A cycloaddition route to novel triazole boronic esters†

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The [3 + 2] cycloaddition of alkynylboronates and azides provides a direct route to novel triazole boronic esters, the regioselectivity of this process and functionalisation of the heterocycle products is described.

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.[1] From a synthetic standpoint, these compounds were traditionally accessed by thermal 1,3-dipolar cycloadditions of azides with alkynes.[2] The emergence of the 'click' chemistry concept has however resulted in significant advances in this field and mild, efficient metal catalyzed variants for both terminal- and internal alkyne substrates are now available.[3] Therefore, the recognition of the triazole motif as both a pharmacophore and a 'solid keystone'[4] for the union of molecular entities prompted us to explore the possibility of developing new functionalised variants of these compounds for further organic synthesis. Specifically, we envisaged the synthesis of triazoles bearing appropriate substituents at C-4 and C-5 that would allow these intermediates to be elaborated to new and diverse chemical entities through a series of modular functional group interconversion events. Of the many possibilities that could be envisaged, we felt that a scaffold bearing a boronic acid derivative and a silyl substituent would represent an attractive target; the former functional group enjoys a rich array of synthetic applications[5] which we felt could be carried out without compromising the latter. Moreover, the silyl group could be later employed as a useful synthetic handle in its own right (Fig. 1).

To our surprise, a search of the literature failed to uncover any examples of triazole boronic acid derivatives. Our recent interests in the employment of alkynylboronates in pericyclic reactions[6,7] prompted us to consider the use of a [3 + 2] cycloaddition reaction of these compounds with azides to construct triazole boronic esters. We report herein the employment of this strategy to prepare novel triazole scaffolds and demonstrate the synthetic applicability of these intermediates.

We began our studies by exploring the use of traditional thermal and metal catalysed[8] processes in an effort to uncover suitable conditions for the assembly of triazole boronic ester compounds. We opted to study the cycloaddition of readily available benzyl azide with TMS-substituted alkynylboronate **1**[9] and as outlined in Scheme 1, we were delighted to find that

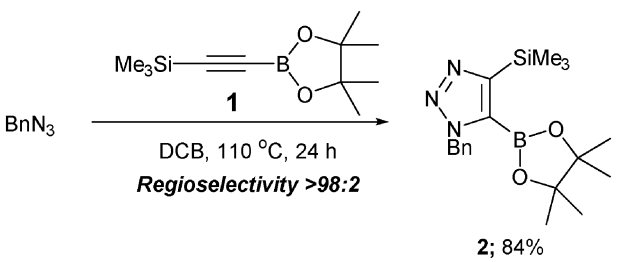
Fig. 1 Molecular triazole scaffold design.

the thermal cycloaddition provided the desired triazole boronic ester cycloadduct **2** in high yield. *Moreover, only a single regioisomer of cycloadduct was observed.*[10] We found this process to proceed with high efficiency in a range of non-polar solvents (toluene, xylenes, mesitylene), in contrast, polar solvents such as dioxane, nitrobenzene and DMF provided significantly lower product yields and complex reaction mixtures. We also took the opportunity to explore the use of Ru-catalysts to accelerate this reaction,[8] unfortunately $Cp^*RuCl(PPh_3)_2$ failed to promote cycloaddition and product **2** was not observed in this case.

We next turned our attention to exploring the scope of azide substrates that would undergo cycloaddition with alkyne **1**, our results are shown in Table 1. We were pleased to find that this process could be extended to substituted benzyl azides with similar yields and regioselectivities (entries 1, 2), and that aryl and alkyl azides performed equally well, albeit over longer reaction times (entries 3, 4). Finally, α-azidoester provided **7** in high yield (entry 5) however, $TMSN_3$ failed to provide the corresponding cycloadduct under these conditions (entry 6).

Having confirmed the potential of the azide cycloaddition chemistry to generate the novel triazole boronic ester intermediates, we next investigated the validity of our proposed functionalisation of these compounds. We began by exploring the Pd-catalysed cross-coupling of the boronic ester moiety, and our results are shown in Scheme 2. We decided to employ the conditions of Netherton and Fu[11] and were pleased to find that the cross-coupling proceeded smoothly for a series of aryl iodides.

With a view to exploring the potential to employ the triazole cycloadducts as the halide partner in cross-coupling reactions, we attempted to convert the boronate to the corresponding chloride and bromide. As outlined in Scheme 3, we were



Scheme 1 Alkynylboronate cycloaddition.

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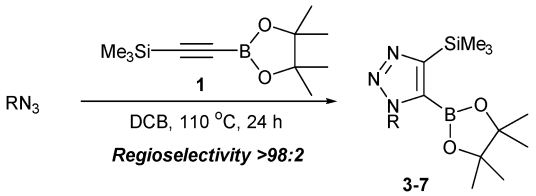
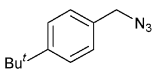
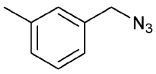
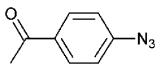
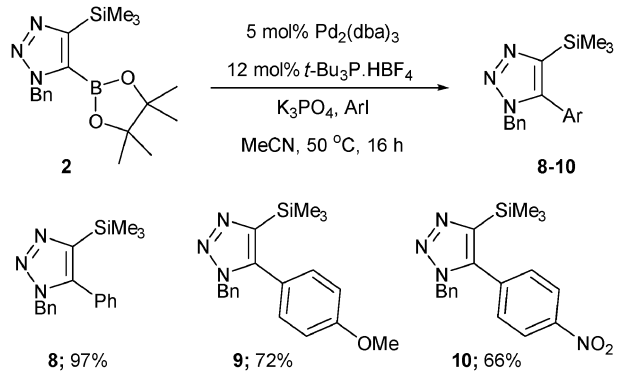
Table 1 Scope of the alkynylboronate/azide cycloaddition

