Kinetics and Mechanism of the Arase-Hoshi R2BH-Catalyzed Alkyne Hydroboration: Alkenylboronate generation via B-H/C-B Metathesis

Kinetics and Mechanism of the Arase-Hoshi R_2BH-Catalyzed Alkyne Hydroboration: Alkenylboronate generation via B-H/C-B Metathesis.

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ABSTRACT: The mechanism of R_2BH-catalyzed hydroboration of alkynes by 1,3,2-dioxaborolanes has been investigated by in situ ^{19}F NMR spectroscopy, kinetic simulation, isotope entrainment, single-turnover labelling ($^{10}B/^{2}H$), and density functional theory (DFT) calculations. For the Cy_2BH catalyzed hydroboration 4-fluorophenylacetylene by pinacolborane, the resting state is the anti-Markovnikov addition product $ArCH{=}CHBCy_2$. Irreversible and turnover-rate limiting reaction with pinacolborane ($k \sim 7\times10^{-3}$ $M^{-1}s^{-1}$) regenerates Cy_2BH and releases *E*-Ar-CH=CHBpin. Two irreversible events proceed in concert with turnover. The first is a Markovnikov hydroboration leading to regioisomeric *E*-Ar-CH(Bpin)=CH_2. This is unreactive to pinacolborane at ambient temperature, resulting in catalyst inhibition every $\sim10^2$ turnovers. The second is hydroboration of the alkenylboronate to give $ArCH_2CH(BCy_2)Bpin$, again leading to catalyst inhibition. 9-BBN behaves analogously to Cy_2BH, but with higher anti-Markovnikov selectivity, a lower barrier to secondary hydroboration, and overall lower efficiency. The key process for turnover is B-H/C-B metathesis, proceeding by stereospecific transfer of the *E*-alkenyl group within a transient, μ-B-H-B bridged, 2-electron-3-centre bonded B-C-B intermediate.

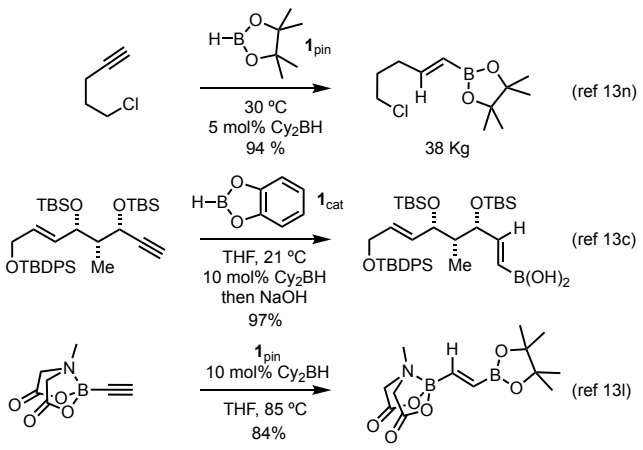
INTRODUCTION

Alkenylboron reagents are ubiquitous in synthesis and pre-eminent in stereospecific cross-coupling reactions to generate alkenes. In such reactions, selection of the appropriate reagent can be crucial.[1] For example, although vinylboronic acid is not especially prone to protodeboronation,[2] in solution,[2b] it does polymerize[3] and self-condense,[4] making protected forms more readily handled.[5] Alkenylboronates are valued for their stability,[6] and as intermediates in the synthesis of alkenyl-boronic acid,[7a] -trifluoroborate,[7b] -tin,[7c] and -aluminium reagents,[7d] alkenyl iodonium salts,[7e] allyl boronates,[7f] epoxyboronates,[7g] and cyclopropylboronates.[7h]

Alkyne hydroboration allows regio- and stereo-selective synthesis of alkenylboron reagents.[8] Although many B-H species hydroborate alkynes at ambient temperature,[8] 1,3,2-dioxaborinanes,[9a] and 1,3,2-dioxaborolanes, such as catecholborane ($\mathbf{1}_{cat}$)[9b] and pinacolborane ($\mathbf{1}_{pin}$),[9c] are inert.[9] This has prompted the development of numerous catalysts,[10,11] and initiators,[12] for the process,[8] including Ca, Ti, Zr, Fe, Ru, Ni, Co, Rh, Ir, Cu, Au and Ag complexes/salts,[10a-t] carboxylic acids,[10u] amides,[10v] NaOH,[10w] Et_3P,[10x] Al hydrides and alkyls,[10yz] and a wide range of boron species.[11a-o]

In 1995, Arase and Hoshi reported that Cy_2BH and 9-BBN both efficiently catalyze the regioselective *cis*-hydroboration of alkynes with $\mathbf{1}_{cat}$ in THF at ambient temperature.[11d] The process was later extended to hydroboration with $\mathbf{1}_{pin}$, allowing preparation of *E*-alkenyl pinacolboronates in good yield,[11f] without contamination by metal catalysts. Over the last two decades, the Arase-Hoshi R_2BH-catalyzed alkyne hydroboration[11d-g] has been deployed extensively,[13] for example in the synthesis of Dictyostatin,[13a] Mandelalide A,[13b] (-)-FR182877,[13cd] Amphidinolide V,[13e] (+)-Herboxidiene,[13f] (-)-Bafilomycin A1,[13gh] Aigialomycin D,[13i] 1α,25-dihydroxyvitamin D analogues,[13j] Lejimalide B and analogues,[13k] Burke's *E*-1-Bpin-2-MIDA ethene,[13l] enantioenriched geminal silylboronates,[13m] and at multikilo-scale in the preparation of an alkenylboronate for cyclopropanation.[13n] However, despite diverse and extensive application of the Arase-Hoshi hydroboration, remarkably little mechanistic detail has emerged regarding why it is highly effective in many cases,[13] e.g. Scheme 1, yet fails in others.[14]

Scheme 1. Selected applications of Arase-Hoshi hydroboration.[13cln]

