ROYAL SOCIETY
OF CHEMISTRY

COMMUNICATION

Check for updates

Formal (2+2) ring expansion prevails over (4+2) cycloaddition of a kinetically stabilized benzoborirene with reactive cycloaddends†

Marvin Sindlinger,[a] Sonja Biebl, [ID][a] Markus Ströbele [ID][b] and Holger F. Bettinger [ID] *[a]

Benzoborirene carrying a bulky $Trip_2C_6H_3$ (Trip = 2,4,6-tri-iso-$Pr_3C_6H_2$) group at boron reacts with the dienophile 4-phenyl-1,2,4-triazoline-3,5-dione and the diene 3,6-di(4-pyridyl)-1,2,4,5-tetrazine by opening of the borirene ring rather than undergoing the typical Diels–Alder reactions. The formal insertion results in diazaborole and azaborolo[1,5-*b*][1,2,4,5]tetrazine derivatives, respectively.

Two fundamental concepts of chemistry, strain and aromaticity, are united in the structural motif of benzoborirene.[1] The annulation of the heteroaromatic borirene ring to the aromatic benzene causes high strain and structural deformation of the benzene ring in an anti-Mills-Nixon fashion with a shorter C=C distance between the fusion atoms.[1,2] Benzoborirenes only recently became available for investigation as their high reactivity limited access to gas phase and matrix isolation conditions.[3–5] While coordination of N-heterocyclic carbenes to the boron atom only provides limited stabilization of **A**,[1] the direct substitution with the electron donating di(trimethylsilyl)amino group of **B** results in sufficient electronic stabilization for isolation at room temperature (Scheme 1).[6]

A benzoborirene (**1**) without substantial electronic stabilization was achieved by employing the sterically demanding $Trip_2C_6H_3$ (Trip = 2,4,6-tri-iso-$Pr_3C_6H_2$) substituent.[2] The ring system **1** shows high thermal stability, does not react with typical electrophiles such as ketones and trimethylsilyl chloride, and only sluggishly with aldehydes.[2,7,8] On the other hand, very rapid reactions are observed for benzoborirenes with the polar multiple bonds of phosphine oxides and isonitriles by formal (2+2) and (2+1) cycloadditions involving a C–B bond.[7,8]

The related *o*-carborane-fused aminoboriranes show similar reactivity.[8–11]

Benzoborirene **1** unites an electrophilic boron atom that experiences steric shielding, a strained three-membered ring, and a slightly distorted benzene ring. In order to investigate the relative reactivity of these units, we focus here on potential cycloaddition reactions of **1** with a highly reactive dienophile and diene, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and 3,6-di-(4-pyridyl)-1,2,4,5-tetrazine (4,4′-bptz), respectively. PTAD is among the most reactive bench-stable dienophiles.[12,13] It is known to very readily react with cyclopropa[*b*]naphthalene, an all-carbon analogue of benzoborirene **1**, by formal (2+2) cycloaddition to give an indazole derivative presumably involving a zwitterionic intermediate[13] (Scheme 2a).[14] Triazolinediones are also known to react with strained C–C bonds of, *e.g.*, bicyclo[1.1.0]butane or quadricyclane.[15,16]

On the other hand, 1,2,4,5-tetrazines carrying electron withdrawing substituents at the 2,6-positions, are very reactive dienes in inverse electron demand Diels–Alder reactions and are thus utilized as bioorthogonal reagents.[17–19] Such tetrazines react with cyclopropabenzene to the methano-bridged phthalazine derivative by [π4s + π2s] cycloaddition of the π-bond between the ring fusion atoms, followed by N_2 extrusion (Scheme 2b).[20]

We here report that the behavior of **1** towards PTAD and 4,4′-bptz shows parallels and distinct differences compared to the reactivity reported for cycloproparenes (Scheme 3).

