A Boron–Boron Double Transborylation Strategy for the Synthesis of gem-Diborylalkanes

A Boron-Boron Double Transborylation Strategy for the Synthesis of *gem*-Diborylalkanes

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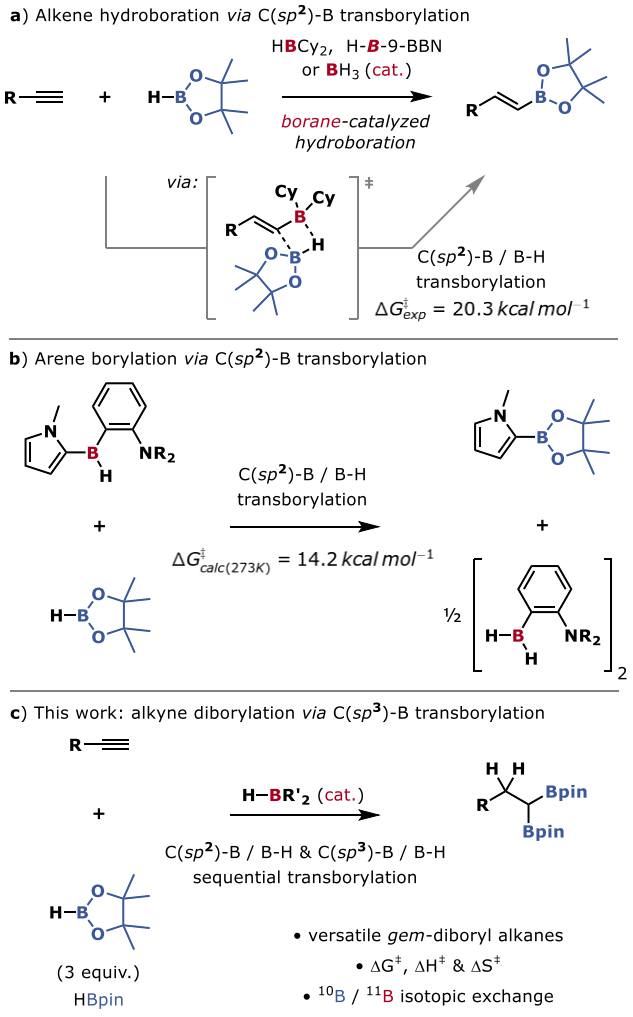
ABSTRACT: Olefin hydroboration reactions provide efficient access to synthetically versatile and easily-handled organoboronic esters. In this study we demonstrate that the commercially available organoborane reagent 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN) can serve as a catalyst for the sequential double hydroboration of alkynes using pinacolborane. This strategy, which is effective for a wide range of terminal alkynes, is predicated upon a key C(sp^3)-B / B-H transborylation reaction. Transition-state thermodynamic parameters and 10-boron-isotopic labeling experiments are indicative of an σ-bond metathesis exchange pathway.

Many organoborane (H-B) species undergo olefin hydroboration reactions under ambient conditions.[1,2] However, dioxaborolane derivatives [*i.e* $HB(OR)_2$] such as pinacolborane (HBpin) or catecholborane (HBcat) do not,[3] and require the use of a catalyst to enable reactivity.[4,5] A wide variety of catalysts and initiators has been reported to perform olefin hydroboration reactions with HBpin as the functional reagent, including transition metals[5] and main group species,[6] amongst others.[7] Of the many methods developed, borane-catalyzed alkyne hydroboration has emerged as a simple and powerful strategy for the formation of (*E*)-alkenylboronic esters (Scheme 1, **a**).[8] As such, this approach has been used in the construction of several natural products and pharmacologically active compounds.[9]

