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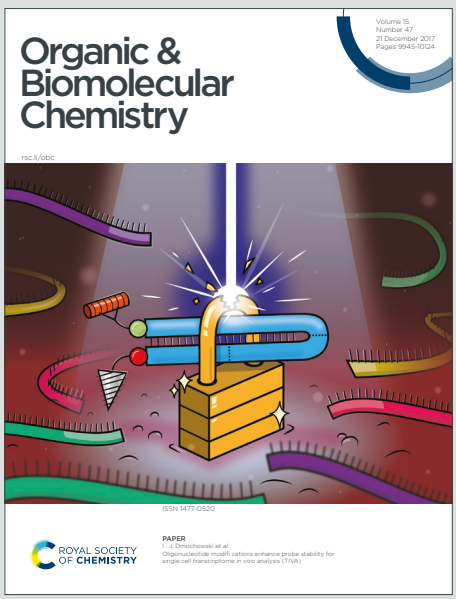

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ARTICLE

Catalytic Synthesis of Saturated Azacycles using Transborylation

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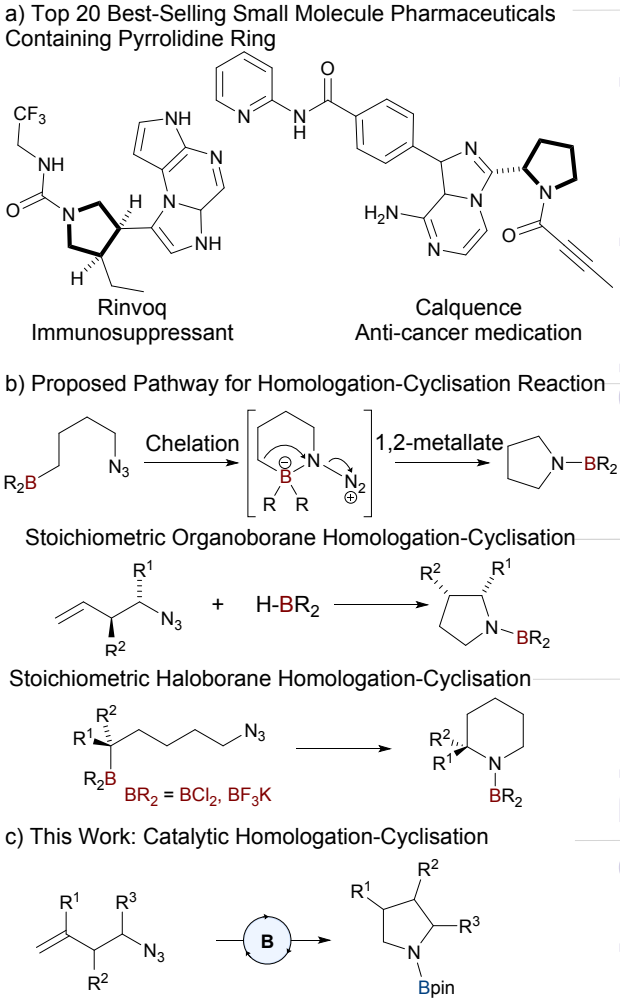
A simple, catalytic synthesis of pyrrolidines through the intermolecular cyclisation-homologation of azido-butenes was enabled by a hydroboration, 1,2-metallate rearrangement and B–N/B–H transborylation reaction sequence. Substitution at the C1; C2; C3-positions of the azido-butenes is well tolerated. Extension of this methodology to azido-propenes and azido-pentenes with the aim of accessing azetidines and pyrrolidines respectively revealed the formation of an aza-bora heterocycle and a saturated azido-pentane boronic acid pinacol ester.