Treatment of **1** with PTAD in benzene over 16 hours results in a pink colored solution. Purification of the crude product by chromatography was not possible on silica, but recycling gel

[a] Institut für Organische Chemie, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany.
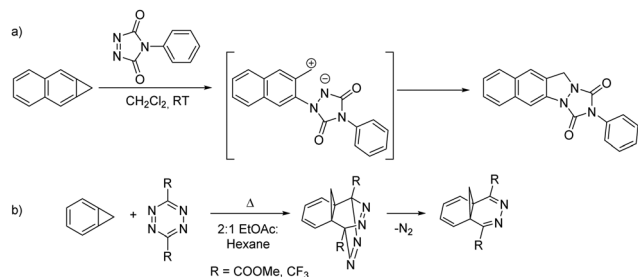*E-mail: holger.bettinger@uni-tuebingen.de*
[b] Institut für Anorganische Chemie, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

Scheme 1 Carbene coordinated benzoborirene **A**, bis(trimethylsilyl)-amino substituted benzoborirene **B**, and kinetically stabilized benzoborirene **1**.
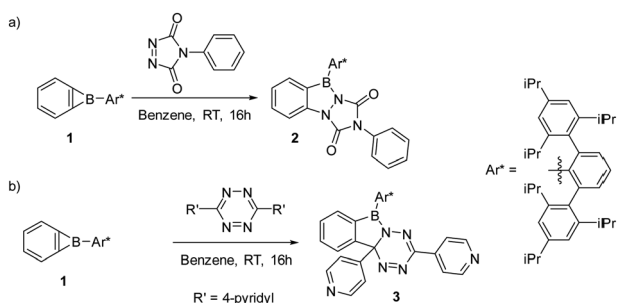
Communication

Scheme 2 (a) Reaction of cyclopropa[b]naphthalene with PTAD gives an indazol presumably involving a zwitterion according to Halton and Russell;[14] (b) reaction of cyclopropabenzene with tetrazines to methanophthalazines as reported by Neidlein and Tadesse.[17]

Fig. 1 Molecular structure of **2** in the solid state. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths [pm] and bond angles [°] for **2**: B–C1 155.4, B–C7 157.0, B–N1 144.8, N1–N2 139.4, N2–C2 138.8, C2–N2–C19–N3 173.84, N1–B–C7–C8 91.74, C19–N3–C21–C22 −41.30. Angle sums [°]: B 360.00, N1 359.81, N2 359.09, C1 359.97, C2 360.00, C19 360.00, C20 360.00, N3 359.86.
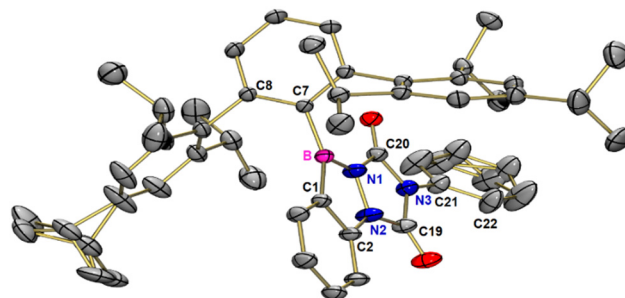
permeation chromatography allowed product isolation in 69% yield. NMR spectroscopy, high-resolution mass spectrometry, and single-crystal X-ray analysis are in agreement with the (2+2) cycloaddition product **2** involving the N=N and one C–B bond (Scheme 3a). Single crystals of **2** grew from a saturated pentane solution at −30 °C. Product **2** crystallizes in the triclinic space group P1̄ with two molecules in the unit cell. The central ring of the terphenyl group is twisted by 91.7° with respect to the planar benzo[d][1,2,3]diazaborol unit (see Fig. 1).

The triazole moiety, on the other hand, is slightly kinked (173.8°, ∠ C2–N2–C19–N3). The phenyl group is rotated by −41.3° (∠ C19–N3–C21–C22) with respect to the triazole unit. All atoms of the five membered rings are in planar trigonal coordination with angle sums of (almost) 360°, with N2 having the smallest angle sum (359.1°). The BN and NN bond lengths are 144.8 ppm and 139.4 ppm, respectively. Their lengths are close to the published values of BN (142.2 pm) and NN (143.7 pm) single bonds in 2,3-dihydro-1,2,3-benzodiazaboroles.[21]