We recently investigated the $HBCy_2$-catalyzed reaction reported by Hoshi to find that the key turnover limiting transborylation step, C(sp^2)-B / B-H (exchange of boron groups), had a barrier of $\Delta G^{\ddagger}_{exp} = 20.3$ kcal mol^{-1} (Scheme 1, **a**).[10] Fontaine similarly demonstrated heteroarene C(sp^2)-B / B-H exchange as a key step for catalytic C-H bond borylation, and determined a transborylation barrier of $\Delta G^{\ddagger}_{calc(273K)} = 14.2$ kcal mol^{-1} (Scheme 1, **b**).[11] While C(sp^2)-B / B-H exchange has been synthetically used and studied, examples of extension to C(sp^3)-B / B-H transborylation have not been reported.[12] In the case of the

Scheme 1. Applications of transborylation



Hoshi-hydroboration, alkyne diborylation was found to inhibit catalysis and C(sp^3)-B / B-H transborylation was not observed.[10] Likewise, Fontaine's heteroarene hydroboration was proposed to proceed by ligand-exchange (O-B / B-H metathesis, $\Delta G^{\ddagger}_{calc} = 23.7$ kcal mol^{-1}) rather than C(sp^3)-B / B-H transborylation, suggesting that exchange at alkyl C(sp^3)-B bonds proceeds by ligand redistribution and not boron-boron transborylation. [13]

We questioned whether careful choice of borane structure could be used to overcome the energetic barrier to C(sp^3)-B / B-H transborylation and therefore provide a mechanism for the borane-catalyzed double hydroboration of alkynes, a transformation currently limited to metal-catalyzed processes.[14-16] The *gem*-diboryl alkane products are a class of synthetically versatile, stable alkyl boronic ester building blocks capable of diverse downstream functionalization.[16,17] Our strategy aimed to use an organoborane catalyst in combination with HBpin as the turnover reagent to access these products. Borane-catalyzed alkyne hydroboration to give an intermediate (*E*)-alkenyl pinacol boronic ester would be followed by a second borane-catalyzed hydroboration passing through an intermediate mixed *gem*-diboryl species (Bpin/B-9-BBN). Conversion of this intermediate to the product *gem*-diboryl alkane (Bpin/Bpin) would be key in establishing the mechanism of catalyst turnover.

Our investigations began by assessing the reactivity of a series of commonly used borane sources as potential catalysts for the sequential double hydroboration of alkynes. Using $HBCy_2$, [H-*B*-9-BBN]$_2$, H_3B•THF and H_3B•DMS as the boron catalyst and HBpin as the turnover reagent, reactivity towards phenylacetylene **1a** was assessed and reaction conditions optimized (Scheme 2, **a**). Of the potential borane catalysts tested, commercially available [H-*B*-9-BBN]$_2$ gave the greatest activity in achieving the borane-catalyzed formation of the *gem*-diboryl alkane product **2a** (Scheme 2, **a**, see also supporting information). However, the question of which mechanistic scenario was operating, ligand redistribution or C(sp^3)-B / B-H transborylation, remained.

In order to confirm the mechanism of catalyst turnover, a series of isotopic labelling experiments were conducted (Scheme 2, **b**-**e**). Use of DBpin gave deuterium incorporation at the benzylic position (d_2-**2a**), however at a level surpassing that expected given the hydride content of the catalyst (Scheme 2, **b**, 60% expected *vs*. 75% observed). This was explained by the observable hydrogen isotope exchange reaction between [H-*B*-9-BBN]$_2$ and DBpin, to give [D-*B*-9-BBN]$_2$ (Scheme 2, **c**). Use of monodeutero alkyne d_1-**1i**, under the standard reaction conditions, showed no deuterium migration from the terminal carbon (Scheme 2, **d**). The key question of ligand redistribution (9-BBN → pinacol) *vs*. C(sp^3)-B / B-H transborylation in the key catalyst turnover step was established using ^{10}B-enriched H^{10}Bpin (Scheme 2, **e**).[10] The *gem*-diboryl alkane $^{10}B_2$-**2a** was obtained with high ^{10}B-incorporation (93%), demonstrating that the boron from the catalyst is not incorporated into the product and thus indicating that catalyst turnover was C(sp^3)-B / B-H transborylation.

