Borane-Catalyzed, Chemoselective Reduction and Hydrofunctionalization of Enones Enabled by B–O Transborylation

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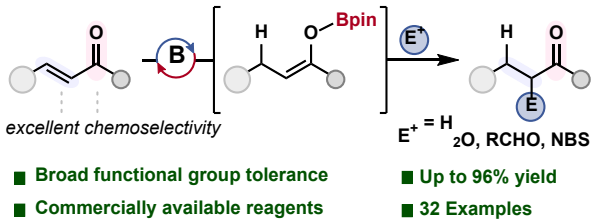
Supporting Information Placeholder



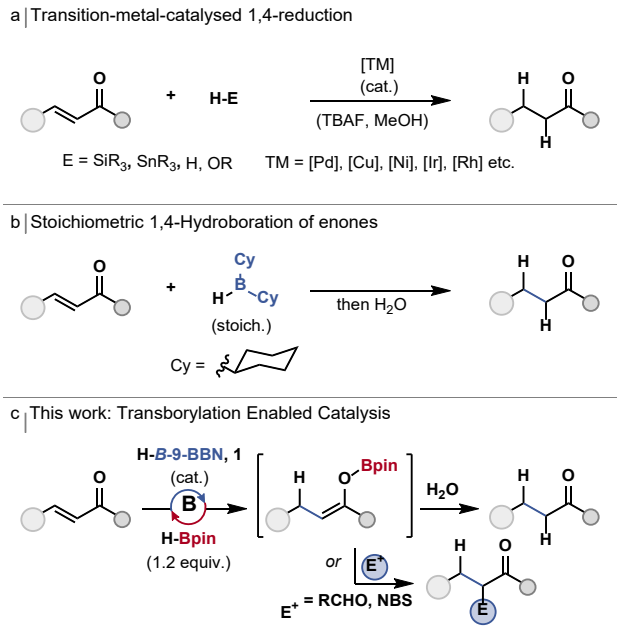
ABSTRACT: The use of stoichiometric organoborane reductants in organic synthesis is well established. Here, these reagents have been rendered catalytic through an isodesmic B−O/B−H transborylation, applied in the borane-catalyzed, chemoselective alkene reduction and formal hydrofucntionalization of enones. The reaction was found to proceed by a 1,4-hydroboration of the enone and B−O/B−H transborylation with HBpin enabling catalyst turnover. Single-turnover and isotopic labelling experiments supported the proposed mechanism of catalysis with 1,4-hydroboration and B−O/B−H transborylation as key steps.

Chemoselective reductions are an important tool in the synthesis of natural products and pharmaceutical targets.[1] The ability to selectively reduce one functional group over another removes the requirement of protecting groups, and results in elegant and atom economic syntheses. The chemoselective reduction and reductive functionalization of enones at the alkene is of interest as the resulting ketones are found in a wide array of biologically active compounds.[2-6]

The chemoselective reduction of enones at the C=C bond is dominated by transition metal catalysis using hydrogenation,[7-12] transfer hydrogenation,[13-27] and silanes[28-39] as the terminal reductants (Scheme 1, a). Main-group strategies for enone reduction have generally focussed on carbonyl reduction, most notably using borohydride reagents[40] and the CBS catalyst to give enantioenriched allylic alcohols.[41] Several stoichiometric, main-group methods for the reduction of the enone C=C bond have been reported including the use of hydride reagents[42] and selenium-[43] and sulfur-derived reductants.[44]