The reaction of **1** with 3,6-(di-4-pyridyl)-1,2,4,5-tetrazine in benzene at room temperature over 16 hours results in a deep red product mixture. NMR spectroscopy (^{1}H and ^{13}C{^{1}H}) as well as high-resolution mass spectrometry of the crude reaction mixture indicates the presence of one major product **3** (Scheme 3b). We could not obtain product **3** in pure form, as sensitivity to moisture precluded purification by chromatography and preparative scale crystallization was impossible. However, crystals

Scheme 3 (a) Reaction of **1** with PTAD yields the 2-hydro-1H,5H-benzo[d][1,2,4]triazolo[1,2-a][1,2,3]diazaborole-1,3-dione scaffold **2**; (b) reaction of **1** with 3,6-(di-4-pyridyl)-1,2,4,5-tetrazine (4,4′-bptz) yields the 6,10b-dihydrobenzo[3,4][1,2]azaborolo[1,5-b][1,2,4,5]tetrazine derivative **3**.

suitable for X-ray structural analysis grew from saturated pentane solution by slow evaporation of the solvent. The main product **3** resulted from formal (2+2) cycloaddition of a C–N bond of the tetrazine to the B–C bond of the benzoborirene ring. Such reactivity is without precedence for 3,6-di-(4-pyridyl)-1,2,4,5-tetrazine.

Product **3** crystallizes in the monoclinic space group Cc with eight molecules in the unit cell and two molecules in the asymmetric unit. In the following, only the (R) enantiomer is considered for a better overview (see Fig. 2). The central ring of the terphenyl unit is rotated by −78.2° (∠ N1–B–C7–C8) relative to the benzo[c][1,2]azaborol subunit, while the plane of the tetrazine subunit is rotated by 30.6° (∠ C3–C1–N2–N4) relative to the benzo[c][1,2]azaborol plane. The boron atom has trigonal planar coordination with a sum of bond angles of 360.0°. The 4-pyridyl group, bound to the five-membered ring, is rotated by an angle of 125.1° (∠ B–C19–C21) relative to the benzo[c][1,2]azaborol plane (see Fig. 2). The N3–N4 bond (126.0 pm) is 10 pm shorter than the N1–N2 bond (136.0 pm). The N2–C20 bond (130.5 pm) is more than 10 pm shorter than the neighboring N4–C20 bond (141.1 pm). This difference is in accord with the Lewis structure drawn in Scheme 3b. For the (S)-enantiomer, the torsion angles are reversed, otherwise, the structural parameters differ only slightly.

Computational chemistry methodology (revDSD-PBEP86-D4/def2-QZVPP/benzene//r^{2}SCAN-3c, see ESI† for details) provides insight into the reactivity of **1** towards PTAD and tetrazine (Fig. 3). Coordination of **1** by a PTAD nitrogen atom is mildly endergonic ($\Delta G° = 3.0$ kcal mol^{-1}) while the transition state **TS1** for insertion into the B–C bond is even lower in energy than the complex ($\Delta G^{\ddagger} = 2.4$ kcal mol^{-1}) indicating a very facile reaction to **INT1** (Fig. 3a). The strongly exergonic ring enlargement from **INT1** to product **2** ($\Delta G° = -87.0$ kcal mol^{-1}) can proceed over **TS2** with a low barrier as well ($\Delta G^{\ddagger} = 9.5$ kcal mol^{-1}). Hence, the formation of **2** from reagents is a low barrier process that is initiated by B···N interaction.

