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Organocatalysed three-component modular synthesis of BN isosteres and BN-2,1-azaboranaphthalenes via Wolff-type rearrangement

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[2,1]-Azaboranaphthalenes represent unique boron–nitrogen (BN) isosteres of naphthalenes, attracting interest for the development of molecules with enhanced therapeutic potency. The existing synthetic strategies are generally two-component reactions with harsh conditions. Here we report an organocatalysed three-component modular synthesis of ring-fused BN isosteres and BN-2,1-azaboranaphthalenes following ring expansion of unstrained cyclic ketones (n = 4–8) via Wolff-type rearrangement. The strategy used 2-formylarylboronic acid as a C–B surrogate and $TMSN_3$ as an exogenous single nitrogen source, allowing the de novo rapid synthesis of BN isosteres by forging C–C, C–N and B–N bonds under a single operation. The developed method proved to be compatible with a broad substrate scope (58 examples), including cyclic ketones and diverse heterocycles, which afforded 1C ring-expanded [2,1]-azaborines. The reaction was also effective with acyclic ketones, yielding BN naphthalene isosteres. Control experiments and density functional theory study dictate the plausible reaction pathways following [1,2]-C–C/C–H shift, analogous to Wolff rearrangement.

The diversification of privileged molecular scaffolds for improving properties is key in drug design and the development of novel pharmaceutical candidates[1–3]. To achieve desired transformations of the underlying key structural core, de novo multistep synthesis is usually required, which inevitably compromises the overall synthetic efficiency and time. Recently, bioisosteric replacement chemistry has emerged as an important tool for modifying existing biologically active compounds, potentially influencing the overall pharmacological activity of related compounds[4–11]. Moreover, the formation of covalent B–N bonds (isoelectronic with C=C) for the generation of novel boron-containing heterocycles has attracted much attention from a broad research community, including synthetic, medicinal and materials chemists[12–19]. In particular, benzazaborines, a class of boron–nitrogen (BN) heterocycles, are viewed as unique BN isosteres of naphthalenes (Fig. 1a)[20–26]. They often exhibit better therapeutic features, such as improved metabolic stability and aqueous solubility, than the parent naphthalene molecules, probably because the NH groups of the azaborines can act as hydrogen-bond donors for better binding to proteins[27–29] (Fig. 1b). In addition to improving the biological activity of lead carbonaceous molecules, it also expands intellectual property space. Despite the great promises of BN isosteres, only a limited number of strategies have been reported so far with certain limitations[30,31]. Furthermore, most of the developments are on the synthesis of BN-1,2-azaboranaphthalene isomers, also named 2,1-borazaronaphthalenes[23–25]. By contrast, the

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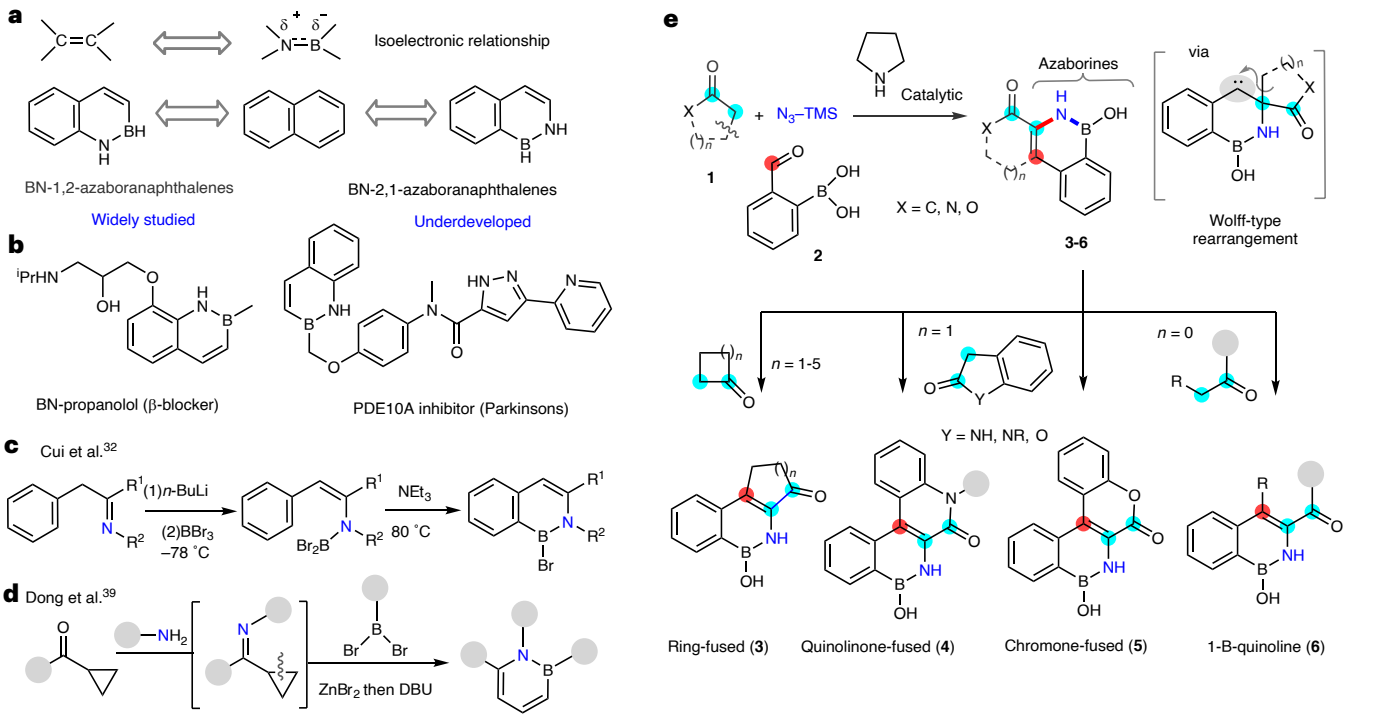

Fig. 1 | Context and importance of this work. a, Isoelectronic relationship and BN isosteres of naphthalene: Regioisomers, BN-[1,2] versus [2,1] azaborines. **b**, Azaboranaphthalene moiety in bioactive molecules. **c**,**d**, Seminal previous works by Cui et al. for 2,1-azaboranaphthalenes via base-promoted C–H borylation (**c**) and by Dong et al. for modular three-component strategy for 1,2-azaborines via a ring-opening closure strategy (**d**). **e**, The present work of organocatalysed three-component synthesis of structurally diverse BN-2,1-azaboranaphthalenes via Wolff-type rearrangement.

