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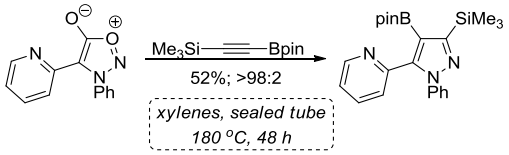
A Mild and Regiospecific Synthesis of Pyrazoleboranes

*Andrew W. Brown, Júlia Comas-Barceló and Joseph P.A. Harrity**

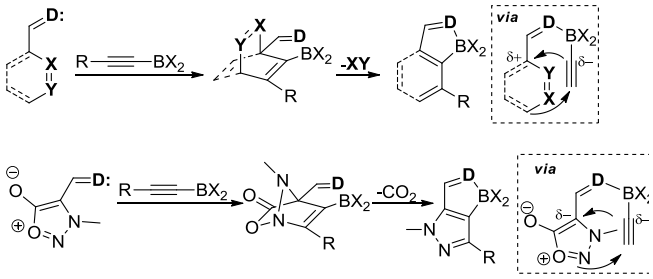
Pyrazoles are commonly employed in the discovery of pharmaceuticals and as crop protection agents.[1] Therefore, methods that allow these compounds to be readily prepared and functionalized are of significant value. However, synthetic approaches to these diazoles can be non-trivial and often result in the formation of isomeric mixtures.[2] Dipolar cycloaddition strategies offer a convenient way to access complex pyrazoles from simple substrates, and this approach is widely used. In this context, the [4 + 2] cycloaddition/retro-cycloaddition of alkynes and sydnones can be particularly effective, as unlike most dipolar reagents, sydnones are bench stable compounds that can be easily generated and stored under ambient conditions for long periods.[3]

Despite widespread interest in the utilization of sydnones for pyrazole synthesis,[4] significant challenges persist with respect to the reaction conditions. Indeed, the synthesis of fully-substituted pyrazoles *via* the reaction of unsymmetrical internal alkynes and 4-substituted sydnones is currently very limited, with relatively few examples, all of which require high reaction temperatures, long reaction times and which often deliver poor reaction regiocontrol.[5] Studies in our group have focused on the cycloaddition of sydnones with alkynyl boronic esters to address this limitation.[6] However, while good regiocontrol can be achieved in some cases, the reactions require temperatures >140 °C over extended reaction times (>24 h). A representative example that illustrates this point is shown in Scheme 1. Attempts to prepare bioactive pyridylpyrazoles[7] by cycloaddition/cross-coupling methods were hampered by low yields encountered during the key cycloaddition step.



Scheme 1. Synthesis of fully substituted pyrazoles by sydnone cycloadditions.

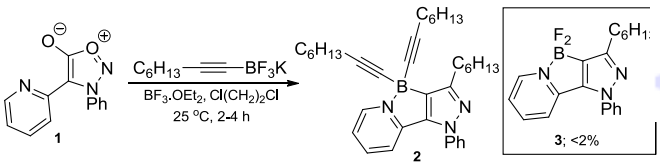
Substrate directed reactions offer an enticing opportunity to control reaction selectivity whilst significantly enhancing reaction rate.[8] In this regard, we have shown that alkynylboranes[9] promote the Diels-Alder reaction of electron deficient 6-membered ring dienes through the formation of a temporary tether. A number of interesting issues become apparent if one envisages the implementation of this strategy with sydnones. Specifically, (i) cycloaddition would require bond formation between two electron rich centers rather than complementary charges and (ii) the initia cycloadduct and final products would engender higher ring strai (Scheme 2). These challenges prompted us to explore the directe cycloaddition reactions of sydnones, and we report herein that thi strategy does offer access to fully-substituted pyrazoles unde unprecedented mild cycloaddition conditions with complet regiocontrol.



Scheme 2. Directed cycloaddition strategy and potential challenges.

We began our investigations by studying the cycloadditio reaction of 4-pyridylsydnone **1** and the alkynyl trifluoroborat derived from 1-octyne. Preliminary experiments showed that the us of 3 equivalents each of alkyne and Lewis acid provided th corresponding pyrazole under ambient conditions and within 3 h i 54% yield (Table 1, Entry 1). A particularly surprising feature of th reaction was that we only observed dialkynylborane **2** rather tha the expected difluoroborane **3**. Reducing the equivalents of Lewi acid had no noticeable effect on reaction conversion (Entry 2), an increasing reaction time to 24 h or steadily increasing the number

Table 1. Preliminary cycloaddition studies and optimization.