A conceivable pathway for the exergonic ($\Delta G° = -48.4$ kcal mol^{-1}) reaction of 4,4′-bptz with **1** to the azaborole **3** that involves an entrance barrier of $\Delta G^{\ddagger} = 25.2$ kcal mol^{-1} was identified (Fig. 3b). Coordination of a tetrazine nitrogen atom is
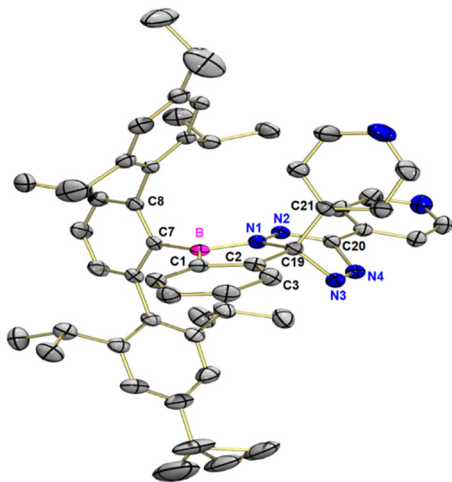
Fig. 2 Molecular structure of the (*R*)-enantiomer of **3** in the solid state. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths [pm] and bond angles [°] for **3**: B–C1 155.6, B–C7 157.3, B–N1 144.5, N1–C19 145.4, N3–C19 149.5, C19–C2 151.1, C19–C21 153.2, N1–N2 136.0, N2–C20 130.5, C20–N4 141.1, N3–N4 126.0, B–C19–C21 125.09, N1–B–C7–C8 −78.16, C3–C1–N2–N4 30.60.

endergonic (ΔG° = 25.1 kcal mol^{-1}), but **TS3** is very close in energy ($\Delta G^\ddagger$ = 25.2 kcal mol^{-1}) and provides **INT2** by a formal [4+2] cycloaddition. The strongly contorted **INT2** can undergo a phenyl shift (**TS4**) to give product **3** with a barrier of $\Delta G^\ddagger$ = 18.7 kcal mol^{-1}. Although the pyridyl nitrogen atoms are more Lewis basic than those of the tetrazine core, the binding energy of the corresponding adduct (ΔG° = −1.8 kcal mol^{-1}) is sufficiently small to have uncoordinated reagents in solution.
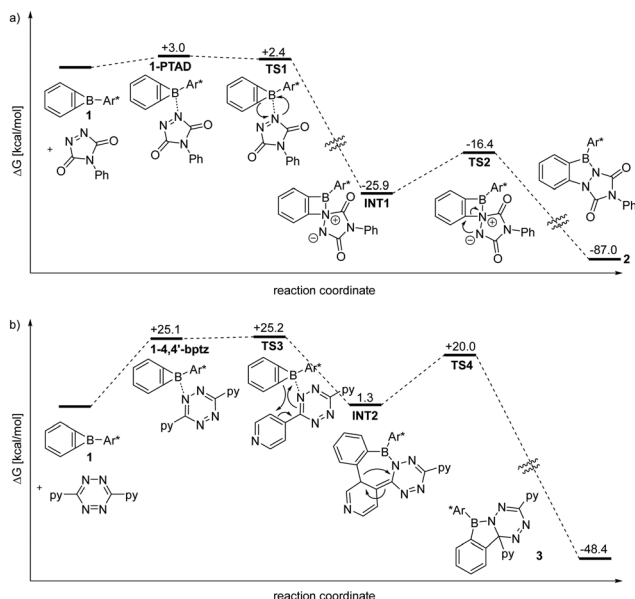
For comparison, we computationally also investigated Diels–Alder reactions between **1** and PTAD and 4,4′-bptz (see ESI,† for details). We find that these reactions involve significantly higher barriers and are mostly strongly endergonic, even when using the phenyl group instead of the large Trip$_2$C$_6$H$_3$ substituent for the modelling.