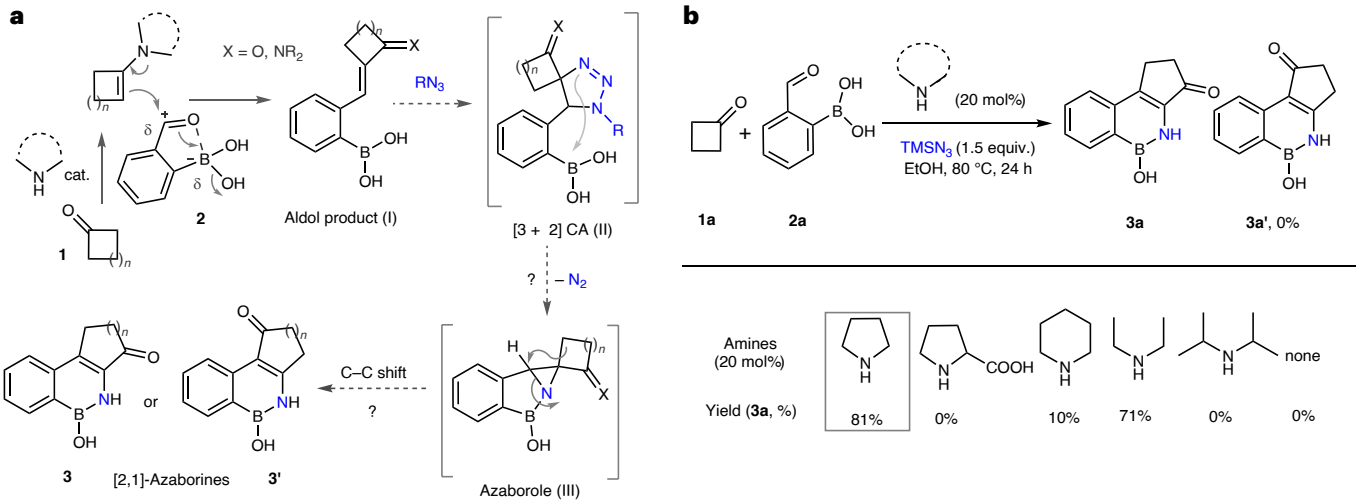

Fig. 2 | Working hypothesis and optimization. a, Working hypothesis for the synthesis of BN-2,1-azaboranaphthalenes. **b**, Optimization and reaction discovery. The reaction was carried out at 0.2 mmol scale. ^{1}H NMR yields are mentioned.

preparation of regio-inverted structure BN-2,1-azaboranaphthalene (or 1,2-borazaronaphthalenes) analogues is still underdeveloped, originally reported by Cui et al.[32], which can be accessed by reacting phenethyl imines, butyllithium and haloboranes followed by electrophilic cyclization (Fig. 1c). In addition, two-component strategies have been reported for BN-2,1-azaboranaphthalenes, although they typically suffer from limited substrate scope and require harsh reaction conditions[33–38]. In these methods, 2-formylphenylboronic acid was used for non-peripheral azaborine synthesis via aldol or Wittig-type reactions with α-amino esters or carbonyl compounds[34–38]. The seminal recent work by Dong et al. reported a three-component two-step synthesis of monocyclic 1,2-azaborines via ring opening of cyclopropyl ketone or imines using amine and dibromoborane in the presence of catalytic $ZnBr_2$ (Fig. 1d)[39].

Given the importance of azaborines in streamlining the rapid synthesis of this class of compounds and their strong potential as naphthalene bioisosteres in drug discovery, we herein disclose an organocatalysed three-component coupling of ketones, 2-formylarylboronic acid and $TMSN_3$ to form BN-2,1-azaboranaphthalenes via a [1,2]-shift and ring expansion of cycloalkanones or ketones (Fig. 1e). This strategy represents a true three-component modular synthesis of structurally diverse ring-fused BN-2,1-azaboranaphthalenes (**3**–**6**) from easily