Scheme 2. Reaction conditions and mechanistic studies

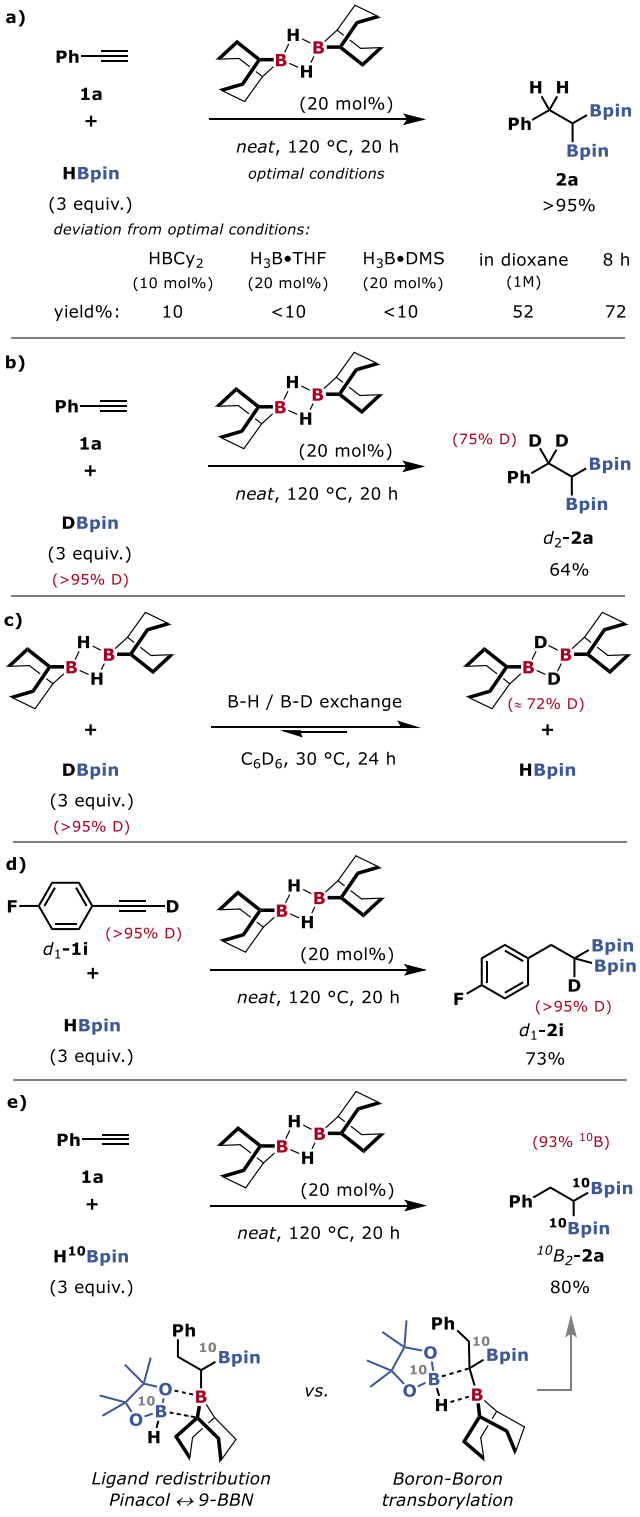
