr. Stephen Flower is thanked for helpful discussions.

Supplementary data

Supplementary data (experimental procedures, compound characterisation data, and X-ray crystal structure data for **1**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.104.

References and notes

1. (a) Cane, D. E.; Walsh, C. T.; Khosla, C. *Science* **1998**, *282*, 63–68; (b) Sharpless, K. B.; Finn, M. G.; Kolb, H. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (c) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137; (d) Boyle, P. M.; Silver, P. A. *J. R. Soc. Interface* **2009**, *6*, S535–S546.
2. Trost, B. M. *Science* **1985**, *227*, 908–916.
3. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
4. (a) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025; (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262; (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015; (d) Sumerlin, B. S.; Vogt, A. P. *Macromolecules* **2010**, *43*, 1–13.
5. (a) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51–65; (b)*Boronic Acids—Preparation, Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; (c) Kotha, S.; Lahiri, K. *Eur. J. Org. Chem.* **2007**, 1221–1236; (d) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658; (e) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.
6. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
7. (a) Bedford, R. B.; Nakamura, M.; Gower, N. J.; Haddow, M. F.; Hall, M. A.; Huwe, M.; Hashimoto, T.; Okopie, R. A. *Tetrahedron Lett.* **2009**, *50*, 6110–6111; (b) Torborga, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027–3043.
8. For selected discussions on the incompatibility, stability and safety of azides, see Refs. 3a and 1b; Conrow, R. E.; Dean, W. D. *Org. Process Res. Dev.* **2008**, *12*, 1285–1286.
9. Fedorov, A. Yu.; Shchepalov, A. A.; Boĺshakov, A. V.; Shavyrin, A. S.; Kurskii, Yu. A.; Finet, J. P.; Zelentsov, S. V. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 370–375.
10. Sviridov, S. I.; Vasil'ev, A. A.; Sergovskaya, N. L.; Chirskaya, M. V.; Shorshnev, S. V. *Tetrahedron* **2006**, *62*, 2639–2647.
11. Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2767–2770.
12. Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2009**, 436–438.
13. Huang, J.; Macdonald, S. J. F.; Cooper, A. W. J.; Fisher, G.; Harrity, J. P. A. *Tetrahedron Lett.* **2009**, *50*, 5539–5541.
14. Naumov, M. I.; Nuchev, A. V.; Sitnikov, N. S.; Malysheva, Y. B.; Shavyrin, A. S.; Beletskaya, I. P.; Gavryushin, A. E.; Combes, S.; Fedorov, A. Yu. *Synthesis* **2009**, 1673–1682.
15. Cho, Y. A.; Kim, D.-S.; Ahn, H. R.; Canturk, B.; Molander, G. A.; Ham, J. *Org. Lett.* **2009**, *11*, 4330–4333.
16. Scrafton, D. K.; Taylor, J. E.; Mahon, M. F.; Fossey, J. S.; James, T. D. *J. Org. Chem.* **2008**, *73*, 2871–2874.
17. Loren, J. C.; Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Synlett* **2005**, 2847–2850.
18. (a) Jin, S.; Choudhary, G.; Cheng, Y.; Dai, C.; Li, M. *Chem. Commun.* **2009**, 5251–5253; (b) Significant binding should reduce the rate of substitution, which was comparable when employing either **1** or 4-bromobenzyl bromide. ^{11}B NMR analysis was also consistent with this conclusion.
19. *p*-Tolylboronic acid (**7**) was synthesised as detailed, or purchased from Frontier Scientific Europe, product code T6078; see Supplementary data for full details.
20. Abbenante, G.; Le, G. T.; Fairlie, D. P. *Chem. Commun.* **2007**, 4501–4503.
21. After 3 h of irradiation (100 W Blak-Ray B100 UV lamp) the single-crystal X-ray structure was unchanged, further details are available in the Supplementary data.
22. (a) Párkányi, L.; Besenyei, G. *J. Mol. Struct.* **2004**, *691*, 97–106; (b) Chesterton, A. K. S.; Jenkinson, S. F.; Jones, N. A.; Fleet, G. W. J.; Watkin, D. J. *Acta Crystallogr., Sect. E* **2006**, *62*, o2983–o2985.
23. Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325.
24. For use of TMS-acetylene in CuAAC reactions and in situ de-silylation of the products, see: Fletcher, J. T.; Walz, S. E.; Keeney, M. E. *Tetrahedron Lett.* **2008**, *49*, 7030–7032.
25. For discussions on atom-economy and protecting groups, see: (a) Clark, J. H. *Green Chem.* **1999**, 1–8; (b) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404–408.
26. Wu, L.-Y.; Xie, Y.-X.; Chen, Z.-S.; Niu, Y.-N.; Liang, Y.-M. *Synlett* **2009**, 1453–1456.
27. Though no particular efforts to scrub any hydroxides from the stream were made, no significant detrimental effect on the boronate was observed. A similar procedure was recently reported: Jiang, Y.; Kuang, C.; Yang, Q. *Synlett* **2009**, 3163–3166.
28. Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.
29. Acetylene (produced from CaC_2 and H_2O) was used to saturate the reaction solution. The reaction was run for 1 h at 60 °C, cooled and the process repeated once more. Full details are available in the Supplementary data.
30. For background discussion, see: (a) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84; For exemplary examples of the CuAAC in this context, see: (b) Manetsch, R.; Krasinski, A.; Radic, Z.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2004**, *126*, 12809–12818; (c) Krasinski, A.; Radic, Z.; Manetsch, R.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 6686–6692.
31. See the discussion of aryl chlorides in: (a) Cai, C.; Rivera, N. R.; Balsells, J.; Sidler, R. R.; McWilliams, J. C.; Shultz, C. S.; Sun, Y. *Org. Lett.* **2006**, *8*, 5161; (b) Bunin, B. A. *Drug Discovery Today* **2003**, *8*, 823–826.
32. Wheless, J. W.; Vazquez, B. *Epilepsy Curr.* **2010**, *10*, 1–6.