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A direct route to triazole boronic esters and their application in the synthesis of small molecule arrays

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ABSTRACT

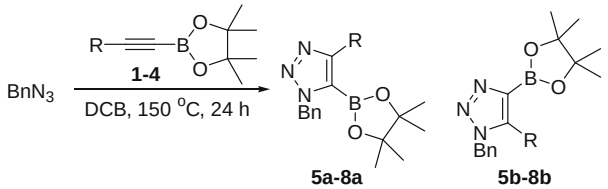
Alkynylboronates represent useful substrates for the direct synthesis of triazole boronic esters by their thermal cycloaddition with azides. A telescoped cycloaddition–cross-coupling protocol is reported and its employment in the synthesis of a small triazole array is disclosed.

Recent studies in our laboratories have focused on the development of thermal- and metal-mediated cycloaddition reactions of alkynylboronates for the synthesis of aromatic and heteroaromatic boronic esters.[1,2] A synthetically useful paradigm has emerged whereby benzene- and azine-based boronic esters can be accessed by cycloaddition–cycloreversion strategies,[3] whilst azole-based analogues are generated by direct cycloaddition.[4,5] In the context of this programme, we recently became interested in the synthesis of triazole boronic esters by a direct cycloaddition route.[6] The 1,2,3-triazole ring is regarded as an important pharmacophore in drug discovery research and is common amongst a plethora of compounds of biological significance.[7] We therefore wished to investigate the potential of the alkynylboronate cycloaddition concept to deliver a range of fully substituted triazole boronic esters, with a view to employing this chemistry in the synthesis of a small library of heterocycles using standard array platform technologies. We report herein the successful realisation of this idea.

Our preliminary goal was to establish the feasibility of the thermally promoted azide 1,3-dipolar cycloadditions with alkynylboronates.[8] Indeed, we were pleased to find that heating a mixture of benzyl azide and a small selection of boronate-substituted alkynes provided the corresponding triazoles in high yield (Table 1). To our surprise however, we observed significant differences in both the reaction regioselectivity and the product stabilities. Specifically, trimethylsilyl-substituted alkyne **1** underwent cycloaddition in high yield to provide **5a** as a single regioisomer. In contrast, phenylacetylene substrate **2** furnished two regioisomers **6a**, **b** with poor levels of selectivity. Nonetheless, the regioisomers were separable by chromatography and the regiochemical assignments of **6a, b** were made by HMBC NMR spectroscopy. On attempting to extend this chemistry to alkyl-substituted alkynes **3** (R = CH_2OMe) and **4** (R = Pr^n), we were surprised to find that the products were extremely unstable and could not be further purified by chromatography. However, the compounds were isolated as relatively clean crude mixtures in high yield. Unfortunately, once again, the regioselectivity was found to be rather disappointing.

These preliminary observations highlighted the potential instability of triazole boronic esters and this prompted us to explore the potential of in situ cross-coupling methods. Moreover, we were mindful that this particular goal complemented our ultimate aim of employing this technique in an array format. Accordingly, we investigated a telescoped cycloaddition–cross-coupling procedure for the synthesis and functionalisation of the unstable boronic esters **7a**, **b** and **8a**, **b**. As outlined in Scheme 1, we were pleased to find that performing the cycloaddition and subsequently cross-coupling the crude boronic ester intermediates with iodobenzene using Fu's protocol[9] provided the corresponding triazoles **9** and **10**. Moreover, these compounds were stable to chromatography

Table 1



Entry	R	Yield (**a**:**b**)
1[a]	Me_3Si; **1**	**5**; 84% (100:0)
2	Ph; **2**	**6**; 63% (2:3)
3	$MeOCH_2$; **3**	**7**; 99%[b,c]
4	Pr^n; **4**	**8**; 99%[b,c]

[a] The reaction was conducted at 110 °C.
[b] Yield of crude product.
[c] A regioselectivity of 3:2 was observed although regiochemical assignments were not made in this case.