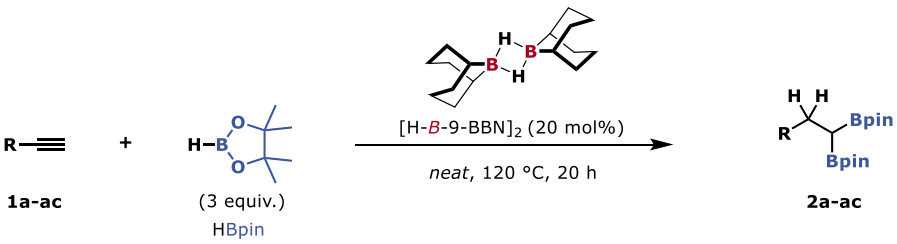
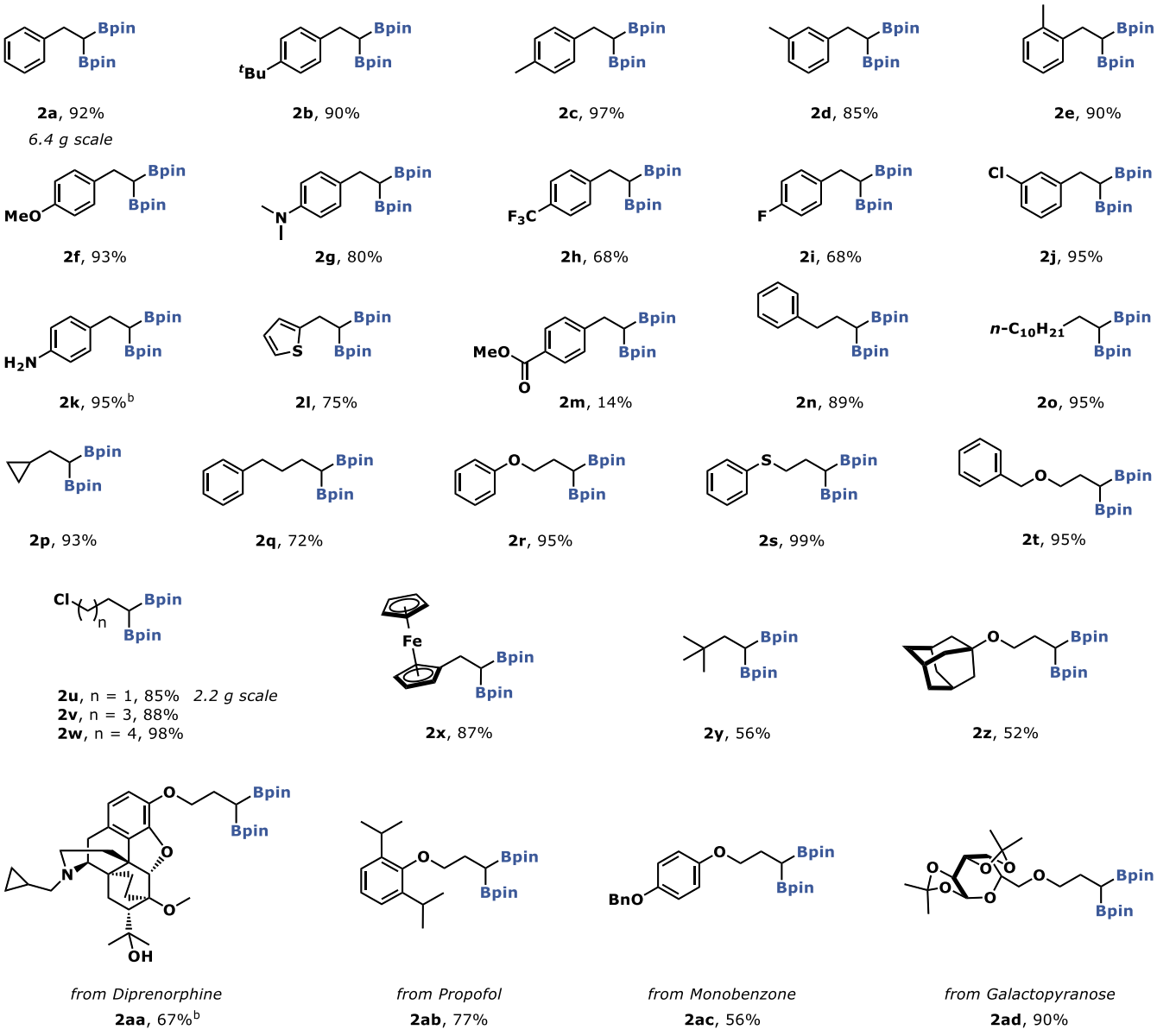