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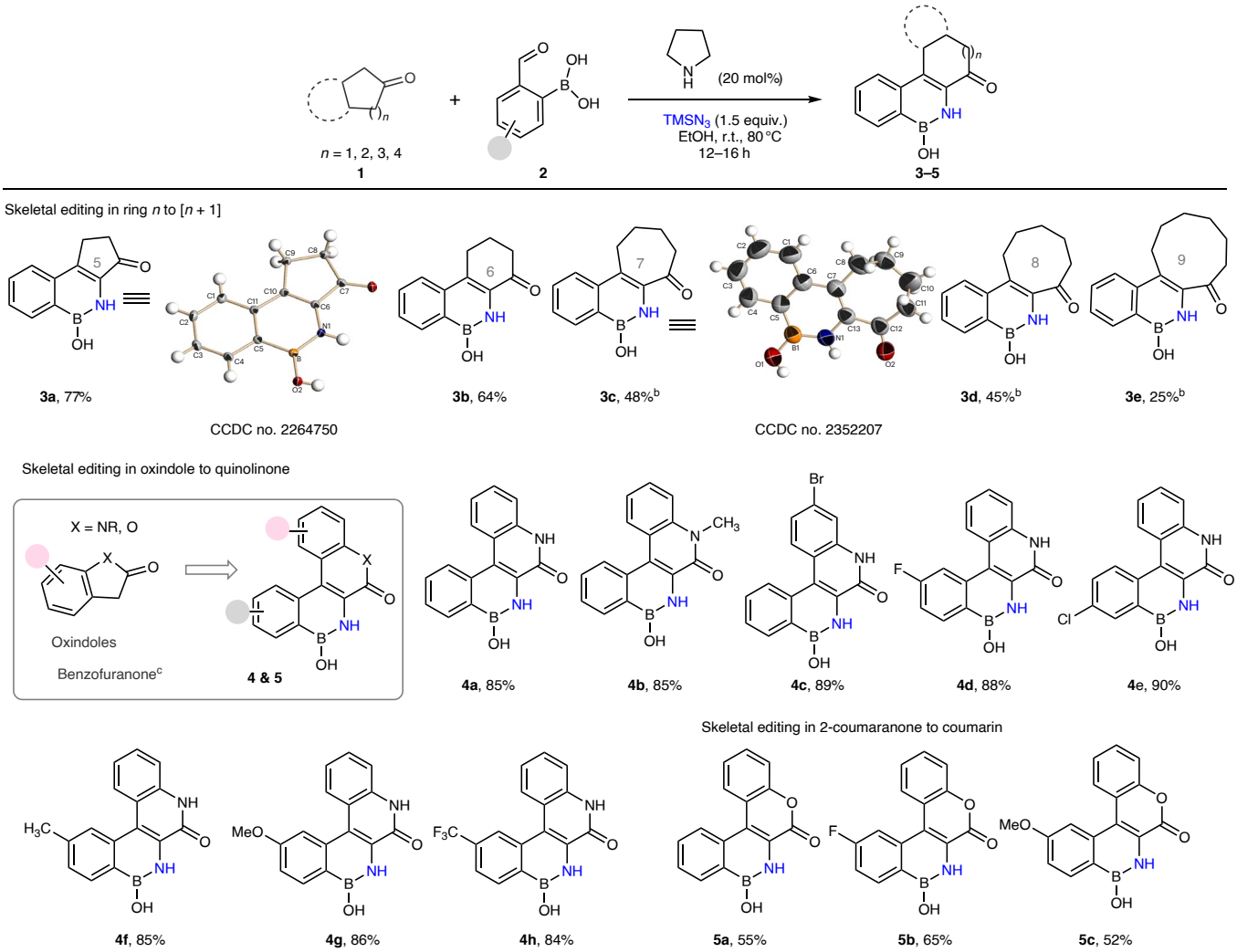
Table 1 | Scope for ring-fused [2,1]-azaborines from cyclic ketones, amides and esters[a]



[a]Reaction was carried out at 0.33 mmol scale. Isolated yields are mentioned. [b]3.0 equiv. of pyrrolidine was used, at 80 °C for 14 h. [c]Reaction was carried out with 20 mol% pyrrolidine in 1,4-dioxane at room temperature.

accessible ketones (**1**), 2-formylarylboronic acid (**2**) and $TMSN_3$. The present innovation could be appealing in aspects of novelty in chemistry pertaining to organocatalysed ring (unstrained; $n = 4–8$) expansion, exploitation of $TMSN_3$ as an exogenous single nitrogen source[40] and regioselective fixation of N and C atoms at the α and β position of C=O (Fig. 1e).

Results and discussion

Reaction discovery and substrate scope

Our proposed hypothesis (Fig. 2a) was based on the formation of an aldol condensation product (**I**) through imine/enamine catalysis between ketones (**1**) and an active formyl group of phenylboronic acid **2** (due to intramolecular activation of the aromatic C=O group by the precisely positioned B centre). Azide was thought to introduce into the activated alkene (**I**) via [3 + 2] cycloaddition to form spiro dihydrotriazole (**II**)[41–45]. It was questioned whether the nitrogen-philic nature of boron could form a stable B–N bond with the extrusion of molecular nitrogen. Due to ring strain, rearrangement was subsequently anticipated to form [2,1]-benzazaborines (**3** and **3′**) via [1,2] C–C shift. This process could also be possible via spiro-aziridine formations[41,42].

To explore our hypothesis, an initial experiment was conducted using relatively strained ring, cyclobutanone (**1a**) and 2-formylphenylboronic acid (**2a**) as model substrates in the presence of different azide sources and activators/catalysts (Fig. 2b). Gratifyingly, $TMSN_3$ (1.5 equiv.) in the presence of 20 mol% pyrrolidine led to the exclusive formation of cyclopentanone ring-fused [2,1]-azaborine **3a** in 81% yield (Fig. 2b) as confirmed by nuclear magnetic resonance (NMR) of the reaction mixture (see 'NMR spectra **A**' in the Supplementary Information). Optimization study further revealed that pyrrolidine is essential for the desired transformation. Other catalytic secondary amines were ineffective or delivered inferior chemical yields (Fig. 2b). Meanwhile, the reaction with NaN_3 in the presence of catalytic pyrrolidine resulted in a mere 12% yield of **3a**. The structure of **3a** was further unambiguously confirmed by NMR and a single crystal X-ray (CCDC no. 2264750; Table 1) analysis, ascertaining the regioselective formation of **3a** (not **3a′**). Medium-to-large cyclic ($n = 5–8$) ketones, which are potentially tricky for ring expansion[46–49], also worked to give corresponding 1C expanded ($n = 6–9$) ring-fused benzazaborines (**3b**–**3e**; 25–77% yields, Table 1; CCDC no. 2352207 for **3c**). Given the importance of azaborines and diversification of privileged molecular structures in the discovery of novel pharmaceuticals[4], azaborine formation was also explored with bioactive scaffolds, such as 2-oxindoles and 2-coumaranones. Under optimal conditions using 20 mol% pyrrolidine, 2-oxindoles underwent 1C ring expansion to