Introduction

Saturated N-heterocycles are prominent structural motifs in pharmaceuticals, agrochemicals and natural products.[1] In 2024, 14 of the top 20 best-selling small-molecule pharmaceuticals contained a saturated azacycle,[2] and thus, the synthesis of saturated *N*-heterocycles is of great importance in synthetic chemistry. The fifth most common *N*-heterocycle in pharmaceuticals is pyrrolidine,[2] which is present in a number of essential medicines, including Rinvoq and Calquence (Scheme 1, a). A variety of methods have been reported for the synthesis of pyrrolidine derivatives;[3-6] however, given the prevalence of azacycles in essential chemicals, orthogonal methods for the synthesis and isolation of these derivatives is of interest.

Homologation-cyclisation reactions of organoboron compounds have been used for the synthesis of N-heterocycle syntheses however these have required stoichiometric borane in all cases and the preinstallation of organoboron group. Homologation-cyclisation reactions proceed by formation of a B–N chelate followed by a 1,2-metallate rearrangement to give the *N*-boryl heterocycle (Scheme 1b, top). Diastereoselective pyrrolidine synthesis using dicyclohexylborane ($HBCy_2$) was achieved by Evans in the synthesis of echinocandin D; however, only a single transformation was reported (Scheme 1b, middle).[7] A similar organoboron cyclisation facilitated by diethylborane was reported later by Carboni.[8] Cyclisation using haloboranes to give pyrrolidines[9] and piperidines have also been reported (Scheme 1b, bottom),[8-12] though suffer from the limiting functional group tolerance of the halide and sensitivity of the haloborane, catalysts and products. Dioxaborolane reagents have also been used in a limited number of cases for a similar cyclisation pathway.[13]

A catalytic homologation-cyclisation of organoboranes remains unreported, to the best of our knowledge. Herein we sought to develop a boron-catalysed pathway, where the reactive borane is a catalyst and turnover achieved using a commercial dioxaborolane.



Scheme 1 a) Pyrrolidine-containing pharmaceuticals; b) Homologation-Cyclisation for N-heterocycle synthesis; c) This work.

We envisaged that *B–N* transborylation (B–N/B–H exchange)[14] could be used to enable the hydroboration-homologation-cyclisation reaction of alkenyl azides, where

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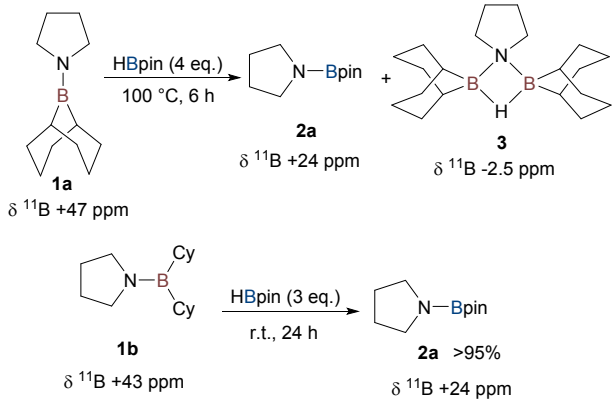
hydroboration followed by an intramolecular cyclisation and 1,2-metallate rearrangement would give *N*-boryl pyrrolidines. The use of a substoichiometric (catalytic) amount of alkyl borane negates the requirement for stoichiometric equivalents of dialkylboranes or boron halides implemented in other methods, expanding substrate scope and avoiding the careful quenching and workup previously required for product isolation.

Results and Discussion

To establish the viability of *B–N* transborylation as the turnover step for the homologation-cyclisation reaction, a series of stoichiometric studies were conducted. Our previous success with 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN) and dicyclohexylborane ($HBCy_2$) prompted their selection as potential catalysts.[14,15] An effective turnover reagent would need to be unreactive, or significantly slower than the borane catalyst, towards alkene hydroboration and azide reduction to avoid competitive reactivity, and thus the bench stable dioxaborolane pinacolborane (HBpin) was selected.

