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Cycloaddition reactions between dicyclohexylboron azide and alkynes†

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The room temperature 1,3-dipolar cycloaddition reactions of the boron azide, Cy_2BN_3 with the electron-poor acetylenes $RCO_2C{\equiv}CCO_2R$, $EtC{\equiv}CCOMe$ and $HC{\equiv}CP(=O)Ph_2$ afforded new 1,2,3-triazoles. In the case of $RCO_2C{\equiv}CCO_2R$, a new macrocyclic product was isolated with loss of the R group.

Click chemistry is a powerful synthetic reaction in organic chemistry which allows the rapid assembly of complex organic compounds.[1] Click reactions generate products in high yields with relatively few by-products and support a wide range of substituents and have seen widespread applications in drug synthesis, material science, nanotechnology and polymers *inter alia*.[2] One example of click chemistry is the azide–alkyne cycloaddition which selectively gives 1,2,3-triazoles which are present in many pharmaceuticals, particularly antifungal drugs.[3] However, the thermal Huisgen 1,3-dipolar cycloaddition of alkynes with azides requires elevated temperatures in order to complete the reaction which often results in a mixture of regio-isomers.[4] For example, the reaction between methyl azide and propyne has a high activation barrier of 25–26 kcal mol^{-1}.[5] To overcome this problem, a Cu or Ru catalyst is often employed in a metal-catalyzed Azide–Alkyne Cycloaddition (CuAAC or RuAAC respectively) offering rate enhancements of up to 10^7 times with respect to the uncatalysed process.[5–7] In the case of CuAAC this rate enhancement is thought to be brought about by the formation of a Cu acetylide intermediate and as a result only terminal alkynes can be used, however in RuAAC both terminal and internal alkynes can partake in the reaction which proceeds *via* a ruthenacycle intermediate.[7,8]

Only a handful of boron azide compounds of the type R_2BN_3 (R = alkyl or aryl) have been reported previously[9] and, although triazole derivatives of boron have been reported[10] the chemistry of boron azides and, in particular, their application in cycloaddition chemistry is very rare; currently, the only example is limited to the recent work by Curran *et al.*[11] on the cycloaddition chemistry of the electron-rich NHC-boryl azide reactions with electron-poor alkynes, alkenes and nitriles to give NHC-boryl triazoles, triazolidines, and tetrazoles respectively.

Herein, we explore the ability of the boron azide, Cy_2BN_3 (**1**) to undergo click reactions with acetylenes under ambient conditions. The boron azide **1** was conveniently prepared from the 1 : 1 stoichiometric reaction of Cy_2BCl with Me_3SiN_3. Removal of the Me_3SiCl by-product *in vacuo* afforded pure **1** in high yields (>90%) as a colourless oil.[12] The ^{11}B NMR spectrum displayed a resonance at δ = 61 ppm. The azide **1** was found to be thermally unstable decomposing with release of N_2 above 55 °C.

The first series of reactions explored were those involving the reactions of Cy_2BN_3 with acetylenes RC≡CH (R = Ph, *p*-tol, 4-^{t}BuPh, $SiMe_3$). However, initial attempts proved unsuccessful at room temperature with no reaction observed by ^1H and ^{11}B NMR spectroscopy even after one week. Raising the temperature to 50 °C exhibited no evident effect on the reaction by NMR spectroscopy, whereas more elevated temperatures promoted N_2 release from the mixture and decomposition of the boron azide. The lack of reactivity of **1** prompted us to utilise more reactive acetylenes bearing a lower energy LUMO. The room temperature stoichiometric reactions of **1** with the electron poor acetylenes $EtC{\equiv}CCOMe$ and $Ph_2P(=O)C{\equiv}CH$ cleanly led to the products **2** and **3** in moderate recovered yields (Scheme 1). The synthesis of **2** appears to give the 1,4-regio-isomer selectively as the only product on the basis of *in situ* NMR spectra with no peaks evident due to the 1,5-product. In the case of **3**, both the 1,4- and 1,5-products are formed in a 3 : 2 ratio as seen in the crude ^1H NMR spectrum before recrystallisation. The smaller proportion of the 1,5-regio-isomer is presumably due to the steric conflict between the cyclohexyl groups on boron and the phenyl groups on phosphorus.