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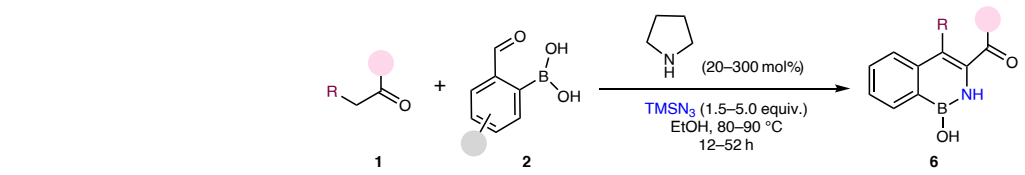
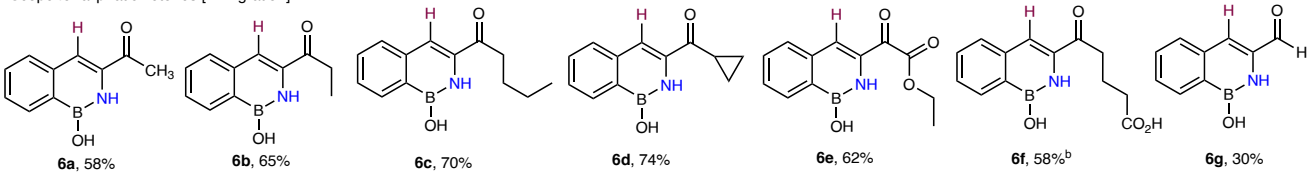
Table 2 | Scope for benzazaborines from acyclic ketones and drug molecules[a]

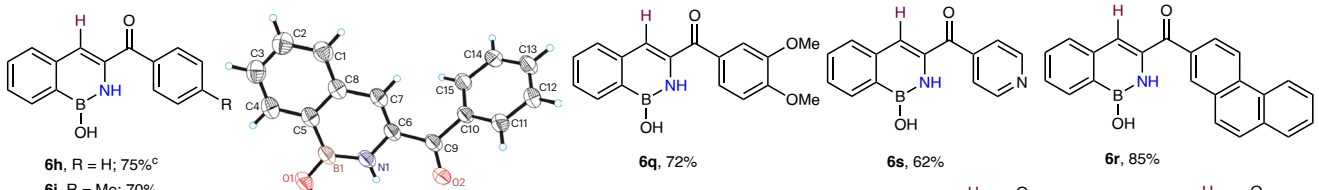


Scope for aliphatic ketones [H migration]



6a, 58% **6b**, 65% **6c**, 70% **6d**, 74% **6e**, 62% **6f**, 58%[b] **6g**, 30%

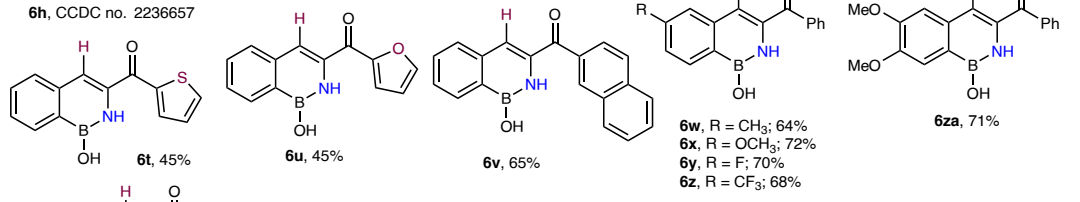
Scope for aromatic ketones [H migration][b]



6h, R = H; 75%[c]
6i, R = Me; 70%
6j, R = Br; 76%
6k, R = I; 74%
6l, R = OH; 75%
6m, R = OMe; 73%
6n, R = *n*-Bu; 65%
6o, R = NO_2; 90%
6p, R = CF_3; 84%

6h, CCDC no. 2236657

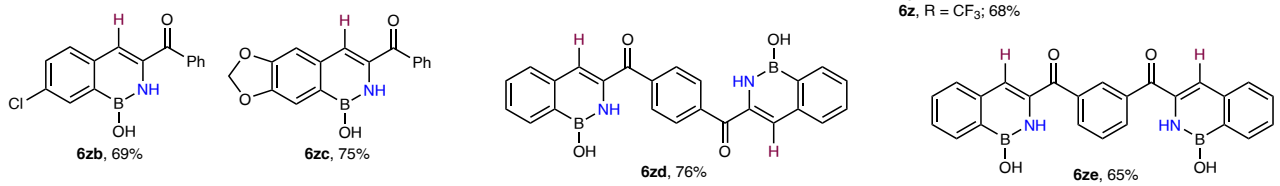
6q, 72% **6s**, 62% **6r**, 85%



6t, 45% **6u**, 45% **6v**, 65%

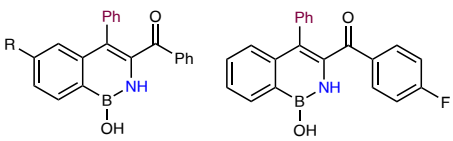
6w, R = CH_3; 64%
6x, R = OCH_3; 72%
6y, R = F; 70%
6z, R = CF_3; 68%

