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A Boron−Oxygen Transborylation Strategy for a Catalytic Midland Reduction

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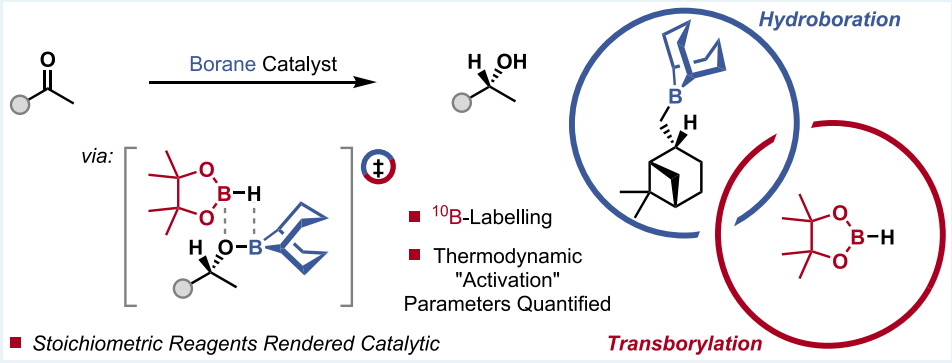

ABSTRACT: The enantioselective hydroboration of ketones is a textbook reaction requiring stoichiometric amounts of an enantioenriched borane, with the Midland reduction being a seminal example. Here, a turnover strategy for asymmetric catalysis, boron−oxygen transborylation, has been developed and used to transform the stoichiometric borane reagents of the Midland reduction into catalysts. This turnover strategy was demonstrated by the enantioselective reduction of ketones, including derivatives of biologically active molecules and those containing reducible groups. The enantioenriched borane catalyst was generated *in situ* from commercially available reagents, 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN) and *β*-pinene, and B−O transborylation with pinacolborane (HBpin) was used for catalytic turnover. Mechanistic studies indicated that B−O transborylation proceeded by B−O/B−H boron exchange through a stereoretentive, concerted transition state, resembling *σ*-bond metathesis.

KEYWORDS: *transborylation, hydroboration, enantioselective, boron, main group, asymmetric catalysis, ketone, reduction*

Catalysis underpins the sustainable future of chemical synthesis yet remains dominated by second- and third-row transition-metal species.[1] The entrenched mechanisms of catalysis—oxidative addition and reductive elimination—are not easily translated beyond the d-block.[2] Although great efforts have been made to force redox activity on main-group species, these have yet to be widely adopted.[3] Many main-group catalysts continue to rely on Lewis and Brønsted acid/base interactions to facilitate substrate binding and catalyst turnover.[4] New turnover mechanisms are needed to further the development and use of main-group catalysts.

Ligand redistribution is well established in the p-block and is routinely used in the synthesis of organoboron and organoaluminum species.[5] The ability to harness this redistribution offers a redox-neutral approach for main-group catalyst turnover. The hydroboration of alkenes and alkynes has been catalyzed by organoborane species[6] and is proposed to occur through a redistribution event between two boron centers.[7] This boron−carbon transborylation, a subclass of *σ*-bond metathesis, is analogous to transmetalation and has enabled the use of primary and secondary borane species as catalysts. Current examples of transborylation in catalysis are limited to boron−carbon bonds. Translation of this turnover pathway to boron−oxygen bonds, B−O transborylation, would open up a new class of reactivity for catalytic turnover.[8]

Asymmetric ketone hydroboration using stoichiometric enantioenriched boranes has found widespread use in total synthesis.[9] The Midland reduction[10] using Alpine-borane **2a** represents the most applied example (Scheme 1a). A major drawback of this method is the concurrent destruction of the stoichiometric enantioenriched reagent **2a** upon hydrolysis of the borinic ester **3** to give the enantioenriched alcohol **5**. Development of B−O transborylation would render this

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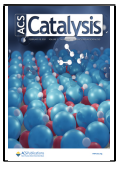