Table 1. Scope of borane-catalyzed double hydroboration.[a]





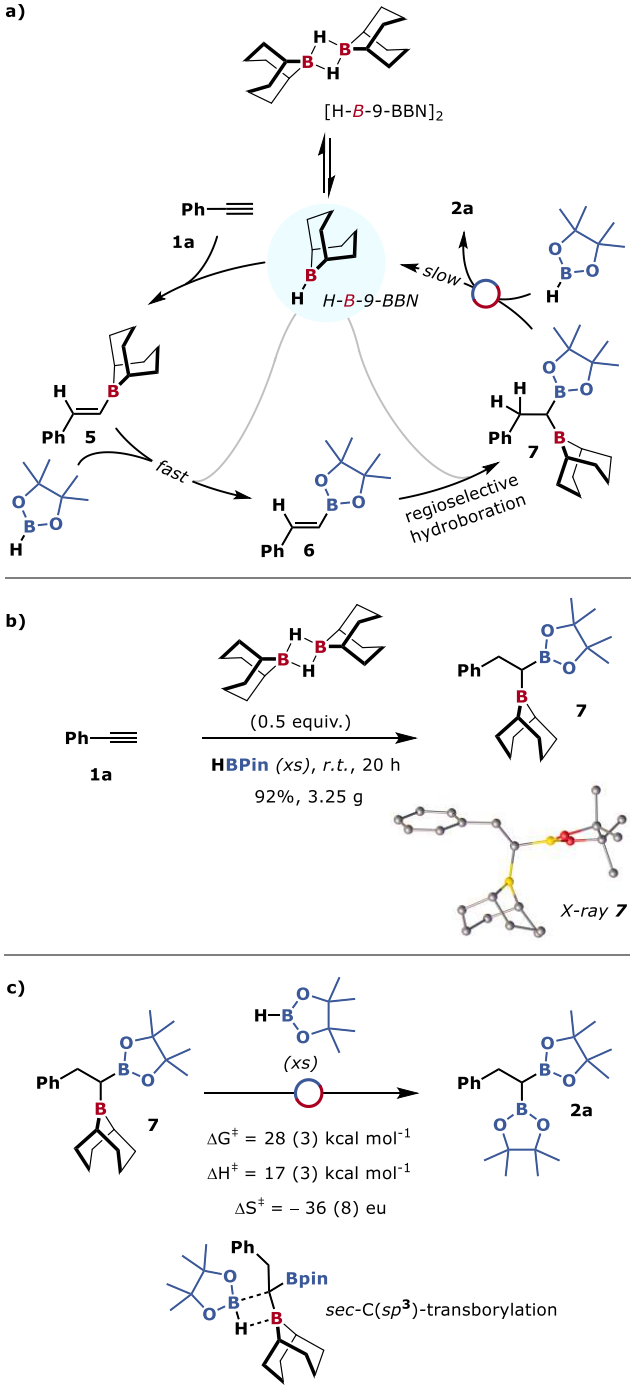
[a]Reaction conditions: alkyne (**1a-ac**), HBpin (3 equiv.), [H-*B*-9-BBN]$_2$ (20 mol%), *neat*, 120°C, 20 h. [b]HBpin (4 equiv.) were used. Reported yields are isolated (see supporting information).