Dehydrocoupling reactions of pyrrolidine and H-*B*-9-BBN and $HBCy_2$ were shown to yield *N*-boryl pyrrolidines **1a-b** in >95% yields as determined by ^{1}H NMR spectroscopy. Single-turnover experiments with HBpin were then monitored by ^{11}B NMR spectroscopy for *N*-boryl-pyrrolidine **1a-b** conversion to the *N*-Bpin-pyrrolidine **2a** (Scheme 2). Upon reaction of *N*-B-9-BBN pyrrolidine **1a** with excess HBpin (4 eq.) for 6-hours at 100 °C only partial *B–N* transborylation was achieve, a 1:2:2 ratio of **1a**, **2a**, and **3,** respectively, was observed by ^{11}B NMR spectroscopy. Additional heating of the reaction mixture or increasing the equivalents of HBpin did not significantly influence the extent of conversion to the *N*-Bpin-pyrrolidine **2a**. A new peak was observed by ^{11}B NMR spectroscopy at δ^{11}B = −2.5 ppm, which was assigned to a bridged dimeric species **3**, by analogy to a bridged B-9-BBN-amine complex (δ^{11}B = −2.7 ppm).[16] The bridged BBN-amine complex **3** appeared stable enough to be unreactive under the reaction conditions preventing formation of *N*-Bpin-pyrrolidine **2a**.



Scheme 2 Single turnover *B–N* transborylation experiments with *N*-borane pyrrolidine adducts and the turnover reagent, HBpin.

Single-turnover experiments between *N*-BCy_2-pyrolidine **1b** and HBpin proceeded in >95% conversion to give *N*-Bpin-pyrrolidine **2a** at room temperature over 24 hours. No dimeric species were observed between *N*-BCy_2-pyrrolidine **1b** and $HBCy_2$, contrasting reactions using *N*-B-9-BBN pyrrolidine **1a**. This was attributed to steric effects, where the larger dicyclohexyl groups on boron prevent formation of a dimeric species akin to **3**. With successful turnover under mild conditions, $HBCy_2$ was selected for catalytic studies.

4-Azido-1-butene was selected as the model substrate for catalysis development and reaction optimisation enabling >95% formation of *N*-Bpin pyrrolidine **2a** by ^{1}H NMR spectroscopy after 16 hours. A range of substituted 4-azido-1-butenes were then tested towards the synthesis of functionalised pyrrolidines, all of which were isolated as the amine hydrochloride salts (Scheme 3). The model substrate 4-azido-1-butene **4a** cyclised in excellent yield and with complete control of regioselectivity, giving pyrrolidine·HCl salt **6a** in 87% isolated yield. Substitution at the C2 position (Scheme 3, R^2) was next investigated. Substituents including Me **6b**, OMe **6c** and tert-butyl **6f** were all tolerated, with the pyrrolidine·HCl products isolated in 92%, 92% and 93% yields, respectively. It should be noted that no coordination to the catalyst or HBpin was observed by the OMe group during the reaction. Substrates with C2 substituents such as *iso*propyl **6d** and cyclohexyl **6e** gave excellent yields by quantitative ^{1}H NMR spectroscopy, both >95%, however they were sensitive to the isolation/purification protocol with the amine hydrochloride salts isolated in moderate 41% and 51% yields, respectively. As anticipated, the sterics and electronic nature of the C2 substituent did not affect catalytic turnover of the reaction as the bond and spatial distance from the site of B–N/B–H exchange presumably prevented any steric encumbrance. It is worth noting that this catalytic hydroboration-homologation-cyclisation enables the access to a diversity of functional groups at C2 of the resulting pyrrolidine, unlike the majority of current stoichiometric[6] and catalytic[5] methods for pyrrolidine synthesis using cycloaddition reactions which require the presence of an electron-withdrawing substituent at this position.