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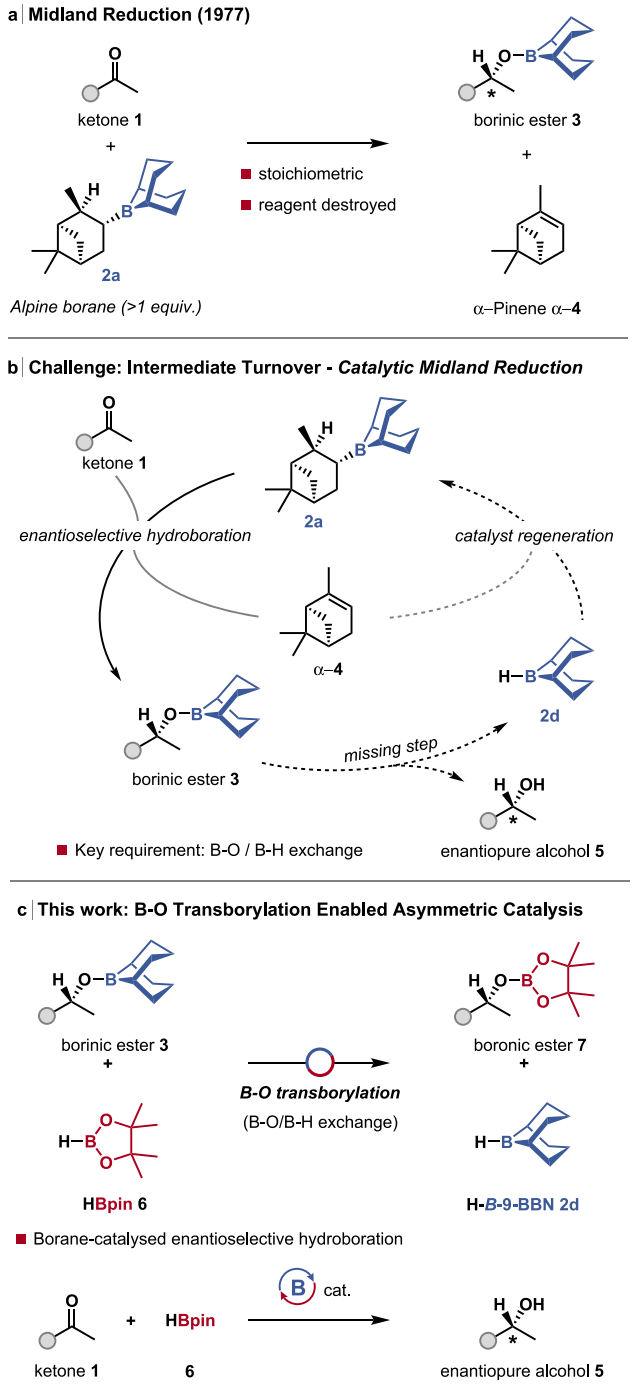
Scheme 1. Transborylation for Catalytic Turnover in Borane Reduction Reactions[a]



[a]Legend: (a) Midland reduction using Alpine borane **2a**; (b) missing step in proposed catalytic Midland reduction; (c) B−O transborylation as a turnover strategy for asymmetric catalysis.

reaction catalytic in borane **2a** and provide an exemplar of this turnover pathway in asymmetric catalysis (Scheme 1b).

The use of an isodesmic B−O/B−H transborylation for catalytic turnover represents a previously unexploited mechanism that enables catalyst regeneration. However, the activation barrier for this exchange poses a challenge in application to the Midland reduction due to the requirement of low temperature to maintain enantioselectivity. A significant requirement of this methodology is the regeneration of the catalyst after transborylation (Scheme 1b). This requires chemoselective alkene hydroboration in the presence of excess ketone. Five key mechanistic challenges must be addressed for the successful realization of B−O transborylation enabled asymmetric catalysis:

(i) establishment of B−O/B−H transborylation.
(ii) conservation of enantiomeric excess during B−O/B−H transborylation.
(iii) chemo- and stereoselective regeneration of the borane catalyst.
(iv) suppression of unselective ketone reduction by achiral boron reagents (H-*B*-9-BBN and HBpin).
(v) suppression of B−C/B−H transborylation to avoid catalyst deactivation.

Herein B−O transborylation has been developed and used as a strategy for catalytic turnover in asymmetric ketone reduction (Scheme 1c). The previously stoichiometric Midland reduction was rendered catalytic, demonstrating this mode of catalysis.