6za, 71%



6zb, 69% **6zc**, 75% **6zd**, 76% **6ze**, 65%

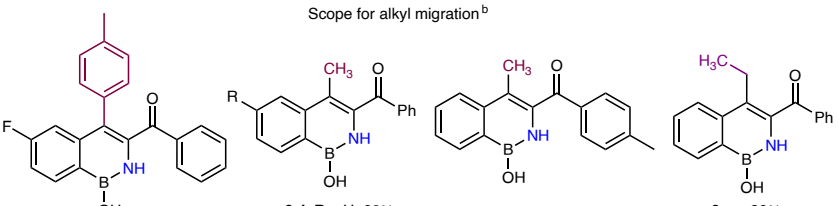
Scope for aryl migration[b]



6zf, R = H; 72%
6zg, R = OMe; 48%

6zh, 44%

Scope for alkyl migration[b]

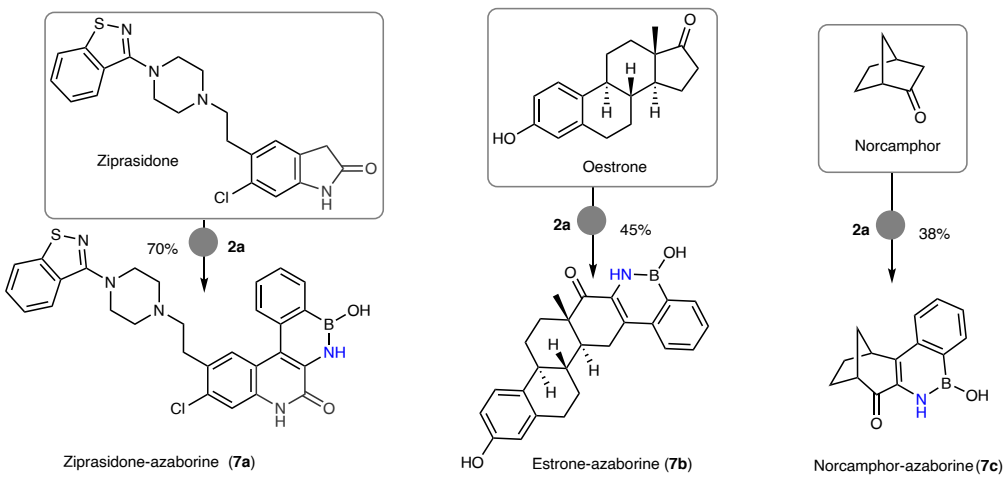


6zi, 40%

6zj, R = H; 62%
6zk, R = F; 65%

6zl, 52% **6zm**, 30%

Scope for drug molecule and natural products[b]



[a]Isolated yields are mentioned. [b]Reaction was carried out with 300 mol% pyrrolidine. [c]Reaction was carried out with at 4.4 mmol scale, 72% yield (0.80 g).

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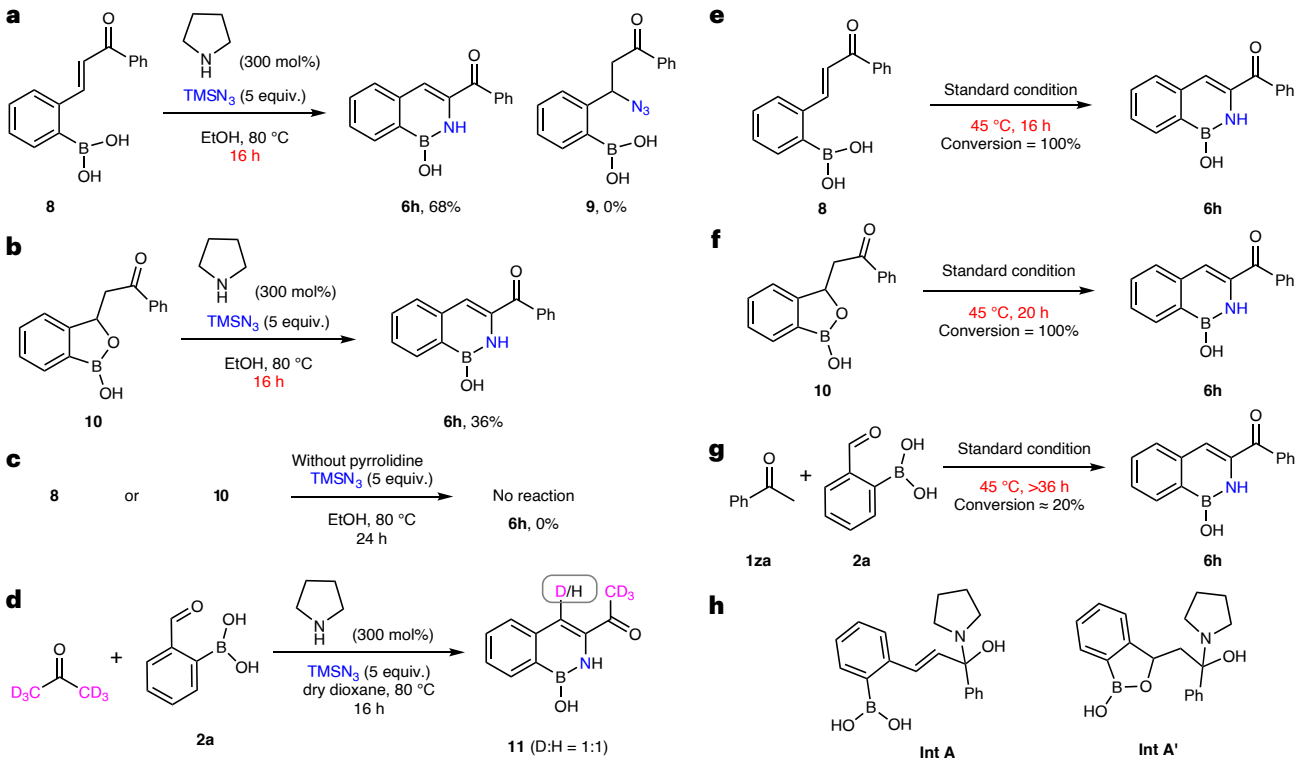