Substitution at the C3 position (Scheme 3, R^3) was then investigated. Excellent yields by ^{1}H NMR spectroscopy were observed for both C3 methyl **6b** and phenyl **6h** substituents, although a lower isolated yield was observed for the C3 methyl substituted pyrrolidine when the methyl substituent on the starting material was at the alkyl versus alkenyl position (R^2 vs R^3, respectively). Compared to contemporary methods for catalytic pyrrolidine synthesis using azides, substitutions at both the C2 and C3 positions are underexplored.[17] Given the minimal influence of substitution at these positions the developed catalytic hydroboration-homologation-cyclisation provides access substituted pyrrolidines at both C2 and C3.

C1 substitution (Scheme 3, R1) with the Me analogue **6i** cyclised in excellent yield of 95% by ^{1}H NMR spectroscopy, though substrates with C1 Cy and Ph substituents required increased reaction temperature to facilitate catalytic turnover and cyclisation resulted in lower conversions compared to other substitution patterns; 74% for Cy **6j** and 62% for Ph **6k** as determined by ^{1}H NMR spectroscopy. A potential steric clash

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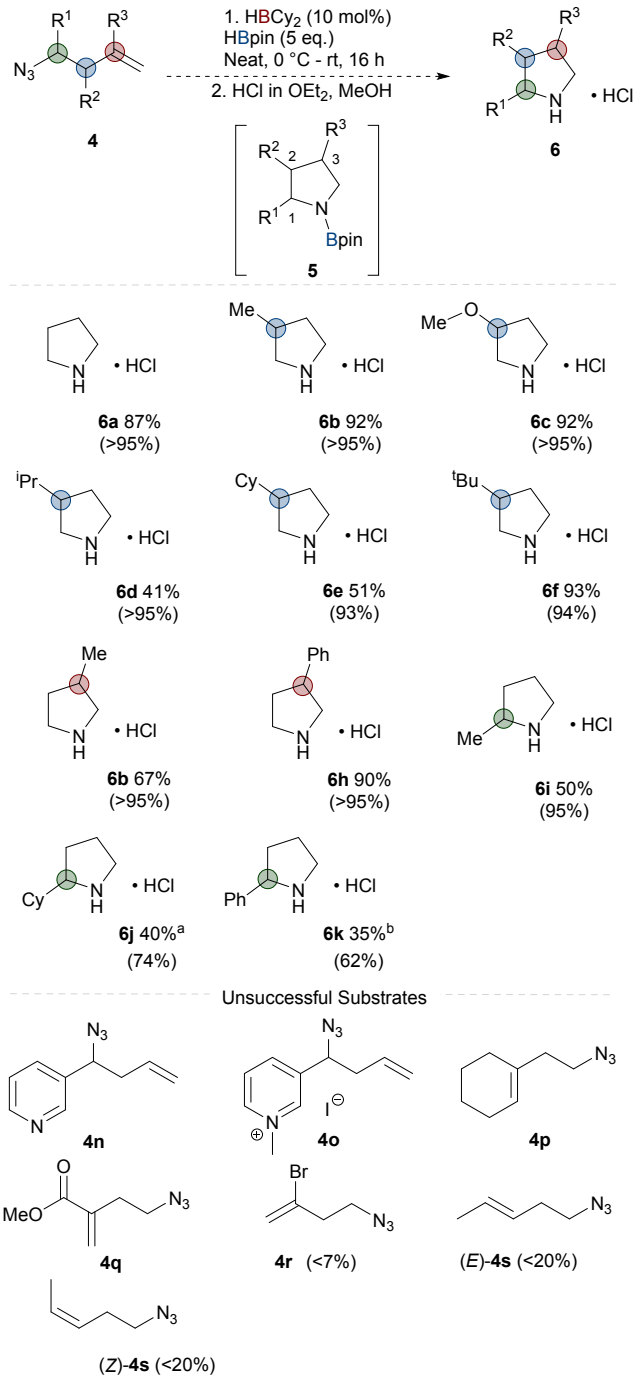