The validity of B−O transborylation was established using single-turnover experiments with a range of enantiopure tertiary boranes (Scheme 2). The stoichiometric reduction of 4-phenyl-3-butyn-2-one **1a** with enantiopure boranes, showed that Alpine borane **2a**, myrtanyl-*B*-9-BBN (myrtanyl borane)[11] **2b**, and Soderquist's borane[12] **2c** gave good enantioselectivity (Scheme 2a). Soderquist's borane **2c** was not investigated further due to the lower ee achieved in comparison to other stoichiometric enantioenriched reductants. The Midland reduction proceeds by reaction of Alpine borane **2a** with a propargylic ketone to give the α-pinene α-**4** and the enantioenriched borinic ester **3a**, which is hydrolyzed to alcohol **5a** on workup. Here, B−O transborylation of the borinic ester **3a** and subsequent catalyst regeneration were investigated by *in situ* ^{1}H and ^{11}B NMR spectroscopy. The reaction of Alpine borane **2a** ($\delta(^{11}B)$ 87 ppm) with 4-phenyl-3-butyn-2-one **1a** gave the borinic ester **3a** ($\delta(^{11}B)$ 56 ppm) and free α-pinene α-**4** (Scheme 2b). Addition of HBpin **6**, to induce B−O/B−H transborylation, gave the alkoxyboronic ester **7a** ($\delta(^{11}B)$ 22 ppm) and H-*B*-9-BBN **2d** ($\delta(^{11}B)$ 28 ppm, dimer). The presence of H-*B*-9-BBN **2d**, rather than catalyst **2a**, suggested that α-pinene α-**4** was too hindered to undergo rapid hydroboration. Preventing catalyst regeneration allowed the unselective background reactions to dominate, giving a product with reduced *e.e.* (Scheme 2a; **2d, 6**). The hydroboration of 1,1-disubstituted alkenes, such as in β-pinene β-**4**, is fast[13] and would enable catalyst regeneration (Scheme 2c). Reaction of β-pinene-derived myrtanyl borane **2b** ($\delta(^{11}B)$ 87 ppm) with 4-phenyl-3-butyn-2-one **1a** gave the corresponding borinic ester **3a** ($\delta(^{11}B)$ 56 ppm) in high enantioselectivity (89% *e.e.*) and β-pinene β-**4**. Significantly, the addition of HBpin **6** showed formation of the alkoxyboronic ester **7a** ($\delta(^{11}B)$ 22 ppm), and re-formation of the borane catalyst **2b** ($\delta(^{11}B)$ 87 ppm). H-*B*-9-BBN **2d** was not observed, indicating that B−O transborylation was followed by rapid, chemoselective alkene hydroboration of β-pinene β-**4** to regenerate the catalyst **2b**.

With the stoichiometric B−O transborylation having been established using myrtanyl borane **2b**, the use of substoichiometric loadings was explored (Scheme 2d). For this catalytic protocol to be viable, the enantiomeric excess (e.e.) of the substoichiometric (catalytic) reaction must match that achieved using stoichiometric borane. This was quantified using enantiofidelity (*e.f.*), defined as the degree of enantiomeric excess retained in the substoichiometric reaction in comparison to the stoichiometric reaction (Scheme 2d). The reaction