In summary, we have subjected the kinetically stabilized benzoborirene **1** to reactions with a potent Diels–Alder dienophile (PTAD) and diene (3,6-(4-pyridyl)-1,2,4,5-tetrazine) and observed that in both cases products result from reactions with the borirene unit of **1**. The reaction of **1** with PTAD, that parallels the reactivity of cyclopropa[*b*]naphthalene, provides access to the novel benzo[*d*][1,2,4]triazolo[1,2-*a*][1,2,3]diazaborole motif. On the other hand, **1** prefers insertion into the C–B bond with the tetrazine to give an unprecedented benzo[3,4][1,2]azaborolo[1,5-*b*][1,2,4,5]tetrazine motif rather than following established behavior of cyclopro-parenes. As both PTAD and 4,4′-bptz are electron poor compounds with low basicity[22,23] that preferentially react with electron rich systems, the attack at the sterically shielded boron center is remarkable. Diels–Alder reactions involving the benzene backbone of **1** with the investigated substrates are not competitive due to significantly higher barriers and unfavorable thermodynamics.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for compounds **2** and **3** have been deposited at the Cambridge Crystallographic Data Centre under 2290575 and 2312526.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 J. Hahn, C. Keck, C. Maichle-Mössmer, E. von Grotthuss, P. N. Ruth, A. Paesch, D. Stalke and H. F. Bettinger, *Chem. Eur. J.*, 2018, **24**, 18634–18637.
2 M. Sindlinger, M. Ströbele, C. Maichle-Mössmer and H. F. Bettinger, *Chem. Commun.*, 2022, **58**, 2818–2821.
3 R. I. Kaiser and H. F. Bettinger, *Angew. Chem., Int. Ed.*, 2002, **41**, 2350–2352.
4 H. F. Bettinger, *Chem. Commun.*, 2005, 2756–2757.
5 H. F. Bettinger, *J. Am. Chem. Soc.*, 2006, **128**, 2534–2535.

Fig. 3 Reaction coordinate (in kcal mol^{-1}) diagrams for the reactions of **1** with PTAD (a) and with 4,4′-bptz (b) as computed at the revDSD-PBEP86-D4/def2QZVPP/CPCM(DCM)//r^{2}SCAN-3c level of theory. Ar* = Trip$_2$C$_6$H$_3$, py = 4-pyridyl.

6 H. Zhang, J. Wang, W. Yang, L. Xiang, W. Sun, W. Ming, Y. Li, Z. Lin and Q. Ye, *J. Am. Chem. Soc.*, 2020, **142**, 17243–17249.
7 M. Sindlinger, M. Ströbele, J. Grunenberg and H. F. Bettinger, *Chem. Sci.*, 2023, **14**, 10478–10487.
8 X. Liu, M. Heinz, J. Wang, L. Tan, M. C. Holthausen and Q. Ye, *Angew. Chem., Int. Ed.*, 2023, **62**, e202312608.
9 J. Wang, L. Xiang, X. Liu, A. Matler, Z. Lin and Q. Ye, *Chem. Sci.*, 2024, **15**, 4839–4845.
10 J. Wang and Q. Ye, *Chem. – Eur. J.*, 2024, **30**, e202303695.
11 Y. Wei, J. Wang, W. Yang, Z. Lin and Q. Ye, *Chem. Eur. J.*, 2023, **29**, e202203265.
12 N. Korol, M. Slivka and O. Holovko-Kamoshenkova, *Org. Commun.*, 2020, **13**, 146–154.
13 K. De Bruycker, S. Billiet, H. A. Houck, S. Chattopadhyay, J. M. Winne and F. E. Du Prez, *Chem. Rev.*, 2016, **116**, 3919–3974.
14 B. Halton and S. G. G. Russell, *Aust. J. Chem.*, 1990, **43**, 2099–2105.
15 M. H. Chang and D. A. Dougherty, *J. Org. Chem.*, 1981, **46**, 4092–4093.
16 H. Olsen, *J. Am. Chem. Soc.*, 1982, **104**, 6836–6838.
17 F. Thalhammer, U. Wallfahrer and J. Sauer, *Tetrahedron Lett.*, 1990, **31**, 6851–6854.
18 A.-C. Knall and C. Slugovc, *Chem. Soc. Rev.*, 2013, **42**, 5131–5142.
19 B. L. Oliveira, Z. Guo and G. J. L. Bernardes, *Chem. Soc. Rev.*, 2017, **46**, 4895–4950.
20 R. Neidlein and L. Tadesse, *Helv. Chim. Acta*, 1988, **71**, 249–253.
21 M. Shigeno, M. Imamatsu, Y. Kai, M. Kiriyama, S. Ishida, K. Nozawa-Kumada and Y. Kondo, *Org. Lett.*, 2021, **23**, 8023–8027.
22 J. Spanget-Larsen, *J. Chem. Soc., Perkin Trans. 2*, 1985, 417–419.
23 W. Kaim and S. Kohlmann, *Inorg. Chem.*, 1987, **26**, 68–77.