between the larger C1 substituents and HBpin during the B–N transborylation step was proposed to prevent the effective coordination of HBpin and ultimately slow catalyst turnover. To test the hypothesis, a single turnover (stoichiometric) B–N transborylation experiment was performed between *N*-BCy_2-2-Ph-pyrrolidine **5k** and HBpin where a significant reduction in reaction conversion was observed; with only 10% of *N*-Bpin-2-Ph-pyrrolidine **6k** formed with 90% *N*-BCy_2-2-Ph-pyrrolidine **5k** unreacted (Scheme 4, a). This suggested that B–N transborylation was sensitive to steric bulk at the C1 position of azido alkene **5** starting material. Unsuccessful substrates **4n-s** could be attributed to Lewis base coordination (**4n**), demethylation (**4o**), the more challenging hydroboration of internal alkenes (**4p**, **4s**), or dehalogenation (**4r**). While cyclisation using substrates bearing C1 substitution was less successful, these can be accessed using other methods.[17,18]

Scheme 3 Conditions: 4-Azido butene (1 eq., 1.5-2.5 mmol), HBpin (5 eq.) and $HBCy_2$ (10 mol%) under N_2 atmosphere. Isolated yields. Yields in parentheses determined by ^{1}H NMR spectroscopy, in cases where less than 95% of product was observed in the crude reaction mixture, dibromomethane was used as an internal standard. [a]Reaction heated at 80 °C for 16 h. [b]Reaction heated at 100 °C for 16 h.

Given the precedent for stoichiometric asymmetric alkene hydroboration,[19,20] enantioselective pyrrolidine synthesis was next targeted. The optimised reaction conditions were found to be compatible with both (*R*)-10-(phenyl)-9-borabicyclo[3.3.2]decane (Soderquist borane)[20] **7**, generated *in situ* from the methoxy analogoue,[21] and diisopinocampheylborane (Ipc_2BH) for the hydroboration-homologation-cyclisation reaction to give pyrrolidine hydrochloride **6a**, albeit with extended reaction times required in both cases (Scheme 4, b). When these conditions were applied to prochiral substrate 4-azido-2-methyl-1-butene **4g**, only trace formation of *N*-Bpin-3-methylpyrrolidine **6g** was observed by ^{1}H and ^{11}B NMR spectroscopy. When both the temperature and catalyst loading was increased and subsequent protection with benzyl chloroformate, the *N*-Cbz-protected 3-methylpyrrolidine **8** was obtained with moderate to low yield (Scheme 4, c) and poor enantioselectivity; 60:40 *e.r.* using Soderquist borane **7** as the catalyst and racemic when using Ipc_2BH. It is unclear why the cyclisation was significantly worse with this substrate, however, slow alkene hydroboration due to the increased steric hindrance[22] cannot be ruled out. More forcing conditions were avoided as elevated temperatures were reported to diminish the enantioselectivities.[21]

Optimised reaction conditions towards the synthesis of pyrrolidines were also tested in the cyclisation of 3-azido-propenes and 5-azido-pentenes to target azetidines and piperidines, respectively. 3-Azido-propene **9** was reacted under standard reaction conditions to give trace amounts of *N*-Bpin-azetidine **10** product as determined by ^{1}H NMR spectroscopy (Scheme 4, d). The formation of a putative cyclic 5-membered aza-borane species **11** in 40% yield was proposed by analogy to reported ^{1}H and ^{11}B NMR spectra of such species.[23] Elevated temperatures and increased catalyst loading enhanced the formation of 1,2-dicyclohexyl-1,2-azaborolidine **11**, but *N*-Bpin-azetidine **10** was not formed in greater than a 5% yield. These results could suggest that the migration of the borane catalyst Cy group during the 1,2-metallate rearrangement outcompetes the migration of the (primary) alkyl group. Presumably a 5-membered transition-state structure gives a better anti-periplanar conformation of the *B*-Cy and *N*-N_2 bonds, though this contrasts the observations of Morken *et al*. for the cyclisation of methoxy-aminoboronates with RBpin[13] so suggesting a boron centre containing ligands with low migratory aptitude are required. The use of the $HBCy_2$ catalyst here gives