Fig. 3 | Control experiments and mechanistic insight. a, Reaction with possible aldol intermediate **8**. **b**, Reaction with possible benzoxaborol intermediate **10**. **c**, Reaction in the absence of pyrrolidine. **d**, Reaction with acetone-D_6. **e**–**g**, Experiments were conducted under standard conditions at 45 °C to identify the slowest steps. **h**, Molecular ion peaks identified (HRMS) correspond to possible intermediates **8** and **10**.

yield quinolinone-fused azaborines **4a**–**4h** in very good to excellent yields (84–90%). This process is highly efficient, requires no column chromatography and is compatible with electronically diverse free (NH) and N-alkyl oxindoles (Table 1). Similarly, 2-coumaranone afforded the corresponding coumarine ring-fused azaborines in moderate to good yields (**5a**–**5c**; 52–65%). Such examples of rapid access to novel azaborine analogues of privileged scaffolds hold great potential in drug development.

After the successful illustration of a three-component strategy with a range of cyclic ketones, unstrained rings, 2-oxindoles and 2-coumaranone for the synthesis of 1C-expanded ring-fused [2,1]-azaborines, acyclic ketones were also investigated (Table 2). Notably, acyclic ketones were initially anticipated to be challenging under the proposed hypothesis (1,2-H or aryl or alkyl shift) due to the absence of ring strain, unlike their cyclic counterparts. Despite the fact that the reaction was found efficient with acetone under the standard conditions in the presence of 20 mol% pyrrolidine, it resulted in the selective formation of [2,1]-azaborine **6a** in 58% yield. Other aliphatic ketones, such as butanone and 2-hexanone, gave the corresponding azaborines (**6b** and **6c**) in moderate to good yields (58–70%; Table 2). Cyclopropyl methyl ketone was also found to be compatible to give the desired product **6d** in 74% yield. Notably, there was no ring opening or closure of cyclopropyl ketone, as reported previously under Lewis acid catalysis[39]. Reaction with methyl pyruvate afforded the corresponding ethyl ester of azaborine **6e** in 62% yield due to trans-esterification with solvent ethanol. Meanwhile, pyruvic acid gave the corresponding decarboxylated azaborine **6g** (30% yield). However, 5-oxohexanoic acid was compatible with retaining its distant CO_2H group in the desired transformation (**6f**, 58% yield); however, it required excess pyrrolidine (300 mol%). While studying aromatic ketones, acetophenone produced only a trace amount of the desired product **6h** with 20 mol% of pyrrolidine, which can be attributed to the low reactivity of aromatic ketones compared with aliphatic ketones. Thus, further efforts (Supplementary Table 1) were made to increase the efficiency of the desired transformation, which led to optimum results with pyrrolidine (300 mol%) and $TMSN_3$ (5 equiv.), resulting in 78% yield (75% isolated) for **6h** (CCDC no 2236657). High amounts of catalyst and $TMSN_3$ facilitate the desired transformation to azaborine **6** and suppress the competitive polymerization of 2-formylphenylboronic acid (Supplementary Table 1). This modified optimum condition was scalable as demonstrated at 4.4 mmol scale (isolated **6h**, 0.8 g, 72% yield) (see reaction procedure of **6h** in the Supplementary Information). Under the above-modified conditions, different aromatic ketones, bearing electron-withdrawing and electron-donating groups at different positions, were examined (**6h**–**6ze**). 4-Substituted (Br, I, Me, OMe, OH, *n*-Bu, CF_3 and NO_2) phenyl and dimethoxyphenyl methyl ketones gave the corresponding azaborines (**6i**–**6q**) in 65–90% yields. The electron-withdrawing groups (NO_2 and CF_3) bearing aryl ketones underwent reactions faster (14 h, 80 °C) than electron-donating counterparts (22–36 h, 90 °C). This result advocates that the reaction might proceed via enolate formation, following iminium/enamine chemistry. Polyarenes (2-naphthyl and phenanthrenyl) and heteroaromatic (4-pyridinyl, 2-furanyl and 2-thiophenyl) methyl ketones also worked well to give corresponding azaborines **6r**–**6v** in moderate to very good yields (45–85%). Reactions were proficiently compatible with substituted 2-formylarylboronic acid having electron-withdrawing and electron-donating groups, such as CH_3, OMe, F, Cl, CF_3, methylenedioxy and dimethoxy groups at different positions (**6w**–**6zc**; 64–75% yields). Bis-azaborines, **6zd** and **6ze**, can be easily synthesized in good yields (76% and 65%) from 1,4- and 1,3-diacetylbenzenes, respectively. After the [1,2-H] shift, we examined aryl and alkyl shifts. Notably, the desired reactions worked proficiently with 2-arylacetophenones and gave **6zf**–**6zi** in good to moderate yields with the migration of the phenyl group. Methyl and ethyl group migrations were also successful when the reaction was