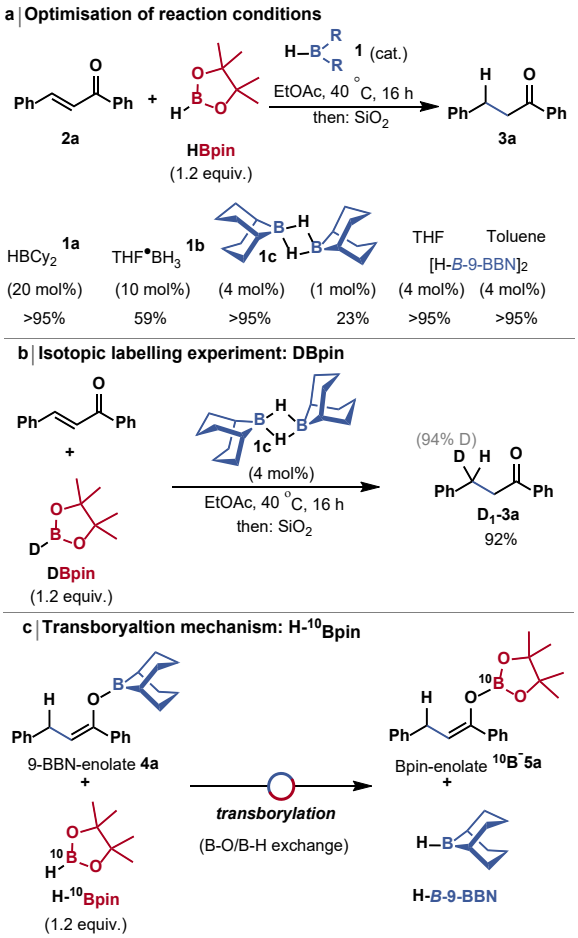
Main-group strategies for the reduction of enones to saturated ketones include the use of dihydropyridines,[45-48] frustrated Lewis pairs,[49,50] bismuth catalysis,[51] and phosphoric acid catalysis using hydroboranes[52] and hydrosilanes[53-55] as the terminal reductants. However, these methods generally have limited substrate scope with respect to chemoselectivity over reducible functional groups, require multi-step synthesis of catalysts, or suffer from limited sustainability of the reaction condotions.[49-55] Alternatively, hydroboranes such as catechol borane (HBcat), dicyclohexyl borane ($HBCy_2$) and 9-borabicyclo[3.3.1]nonane

Scheme 1.



(H-*B*-9-BBN) can be used as stoichiometric reductants for reduction of enones by 1,4-hydroboration, which following hydrolysis give the saturated ketones (Scheme 1, b).[56,57] Significantly, the resulting boron enolate can be trapped by electrophiles so offering further synthetic value.[58]

Scheme 2.



Optimization of reaction conditions, for further details see SI table S2. ^{1}H NMR yields calculated from crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Main-group cataly-sis offers an underutilized and sustainable alternative to transition metal catalysis, however, the redox chemistry of transition metals is not readily translated to main-group species. Although excellent progress has been made to impart the entrenched methods of catalysis on the main-group, the use of oxidative addition and reductive elimination remain limited beyond the d-block.[59] Recently, transborylation has offered a new approach to main-group catalysis, where controlled and directed isodesmic ligand interchange is exploited for catalyst turnover and has enabled previously stoichiometric reagents to be used as catalysts.[60-62]

B−O/B−H transborylation has been used to render the Midland reduction catalytic.[63] If a suitable, secondary organoborane catalyst could be identified it was postulated that B−O/B−H transborylation could be extended to the chemoselective reduction of enones with HBpin as a turnover reagent, and terminal reductant (Scheme 1, c). 1,4-Hydroboration of an enone by a secondary organoborane would give a dialkyl boron enolate which could undergo B−O/B−H transborylation with HBpin to give a Bpin-enolate, and regenerate the secondary borane catalyst. Hydrolysis of the Bpin-enolate on work-up would give the saturated ketone. Alternatively, the Bpin-enolate could be trapped by an electrophile resulting in a reductive α-functionalisation of the enone.