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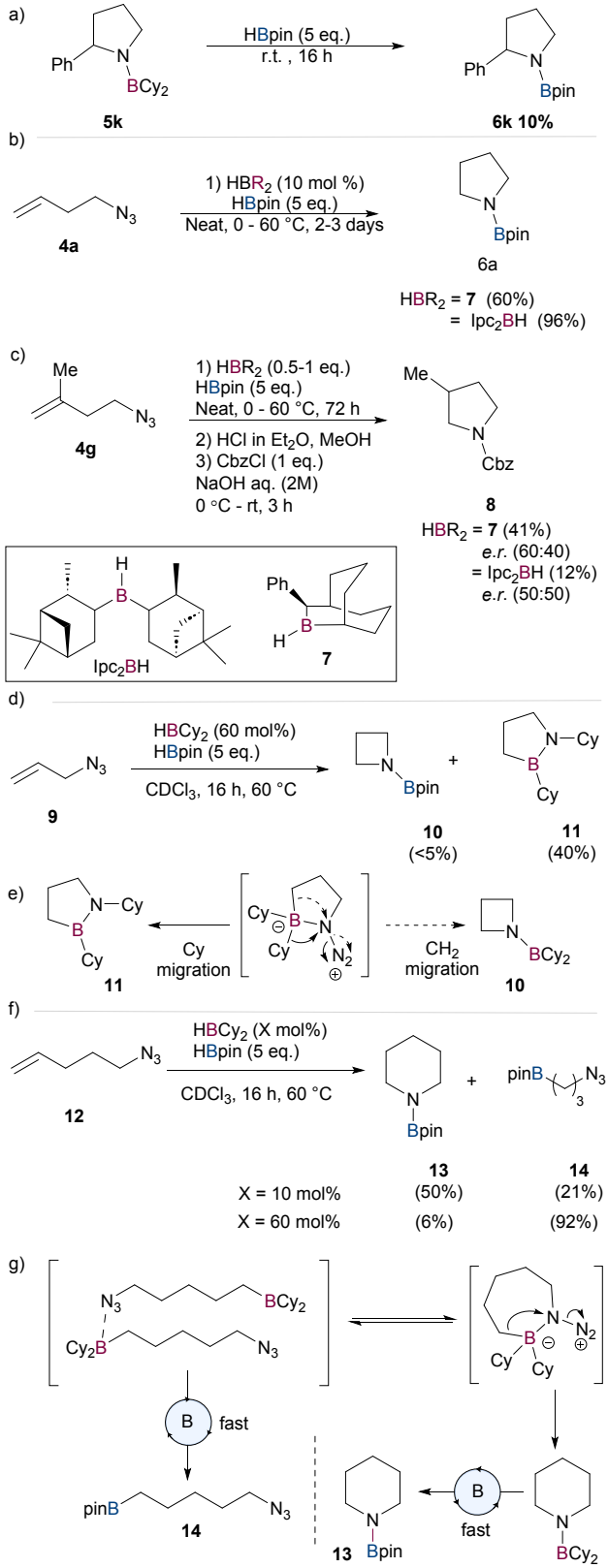
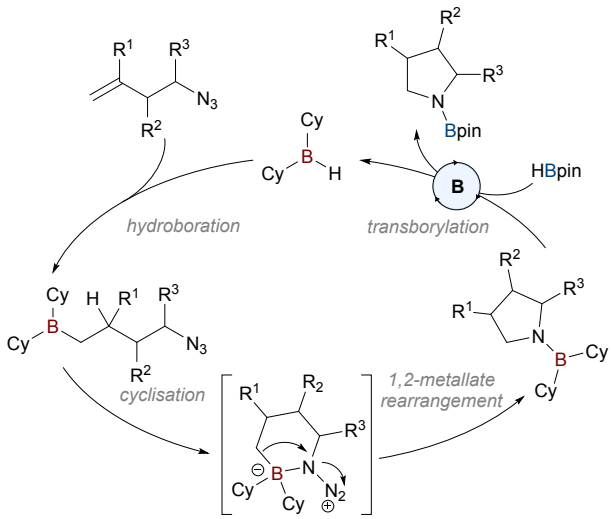