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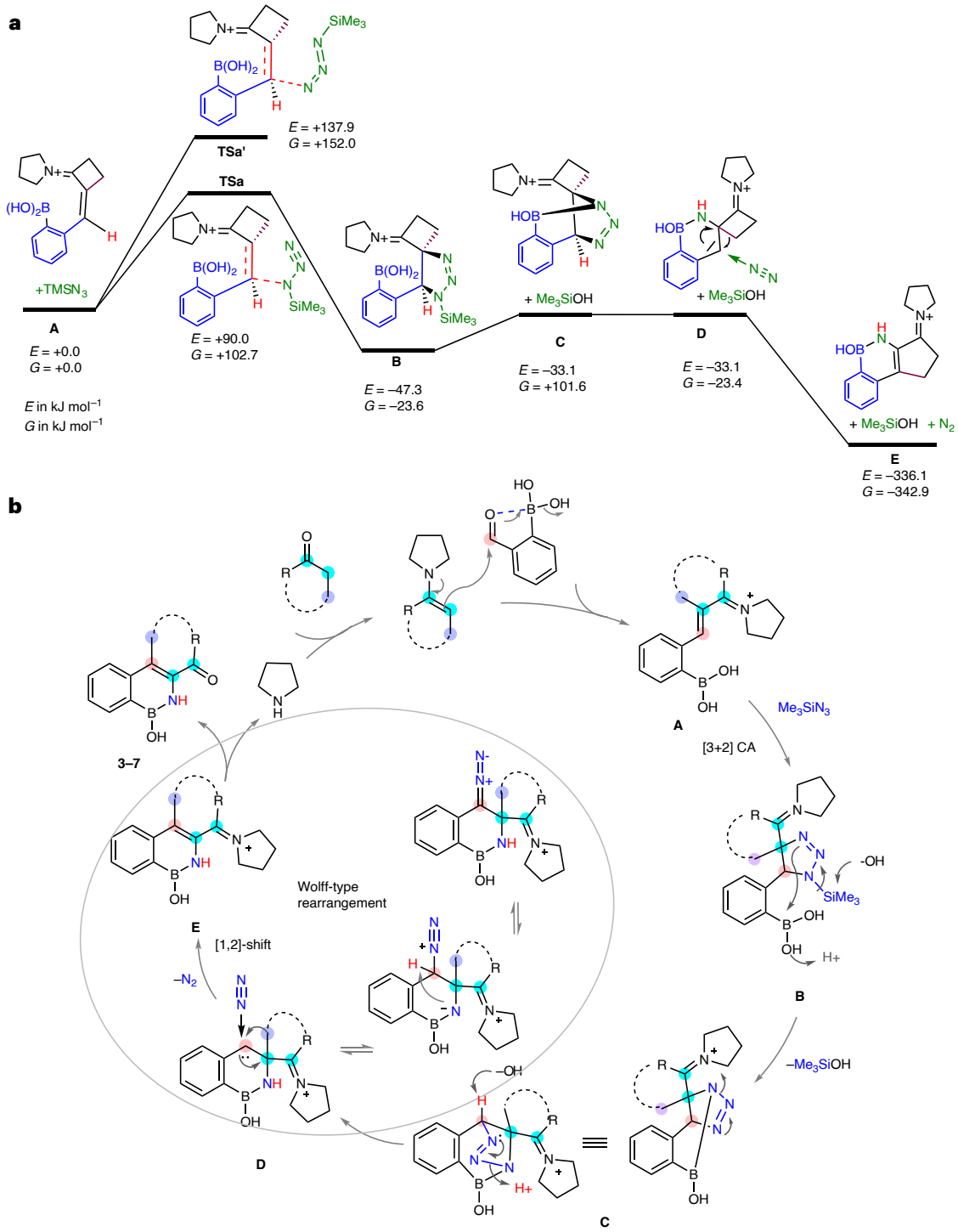

Fig. 4 | Mechanism and energy profile. a, The energy profile based on DFT. **b**, The general proposed mechanism for product formation.

conducted with propiophenone and butyrophenone, respectively (**6zj**–**6zm**; 30–62% yields). Reactions were notably slow as compared with acetophenone and required longer reaction times and slightly elevated temperatures (see the reaction procedure for **6zf**–**6zm** in the Supplementary Information). Finally, the strategy was used for late-stage modification of drugs and complex molecules towards the development of novel potential boron-containing drug candidates (Table 2). Ziprasidone is a US Food and Drug Administration-approved atypical antipsychotic drug that contains a 2-oxindole structural core. It was converted into the corresponding quinolinone-fused azaborine congener (**7a**) in 70% yield. Similarly, estrone was transformed into **7b** by converting its cyclopentanone nucleus to a cyclohexanone ring-fused [2,1]-benzazaborine. Norcamphor, a bicyclo[2.2.1]heptan-2-one core, also underwent molecular transformation to bicyclo[2.3.1]octatan-2-one **7c**. The reaction overall encompasses a wide range of cyclic and acyclic ketones, including bioactive molecules, to furnish BN isosteres of privileged scaffolds under very mild conditions.

Mechanistic studies

To understand the mechanistic pathways for the developed three-component azaborine synthesis and ring expansion, a series of control experiments were conducted. Initially, we attempted