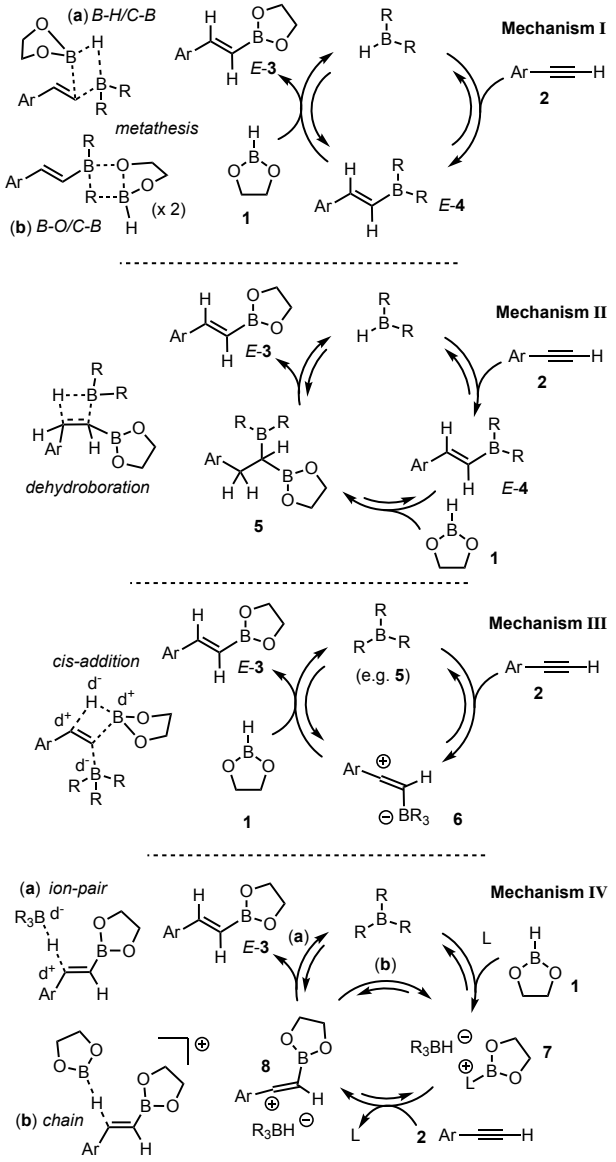


RESULTS AND DISCUSSION

1. Prior Studies. In their seminal report,[11df] Arase and Hoshi suggested general mechanism I, Scheme 2, to account for the catalytic effect of R_2BH on alkyne hydroboration. The mechanism is analogous to that proposed in 1990 by Periasamy for catalysis by $[H_3B{\cdot}N(Ph)Et_2]$[11ac] and was primarily based on two known stoichiometric processes: the hydroboration of alkynes by dialkylboranes,[15] and the thermal redistribution of trialkyl boranes with borate esters,[10v,16] including *o*-phenylene borate,[16b] and $\mathbf{1}_{cat}$.[10v]

Thermal redistribution of boranes with borates is catalyzed by *B*-H boranes.[16d] It may proceed by B-H/C-B metathesis (pathway Ia), as suggested by Köster,[16d] or by alkoxy ligand exchange (B-O/C-B metathesis; pathway Ib), as suggested by Brown,[16b] or by analogous processes where R = H.[17]

Scheme 2. Mechanisms I-IV for R_2BH/BR_3-catalyzed alkyne (**2**) hydroboration with a generic 1,3,2-dioxaborolane (**1**). Key product-generating steps are indicated on the left-hand side of each cycle. R = H, alkyl or Ar; L = neutral ligand, e.g. solvent.



Whilst the mechanism under Arase-Hoshi catalysis conditions has not been explored, a number of studies on related alkyne hydroborations using $\mathbf{1}_{pin}$, that are catalyzed or initiated[12] by $[Ar_{(3-n)}BH_n]$ species have been reported.[11i-j,l,n] Detailed NMR spectroscopic studies by Oestreich[11i] revealed that Ar_3B catalyzed hydroboration, where Ar = 3,5-$(CF_3)_2C_6H_3$), involves *in situ* Ar_3B / $\mathbf{1}_{pin}$ redistribution to generate a range of species, including dimers of Ar_2BH, and $ArBH_2$. These were proposed to be the active catalysts for alkyne hydroboration via mechanism I. In contrast, Stephan and Glorius, found that alkyne hydroboration catalyzed by $B(C_6F_5)_3$, and by $HB(C_6F_5)_2$, involved generation of alkyldiaryl borane intermediates, including diboryl $\mathbf{5}_{pinAr}$ (Scheme 2, Mechanism II, R = C_6F_5) that was isolated and characterized as an isonitrile complex.[11j] Alkyl boranes undergo thermal dehydroboration,[17] and a three-stage hydroboration, hydroboration, dehydroboration sequence (**2**→**4**→**5**→**3**; mechanism II) provides a pathway for catalysis.[18] Independently prepared $\mathbf{5}_{pinAr}$ is an efficient catalyst for the alkyne hydroboration process; however, tests for dehydroboration from $\mathbf{5}_{pinAr}$ proved negative.[11j] This led to the suggestion that Ar_3B, or $\mathbf{5}_{pinAr}$, or analogous $RBAr_2$ species, exert catalysis through the Lewis-acid polarization[19] of the alkyne to facilitate the direct addition of the pinacolborane $\mathbf{1}_{pin}$ B-H, *cis* across a formally zwitterionic intermediate (**6**, mechanism III).[11j] Vasko, Kamer, and Aldrich recently reported on alkyne hydroboration catalyzed by a dimethylxanthene-based frustrated Lewis pair (FLP).[11o] It was elucidated that the active catalyst is generated in two stages: the FLP undergoes metathesis with $\mathbf{1}_{pin}$ to generate a $(C_6F_5)_2(H)B{\cdot}PAr_3$ complex, and this then reacts with the alkyne (**2**) to generate *E*-**4** (R = R = C_6F_5). By analogy to prior work,[11j] *E*-**4** was assumed to undergo hydroboration to generate $\mathbf{5}_{pinAr}$ and thus initiate mechanism III.[11o] An additional process to be considered is one in which a borenium–borohydride ion-pair (**7**, mechanism IV) is generated by hydride transfer from 1,3,2-dioxaborolane **1** to R_3B. Borenium-catalyzed hydroborations involving NHC species are well-described.[20] Propagation of Arase-Hoshi catalysis by mechanism IV would require H-transfer to alkyne adduct **8**, within the ion-pair (pathway IVa), or by a chain-reaction involving **1** (pathway IVb). Mechanisms III and IV are partially analogous to that proposed by Ingleson for the addition of Lewis-base adducts of 9-BBN to alkynes,[21] however, the latter proceeds with overall *trans* addition of B and H.[22]

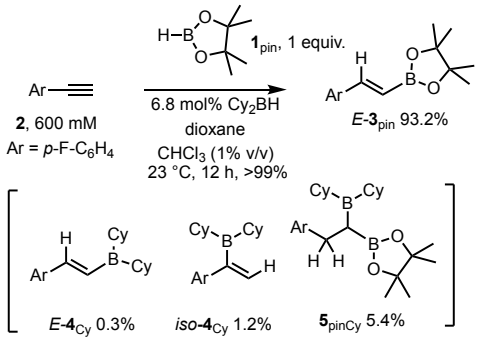
Herein we report on a mechanistic investigation of Arase-Hoshi hydroboration catalysis,[11d-g] Scheme 1, employing Cy_2BH, and 9-BBN, with $\mathbf{1}_{pin}$. We have focussed in particular on the mode of addition of $\mathbf{1}_{pin}$ to *p*-fluorophenylacetylene (**2**) with the aim of distinguishing stepwise 1,2-addition involving metathesis (mechanism I), from direct *cis*-1,2-addition then dehydroboration (mechanism II), from direct *cis*-1,2-addition (mechanism III), from stepwise 1,2-addition, that does not involve C-B bond formation with the catalyst (mechanism IV).