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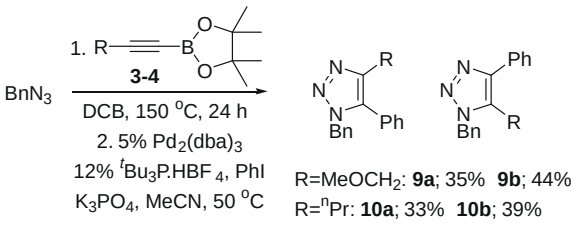


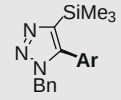
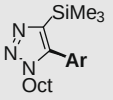
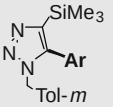
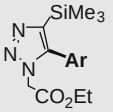
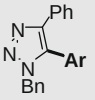
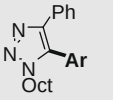
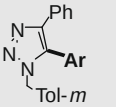
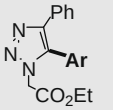
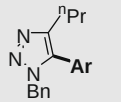
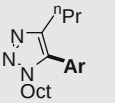
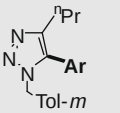
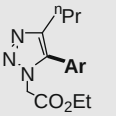
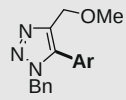
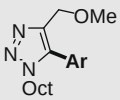
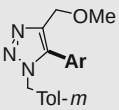
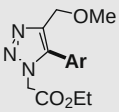
Scheme 1.

and the regioisomers could be isolated as separate compounds in good overall yield.

Having established that the cycloaddition and cross-coupling processes could be successfully telescoped, we next demonstrated that this chemistry could be exploited to make available a small library of triazoles, thereby making the cycloaddition–coupling technique of potential utility in the discovery of small bioactive compounds. Specifically, we decided to prepare a 48-membered library of triazoles with variable substitution at all 3 positions of the triazole ring. Accordingly, we prepared a 4×4×3 component array consisting of azides bearing alkyl, benzyl and 2-ethanoate groups, alkynylboronates consisting of silyl, phenyl, alkyl and propargylic ether groups and electron neutral, rich and deficient cross-coupling partners. The general scheme and structures of the cycloaddition substrates are highlighted in Figure 1.

The cycloadditions were carried out in 1,2-dichlorobenzene at 150 °C in reaction tubes using a Radleys GreenHouse™ parallel synthesiser. After 24 hours, each crude cycloadduct was portioned between three reaction tubes and a mixture of Pd_2dba_3 (5 mol %), $^tBu_3P{\cdot}HBF_4$ (12 mol %), K_3PO_4 and aryl iodide in MeCN was added. After stirring at 50 °C overnight, the crude reaction mixture was purified using a Flashmaster platform on a 10 g ISOLUTE® flash column to provide the corresponding triazole products. In the event, the 4×4×3 array provided 30 members which had purities ⩾90%. Upon closer inspection, it is clear that the less effective members of the array are largely those compounds that originate from the cross-coupling of 4-iodoanisole. Whilst it is not the purpose of this study to optimise the cross-coupling reaction of this particular aryl halide, we would expect that catalyst screening

Table 2

	a	b	c	d
A	 Ar:Ph; 53% (95%) Ar:*p*-MeOC$_6$H$_4$; 40% (70%) Ar:*p*-NO$_2$C$_6$H$_4$; 37% (50%)	 Ar:Ph; 32% (95%) Ar:*p*-MeOC$_6$H$_4$; 29% (50%) Ar:*p*-NO$_2$C$_6$H$_4$; 23% (20%)	 Ar:Ph; 39% (95%) Ar:*p*-MeOC$_6$H$_4$; --[b] Ar:*p*-NO$_2$C$_6$H$_4$; 37% (95%)	 Ar:Ph; 28% (95%) Ar:*p*-MeOC$_6$H$_4$; 47% (20%) Ar:*p*-NO$_2$C$_6$H$_4$; 30% (95%)
B	 Ar:Ph; 26% (95%) Ar:*p*-MeOC$_6$H$_4$; --[b] Ar:*p*-NO$_2$C$_6$H$_4$; 15% (90%)	 Ar:Ph; 22% (95%) Ar:*p*-MeOC$_6$H$_4$; 23% (30%) Ar:*p*-NO$_2$C$_6$H$_4$; 18% (90%) 25% (90%)[c]	 Ar:Ph; 19% (90%) Ar:*p*-MeOC$_6$H$_4$; 18% (30%) Ar:*p*-NO$_2$C$_6$H$_4$; 32% (60%)	 Ar:Ph; 30% (95%) Ar:*p*-MeOC$_6$H$_4$; 14% (95%) Ar:*p*-NO$_2$C$_6$H$_4$; 21% (50%)
C	 Ar:Ph; 20% (95%) 17% (95%)[c] Ar:*p*-MeOC$_6$H$_4$; 33% (60%)[d] Ar:*p*-NO$_2$C$_6$H$_4$; 12% (95%)	 Ar:Ph;16% (95%) 18% (90%)[c] Ar:*p*-MeOC$_6$H$_4$; 45% (60%)[d] Ar:*p*-NO$_2$C$_6$H$_4$; 16% (95%) 14% (95%)[c]	 Ar:Ph; 15% (95%) 24% (95%)[c] Ar:*p*-MeOC$_6$H$_4$; 37% (60%)[d] Ar:*p*-NO$_2$C$_6$H$_4$; 16% (95%) 22% (40%)[c]	 Ar:Ph; 27% (95%)[d] Ar:*p*-MeOC$_6$H$_4$; 26% (85%)[d] Ar:*p*-NO$_2$C$_6$H$_4$; 21% (95%) 23% (95%)[c]
D	 Ar:Ph;21% (95%) 25% (95%)[c] Ar:*p*-MeOC$_6$H$_4$; 23% (95%) 19% (90%)[c] Ar:*p*-NO$_2$C$_6$H$_4$; 43% (85%)[d]	 Ar:Ph; --[b] Ar:*p*-MeOC$_6$H$_4$; 11% (95%) 27% (40%)[c] Ar:*p*-NO$_2$C$_6$H$_4$; 13% (95%) 16% (95%)[c]	 Ar:Ph; 10% (95%) 27% (80%)[c] Ar:*p*-MeOC$_6$H$_4$; 15% (95%) 19% (95%)[c] Ar:*p*-NO$_2$C$_6$H$_4$; 22% (95%) 30% (95%)[c]	 Ar:Ph; 20% (95%) 24% (95%)[c] Ar:*p*-MeOC$_6$H$_4$; 16% (90%) 15% (90%)[c] Ar:*p*-NO$_2$C$_6$H$_4$; 27% (95%) 22% (95%)[c]