Crystals of **2** suitable for X-ray diffraction were grown from a saturated solution of **2** in CH_2Cl_2 at −35 °C and crystals of **3** were formed by the slow evaporation of the solvent from a

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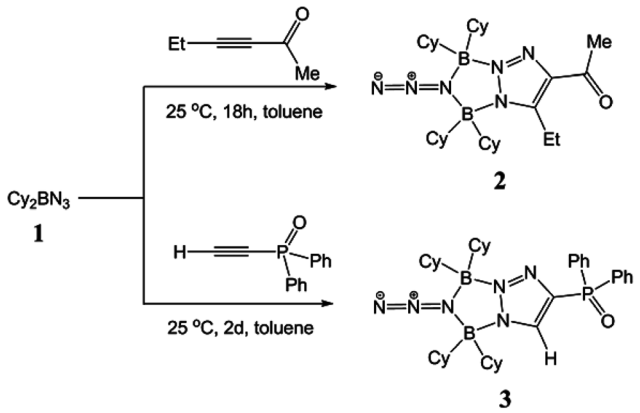
†Electronic supplementary information (ESI) available: Experimental details, NMR data, DFT calculations and details of the crystal structure determination of **2**, **3** and **5**. CCDC 918102–918104. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3dt00068k



Scheme 1 Synthesis of compounds **2** and **3**.

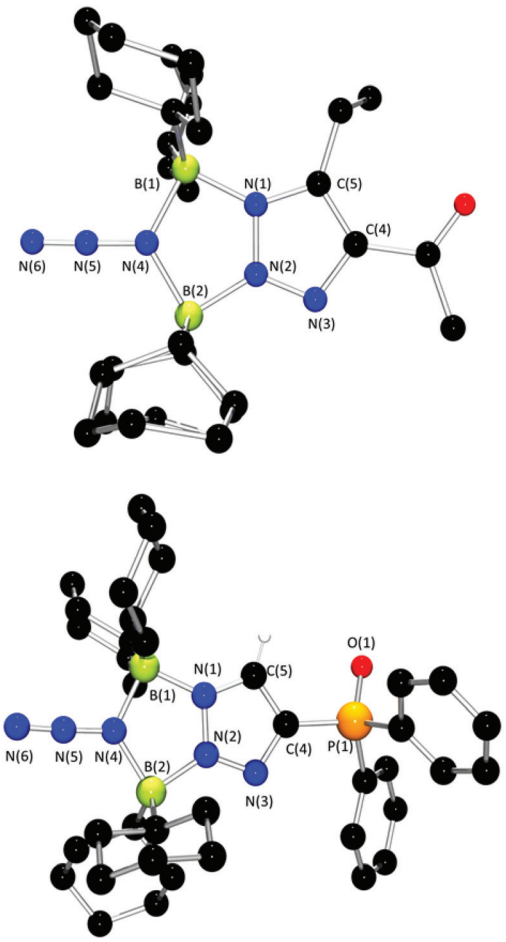


Fig. 1 POV-ray depiction of **2** (top) and **3** (bottom). Hydrogen atoms are omitted for clarity.

saturated solution of **3** in toluene. Both **2** and **3** crystallise in the triclinic space group $P\bar{1}$ with one molecule in the asymmetric unit (Fig. 1).‡ Previously, boron azides bearing bulky substituents have been shown to be dimeric in solution and the solid state.[13] Thus the structures of both **2** and **3** can been viewed as arising from the 1,3-dipolar cycloaddition of the alkyne with one azide group of the $[Cy_2BN_3]_2$ molecule.