Entry	Equiv. BF_3	Equiv. alkyne	Conversion[a,b]
1	3.0	3.0	65% (54%)
2	1.1	3.0	65%
3	1.1	5.0	65%
4	2.0	5.0	100% (100%)

[a] Conversion estimated by 400 MHz ^{1}H NMR spectroscopy. [b] Isolated yields in parenthesis.

equivalents of alkyne also failed to improve conversion to pyrazole (Entry 3). As the reaction formally requires a 3:1 stoichiometry of

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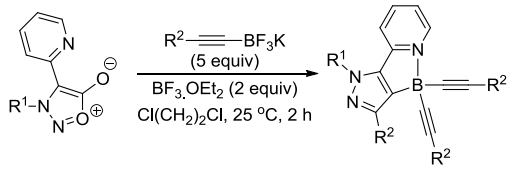
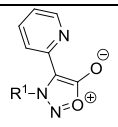
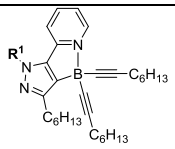
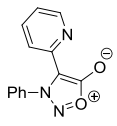
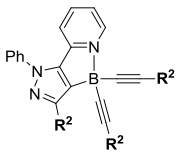
alkyne:BF_3·OEt_2 for complete conversion to **2**, it is perhaps unsurprising that increasing the number of equivalents of alkyne but not Lewis acid did not affect conversion. However, it is notable that this variation in stoichiometry did not lead to other borane-containing pyrazoles (ie mono- or di-fluoroboranes) either. Finally, increasing the equivalents of Lewis acid in the presence of 5 equivalents of trifluoroborate salt provided a significant improvement in conversion, allowing the isolation of pyrazole **2** in quantitative yield after 2 hours (Entry 4). This study therefore confirmed that fully-substituted pyrazoles could be accessed from sydnones within a few hours under ambient conditions for the first time. This result represents a significant rate acceleration in these reactions, and offers a mild and regiocontrolled means for accessing functionalized pyrazoles.

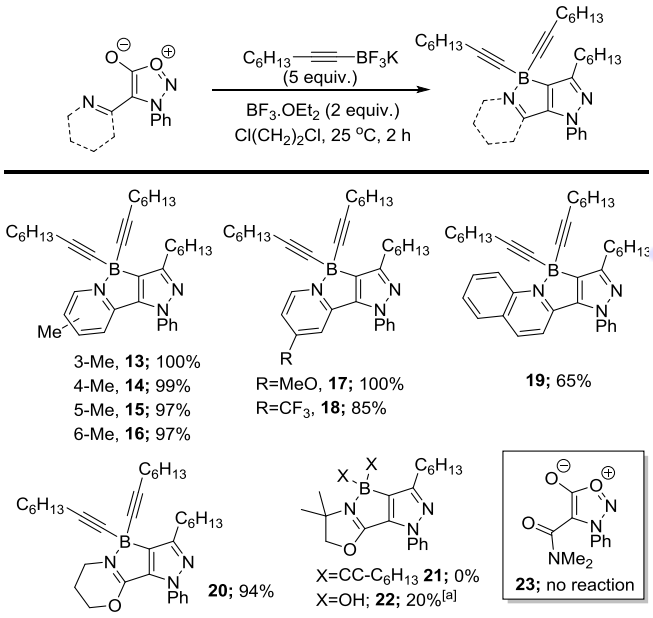
With optimal conditions in hand, we turned our attention to investigating the reaction scope (Table 2). Beginning with the nature of the sydnone *N*-substituent, we were pleased to find that both aromatic and aliphatic groups were tolerated, providing the corresponding pyrazoles **4-7** in high yield (entries 1-4). This methodology is therefore especially well suited to the cycloaddition of *N*-alkyl sydnones, which are typically less stable and less reactive than the *N*-aryl analogs and often perform poorly in cycloadditions.[10] To further demonstrate the versatility of the chemistry, the cycloaddition scope with respect to the alkynyl trifluoroborate salts was undertaken (entries 5-9). We found the reaction to be tolerant of a selection of substituent types including aryl, alkenyl, *tert*-alkyl, silyl and the corresponding terminal alkyne. The regiochemistry of formation of **9** is especially noteworthy as the 1,4,5-trisubstituted pyrazole boronate substitution pattern complements the natural 1,3,5-substitution observed in thermally promoted reactions of sydnones and terminal alkynylboronates.[4]

Table 2. Pyrazole synthesis scope.