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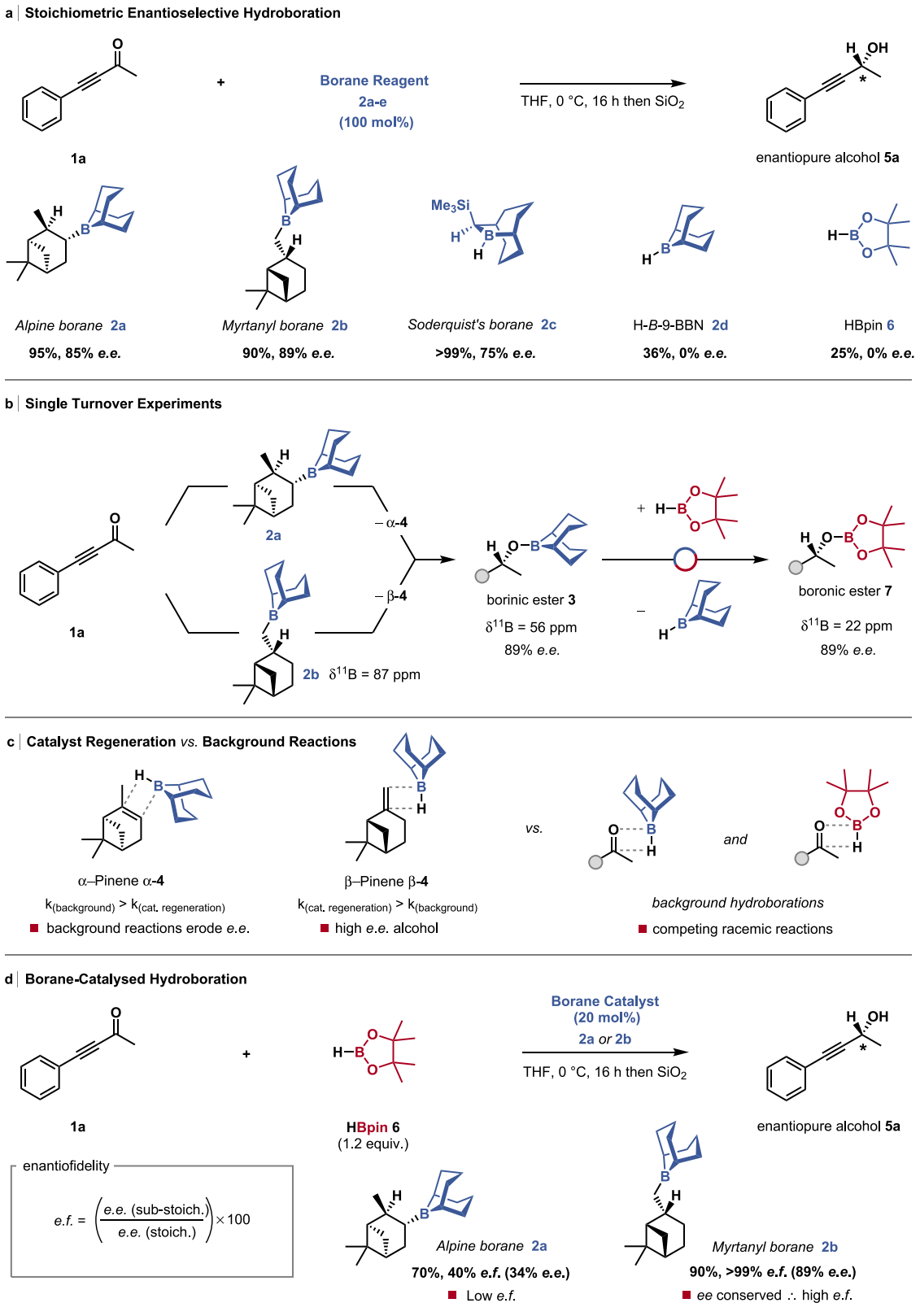
Scheme 2. Assessment of Stoichiometric Borane Reagents for Asymmetric Ketone Reduction and Translation to a Catalytic Method[a]



[a]Legend: (a) stoichiometric reduction of 4-phenyl-3-butyn-2-one **1a**; (b) single-turnover experiments using boranes **2a** and **2b** (chemical shifts and e.e. values refer to the reaction using myrtanyl borane **1b, corrected for use of 92% e.e. *β*-pinene**); (c) hydroboration of *β*-pinene versus *α*-pinene ***α*-4** and comparison to background unselective reductions; (d) catalytic reactions using boranes **2a** and **2b**.

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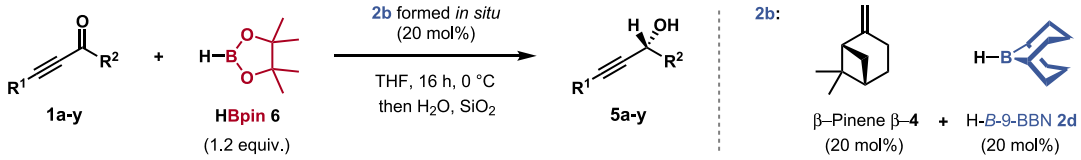
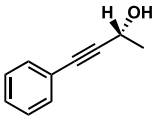
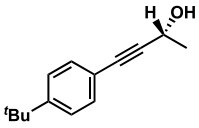
Table 1. Substrate Scope for the Transborylation-Enabled Asymmetric Ketone Reduction[f]

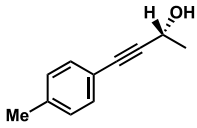




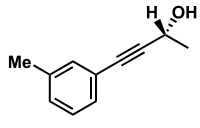
5a[a]
76%, 99% *e.f.*
(89% *e.e.*)