2. Elimination of 'Uncatalyzed' Reactions. There are conflicting reports in the literature regarding the direct hydroboration of alkynes by 1,3,2-dioxaborolanes (**1**)[9] Thus, although it is widely accepted that $\mathbf{1}_{cat}$[9b] is relatively unreactive to simple alkynes, frequently requiring heating under solvent-free conditions,[23] pinacolborane, $\mathbf{1}_{pin}$,[9c] is sometimes reported to react efficiently with alkynes at ambient temperature in solution.[9c,24,,25] 1,3,2-Dioxaborolanes (**1**) can undergo disproportionation,[26] especially in the presence of nucleophilic Lewis bases,[26a] to generate borates and BH_3. The latter is a known catalyst for alkyne hydroboration,[11mn] and thus impure or aged solutions, of $\mathbf{1}_{pin}$, or those prepared *in situ* from pinacol and $H_3B{\cdot}SMe_2$,[9c] can contain sufficient BH_3 to undergo efficient but *indirect* (i.e. catalyzed)[11n] reaction with alkynes. We began by confirming[25] that, in the absence of a deliberately introduced catalyst,[10,11] $\mathbf{1}_{pin}$ does not react with alkyne **2** in solution at 23 °C, or undergo disproportionation to generate B_2pin_3 + BH_3, and hydroboration products thereof. Of a range of solvents explored, a mixture of dioxane and $CHCl_3$ (1%) emerged as highly effective at stabilizing $\mathbf{1}_{pin}$,[27] and there was no detectable reaction of $\mathbf{1}_{pin}$ with **2** (600 mM) over a period of 24 hours at ambient temperature (99.9 % **2**, ^{19}F NMR spectroscopy; >99% $\mathbf{1}_{pin}$, <0.2 % B_2pin_3, ^{11}B NMR spectroscopy).

3. In situ ^{19}F NMR Spectroscopic Analysis. Addition of Cy_2BH to the stable solution of $\mathbf{1}_{pin}$ and **2** induces catalytic hydroboration, Scheme 3. Endpoint ^{19}F NMR spectroscopic analysis indicates that the product mixture contains *E*-$\mathbf{3}_{pin}$ (93%) and three minor components, linear alkenylborane *E*-$\mathbf{4}_{Cy}$ (0.3 %), branched alkenylborane *iso*-$\mathbf{4}_{Cy}$ (1.2 %), and 1,1-diborylalkane $\mathbf{5}_{pinCy}$ (5.4%). Variation of the catalyst loading led to changes in the relative proportions of the endpoint reaction products. Diboryl $\mathbf{5}_{pinCy}$, the product of formal double hydroboration,[28] was always generated in quantities directly

proportional to the Cy_2BH catalyst loading. In contrast, higher Cy_2BH loadings led to reduced quantities of *E*-**3**$_{pin}$.

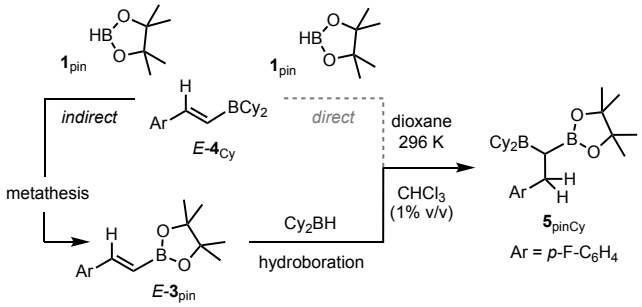
Scheme 3. $HBCy_2$-catalyzed hydroboration of alkyne **2**, together with intermediates and side-products detected by ^{19}F-NMR spectroscopy after 12 h at 23 °C.



In situ ^{19}F NMR spectroscopic monitoring of the reaction evolution, Scheme 3, indicates that the branched alkenylborane *iso*-**4**$_{Cy}$ is generated in concert with product *E*-**3**$_{pin}$, in a constant ratio of 1:89±1. In contrast, alkenylborane *E*-**4**$_{Cy}$ is generated transiently, reaching a maximum pseudo steady-state concentration after a short induction period. Increased catalyst loadings result in directly proportional increases in the concentration of transient alkenylborane *E*-**4**$_{Cy}$.[29] In contrast, diboryl **5**$_{pinCy}$ is present in low concentrations until >99% of alkyne **2** has been consumed. At this stage, the concentration of product (*E*-**3**$_{pin}$) becomes constant, the concentration of alkenylborane *E*-**4**$_{Cy}$ decays to zero, and diboryl **5**$_{pinCy}$ appears in direct inverse proportion to the decay in *E*-**4**$_{Cy}$. Identical kinetics were obtained in the absence of $CHCl_3$ (1%).[30] Changing from dioxane to THF as solvent had negligible impact on the temporal concentrations of the species detected by ^{19}F NMR spectroscopy (**2**, *E*-**3**$_{pin}$, *E*-**4**$_{Cy}$, *iso*-**4**$_{Cy}$, and **5**$_{pinCy}$). Standard graphical analysis of the concentration of **2** during its Cy_2BH-catalyzed reaction (Scheme 3) with **1**$_{pin}$, and systematic variation in the concentrations of all three components led to an empirical rate equation $d[\mathbf{3}_{pin}]/dt \approx k_{obs}[Cy_2BH]_0[\mathbf{1}_{pin}]_t$, consistent with all four mechanisms (I-IV), under specific constraints.

The generation of *E*-**4**$_{Cy}$, *iso*-**4**$_{Cy}$ and 1,1-diborylalkane **5**$_{pinCy}$ were further investigated by stoichiometric reactions. In the absence of **1**$_{pin}$, 1 equiv. of $(Cy_2BH)_n$ reacted instantly with **2** to give *E*-**4**$_{Cy}$ and *iso*-**4**$_{Cy}$ in an 89/1 ratio. Addition of 1 equiv. **1**$_{pin}$ to the mixture cleanly generated 1,1-diborylalkane **5**$_{pinCy}$ from *E*-**4**$_{Cy}$, Scheme 4. The same product (**5**$_{pinCy}$) was also cleanly generated on reaction of isolated purified *E*-**3**$_{pin}$ with 1 equiv. $HBCy_2$. Deconvolution of the direct versus indirect pathways from *E*-**4**$_{Cy}$ to **5**$_{pinCy}$ (Scheme 4) was achieved by isotopic labelling, *vide infra*.

Scheme 4. Stoichiometric hydroboration of alkenylboron species.[15,28] See text for full discussion of direct versus indirect reaction pathways from *E*-**4**$_{Cy}$ to **5**$_{pinCy}$.



4. Validation of Alkenylborane *E*-4 as an On-Cycle Intermediate. Having identified that *E*-**4**$_{Cy}$ is generated at a pseudo steady-state concentration that corresponds to the Cy_2BH catalyst loading, and that 1,1-diborylalkane **5**$_{pinCy}$ primarily accumulates after **2** has been consumed, we sought to test whether *E*-**4**$_{Cy}$ and **5**$_{pinCy}$ are intrinsic to the catalytic cycle (e.g. in mechanisms I and II), or are peripheral to the cycle, e.g. generated by non-productive side reactions. Preparation of d_4-**2**, in which the aromatic ring is perdeuterated, results in an upfield shift ($\Delta\delta$ = 0.5 ppm) in the ^{19}F NMR spectra of d_4-**2**, relative to **2**, and analogously into any products thereof. This facilitates detailed interrogation of mechanisms I-IV, by way of isotope-entrainment.[31]