[a] Compound purities indicated in parentheses, as judged by LC–MS and NMR spectroscopy.
[b] The desired compounds were not isolated in this case.
[c] Yield (purity) of separated regioisomers. Regiochemical assignment was not carried out.
[d] Yield (purity) of inseparable regioisomeric mixtures.

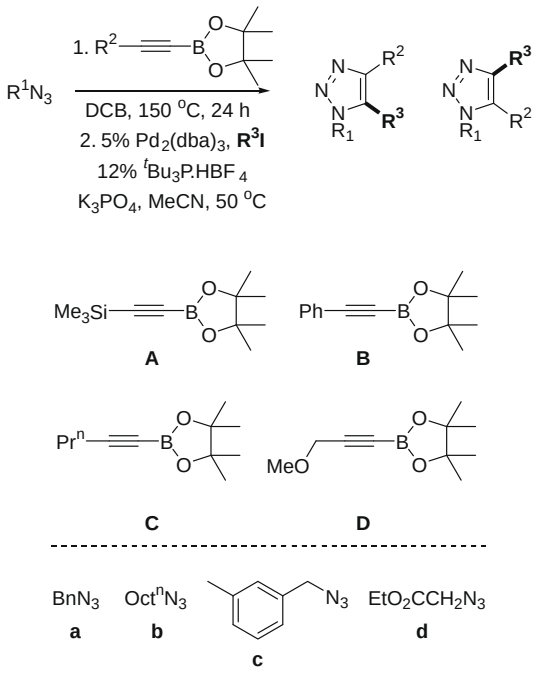


Figure 1.

would ultimately overcome this issue. Significantly however, there are no such trends with respect to the azide/alkynylboronate combinations, suggesting that there is potential for these cycloadditions to be widely applied on the array platform.[10] Moreover, the yield would likely be generally higher if any given analogue was repeated as a single reaction (compare yields of **9a, b** in Scheme 1 with array grid point **D**×**a**×Ph in Table 1 and **10a**, **b** with grid point **C**×**a** ×Ph) (Table 2).

In summary, we have reported a direct route to novel triazole boronic esters by the thermal cycloaddition of alkynylboronates and azides. Alkynes bearing a range of alkyl/aryl groups undergo cycloaddition in good yield but with poor regiocontrol. In sharp contrast, the trimethylsilyl-substituted alkynes react with a range of azides to provide the corresponding triazoles in high yield and with excellent regiocontrol. Furthermore, the power of this chemistry to prepare libraries of triazoles using standard protocols for the assembly of small molecule arrays has been exemplified.

Acknowledgements

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Supplementary data

Supplementary data (synthetic procedures, ^{1}H and ^{13}C NMR spectra of all compounds and LC–MS spectra of compounds listed in Table 2) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.085.

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10. The presence of regioisomers ultimately provides >48 compounds and these were generally separable by LC–MS. In some cases both regioisomers could not be isolated in sufficient yield and only a single compound is noted where appropriate. Nonetheless, the solution phase studies outlined herein suggest that all processes should give rise to an approximately equal ratio of regioisomers, except in the case of the trimethylsilyl alkynylboronate **1**.