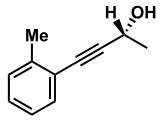
5b
65%, 89% *e.f.*
(89% *e.e.*)



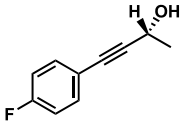
5c[b]
46%, 94% *e.f.*
(86% *e.e.*)



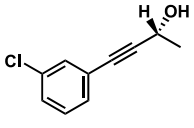
5d
36%, >99 *e.f.*
(84% *e.e.*)



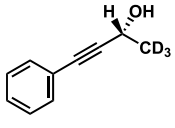
5e
62%, 97% *e.f.*
(77% *e.e.*)



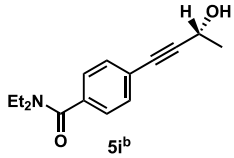
5f
65%, 87% *e.f.*
(73% *e.e.*)



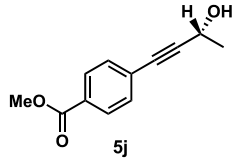
5g
32%, 66% *e.f.*
(46% *e.e.*)



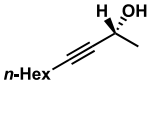
5h
70%, 86% *e.f.*
(62% *e.e*)



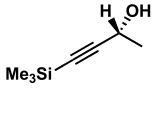
5i[b]
52%, >99% *e.f.*
(89% *e.e.*)



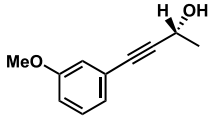
5j
78%, 74% *e.f.*
(67% *e.e.*)



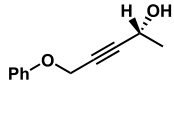
5k
60%, 79% *e.f.*
(34% *e.e.*)



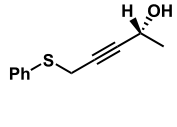
5l
75%, 94% *e.f.*
(64% *e.e.*)



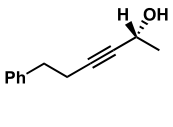
5m[a,b]
74%, 94% *e.f.*
(74% *e.e.*)



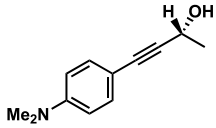
5n
35%, 84% *e.f.*
(70% *e.e.*)



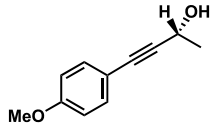
5o
43%, 90% *e.f.*
(78% *e.e.*)



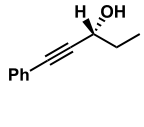
5p
53%, 65% *e.f.*
(59% *e.e.*)



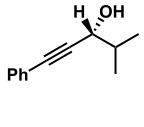
5q[c]
55%, 60% *e.f.*
(52% *e.e.*)



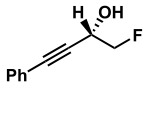
5r
54%, 50% *e.f.*
(44% *e.e.*)



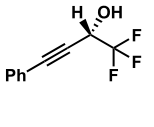
5s[a,d]
57%, 82% *e.f.*
(65% *e.e.*)



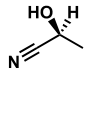
5t
57%, 39% *e.f.*
(24% *e.e.*)



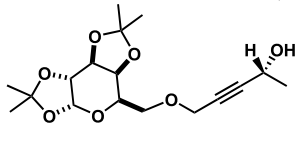
5u
60%, 44% *e.f.*
(35% *e.e.*)



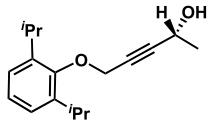
5v[a,d]
80%, 83% *e.f.*
(58% *e.e.*)



5w
62%, 91% *e.f.*
(65% *e.e.*)



5x[e]
63%, >95% *d.f.*
(64:36 *d.r.*)



5y
68%, 99% *e.f.*
(91% *e.e.*)