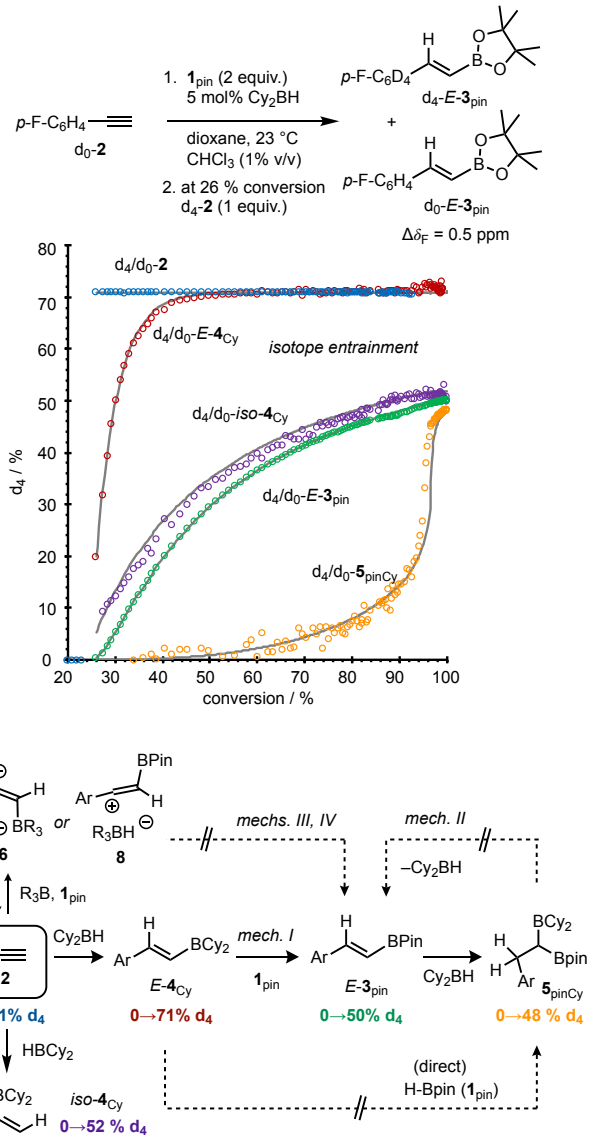


Figure 1. Isotope entrainment into the catalytic cycle, confirming on-cycle productivity of intermediate *E*-**4**$_{Cy}$ (→ *E*-**3**$_{pin}$) and its *indirect* conversion to **5**$_{pinCy}$ *via* *E*-**3**$_{pin}$. Open circles: experimental data (^{19}F NMR spectroscopy) for d_4-incorporation (%) versus net conversion of d_4/d_0-**2** + d_4/d_0-**4**$_{Cy}$ into d_4/d_0-*E*-**3**$_{pin}$, d_4/d_0-*iso*-**4**$_{Cy}$, and d_4/d_0-**5**$_{pinCy}$ (%). Solid lines: simulation of d_4-incorporation based on the kinetic model in Figure 3. Conditions: **1**$_{pin}$ (600 mM), **2** (295 mM), Cy_2BH, (30 mM), dioxane/$CHCl_3$ (99:1) at 296 K, with d_4-**2** (297 mM), added at 26% conversion.

Addition of d_4-**2** (0.5 equiv.) to a reaction of **2** (0.5 equiv.) and **1**$_{pin}$ (1 equiv.) undergoing turnover (Cy_2BH, 5 mol%) induces an isotopic perturbation. At the point of addition (26 % total conversion) the d_4/d_0-isotope ratio in the substrate pool **2**, is immediately raised from 0% to 71%-d_4. In situ ^{19}F NMR spectroscopic monitoring of the subsequent evolution of the d_4/d_0-isotope ratios (%) in **2**, *E*-**4**$_{Cy}$,

iso-**4**$_{Cy}$, *E*-**3**$_{pin}$, and **5**$_{pinCy}$, as a function of conversion, Figure 1, reveals numerous features:

i) There are no significant reversible reactions connecting **2** with any intermediates or products, on or off cycle: **2** remains 71%-d_4 throughout.

ii) The isotope ratio in transient intermediate *E*-**4**$_{Cy}$ grows, in advance of all other species except for **2** (which undergoes a step-change at the point of addition) and soon approaches the same level as **2**, i.e. 71%-d_4.

iii) The isomeric alkenylborane *iso*-**4**$_{Cy}$, generated in low proportion (1.2 % of total product), also accumulates d_4, at a slower rate than *E*-**4**$_{Cy}$, but in advance of *E*-**3**$_{pin}$. It eventually reaches 52%-d_4; this value corresponds exactly to that predicted for irreversible generation of *iso*-**4**$_{Cy}$ from **2**, as an inert product.

iv) Product *E*-**3**$_{pin}$ accumulates d_4 after addition of d_4-**2**, rising to 50%-d_4 after a short induction period. The accumulation of d_4 in *E*-**3**$_{pin}$ is thus dependent on the growth of d_4 in an intermediate that connects it (mechanisms I, II) with the substrate **2**. Thus, *E*-**3**$_{pin}$ is not generated directly from **2**, or transiently complexed **2**, mechanisms III, IV).

v) On complete consumption of **2**, the intermediate, *E*-**4**$_{Cy}$ undergoes decay, but retains its isotope ratio throughout (71%-d_4); it is thus generated and consumed irreversibly.

vi) 1,1-Diborylalkane **5**$_{pinCy}$ is present in low quantities (0.5%) throughout the first 95 % of the reaction evolution, during which the isotope ratio in **5**$_{pinCy}$ rises from 0 to 30%-d_4. In the final stage of reaction evolution there is a surge in the concentration of **5**$_{pinCy}$, where it is generated in inverse proportion to the decay in *E*-**4**$_{Cy}$ (~5 mol%). However, the isotope ratio maximum in **5**$_{pinCy}$ is 48%-d_4, demonstrating that that **5**$_{pinCy}$ is not generated via turnover of *E*-**4**$_{Cy}$ (71%-d_4) (mechanism II), but from *E*-**3**$_{pin}$ (≤50%-d_4) - i.e. the 'indirect' route, Scheme 4.

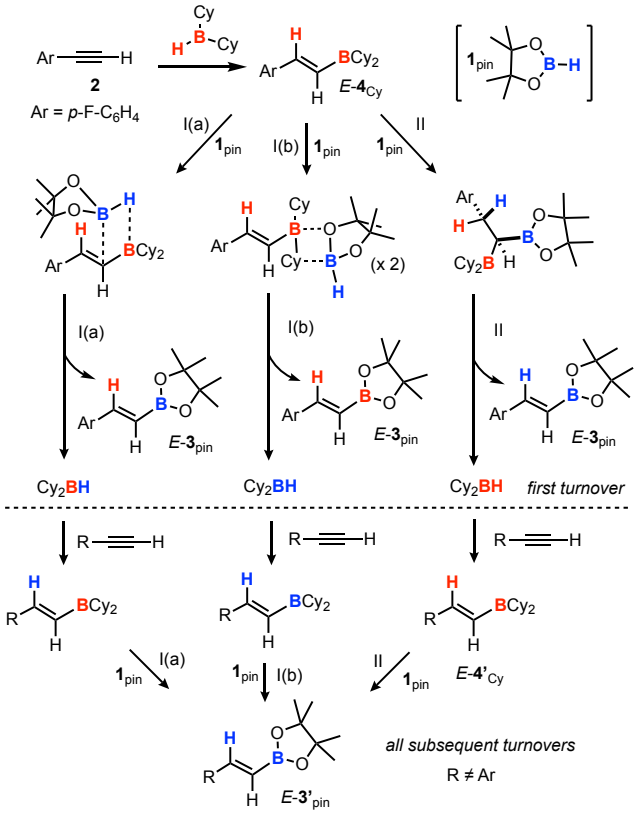
After complete consumption of **2**, addition of further **2** to the system (comprising *E*-**3**$_{pin}$, *iso*-**4**$_{Cy}$, **5**$_{pinCy}$, and **1**$_{pin}$) does not result in generation of *E*-**4**$_{Cy}$, or recovery of any significant turnover, or perturbation in the isotope ratios of *E*-**3**$_{pin}$, *iso*-**4**$_{Cy}$, **5**$_{pinCy}$, confirming that all of observed species are generated irreversibly under the conditions of catalysis. Together with the empirical rate equation, the isotope entrainment analysis (Figure 1) eliminates mechanisms II, III and IV; and places considerable constraints on I in terms of (lack of) reversibility at all stages. Inclusion of these constraints, as illustrated in the simplified mechanism I at the bottom of Figure 1, allows quantitative prediction of the isotope ratios as function of conversion when the resting state is *E*-**4**$_{Cy}$; see solid lines passing through data points in Figure 1, generated using the holistic kinetic model described below.