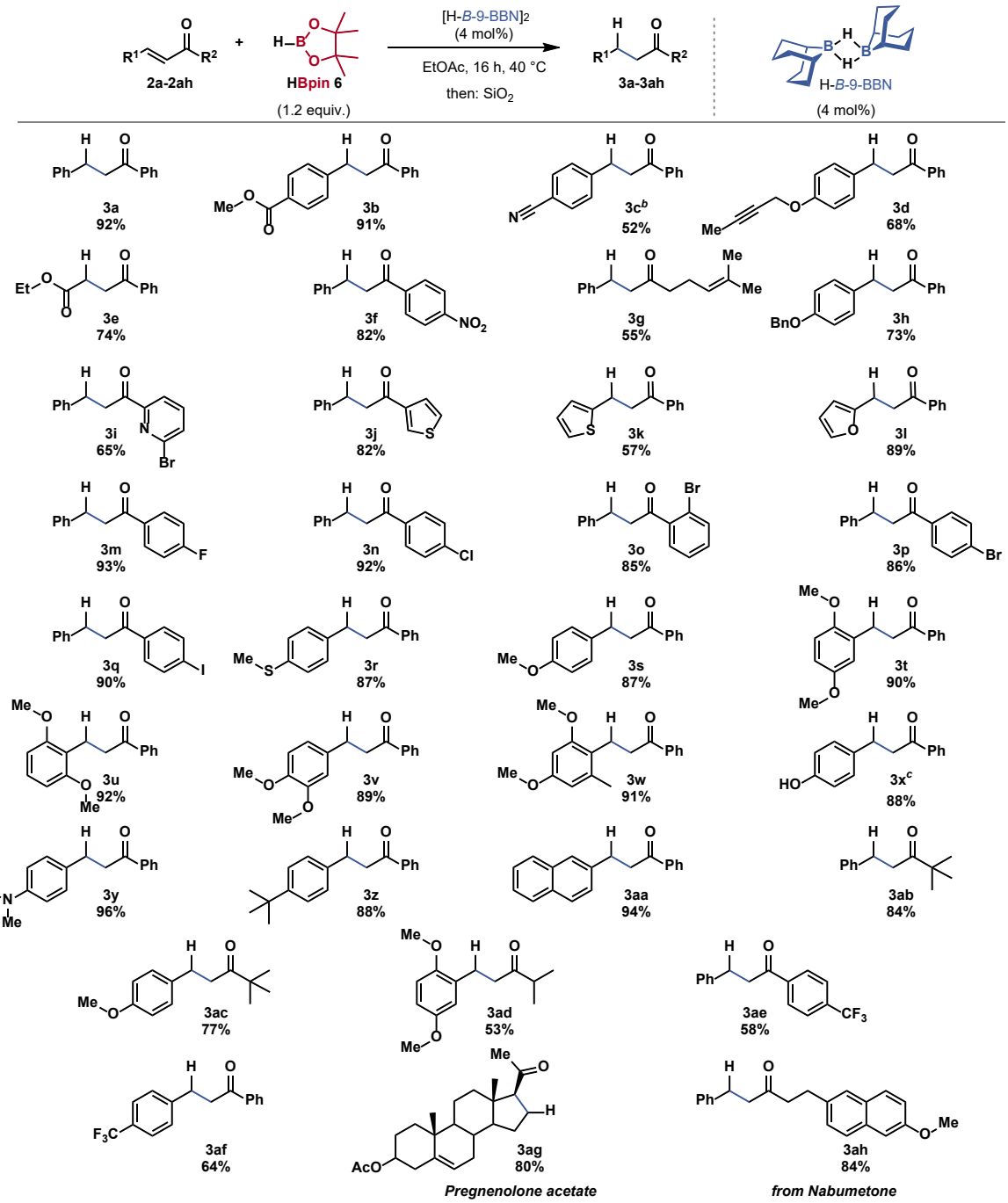
Commonly used boranes **1a-c** for the stoichiometric 1,4-hydroboration of enones were assessed as potential catalysts for the chemoselective alkene reduction of enones using chalcone **2a** as a model substrate and HBpin as the turnover reagent (Scheme 2, a). Commercially available [H-*B*-9-BBN]$_2$ **1c** achieved the best results giving dihydrochalcone **3a** without any observed ketone reduction. Equal catalytic activity was observed in several solvent systems including EtOAc, THF and toluene. EtOAc was chosen for further study due to the high product yield and its status as a 'green' solvent.[64] Cyclic enones, such as cyclohexenone, were unreactive, presumably due to the inability to orientate into the s-cis conformation required for 1,4-hydroboration. In accordance with previous reports,[65] α,β-unsaturated esters and amides were unreactive (see SI, Table S2).

In order to support the proposed mechanism of catalysis, isotopic labelling experiments were conducted (Scheme 2, c). The use of D-Bpin resulted in deuterium incorporation solely at the β-position, consistent with 1,4-hydroboration of the enone by D-*B*-9-BBN D$_1$-**1c**, generated by B−O/B−D transborylation (Scheme 2, b). The mechanism of B−O/B−H transborylation was investigated with ^{10}B enriched H-^{10}Bpin in a single-turnover experiment with the O-*B*-9-BBN enolate **4a**. The resulting O-Bpin-enolate ^{10}B-**5a** was obtained with complete ^{10}B incorporation showing that the B−O bond of the O-*B*-9-BBN enolate **4a** was exchanged alongside catalyst regeneration rather than a ligand redistribution which would break the B−C bonds.