Having found efficient reaction conditions and developed a mechanistic understanding, we assessed the generality of this strategy by application to a diverse scope of alkynes (Table 1). The gram-scale reaction of phenylacetylene **1a** with HBpin gave *gem*-diboryl alkane **2a** in high yield (6.4 g, 92%), without the formation of any observable minor regioisomers or mono-boryl products, as can be formed in metal-catalysed double hydroboration reactions.[14a,f] Extension to *para*-, *meta*- and *ortho*-substituted phenylacetylene derivatives **1b-e** generated the corresponding *gem*-diboryl compounds **2b-e** in excellent yields. Phenylacetylene derivatives bearing both electron-donating- **1f-g** and electron-withdrawing substituents **1h-j** were tolerated and gave the expected boronic esters **2f-j** in good to excellent yields. Examples containing basic nitrogen units such as 4-ethynyl-*N*,*N*-dimethylaniline **1g** reacted efficiently, while unprotected aniline derivative **1k** was 'protected' in situ by HBpin (4 equiv. instead of 3 equiv.)[18] to give the *gem*-diboryl alkane **2k** in excellent yield. However, application to ester **1m** gave only a low yield of *gem*-diboryl alkane **2m** due to concomitant ester reduction. Importantly the methodology was applicable to examples beyond aryl-alkyne derivatives, including a range of alkyl-alkynes **1n-ad**, and alkynes derived from pharmaceuticals; diprenorphine **1aa**, propofol **1ab** and monobenzone **1ac** and from a saccharide **1ad**.

Considering the observed reactivity, and that understood from C(sp^2)-B / B-H transborylation, a catalytic cycle could be proposed (Scheme 3, **a**). Firstly, [H-*B*-9-BBN]$_2$ dimer dissociation gives the reactive monomeric H-*B*-9-BBN that undergoes alkyne hydroboration to give (*E*)-alkenyl-B-9-BBN **5**.[19] Subsequent C(sp^2)-B / B-H transborylation generates (*E*)-alkenyl boronic ester **6** with concurrent regeneration of H-*B*-9-BBN, both of which react again to give mixed *gem*-diboryl intermediate **7**. A final, key, C(sp^3)-B / B-H transborylation gives the product *gem*-diboryl alkane **2a** and regenerates the catalyst (H-*B*-9-BBN).

Further investigation of the successfully demonstrated C(sp^3)-B / B-H transborylation relied on the formation and isolation of the mixed *gem*-diboryl alkane **7** (Bpin/*B*-9-BBN) intermediate which was observed during catalysis. Reaction of phenylacetylene **1a** with [H-*B*-9-BBN]$_2$ in excess HBpin as the reaction solvent at ambient temperature gave the mixed *gem*-diboryl intermediate **7** in multi-gram quantity, which could be characterized by X-ray crystallography (Scheme 3, **b**). Eyring analysis of the reaction between the mixed *gem*-diboryl alkane **7** and HBpin over 70 °C - 120 °C gave the thermodynamic parameters; $\Delta G^{\ddagger}$ = 28 (3) kcal mol^{-1}, $\Delta H^{\ddagger}$ = 17 (3) kcal mol^{-1} and $\Delta S^{\ddagger}$ = –36 (8) eu (Scheme 3, **c**, and see supporting information).[20] It is notable that the free energy value obtained for this C(sp^3)-B / B-H transborylation is significantly higher than those observed and calculated for C(sp^2)-B / B-H transborylation, and in line with the thermal barrier to productive catalysis.[10,13] Additionally, the large negative entropy term suggests a highly ordered transition-state structure, with significant loss of vibrational and rotational freedom; typical of σ-bond metathesis pathways.[21]

Scheme 3. Proposed mechanism and transborylation thermodynamics



In summary, we have discovered a double hydroboration-transborylation sequence for the borane-catalyzed formation of *gem*-diboryl alkanes. This strategy is a synthetically useful methodology which exploits a fundamental C(sp^3)-B / B-H transborylation from a secondary alkyl-*B*-9-BBN intermediate. Mechanistic studies demonstrated a boron-boron exchange with a large, negative, entropy value which is indicative of a σ-bond metathesis pathway in the key C(sp^3)-B / B-H transborylation step.

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Author Contributions

J.H.D and K.N carried out the practical work. J.H.D and S.P.T conceived the concept. A.P.D and S.P.T advised investigations. All authors contributed to the manuscript.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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