[a]Reaction at 18 °C: **5a** (92% yield, 35% *e.e.*), **5m** (88% yield, 49% *e.e.*), **5s** (92% yield, 34% *e.e.*) and **5v** (83% yield, 26% *e.e.*). [b]Reaction over 40 h. [c]An additional 1 mL of THF added (0.08 M, H-*B*-9-BBN **2d**). [d]HBpin **6** addition at 5.4 μL h^{-1}. [e]*d.f.* = 100 × (stoichiometric diastereomeric excess)/(catalytic diastereomeric excess). [f]Reaction conditions unless specified otherwise: (*S*)-*β*-pinene *β*-**4** (0.2 equiv), H-*B*-9-BBN **2d** (0.5 M in THF, 0.2 equiv), substrate **1a**–**y**, HBpin **6** (1.2 equiv), 16 h, 0 °C, then addition of H_2O and SiO_2. Isolated yields are reported. *e.e.* values for catalytic reactions are shown in parentheses, with the ee values corrected for the use of 92% *e.e.* (*S*)-*β*-pinene.

development was focused on achieving high enantiofidelity and not absolute enantioselectivity. To achieve high enantiofidelity, the rate of catalyst regeneration must exceed the rate of background reduction by the achiral boranes. The stoichiometric reaction of H-*B*-9-BBN **2d** and HBpin **6** with 4-phenyl-3-butyn-2-one **1a** gave the racemic alcohol (±)-**5a** in 25% and 36% yields, respectively, under conditions mimicking those of catalysis (Scheme 2a).

After optimization of the catalytic reaction conditions (Section S2 in the Supporting Information), the use of myrtanyl

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borane **2b** (20 mol %) and HBpin **6** (1.2 equiv) at 0 °C enabled the asymmetric reduction of 4-phenyl-3-butyn-2-one **1a** in 76% yield and 89% *e.e.* This matched the yield and enantioselectivity obtained using stoichiometric myrtanyl borane **2b** (90% yield, 89% *e.e.*), giving 99% *e.f.* and establishing B−O transborylation as a mechanism of turnover for asymmetric main-group catalysis. The catalytic asymmetric reduction was further applied to other substrate classes; however, this proved unsuccessful in the cases of acetophenone and 4-phenyl-3-buten-2-one (no reaction) and an α-keto ester and an α-keto thioester (poor *e.e.*) (see Table S1 in the Supporting Information).

The substrate scope of the catalytic asymmetric hydroboration was explored using myrtanyl borane **2b** as the catalyst, generated *in situ* by reaction of H-*B*-9-BBN **2d** (20 mol %) and β-pinene β-**4** (20 mol %) (Table 1). 4-Phenyl-3-butyn-2-one **1a** underwent hydroboration with excellent yield (90%) and enantiofidelity (99% *e.f.*). Substitution on the aromatic ring was tolerated, with excellent enantiofidelity observed for 4-*tert*-butyl (**1b**, 89% *e.f.*), 4-methyl (**1c**, 94% *e.f.*), 3-methyl (**1d**, >99% *e.f.*), and 2-methyl (**1e**, 97% *e.f.*) groups. Use of the 4-fluoro derivative **1f** gave good enantiofidelity (88% *e.f.*) whereas decreased enantiofidelity was observed for the 3-chloro analogue **1g** (66% *e.f.*). Lewis basic ether substituents **1n** (84% *e.f.*) and **1m** (92% *e.f.*) and the thioether **1o** (90% *e.f.*) gave high enantiofidelity, although the 4-methoxy-substituted **1r** gave lower enantiofidelity (50% *e.f.*). Reduced enantiofidelity was observed with the dimethylamino-bearing ketone **1q** (60% *e.f.*). Excellent chemoselectivity was observed, with groups expected to react with boranes being tolerated. Nitrile (**1w**, 91% *e.f.*), ester (**1j**, 74% *e.f.*), and amide substituents (**1i**, >99% *e.f.*) all gave excellent enantiofidelity. Propargylic ketones bearing electron-withdrawing substituents, such as **1f** (73% *e.e.*), **1g** (46% *e.e.*), and **1j** (67% *e.e.*), were reduced in moderate to good *e.e.*, presumably due to a greater rate of background, unselective reduction by HBpin. Propargylic ketones bearing electron-donating substituents **1a**−**e** consistently gave improved enantioselectivities (89−77% *e.e.*). However, in contrast to ketones bearng electron-donating groups about the arene, substrates bearing a mesomeric donor in the para position, **1q** (52% *e.e.*) and **1r** (44% *e.e.*), gave moderate to poor enantioselectivty. The greater Lewis basicity of these substrates may increase the rate of unselective reduction, by greater coordination to the achiral boranes. Although a higher rate of reaction was achieved at 18 °C, the enantioselectivity was decreased (**5a** (92% yield, 35% *e.e.*), **5m** (88% yield, 49% *e.e.*), **5s** (92% yield, 34% *e.e.*), and **5v** (83% yield, 26% *e.e.*), presumably as a result of the low temperature required for enantioselectivity in the Midland reduction.