to isolate a proposed aldol/enone intermediate (**I**; Fig. 2) from 2-formylphenylboronic acid and cyclohexanone/cyclopentanone under base-mediated aldol condensation conditions. However, our endeavour failed to isolate it. Pleasingly, we were able to isolate a model aldol intermediate **8** from 2-formylphenylboronic acid and Wittig ylide of acetophenone[50] (see the reaction procedure of **8** in the Supplementary Information). Subsequently, product **8** was exposed to $TMSN_3$ under standard conditions in the presence of pyrrolidine, which afforded the desired product **6h** in 68% yield (Fig. 3a). To our surprise, another anticipated Michael addition product, azide (**9**) was not observed at all[51]. As chalcone/aldol product **8** is easily convertible to benzoxaborole **10**, which can be anticipated to be another intermediate[47]. Thus, intermediate **10** was synthesized by simply stirring **8** in the presence of acidic alumina and exposing it to identical conditions using 300 mol% of pyrrolidine, resulting in the formation of the desired product **6h** in 36% yield (Fig. 3b). These two experiments revealed that **8** could be the primary—or even the sole—contributory intermediate towards azaborine (**6h**) formation. These intermediates (**8** or **10**) did not give any products in the absence of pyrrolidine (Fig. 3c), thus suggesting that pyrrolidine plays an important role in the subsequent step (**8** or **10** to **6h**). The imine activation of the carbonyl of **8** or **10** is probably essential for the [3 + 2] cycloaddition reaction with $TMSN_3$. The reaction with acetone-d_6 in dry dioxane (Fig. 3d) gave the corresponding desired product **11** (D:H, 1:1), suggesting that there is [1,2]-deutrium transfer from the CD_3 group of acetone-D_6. To determine the slowest and rate-determining step in the present transformations, a model reaction was conducted at lower temperature (45 °C), independently with chalcone (**8**; Fig. 3e), benzoxaborole (**10**; Fig. 3f) and standard three-component reactions using acetophenone and 2-formylphenylboronic acid (Fig. 3g). It was observed that intermediates **8** and **10** underwent complete reaction in 16 h and 20 h, respectively (Fig. 3e,f), whereas the third set of reaction was sluggish and underwent merely 20% conversion in 36 h (Fig. 3g). The above three sets of reactions revealed that the first step, that is, the formation of intermediate (**8** or **10**), might be the slowest step in the present process. Furthermore, the trimethylsilyl group was shown to be crucial, as confirmed by control experiments showing poor yield with NaN_3 (Supplementary Table 1). The possible rationale is that the silyl group (TMS) may act as a Lewis acid, activating the carbonyl group to facilitate the reaction and imine formation. High-resolution mass spectrometry (HRMS) analysis was conducted at specific time intervals to identify potential intermediates. Characterization of molecular ion peaks (Int. **A**/**A′**) (Fig. 3h) suggested the formation of alkene or benzoxaborol adducts **8** and **10** (as also confirmed by experiments; Fig. 3a,b).

An initial density functional theory (DFT) computational study was then conducted to get further insight into our hypothesis (Fig. 4a). The mechanism has been studied with cyclobutanone as a benchmark. As enone (analogous to **8**; Fig. 3) was shown to be the key intermediate for the above transformation, we began our DFT study from an iminium compound (**A**), formed in situ in the presence of pyrrolidine, and computed different possible intermediates (Fig. 4a). 1,3-Dipolar cycloaddition of the olefinic moiety of iminium intermediate (**A**) and $TMSN_3$ gave spiro dihydrotrizazole (**B**)[41,42]. The regioselectivity of the addition of the $TMSN_3$ is mainly under kinetic control, with an energy difference of 49.3 kJ mol^{-1} (**TS-a**; G = +102.7 kJ mol^{-1} versus **TS-a′**; 152.0 kJ mol^{-1} for the other isomer) (see DFT calculation data in the Supplementary Information). Intermediate **B** undergoes B–N bond formation due to the electrophilic nature of boron, leading to a bridged type intermediate **C** with the elimination of Me_3Si–OH. Subsequent opening of strained and unstable dihydrotriazole ring **C** and nitrogen extrusion leads to carbene or diazo-type intermediate **D**, which in turns leads to [1,2]-C–C or C–H shift, analogous to Wolff-type rearrangement to an intermediate **E**[52]. [1,2]-Migration is energetically driven by the formation of thermodynamically stable benzazaborine **E**[20–26]. We have not been able to determine any other potential transition states between **B** and **E**. One possible explanation is the difficulty in accurately accounting for the influence of proton and hydroxyl fragments during the concerted rearrangement steps (Fig. 4b). The hydrolysis of the iminium **E** led to the final isolated products. Accordingly, the general mechanism is proposed in Fig. 4b.

Conclusions

In summary, a rare organocatalysed approach has been devised for ring expansion of unstrained cyclic ketones (n = 4–8) and modular synthesis of [2,1]-benzazaborines via Wolff-type rearrangement. The present strategy represents an efficient three-component synthesis of ring-fused [2,1]-benzazaborines using cyclic ketones, 2-formylboronic acids and $TMSN_3$ as an exogenous single nitrogen source. The strategy was also compatible with acyclic ketones to give BN naphthalene isosteres via [1,2]- shift of H, aryl and alkyl groups. The reaction was highly efficient and scalable, with diverse substrate scopes and functional group tolerance. The strategy was well suited to tune privileged scaffolds and drug molecules to potential high-valued azaborine congeners. Control experiments and DFT studies were conducted to propose the putative reaction mechanism for the selective formation of [2,1]-azaborines.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-025-01938-1.

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Methods

The general procedure of 2,1-azaboranaphthalene synthesis was as follows. In a reaction vial, 2-formylphenylboronic acid (**2**, 0.59 mmol, 1.8 equiv.) was dissolved in ethanol (0.1 M) to which cyclic/acyclic aliphatic ketone (**1**, 0.33 mmol, 1.0 equiv.), pyrrolidine (0.066, 0.20 equiv.) and $TMSN_3$ (0.495 mmol, 1.5 equiv.) were added at room temperature and transferred for heating at 80 °C for 12–52 h. After the completion of the reaction monitored by thin layer chromatography, the reaction was cooled down to an ambient temperature, quenched with water and extracted with dichloromethane (3 × 15 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography and eluted with hexane:EtOAc to furnish the desired products.

Data availability

The data that support the findings of this study are available within the Article and its Supplementary Information. Crystallographic data for the structure reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2264750 (**3a**), CCDC 2352207 (**3c**) and CCDC 2236657 (**6h**). Copies of the data can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

R.Ku. conceived and directed the project. A.S. performed experiments. M.G. performed the DFT calculations and drafted the DFT parts. R.Ka. analysed the X-rays. A.S. and R.Ku. prepared the Article and its Supplementary Information. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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