Having optimized the reaction conditions and confirmed the mechanism through isotopic labelling, the reaction was applied to a diverse scope of enones (Scheme 3). Dihydrochalcone, **3a**, was isolated in high yield (92%) with complete chemoselectivity for alkene reduction, and without the formation of any allylic alcohol observed. The reaction tolerated the presence of an excellent array of reducible functional groups including ester **3b** (91%) and **3e** (74%), nitrile **3c** (52%), alkyne **3d** (68%), nitro **3f** (82%), and alkene **3g**, (55%) substituents. These functionalities react with stoichiometric borane reagents and are can be reduced by transition-metal-catalyzed hydrogenation or transfer hydrogenation.[66] A benzyl ether **3h** (73%) was retained during the alkene reduction, demonstrating orthogonality to Pd/H$_2$, which cleaves benzyl ethers by hydrogenolysis. The inclusion of heteroaromatic structures was tolerated, including pyridine **3i** (65%), thiophenes **3j** (82%) and **3k** (57%) and furan **3l** (89%). In the case of pyridine **3i** a 2-bromo substituent was required to prevent coordination and deactivation of the borane catalyst. Halide substituents were also tolerated with fluoro **3m** (93%), chloro **3n** (92%), bromo **3o** (85%) and **3p** (86%), and iodo **3q** (90%) bearing substrates all chemoselectively reduced at the alkene without any deleterious side reactions. This is notable as halide substituted substrates can be challenging using transition metal catalysis due to unwanted oxidative addition-and protodehalogenation.[67]

The Lewis acidic catalyst achieved good yields in the presence of substrates bearing Lewis basic functionalities such as a thioether **3r** (87%), di-methylamino **3y** (96%) and an ether **3s** (87%). Several dimethoxydihydrochalcones of biological interest **3t**–**3w** were isolated in good yields and with complete selectivity for alkene reduction. A substrate bearing an unprotected phenol **3x** was successfully reduced (88%), using in situ protection with an additional equivalent of HBpin. The protection prevented non-productive reaction of the catalyst, H-*B*-9-BBN.

Scheme 3. Substrate scope[a]

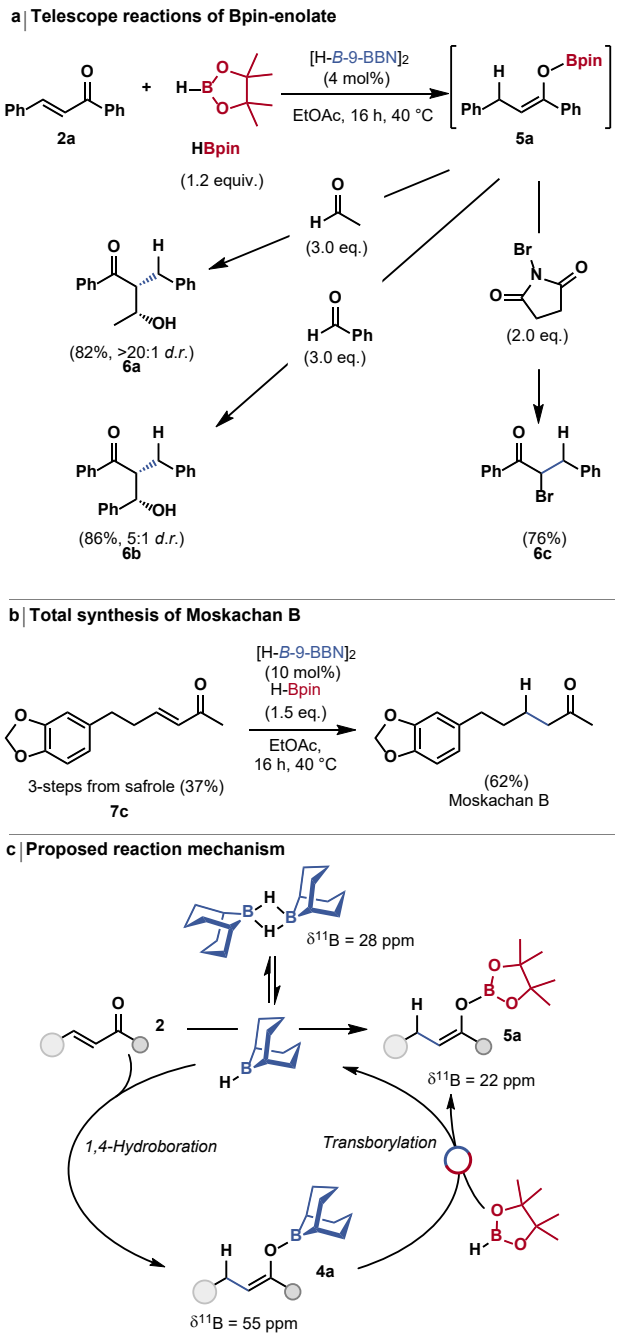


[a]Reaction conditions: [H-*B*-9-BBN]$_2$ 4 mol%, HBpin (1.2 equiv.) EtOAc, 40 °C, 16 h, then SiO_2 (0.5 g, excess). [i]Isolated as an inseparable mixture with starting material (see SI for details). [c]An additional equivalent of HBpin was added.