Entry[a]	Sydnone	R^1, R^2	Product	Yield
1		4-FC_6H_4, C_6H_{13}		**4;** 85%
2		4-$MeOC_6H_4$, C_6H_{13}		**5;** 99%
3		Me, C_6H_{13}		**6;** 76%
4		Bn, C_6H_{13}		**7;** 70%
5		Ph, Ph		**8;** 100%
6		Ph, H		**9;** 78%
7		Ph, *t*-Bu		**10;** 81%
8		Ph, C(Me)=CH_2		**11;** 72%
9		Ph, $SiMe_3$		**12;** 61%

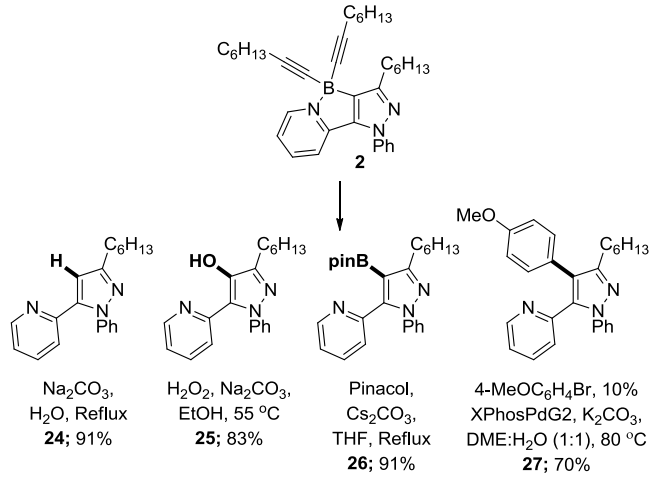
Finally, we explored the effect of the directing group on the reaction (Scheme 3). Gratifyingly, incorporation of a methyl group at all positions on the pyridine ring did not have a significant effect on reactivity and boranes **13-16** were all formed in high yield. Both electron donating and electron withdrawing groups positioned *para* to the pyridine nitrogen were tolerated, and the reaction was successfully extended to include a quinoline and an oxazine directing group, all of which afforded the corresponding pyrazoles **17-20** in excellent yield. In contrast, the oxazoline substituted sydnone did not afford the expected cycloadduct **21**. In this case, the borane appeared to be sensitive towards protodeborylation such that the alkyne moieties were cleaved upon workup and purification to deliver the corresponding boronic acid **22** which was isolated in low yield. Finally, we were surprised to find that amide **23** did not promote cycloadditions as this had previously proven to be a rather general directing group.[9]



Scheme 3. Directing group scope. [a] Reaction conducted over 4 h.

The regiochemistry of the reaction was unambiguously confirmed by X-ray crystallography in the case of pyrazole **8**,[11] and other substrates were assigned by analogy. The crystal structure confirmed the existence of a bonding interaction between the pyridine nitrogen and boron.

After demonstrating the versatility of the chemistry in accessing a broad library of pyrazole dialkynylboranes, we sought to demonstrate that the dialkynylborane motif could be used as handle for functionalization. To the best of our knowledge, the reactivity of



Scheme 4. Functionalization of dialkynylboranes.

this unusual motif has never been investigated. We first sought conditions for protodeboronation. Pleasingly, heating **2** in THF/H_2O in the presence of sodium carbonate furnished **24** in excellent yield (Scheme 4). We next turned our attention to oxidation. Gratifyingly, gentle heating of **2** with hydrogen peroxide afforded phenol **25** in good yield. We were also pleased to find that heating **2** with pinacol and caesium carbonate furnished the pinacol ester **26** in excellent yield, even when carried out on 0.5 g scale. Finally, we found **2** to be a rather demanding substrate for Suzuki-Miyaura coupling. However, the use of the 2nd generation XPhos precatalyst successfully promoted formation of cross-coupled product **27** using 4-bromoanisole.