5. Single-Turnover ^{10}B,^{2}H-analysis of Metathesis Pathways. Attention was next focussed on the productive turnover of *E*-**4**$_{Cy}$ by **1**$_{pin}$ to give Cy_2BH + *E*-**3**$_{pin}$. In common to metathesis mechanisms Ia and Ib, Scheme 2, is the retention of the *cis*-H in *E*-**4**$_{Cy}$ in the product *E*-**3**$_{pin}$; see upper left-hand side of Scheme 5 where the *cis*-H in both *E*-**4**$_{Cy}$ and *E*-**3**$_{pin}$ is colored red. This provides simple differentiation of mechanism I from mechanism II. In the latter, the *cis*-H in *E*-**4**$_{Cy}$ is eliminated via *syn*-stereospecific dehydroboration during generation of *E*-**3**$_{pin}$; see upper right-hand side of Scheme 5, where the liberated Cy_2BH has *B*-H colored red. The two pathways for metathesis (Ia, 1b) are differentiated from each other by the boron atom in *E*-**4**$_{Cy}$ (colored red in the upper part of Scheme 5) which is transferred into Cy_2BH in mechanism Ia, but retained in *E*-**3**$_{pin}$ in mechanism Ib.

In principle then, it is simple to distinguish mechanisms Ia, Ib, and II by ^{1}H/^{2}H and ^{10}B/^{11}B labelling of the Cy_2BH catalyst and reagent **1**$_{pin}$, and analysis of the isotopic provenance of *cis*-H and B in the product *E*-**3**$_{pin}$, as illustrated by red/blue coloring in Scheme 5. However, two factors corrupt this analysis: i) for mechanism I, repeated catalytic turnover of Cy_2BH generates *E*-**3**$_{pin}$ with a different label distribution to the first turnover, see lower section to Scheme 5; and ii) reversible generation of μ-H borane dimers, scrambles the *B*-H/D labelling patterns in **1**$_{pin}$ / Cy_2BH. Neither problem is solved by stoichiometric reaction between *E*-**4**$_{Cy}$ and **1**$_{pin}$, because 1,1-diborylalkane **5**$_{pinCy}$ is rapidly generated from Cy_2BH + *E*-**4**$_{Cy}$ (Scheme 4) when there is no alkyne (**2**) present.

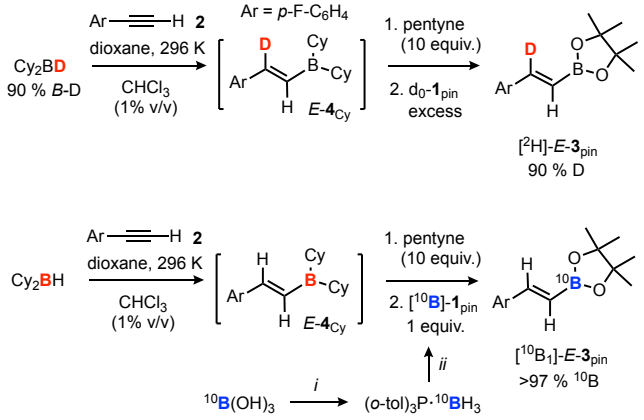
To bypass these complications, we conducted single turnover analysis[32] via sequential-additions of Cy_2BH (cat.), then RC≡CH (R ≠ Ar), then **1**$_{pin}$, to the alkyne **2**. As illustrated schematically in the lower section of Scheme 5, this effects *in situ* generation of *E*-**4**$_{Cy}$ and its conversion to *E*-**3**$_{pin}$, with the regenerated Cy_2BH catalyst being sequestered in further turnover that converts RC≡CH to *E*-**3'**$_{pin}$ *via* *E*-**4'**$_{Cy}$. The *E*-**3**$_{pin}$ emerging from the first turnover is then separated, and analyzed by ^{1}H and $^{10/11}$B NMR spectroscopy, and by MS.

Scheme 5. H and B migrations (red, blue) under catalytic conditions during the first, and all subsequent turnovers, during conversion of on-cycle intermediate *E*-**4**$_{Cy}$ to *E*-**3**$_{pin}$ by **1**$_{pin}$. Coloring illustrates differentiation of B-H/C-B metathesis (Ia), B-O/C-B metathesis (Ib), and *syn*-dehydroboration (II) mechanisms.



Commercially-available D_3B·THF was reacted with cyclohexene to generate (d_n-Cy_2)BD *in situ*. Control experiments (see SI) indicated 90% *B*-D. Single turnover analysis, using pentyne to sequester Cy_2BH and **1**$_{pin}$, gave *E*-**3**$_{pin}$ that was 90 % deuterated at *cis*-H, Scheme 6. This is fully consistent with metathesis pathways Ia and Ib, and eliminates mechanism II. Labelling of the boron intermediates required development of a reliable synthesis of stable solutions of pure [^{10}B]-**1**$_{pin}$, ≥ 97% ^{10}B, in dioxane/$CHCl_3$, Scheme 6 lower; see SI for full details. With [^{10}B]-**1**$_{pin}$ in hand, single-turnover, followed by isolation of *E*-**3**$_{pin}$ and analysis by ^{10}B/^{11}B NMR spectroscopy using natural abundance $ArBF_3K$ as an internal reference, indicated that [^{10}B]-*E*-**3**$_{pin}$ (≥ 97% ^{10}B) is generated. This result is fully consistent with metathesis pathway Ia, and eliminates B-O/C-B metathesis (alkoxy ligand exchange, pathway Ib), Scheme 6.

Scheme 6. Single-turnover analysis[a] of *E*-**3**$_{pin}$ generated from Cy_2BD + **1**$_{pin}$ and Cy_2BH + ^{10}B-**1**$_{pin}$.[b]



[a]Analyses by ^{1}H and $^{10/11}$B NMR spectroscopy, and MS; see SI. [b]Conditions: i) iPrOH, 3 equiv. CaH_2, 4 equiv. 90 °C; distill 60 °C, 40-60 mBar; then $LiAlH_4$ 0.8 equiv, *o*-tol_3P, 1.5 equiv. THF, 0 °C; then Rochelle salt, aq.; then 3% aq. H_2O_2; 52-72% ii) pinacol, 0.77 equiv., dioxane / $CHCl_3$ (1%), 57 °C, 16h, then distil, 40°C, 60-90 mBar; 1.09 M solution in dioxane / $CHCl_3$, 50% yield from pinacol.