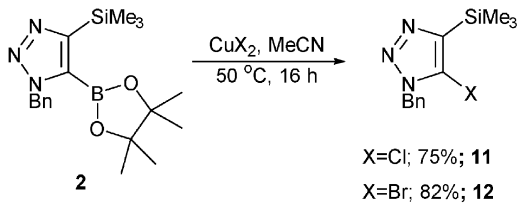


Entry	Azide	Yield (%)
1		**3**; 69
2		**4**; 73
3[a]		**5**; 65
4[a]	*n*-OctN$_3$	**6**; 68
5[a]	EtO$_2$CCH$_2$N$_3$	**7**; 75
6	TMSN$_3$	0

[a] Reaction run over 48 h.



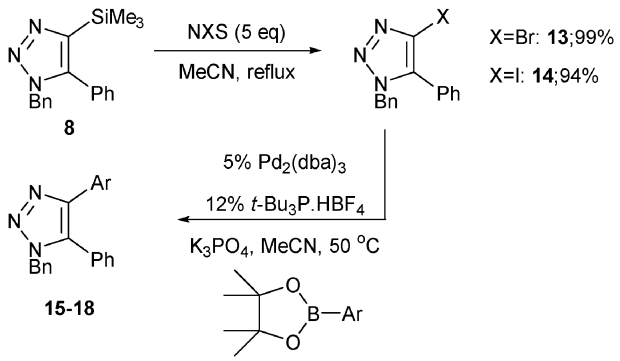
Scheme 2 Suzuki coupling reactions.



Scheme 3 Boronate–halogen exchange.

pleased to find that simply heating **2** in the presence of the appropriate copper(II) halide provided the corresponding products **11** and **12** in good yield.[12]

Our next objective was to exploit the trimethylsilyl group as a synthetic handle. Specifically, we chose to convert this group into the corresponding bromide and iodide, this was readily achieved with compound **8** through the use of the appropriate



Scheme 4 Silyl–halogen exchange and cross-coupling.

Table 2 Cross coupling reactions of **13** and **14**

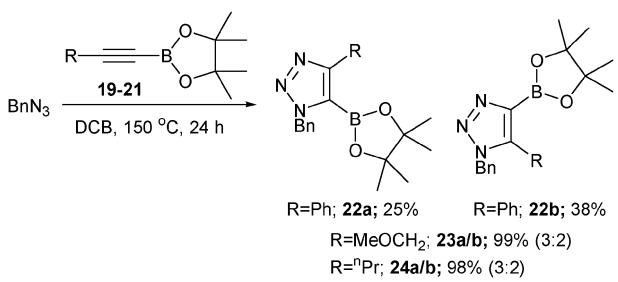
Entry	X	ArB(pin)	Yield (%)
1	I	4-ClC$_6$H$_4$B(pin)	**15**; 75
2	I	3-MeOC$_6$H$_4$B(pin)	**16**; 65
3	I	3-O$_2$NC$_6$H$_4$B(pin)	**17**; 70
4	I	4-Me$_2$NC$_6$H$_4$B(pin)	**18**; 68
5	Br[a]	3-O$_2$NC$_6$H$_4$B(pin)	**17**; 59
6	Br[a]	4-Me$_2$NC$_6$H$_4$B(pin)	**18**; 72

[a] Reactions run with 5 mol% $PdCl_2(PPh_3)_2$, Cs_2CO_3 in refluxing dioxane.

N-halosuccinimide. Unsurprisingly, these compounds could then be readily elaborated by subsequent Suzuki coupling reactions. Notably, the high regioselectivity provided by the alkynylboronate cycloaddition combined with the site-specific cross-coupling reactions allows access to a range of 4,5-diaryl triazoles *with reliable and controllable incorporation of the aryl groups at specific positions on the aryl ring* (Scheme 4 and Table 2).

Having demonstrated that a triazole scaffold bearing trimethylsilyl and boronate moieties could be orthogonally functionalised *via* cross-coupling reactions, we decided to examine the cycloaddition of a selection of alternative alkynylboronates and our results are depicted in Scheme 5. Phenylacetylene substrate **19** underwent cycloaddition to provide two regioisomers **22a**/**b** as a seperable mixture in good overall yield. On attempting to extend this to alkyl substituted alkynes **20** (R = CH_2OMe) and **21** (R = ^{n}Pr) we were surprised to find that the products were extremely unstable and could not be further purified by chromatography, although they were isolated as clean crude mixtures in high yield.[13]

In conclusion, we have developed a direct route to novel triazole boronic esters *via* thermal [3 + 2] cycloadditions of



Scheme 5 Alternative alkynylboronate cycloadditions.

azides and alkynylboronates. Trimethylsilyl-substituted alkynes undergo highly regioselective cycloaddition and the corresponding products can be manipulated *via* functionalisation of the boronate and the TMS-groups. The chemistry can be extended to include other alkynylboronates although regioselectivities appear to be significantly lower. Mechanistic studies on this reaction and the application of this chemistry for the synthesis of heterocycle arrays is underway and will be reported in due course.

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