Overall therefore, the experimentally observed directed cycloaddition reaction of sydnones and alkynylboranes was found to proceed under mild conditions and in high yields. A number of unexpected observations were made during the course of these studies; i) the strategy is successful for a number of pyridine based directing groups; ii) directing group ring size may be important; whilst 1,3-oxazines are effective, the corresponding 1,3-oxazolines and oxazoles are poor directing groups; iii) amides do not promote the cycloaddition process; iv) the products are generated as dialkynylboranes with no trace of the corresponding difluoroboranes. The products are probably formed via disproportionation of the in situ generated alkynyldifluoroborane followed by cycloaddition,[9d] although the lack of further disproportionation to difluoroboranes is unexpected. In order to understand the surprising differences observed in this study, both theoretical and mechanistic investigations have been undertaken and these will be reported elsewhere.

In conclusion, sydnones bearing pyridines and related azines at *C*4 undergo rapid cycloaddition with alkynylboranes to generate pyrazoleboranes with complete control of regioselectivity. These reactions proceed under ambient conditions, demonstrating unprecedented reactivity for the [4 + 2] cycloaddition of sydnones with simple alkynes. The pyrazoleboranes undergo typical organoboron functionalization reactions such as oxidation and cross-coupling, confirming the value of these products for organic synthesis.

Experimental Section

Typical cycloaddition procedure as exemplified by the formation of **8**: to a suspension of **1** (50 mg, 0.21 mmol) and potassium(1-phenylethyn-2-yl)triflouroborate (218 mg, 1.05 mmol) in dichloroethane (1 mL, 0.2 M) under an atmosphere of nitrogen at 25 ^oC was added a solution of $BF_3.OEt_2$ (60 mg, 0.42 mmol) in dichloroethane (1 mL, 0.4 M). The reaction was stirred for 2 hours at 25 ^oC before brine was added. The resulting mixture was extracted with dichloromethane and the combined organic layers dried over $MgSO_4$, filtered through a short pad of celite® and concentrated *in vacuo*. Flash silica chromatography (gradient starting with 100% 40-60 petroleum ether and ending with 40% ethyl acetate in 40-60 petroleum ether) afforded **8** as a tan solid (107 mg, 100%). M.p.: 246-248 °C (dec.); ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.23 (6H, m), 7.29-7.54 (10H, m), 7.59 (2H, t, *J* = 8.5 Hz), 7.65-7.72 (2H, m), 7.90-7.99 (1H, m), 8.39 (2H, dd, *J* = 8.0, 1.0 Hz), 8.96-9.05 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 96.5, 98.8 (b), 117.5, 122.3, 125.0, 125.1, 127.1, 127.3, 127.9, 128.0, 128.6, 128.7, 129.7, 131.9, 133.8, 137.1 (b), 139.8, 142.0, 143.5, 145.9, 146.9, 152.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ -10.0; FTIR: ν_{max} 3216 (s), 2262 (w), 2178 (w), 1623 (m), 1597 (m), 1488 (s), 1441 (s), 1195 (m), 986 (m), 919 (m); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{36}H_{25}{}^{11}BN_3$: 510.2142. Found: 510.2166.

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[11] CCDC 1453893 contains the supplementary crystallographic data for this compound. This data is provided free of charge by the Cambridge Crystallographic Data Centre.

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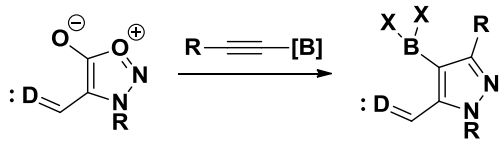
A Mild and Regiospecific Synthesis of Pyrazoleboranes



Thermal Cycloaddition	Directed Approach
☒ *High temperature (>140 °C)*	☑ *Ambient conditions*
☒ *Reaction time (> 24 h)*	☑ *Complete in 2 h*
☒ *Variable regioselectivity*	☑ *High yields*
	☑ *Regiospecific*
	☑ *Functionalizable scaffolds*

Go direct! Alkynylboranes show unprecedented reactivity in their [4 + 2] cycloaddition of sydnones offering access to fully substituted pyrazoles within a few hours at room temperature. This method delivers synthetically valuable pyrazoleboranes with complete control of regioselectivity, and these intermediates can be further elaborated through functionalization of the C-B bond.

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