6. Mechanism and Kinetics of Cy_2BH Catalysis via Alkenyl B-H/C-B Metathesis (pathway Ia). The full catalytic cycle for Mechanism Ia was explored using the M06L/6-311++G** level of theory, which had previously been found effective for the protodeboronation reaction.[33] All calculations were performed in Gaussian09,[34] with dioxane solvation incorporated via a polarizable continuum model (PCM) single point at the same level of theory. Free energy corrections were computed with 'goodvibes'[35] at T = 298 and standard state concentration of 1M. Geometries and energies (including a description of the low energy conformations) are provided as supporting information.

The calculated barrier for the direct (uncatalyzed) reaction of **1**$_{pin}$ with **2** is very high ($\Delta G^{\ddagger}_{calc.}$= 46 kcal mol^{-1}), consistent with the requirement for catalysis.[11j,m,o,25] For catalysis by Cy_2BH, the resting state was found to be *E*-**4**$_{Cy}$. Metathesis by **1**$_{pin}$ (k_2) is calculated to be turnover-rate limiting ($\Delta G^{\ddagger}_{calc.}$= 19.7 kcal mol^{-1}; Figure 2), in excellent agreement with the experimental rate of turnover, $\Delta G^{\ddagger}_{exp.}$= 20.3 kcal mol^{-1}. Rapid capture of the liberated Cy_2BH by **2** ($\Delta G^{\ddagger}_{calc.}$= 14 kcal mol^{-1}), completes the cycle, which is thus consistent with the empirical rate-equation in which the turnover frequency is first order in both **1**$_{pin}$ and [BCy_2]$_{tot}$. The B-H/C-B metathesis (pathway Ia) is calculated to proceed in a step-wise manner involving a transient μ-H bridged intermediate (*E*-**9**$_{pinCy}$) where a B-C-B assembly is midpoint between transfer of the alkene from one boron to the other, with retention of *E*-configuration (see lower section of Figure 2). Intermediate *E*-**9**$_{pinCy}$ is somewhat analogous to a number of isolated B-C-B and Al-C-Al complexes.[36] In a detailed study of a closely related structure, Holthausen and Wagner determined the bonding in this type of intermediate to involve two 2-electron-3-centre ('2e3c') bonds.[36a] The first employs the 1s orbital of the bridging hydrogen while the second employs an sp2 hybrid orbital from the bridging carbon, see schematic illustration at the bottom Figure 2. In accordance with the nature of these previously described structures, the double bond is almost unperturbed in the intermediate *E*-**9**$_{pinCy}$ (C=C 1.36 Å, C=C-H 116°).

Whilst the thermodynamic driving force for overall hydroboration (**2** +**1**$_{pin}$ → *E*-**3**$_{pin}$) is substantial[37] ($\Delta G_{calc.}$= –33 kcal mol^{-1}), that for the metathesis step *E*-**4**$_{Cy}$ + **1**$_{pin}$ → *E*-**3**$_{pin}$ + Cy_2BH is low. The calculations, see Figure 2, also confirm that the disfavored Markovnikov hydroboration product *iso*-**4**$_{Cy}$ has a large barrier to metathesis by **1**$_{pin}$ ($\Delta G^{\ddagger}_{calc.}$= 25.7 kcal mol^{-1}) and that **5**$_{pinCy}$ is generated irreversibly: dehydroboration to regenerate *E*-**3**$_{pin}$ + Cy_2BH, $\Delta G^{\ddagger}_{calc.}$= 29 kcal mol^{-1}. These features render generation of *iso*-**4**$_{Cy}$ and **5**$_{pinCy}$ catalyst termination steps, at ambient temperature.

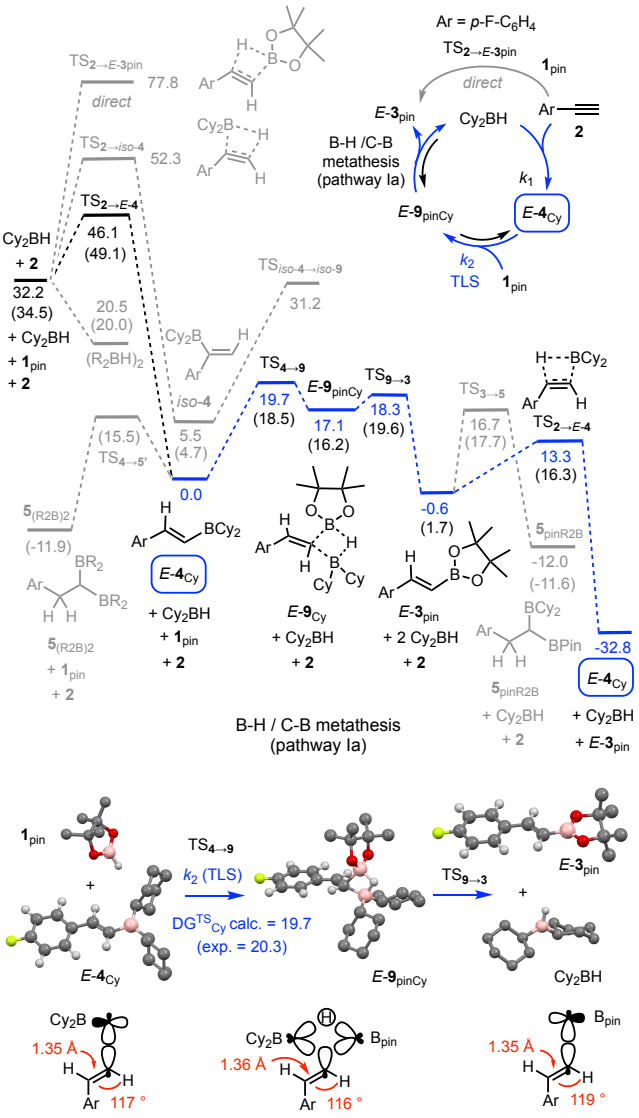


Figure 2. Upper: free energies (kcal mol^{-1}, M06L/6-311++G** PCM (dioxane, single point with M06L/6-311++G**) standard state, 1M, 298 K) of species in the reaction of **1**$_{pin}$ with **2** to generate *E*-**3**$_{pin}$, via intermediates *E*-**4**$_{Cy}$ and *E*-**9**$_{pinCy}$. Kinetically disfavored and inhibition pathways in grey; values in parentheses are for the analogous process with 9-BBN. Lower: calculated structures (H atoms on cyclohexyl and pinacolyl groups omitted for clarity) for the B-H/C-B metathesis process, with schematic illustration of the key orbitals and 2-electron-3-centre bonds.[36a]

With a more detailed mechanistic picture in hand, the full reaction evolution, as determined by in situ ^{19}F NMR spectroscopy, was explored across a range of initial concentrations. The kinetic model outlined in Figure 3, satisfactorily accounts for the temporal concentrations of all species detected by ^{19}F-NMR spectroscopy, Scheme 3, including generation of side product *iso*-**4**$_{Cy}$ and the secondary process that indirectly converts *E*-**4**$_{Cy}$ to **5**$_{pinCy}$, *via* **3**$_{pin}$, predominantly after complete consumption of **2**. The optimization of the model includes isotope entrainment of d_4-**2** into the catalytic cycle, see solid lines through datapoints in Figure 1. Five key features emerge from the analysis:

i) The rate of hydroboration of alkyne **2** by Cy_2BH (k_1) is far greater than the rate of reaction of *E*-**4**$_{Cy}$ with **1**$_{pin}$ (k_2), leading to *E*-**4**$_{Cy}$ being the dominant catalyst species throughout the reaction.