Table 1 Geometric parameters for the triazole rings in **2**, **3** and **5** in relation to previously reported triazole structures found on the CSD

Compound	Average[a]	2	3	5
Bond length/Å				
N(1)–N(2)	1.348	1.352(2)	1.346(3)	1.332(2)
N(2)–N(3)	1.436	1.302(2)	1.311(3)	1.333(3)
N(3)–C(4)	1.383	1.350(3)	1.358(3)	1.351(3)
C(5)–N(1)	1.371	1.349(3)	1.333(3)	1.343(3)
C(4)–C(5)	1.400	1.395(3)	1.380(3)	1.370(3)

[a] Search of the CSD.

In both cases the fused $C_2N_4B_2$ bicyclic frameworks are essentially planar (max. deviation from planarity 0.054 Å for **2** and 0.084 Å for **3**) with the unreacted azide moiety lying slightly out of the plane of the heterocyclic ring; the plane of the BN_3B moiety forming an angle to the heterocyclic B_2N_2 plane of 2.62° and 8.15° for **2** and **3** respectively. However there are some marked variations in N–N, C–N and C–C bond lengths in relation to previously reported 1,2,3-triazoles (Table 1); the bonding in triazoles typically exhibits C–N bond lengths consistent with a delocalised bonding pattern comparable to pyridine (C···N at 1.34 Å) rather than imines or amines (C=N at 1.28 Å and C–N at 1.47 Å). With the exception of the N(1)–N(2) bond in **2** the structures of **2** and **3** exhibit shorter bonds than in conventional triazoles with a particularly marked shortening of N(2)–N(3). The nature of the bonding within the fused heterocycle was further probed by DFT (B3LYP/6-311G*+) calculations and NBO studies (see ESI†). The NBO analysis based on the gas-phase geometry-optimised structure revealed substantial delocalisation and a strongly polar structure with considerable bis-imine character within the triazole ring (Fig. 2).

NMR spectroscopic studies of **2** and **3** show that each species is *intact* in solution with no indication of dissociation of the coordinating Cy_2BN_3 moiety. Even the addition of coordinating solvents such as THF or pyridine did not promote the dissociation of the Cy_2BN_3 group or azide (*vide infra*), suggesting that the bicyclic frameworks of **2** and **3** are robust and that the remaining azide moiety is deactivated towards a further cycloaddition reaction. The lack of reactivity of **1** with acetylenes bearing mildly electron-withdrawing groups indicates that the acetylene–azide reaction occurs through interaction of the HOMO of the azide with the LUMO of the alkyne. However the DFT calculations indicate that the HOMO of both **1** and **2** are of similar energy and both of π-non-bonding character. This suggests that the lack of reactivity may be due to greater steric shielding (by the cyclohexyl groups) of the azide

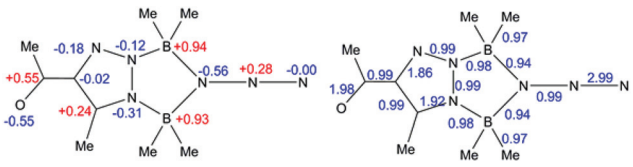
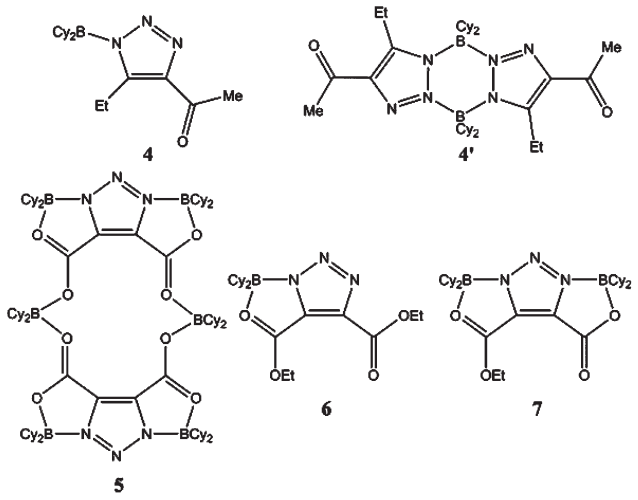


Fig. 2 NBO partial charges (left) and bond orders (right) for **2** based on the DFT-optimised (B3LYP/6-311G*+) geometry.