Sterically encumbered ketones **1s** (63% *e.f.*) and **1t** (39% *e.f.*) gave poor to moderate enantiofidelity. Presumably, slow hydroboration by the enantioenriched borane allowed significant background reduction by the less sterically demanding, achiral boranes H-*B*-9-BBN **2d** and HBpin **6**. The trideuteriomethyl-substituted ketone **1h** was tolerated, but electron-withdrawing groups such as monofluoromethyl (**1u**, 44% *e.f.*) and trifluoromethyl (**1v**, 19% *e.f.*) gave reduced enantiofidelity. The trifluoromethyl ketone **1v** was reduced to the racemic alcohol (±)-**5v** by HBpin **6** in 86% yield under the reaction conditions, indicating that unselective hydroboration by HBpin **6** outcompetes the enantioselective reaction.

Controlling the concentration of achiral boranes (H-*B*-9-BBN **2d** and HBpin **6**) could suppress the rate of unselective hydroboration. The slow addition of HBpin improved the enantiofidelity in the reduction of ethyl- (**1s**) and trifluoromethyl-substituted (**1v**) ketones, with the enantiofidelity increasing from 63% to 82% *e.f.* and from 19% to 83% *e.f.*, respectively. The enantiofidelity could also be improved by reducing the H-*B*-9-BBN **2d** loading (10 mol %) while maintaining the β-pinene β-**4** loading (20 mol %); the enantiofidelity of ethyl ketone **1s** increased from 63% to 85% *e.f.* Reducing the reaction temperature to −20 °C improved the enantiofidelity (to 85% *e.f.*), albeit with reduced yield (22%).

Applying B−O transborylation to substrates derived from biologically active compounds proved successful. Asymmetric reduction of the galactopyranose-derived substrate **1x** gave high diastereofidelity (95% *d.f.*). Ketone **1y**, derived from propofol (Diprivan), was reduced with excellent enantiofidelity (99% *e.f.*). Gram-scale reduction of ketone **1a** under the standard conditions gave excellent enantiofidelity and yield (80% yield, 98% *e.f.*).

Two mechanisms of boron−boron exchange have been proposed: ligand redistribution and transborylation (Scheme 3a).[7,8,14] For ligand redistribution, the B−O bond of the borinic ester **3a** is maintained and the supporting ligands are exchanged with HBpin. Transborylation breaks the B−O bond on the borinic ester **3a** by σ-bond metathesis, with the boron atom of alkoxyboronic ester **7a** originating from HBpin. The reaction of H^{10}Bpin with borinic ester **3a** gave only the ^{10}B-labeled alkoxyboronic ester **^{10}B-7a**, as determined by ^{10}B and ^{11}B NMR spectroscopy (Scheme 3a). Therefore, exchange proceeded by B−O transborylation, not ligand redistribution. The thermodynamic properties of the B−O transborylation were determined using an Eyring plot constructed over the temperature range 301−315 K (Scheme 3b; see section S9 in the Supporting Information).[15] This supported a highly ordered transition-state structure for B−O transborylation with a large negative entropy value ($\Delta S^{\ddagger}$ = −21.5 eu)[16] and a Gibbs free energy ($\Delta G^{\ddagger}_{298}$ = 22.7 kcal mol^{-1}) similar to those of B−C(sp^2) ($\Delta G^{\ddagger}$ = 20.3 kcal mol^{-1})[7b] and B−C(sp^3) ($\Delta G^{\ddagger}$ = 28 kcal mol^{-1})[7a] transborylation reactions.

When all mechanistic investigations were taken into account, a catalytic cycle for the B−O transborylation-driven asymmetric ketone reduction was proposed (Scheme 3c). Enantioselective hydroboration of the ketone **1** by the borane catalyst **2b** through a Meerwein−Ponndorf−Verley-type transition state gives the enantioenriched borinic ester **3** and releases β-pinene β-**4** (*enantioselective hydroboration*).[11,17] B−O/B−H transborylation of borinic ester **3** with HBpin **6** gives the alkoxyboronic ester product **7** and releases H-*B*-9-BBN **2d** (*transborylation*). The borane catalyst **2b** is regenerated by highly chemo-, regio-, and diastereoselective hydroboration of β-pinene β-**4** by H-*B*-9-BBN **2d** (*alkene hydroboration*).