a cyclic 5-membered boronate complex where 3 B–C bonds of a similar bond strength must be differentiated, therefore orbital overlap becomes the controlling factor governing bond migration.

Scheme 4 a) Transborylation of *N*-BCy$_2$ pyrrolidine5k with HBpin; b) Cyclisation of azido alkene 4a to *N*-BCy$_2$ pyrrolidine 6a; c) Cyclisation using enantioenriched boranes 7 and Ipc$_2$BH; d) Cyclisation of 3-azido-propene; e) Formation of azetidine 10 or pyrrolidine 11 from a common intermediate; f) Cyclisation of 5-azido-pentene; g) Formation of *N*-Bpin piperidine 13 or linear boronic ester 14.

The reactivity of 5-azido-pentene **12** was similar to that of 4-azido-1-butene **4a**. At 60 °C a 50% yield of *N*-Bpin piperidine **13** was observed, and 21% yield for *N*-Bpin-5-azidopentane **14** (Scheme 4, f). Increasing the catalyst loading resulted in a dramatically shifted product ratio; *N*-Bpin-5-azidopentane **14** was formed in 92% yield, and *N*-Bpin piperidine **13** only in 6%. These results indicate that the reaction temperature and catalyst loading are determining factors influencing both the formation of a cyclic 7-membered boron 'ate' complex and the B–C/B–H transborylation step. Concentration has been shown to have an effect on the propensity for intra- versus intermolecular coordination in molecules bearing both a Lewis acidic and basic site.[24] At high concentrations of substrate, intermolecular coordination is favoured, while at more dilute concentrations, intramolecular coordination is favoured. In reactions with pentenyl azide **12**, at 10% HBCy$_2$ loading, the concentration of R-BCy$_2$ in solution is low, favouring the intramolecular cyclisation to give the *N*-Bpin piperidine **13**, following a 1,2-metallate and transborylation (Scheme 4g, left). At 50 mol% loading of borane, the concentration of R-BCy$_2$ is high, favouring intermolecular coordination and the observance of linear alkyl boronic ester **14**, following transborylation of the linear trialkyl borane (Scheme 4g, right).

From the results of boron-catalysed pyrrolidine, azetidine and piperidine formation, a catalytic cycle for homologation-cyclisation was proposed (Scheme 5). The cycle begins by (chemoselective) alkene hydroboration to give trialkyl borane (R–BCy$_2$). B–N adduct formation to form an intramolecular boron 'ate' complex triggers 1,2-metallate rearrangement of the primary alkyl group to give the *N*–BCy$_2$ pyrrolidine. The cycle is completed by B–N transborylation to give the *N*-Bpin pyrrolidine, and regenerate the dialkyl borane catalyst.



Scheme 5 Proposed catalytic cycle for the homologation-cyclisation of alkenyl azides.

Conclusions

In summary the catalytic organoboron-catalysed pyrrolidine synthesis has been developed. The reaction has been successfully applied to substitution in the C1-C3 positions of the pyrrolidine ring and the influence of sterics on the cyclisation has been examined. The generality of this cyclisation was tested in the synthesis of azetidines and piperidines with varying success.

Author contributions

Experimental work was conducted by NC, NM, JS and SLM. Initial draft of manuscript was completed by NC. All authors contributed to manuscript editing. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

All experimental details, characterisation data, and optimisation are provided in the supplementary information.

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Data availability

All experimental details, characterisation data, and optimisation are provided in the supplementary information.