Scheme 2 Structures of **4–7**.

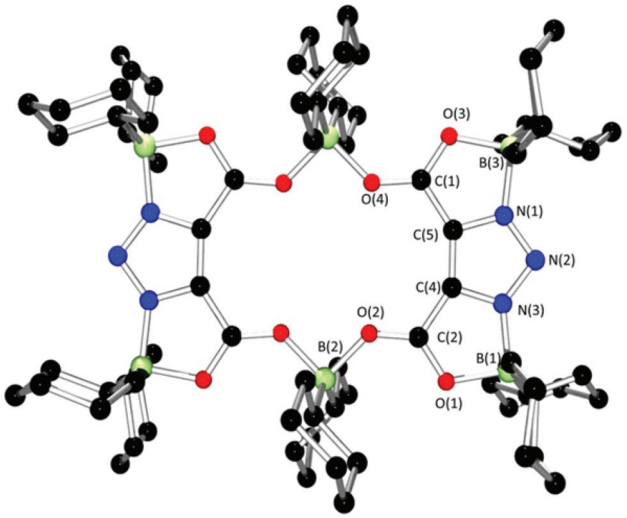


Fig. 3 POV-ray depiction of the dimeric structure of **5**. Hydrogen atoms are omitted for clarity.

functionality in **2** than in **1**, consistent with the increase in ring size from a 4 to a 5-membered ring.

Interestingly, the high-resolution DART (and ESI+) mass spectrometry on **2**, did not show the presence of **2** but instead displayed peaks at m/z = 316.3 and 631.5 corresponding to $[\mathbf{4} + H]^+$ and the dimer $[\mathbf{4}' + H]^+$ (Scheme 2) with the correct isotope distribution pattern, suggesting that heating **2** may result in the release of Cy_2BN_3 to generate **4** which could dimerise to form **4′**. Formation of **4′** may also occur *via* cycloaddition of a further equivalent of alkyne with **2**. In order to investigate this reactivity, a solution of **2** and excess EtC≡COMe in d_8-toluene was heated for 6 h at 80 °C. The resulting *in situ* ^{1}H spectrum showed that a different product was formed in high yield which we tentatively assign to the click product **4** or **4′** (Scheme 2), though crystals have proved elusive to date. In this context, the formation of the mono-cycloaddition product **2** can be viewed as a stable intermediate on the way to the formation of the double cycloaddition product **4′**.

Subsequent investigations to assess further the effects of the electron withdrawing substituents on the acetylene, led us to examine the 1 : 1 stoichiometric reactions of **1** with $RCO_2C{\equiv}CCO_2R$ (R = Me, Et, ^{t}Bu) in toluene. In all cases the product was unexpectedly found to be the macrocycle **5**. Storage of a saturated toluene solution at room temperature or at −35 °C afforded colourless cubic crystals of **5** suitable for X-ray diffraction (Fig. 3). Changing the reaction stoichiometry (**1** : alkyne = 3 : 2) also afforded **5** but in lower isolated yields.

Compound **5** crystallises in the triclinic space group $P\bar{1}$.‡ The structure comprises a central $C_8O_4B_2$ macrocycle located about a crystallographic inversion centre with two sets of three crystallographically related fused 5-membered rings (Fig. 3). The hepta-cyclic framework is essentially planar (max. deviation 0.145 Å). Whilst the 14-membered macrocycle offers a potential O_4-donor set for metal coordination, the cyclohexyl groups appear to sterically hinder coordination (see later). Compound **5** was found to be insoluble in all common organic solvents (pentane, hexane, diethyl ether, toluene, THF, CH_2Cl_2) and even the more polar coordinating solvents (water, alcohols, DMSO and DMF). Owing to the insoluble nature of **5**, solution state characterisation by either NMR or mass spectroscopy proved impossible but the composition of **5** was additionally confirmed by elemental analysis and solid state NMR spectroscopy.