The reaction tolerated the inclusion of aryl-, alkyl-, including ^{t}Bu, and napthyl substituents (**3z-3ad**) to give the corresponding ketones in high yields. The presence of electron-withdrawing trifluoromethyl substituents **3ae** (58%) and **3af** (64%) resulted in reduced chemoselectivity and thus reduced yield, with elevated levels of 1,2-hydroboration observed (**3ae** = 8%, **3af** = 14%). Presumably this occurred due to the electron-withdrawing substituent causing a lowering of the LUMO energy and thus biasing chemoselectivity, although this effect was not observed in the reaction of other substrates bearing electron-withdrawing groups. The chemoselective reduction was applied to molecules of pharmaceutical interest, a derivative of the anti-inflammatory Nabumetone **3ah** was chemoselectively reduced in good yield (84%). 16-Dihydropregnenolone acetate, a precursor to 4 pharmaceuticals on the WHO Model List of Essential Medicines,[68] was reduced in good yield to pregnenolone acetate **3ag** (80%). This strategy provides an alternative to the Pd/H_2 approach used in the Marker degradation,[69] a semi-synthesis of progesterone.

In order to further expand the synthetic utility of this reduction protocol and exploit the O-Bpin-enolate **5a** a range of electrophiles were screened for telescope reactivity to interpret this

Scheme 4.



a) Telescope reactions for hydrofunctionalization of enones, see SI for details b) Total synthesis of Moskachan B c) Proposed reaction mechanism.

and achieve a formal hydrofunctionalization of the enone. (Scheme 4, a).

The catalytic generation of boron enolates demonstrated comparable reactivity to that of stoichiometric enolate generation.[57] Several reductively functionalised chalcone derivatives were prepared by this method. 1,4-Hydroboration of enones has previously been reported to give (Z)-enolates [56,65] the generation of syn aldol products (**6a** 82% >20:1 d.r., **6b** 86% 5:1) is consistent with this. The reaction was also applicable to bromination (**6c** 76%) reactions.

Finally, the transborylation strategy for chemoselective enone reduction was applied to the total synthesis of Moskachan B (Scheme 4, b).[70] Enone **7c**, readily prepared from safrole in 3-steps, underwent chemoselective 1,4-reduction with H-*B*-9-BBN/HBpin to give Moskachan B.

Using *in situ* ^{11}B NMR spectroscopy and the isotopic labelling studies a mechanism was proposed (Scheme 4, c). Dissociation of [H-*B*-9-BBN]$_2$ (δ ^{11}B =28 ppm) to solvent coordinated monomer followed by 1,4-hydroboration on the enone, gives a O-*B*-9-BBN-enolate **4a** (56 ppm) which undergoes an isodesmic B−O/B−H transborylation with HBpin to regenerate the H-*B*-9-BBN catalyst and give a O-Bpin-enolate **5a** (22 ppm). Hydrolysis of the O-Bpin enolate **5a** gives the saturated ketone **3** or reaction with an electrophile the formal hydrofunctionalization product.

In summary, we have demonstrated the application of B−O/B−H transborylation as a turnover strategy for the chemoselective reduction of enones, thus enabling previously stoichiometric borane reductants to be used as catalysts and providing a main group alternative to transition metal catalysis for this transformation. Catalysis showed excellent functional group tolerance and wide applicability with chemo- and regioselective alkene reduction in all cases. The synthetic applicability was extended by intercepting the intermediate O-Bpin-enolates with electrophiles for the diastereoselective formation of C−C bonds through aldol-type reactions and formal hydrofunctionalizations. The use of DBpin as the stoichiometric turnover reagent supported the proposed pathway of 1,4-hydroboration by incorporation of the deuterium in the β-position of the ketone. Single turnover experiments with ^{10}B-HBpin showed a B−O/B−H transborylation was occurring as the key turnover step for catalyst regeneration.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental information, experimental setup and procedures, reaction monitoring, NMR spectra and associated references (PDF)

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Author Contributions

KN carried out all practical work. KN and SPT devised the concept. TL and SPT supervised the work. All authors have given approval to the final version of the manuscript.

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