ii) The selectivity for anti-Markovnikov hydroboration (k_1/k_3) of **2** by Cy_2BH is moderate, leading to catalyst inhibition *via* generation of *iso*-**4**, occurring on average, once in every 89 turnovers.

iii) The rate of hydroboration of **2** by Cy_2BH (k_1) is around three orders of magnitude faster than *E*-**3**$_{pin}$ (k_4), leading to the majority of **5**$_{pinCy}$ being generated in the very last stages of reaction, when all of the alkyne **2** has been consumed.

iv) The impact of Cy_2BH aggregation,[38] which is extensive in the absence of alkyne **2**, is negligible, due to the low concentration of free borane.

v) Generation of *iso*-**4**$_{Cy}$ and **5**$_{pinCy}$ reduces the yield of *E*-**3**$_{pin}$. In principle, the highest yield of *E*-**3**$_{pin}$ attainable under these conditions is 98.5%, by use of 1.25 mol% Cy_2BH. This value assumes no catalyst deactivation pathways other than generation of *iso*-**4**$_{Cy}$ and **5**$_{pinCy}$.

vi) Unlike 9-BBN, *vide infra*, competing hydroboration of *E*-**4**$_{Cy}$ by Cy_2BH is negligible: **5**$_{(Cy)2}$ was not detected under the reaction conditions (≤0.1 %; $k_1/k_5 \geq 2.7\times10^3$).

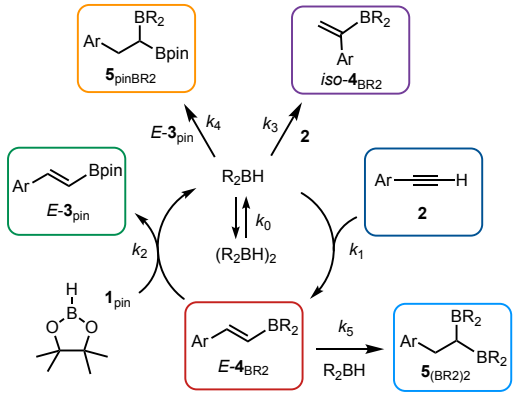
7. Catalysis by 9-BBN. Unlike the air-sensitive, in situ-prepared suspension of $(Cy_2BH)_n$,[38] the related secondary borane $(9\text{-BBN})_2$, is commercially-available as a crystalline solid, and as a readily-handled solution in THF. Although the majority of applications of $(9\text{-BBN})_2$ catalysis in Arase-Hoshi alkyne hydroboration have employed **1**$_{cat}$; it is also effective with **1**$_{pin}$ and has recently been used by Werner in the synthesis of *E*-stilbenes;[39] see SI for further examples. In situ ^{19}F-NMR spectroscopic analysis of the reaction of alkyne **2** with **1**$_{pin}$ catalyzed by $(9\text{-BBN})_2$, revealed a similar but not identical set of intermediates to those found for Cy_2BH. In situ ^{11}B NMR spectroscopic analysis also confirmed that the free 9-BBN is predominantly dimeric (K_0 <1.4×10^{-4} M; k_0 ~1 ×10^{-3} s^{-1})[40] under the reaction conditions. Independent reaction of alkyne **2** with 9-BBN generated *E*-**4**$_{9BBN}$ and the double hydroboration[28] product **5**$_{(9BBN)2}$, which was also detected (0.8%) during catalytic turnover. Reaction of isolated *E*-**3**$_{pin}$ with 9-BBN generated **5**$_{pin9BBN}$.

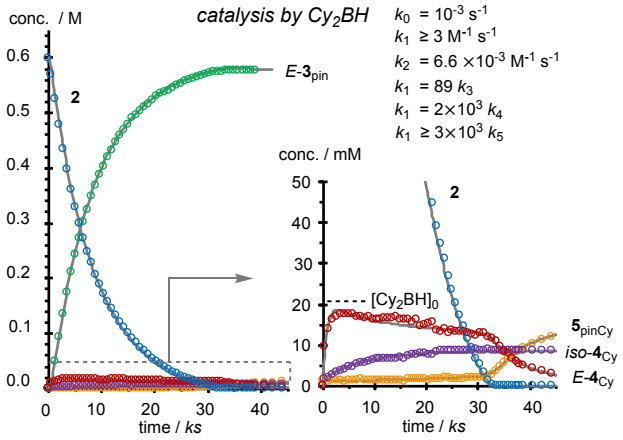
The catalytic cycle involving 9-BBN, generated by reversible dissociation from $(9\text{-BBN})_2$, was also explored using the M06L/6-311++G** level of theory, and the computed energies (see values in parentheses in Figure 2 and further detail of inhibition processes) used to guide simulation of the full reaction evolution, as determined by in situ ^{19}F NMR spectroscopy, at two $(9\text{-BBN})_2$ loadings. Hydroboration catalyzed by $(9\text{-BBN})_2$ (Figure 3, lower graphs) has a distinct profile, with three key points identified by computational and kinetic analysis:

i) Dimerization of the free 9-BBN (k_{-0}) leads to a low pseudo steady-state concentration of *E*-**4**$_{9BBN}$. Higher catalyst concentrations result in decreased selectivity (k_2/k_5) for *E*-**3**$_{pin}$ over **5**$_{(9BBN)2}$ (165/1 at 3 mol%; 75/1 at 6.8 mol% $(9\text{-BBN})_2$). Increasing the [**1**$_{pin}$]$_0$/[**2**]$_0$ ratio leads to less **5**$_{(9BBN)2}$ generation; however, with this substrate (**2**), this is only a minor inhibition pathway.

ii) The anti-Markovnikov selectivity (k_1/k_3) in hydroboration of **2** by 9-BBN is high (>400/1) leading to negligible inhibition.

iii) The rate of hydroboration of the product *E*-**3**$_{pin}$ by 9-BBN (k_4; to generate **5**$_{pin9BBN}$) competes significantly with hydroboration of **2** (k_1/k_4~5), leading to irreversible inhibition *throughout* the reaction, Figure 3. This reduces the maximum yield of *E*-**3**$_{pin}$ under these conditions to 65 %, using 11 mol% $(9\text{-BBN})_2$.