The loss of alkyl groups in these cycloaddition reactions is unprecedented. Indeed, in the equivalent reaction reported by Curran,[11] there was no evidence for loss of alkyl groups during the cycloaddition of the NHC-stabilised boron azide with $RCO_2C{\equiv}CCO_2R$ (R = Me or Et). However, the recurrent formation of **5** indicates that **5** is not only a thermodynamic sink but that this appears a preferred outcome for these ester derivatives and would appear to suggest that the O-donor is capable of displacing azide from the boron centre. Notably the ketone EtC≡CCOMe does not react in the same manner nor does addition of THF to **2** or **3** reveal any evident reactivity. Formation of the triazole ring would indicate that the boron azide initially undergoes the expected cycloaddition with the alkyne but the ester carbonyl appears then to undergo intramolecular coordination to the boron centre with concomitant elimination of the alkyl group from the ester.

In an attempt to determine the fate of the R group the 1 : 1 and 1 : 3 [$RCO_2C{\equiv}CCO_2R$ (R = Me, Et):azide] stoichiometric reactions were followed by *in situ* ^{1}H NMR spectroscopy. Although the ^{1}H NMR spectra are complicated by the presence of the cyclohexyl groups, throughout these experiments three signals corresponding to two compounds in the ^{1}H NMR spectrum were always observed due to the ethyl (or methyl) groups. We assign these resonances tentatively to the model intermediates **6** and **7** in the formation of the macrocycle **5**. Since the reactions were performed under rigorously anhydrous conditions the loss of RO^- by ester hydrolysis can be excluded. It is plausible that RN_3 could be formed in the reaction, although this was not observed presumably due to its high volatility.

The macrocycle **5** was found to be remarkably robust being air and water stable. Indeed, attempted alkylation reactions with MeI, BnCl and EtBr at N(2) in the triazole ring and attempts to encapsulate a Li^+ cation within the macrocyclic core have, to date, proved unsuccessful.

In conclusion studies of the reactivity of the boron azide Cy_2BN_3 with acetylenes RC≡CR reveal that electron-donating substituents show no reactivity suggesting the dominant interaction can be considered as a normal electron-demand cycloaddition, *i.e.* the dominant orbital interaction is between the HOMO of the 4π 1,3-dipole (azide) and the LUMO of the 2π dipolarophile (alkyne). The use of electron deficient acetylenes results in a lowering of the LUMO leading to a cycloaddition reaction forming the expected triazole. Unlike other 'click' reactions of this type, these reactions proceed rapidly at room temperature in the absence of a catalyst. The boron azide (**1**) is considered to be dimeric in solution and the second azide appears deactivated and NMR evidence for cycloaddition at this second site only appears to occur at elevated temperatures. In the case of $RCO_2C{\equiv}CCO_2R$ an unprecedented rearrangement occurs generating an incredibly stable macrocyclic product contain 7 fused rings *via* elimination of the alkyl (R) groups. Perhaps most importantly this work demonstrates fine-tuning of the electronics of the acetylene is key to the modulation of the reactivity and the nature of the products formed.

Acknowledgements

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Notes and references

‡Crystal data for **2**, **3** and **5** were collected on a Bruker APEX-II diffractometer. Structures were solved by direct methods and refined by full matrix least squares based on F^2 using the SHELXTL program package.[14]

Crystal data for **2**: $C_{30}H_{52}B_2N_6O$, M = 534.40, triclinic $P\bar{1}$, a = 9.1297(4), b = 9.2734(4), c = 19.1974(8) Å, α = 79.937(2), β = 80.421(2), γ = 73.642(2)°, V = 1523.67(11) Å^3, μ(Mo-Kα) = 0.71, T = 150(2) K, Z = 2, D_c = 1.165 Mg m^{-3}, F(000) = 584, independent reflections 5345 (R_{int} = 0.026). Two of the four cyclohexyl groups were found to be disordered over two sites and refined with 50 : 50 disorder and a constrained geometry R_1 ($I > 2\sigma(I)$) = 0.055, wR_2 (all data) = 0.136, S = 1.192 (all data).