In summary, B−O transborylation has been established and applied as a turnover mechanism for asymmetric main-group catalysis. A catalytic Midland reduction has been enabled, using B−O/B−H transborylation and myrtanyl borane **2b** as the asymmetric catalyst, across a range of functionalized substrates with excellent enantiofidelity. B−O transborylation was found to proceed by a σ-bond metathesis mechanism. Modification of the catalytic protocol to reduce racemic background reductions by achiral boron reagents (H-*B*-9-BBN **2d** and HBpin **6**) ensured high enantiofidelity for challenging substrates. This application of B−O/B−H transborylation demonstrates the potential of transborylation to be used as a general platform for main-group catalysis.

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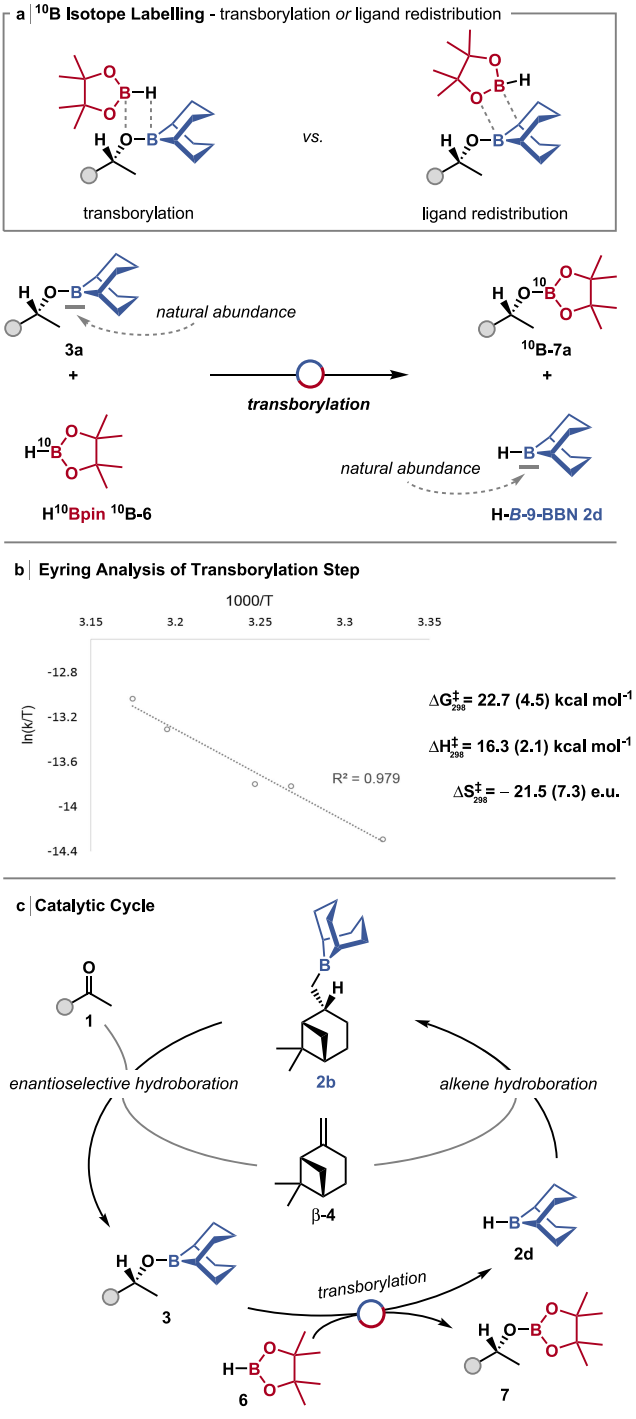
Scheme 3. Mechanistic Investigations[a]



[a]Legend: (a) ^{11}B NMR and ^{10}B NMR labeling experiments; (b) Eyring analysis of B−O/B−H transborylation (c) proposed catalytic cycle. Ketone = 4-phenyl-3-butyn-2-one **1a**.

■ ASSOCIATED CONTENT

Supporting Information

this material is available free of charge via the Internet at . The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05168.

Additional discussion, experimental procedures, kinetic data and analysis, computational details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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