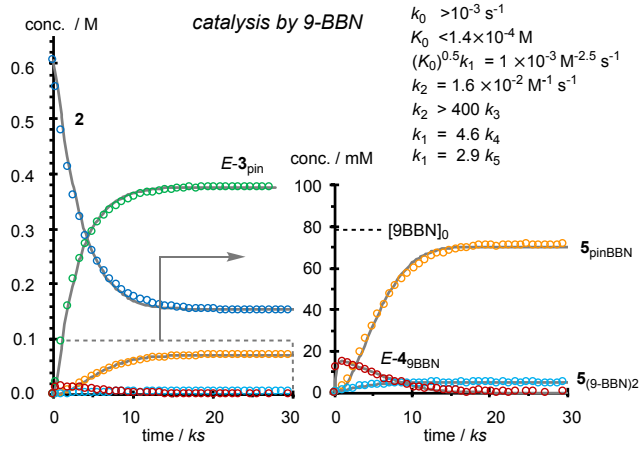


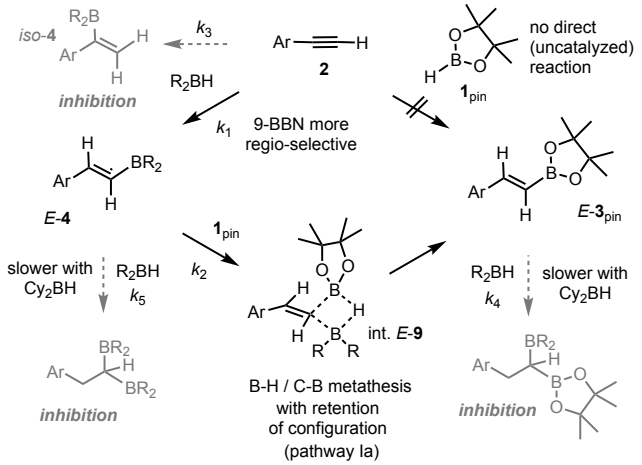
Figure 3. Temporal evolution of **2** (600 mM) + **1**$_{pin}$ (606 mM) at 296 K, in dioxane, containing 1 % v/v $CHCl_3$ stabilizer, after addition of $(Cy_2BH)_n$, 3.5 mol% (upper graphs) and $(9\text{-BBN})_2$, 6.8 mol% (lower graphs). Open circles experimental data (*in situ* ^{19}F NMR spectroscopy). Solid lines: simulations according to the kinetic models shown. For Cy_2BH, k_0 represents quasi-irreversible reactive dissolution of its suspension. For the 9-BBN simulation, K_0 represents a upper limit based on ^{11}B NMR spectroscopic analysis; the absolute rate constants should not be applied in isolation. See SI for full details.

8. Catalyst Inhibition in Arase-Hoshi Hydroboration.

The secondary boranes Cy_2BH and 9-BBN catalyse Arase-Hoshi hydroboration of alkyne **2** with different efficiencies. As discussed above, the dominant 'on-cycle' catalytic species for the reaction is identified as Ar-CH=CH-BR_2 (*E*-**4**), generated by irreversible anti-Markovnikov addition of the borane R_2BH to the alkyne (**2**). The relatively low barrier to irreversible reaction of *E*-**4** with **1**$_{pin}$ (~20

kcal mol^{-1}) allows the overall process to undergo turnover at ambient temperature. For both catalyst systems, a number of competing and irreversible hydroborations by R_2BH proceed in concert with turnover. These include Markovnikov hydroboration of the alkyne (to generate *iso*-**4**), addition to the on-cycle intermediate (*E*-**4**) to generate $\mathbf{5}_{(R2B)2}$, and addition to the net hydroboration product (*E*-$\mathbf{3}_{pin}$) to generate $\mathbf{5}_{pinR2B}$, all of which lead to catalyst inhibition and reduced yields.. As a result, the two catalysts Cy_2BH and 9-BBN have different optimum catalyst loadings; these reflect a compromise between total conversion of alkyne **2**, and overall yield of *E*-$\mathbf{3}_{pin}$. Conducting the reaction at higher temperatures and in different solvents will change selectivity and may also facilitate turnover of what are inhibited species at ambient temperature in dioxane.

Scheme 7. Arase-Hoshi catalysis by Cy_2BH versus 9-BBN.[11df,13,37]



For $\mathbf{1}_{pin}$ + *E*-**4**, the B-H/C-B-metathesis proceeds at a similar rate with 9-BBN (k_2 ~2 ×10^{-2} M^{-1}s^{-1}) as compared to Cy_2B (k_2 ~7×10^{-3} M^{-1}s^{-1}), but with the addition of R_2BH across the alkyne **2** proceeding with considerably higher regioselectivity (9-BBN, k_1/k_3 > 400; Cy_2B, , k_1/k_3 ~89), Scheme 7. Ostensibly, this suggests 9-BBN to be the superior catalyst. Indeed, many of the early applications of Arase-Hoshi hydroboration employed 9-BBN with $\mathbf{1}_{cat}$.[13] However, 9-BBN has a higher propensity than Cy_2BH to undergo secondary hydroboration[28] (k_4, *E*-$\mathbf{3}_{pin} \rightarrow \mathbf{5}_{pin9BBN}$; and k_5, *E*-$\mathbf{4}_{9BBN} \rightarrow \mathbf{5}_{(9BBN)2}$) leading to an earlier onset of termination of turnover. Hindered alkyne substrates that inhibit B-H/C-B-metathesis by **1**, or those bearing B-coordinating groups that can direct secondary hydroboration,[14] will exacerbate catalyst termination. Lack of turnover of intermediates analogous to *E*-**4**, by $\mathbf{1}_{pin}$ or $\mathbf{1}_{cat}$ explains why some alkynes that fail to undergo Arase-Hoshi catalysis, readily undergo stoichiometric hydroboration with 9-BBN,[14c] or Cy_2BH,[14a] and then direct cross-coupling.

CONCLUSIONS

In 1990, Periasamy described modest acceleration of alkyne hydroboration by catecholborane $\mathbf{1}_{cat}$, in the presence of $[H_3B{\cdot}N(Ph)Et_2]$[11ac] Five years later, Arase and Hoshi demonstrated that dialkyl boranes (R_2BH) are very efficient catalysts for alkyne hydroboration by $\mathbf{1}_{cat}$[11d] and pinacolborane ($\mathbf{1}_{pin}$)[11f] to generate synthetically useful alkenylboronate reagents.[6,8] This mild, efficient, and highly-selective procedure has enjoyed diverse applications in synthesis,[13,14] Scheme 1. Herein we have described a mechanistic analysis of Cy_2BH[13] and 9-BBN[13,37] catalyzed hydroboration of 4-fluorophenylacetylene (**2**) by $\mathbf{1}_{pin}$. Isotopic entrainment (Figure 1) confirms the major catalyst-derived species, Ar-CH=CH-BR_2 (*E*-**4**), is productive and 'on-cycle', undergoing turnover-limiting reaction with pinacolborane[9c] ('H-Bpin', $\mathbf{1}_{pin}$). M06L/6-311++G** calculations (Figure 2), and single-turnover isotopic labelling (^{2}H,^{10}B; Scheme 6) indicate stereospecific two-stage B-H/C-B metathesis, proceeding via a fleeting intermediate in which the alkene is pincered between two boron centres, by way of a μ-B-H-B bridge and a 2-electron-3-centre ('2e3c') B-C-B bond; Figure 2 and Scheme 7. This is the first direct experimental evidence for R_2BH generation from an alkenylboron proceeding via B-C-B transfer (mechanism Ia),[16d] rather than by alkoxy ligand exchange (mechanism Ib).[16a] The process is directly analogous to the mechanism for redistribution reactions of alkylboranes proposed by Köster in the 1960s,[16d] and the B-Ar-B species isolated and characterized in great detail by Holthausen and Wagner.[36a] It is also related to the generation of arylboronate products in the FLP-catalyzed borylation of heteroarenes,[41] the $\mathbf{1}_{pin}$-mediated liberation of Ar_2BH and Ar_2BH_2 from Ar_3B species,[11i] and to Ar_2BH liberation from a dimethylxanthene-based FLP.[11o] The kinetic and mechanistic details elucidated herein, will aid in the rational selection of conditions for application of Arase-Hoshi hydroboration,[13,14] as well as in the design of new selective boron-catalyzed reactions and processes.

ASSOCIATED CONTENT

Supporting Information: Additional discussion, experimental procedures, kinetic data and analysis, computational details, characterization data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author contributions

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Notes

The authors declare no competing financial interest.

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GRAPHICAL ABSTRACT