Crystal data for **3**: $C_{38}H_{55}B_2N_6OP$, M = 664.47, triclinic $P\bar{1}$, a = 9.5954(13), b = 11.2785(15), c = 17.351(2) Å, α = 97.004(4), β = 97.151(4), γ = 101.004(5)°, V = 1808.3(4) Å^3, μ(Mo-Kα) = 0.116, T = 150(2) K, Z = 2, D_c = 1.220 Mg m^{-3}, F(000) = 716, independent reflections 6296 (R_{int} = 0.033). R_1 ($I > 2\sigma(I)$) = 0.058, wR_2 (all data) = 0.123, S = 1.121 (all data).

Crystal data for **5**: $C_{80}H_{132}B_6N_6O_8$, M = 1370.78, triclinic $P\bar{1}$, a = 10.3184(10), b = 14.6317(15), c = 15.0290(16) Å, α = 69.271(5), β = 88.761(5), γ = 75.300(5)°, V = 2046.8(4) Å^3, μ(Mo-Kα) = 0.069, T = 150(2) K, Z = 1, D_c = 1.112 Mg m^{-3}, F(000) = 748, independent reflections 7186 (R_{int} = 0.040). R_1 ($I > 2\sigma(I)$) = 0.070, wR_2 (all data) = 0.161, S = 1.210 (all data).

1 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
2 J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, 2007, **28**, 15; J. F. Lutz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1018; M. V. Gil, M. J. Arévalo and O. López, *Synthesis*, 2007, 1589.
3 R. S. Bohacek, C. McMartin and W. C. Guida, *Med. Res. Rev.*, 1996, **16**, 3.
4 K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 863.
5 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.
6 For examples of CuAAC see: C. Spiteri and J. E. Moses, *Angew. Chem., Int. Ed.*, 2010, **49**, 31; V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; V. D. Bock, H. Hiemstra and J. H. Van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51; M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302; L. Liang and D. Astruc, *Coord. Chem. Rev.*, 2011, **255**, 2933.
7 For examples of RuAAC see: B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923; L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998; L. K. Rasmussen, B. C. Boren and V. V. Fokin, *Org. Lett.*, 2007, **9**, 5337.
8 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.
9 P. I. Paetzold, *Z. Anorg. Allg. Chem.*, 1966, **345**, 79; H. U. Meier, P. I. Paetzold and E. Schroeder, *Chem. Ber.*, 1984, **117**, 1954; P. I. Paetzold, P. P. Habereder and R. Muellbauer, *J. Organomet. Chem.*, 1967, **7**, 45; J. Muenster, P. I. Paetzold, E. Schroeder, H. Schwan and T. von Bennigsen-Mackiewicz, *Z. Anorg. Allg. Chem.*, 2004, **630**, 2641; P. I. Paetzold, *Chem. Ber.*, 1983, **116**, 1531; S. Biswas, H. F. Bettinger and I. M. Oppel, *Inorg. Chem.*, 2010, **49**, 449.
10 K. Niedenzu and K. R. Woodrum, *Inorg. Chem.*, 1989, **28**, 4022; C. P. Brock, A. L. Companion, L. D. Kock and K. Niedenzu, *Inorg. Chem.*, 1991, **30**, 184.
11 E. Merling, V. Lamm, S. J. Geib, E. Lacôte and D. P. Curran, *Org. Lett.*, 2012, **14**, 2690.
12 Covalent azides are potentially explosive and reactions were performed on small scale behind blast shields. $Cy_2BN_3{\cdot}Py$ has been synthesised previously from the reaction on (Cy)-(Ph)BCl and NaN_3 in pyridine. See: Gmelin Handbook: B: B-Verb.4, **8**, 260.
13 W. Fraenk, T. M. Klapötke, B. Krumm, P. Mayer, H. Nöth, H. Piotrowski and M. Suter, *J. Fluorine Chem.*, 2001, **112**, 73; W. Fraenk, T. M. Klapötke, B. Krumm and P. Mayer, *Chem. Commun.*, 2000, 667.
14 *SHELXTL*, Bruker AXS, Madison, WI, USA.

