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# Lewis Acid Catalyzed Borotropic Shifts in the Design of Diastereo- and Enantioselective γ-Additions of Allylboron Moieties to Aldimines

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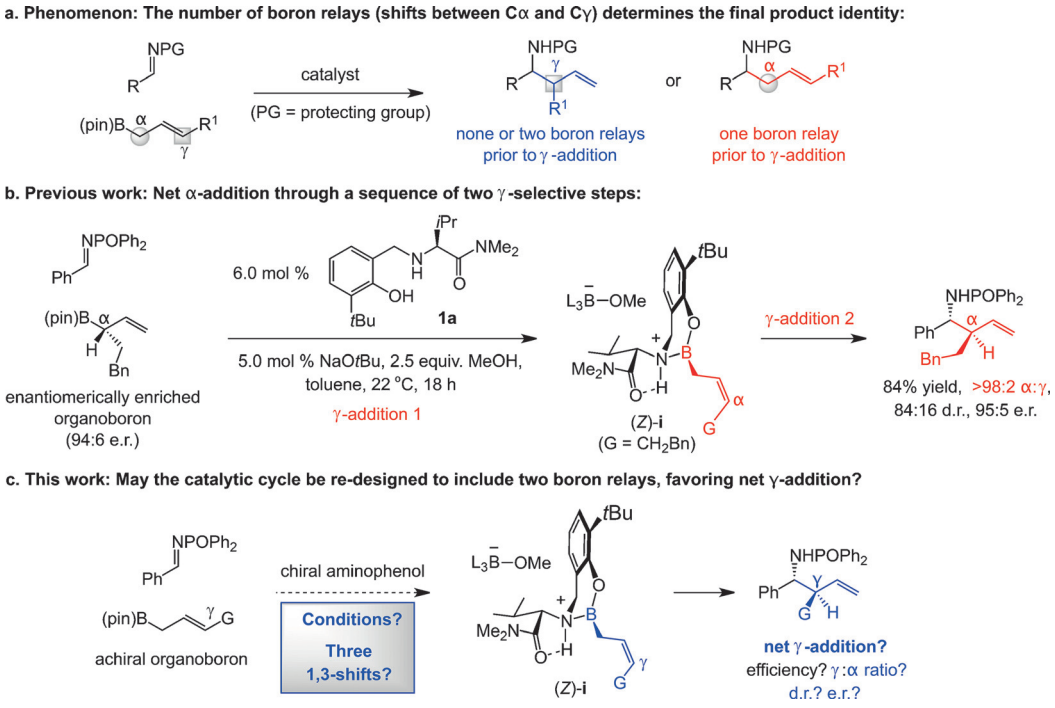
***Abstract:*** *Catalytic allylboron additions to aldimines are presented for which small amounts of $Zn(OMe)_2$ serve as the co-catalyst to accelerate allyl exchange and 1,3-borotropic shift processes. Low-yielding and moderately α- and diastereoselective reactions are thus turned into highly efficient γ-, diastereo-, and enantioselective transformations that exhibit considerable scope.*

Catalytic enantioselective additions of unsaturated organoboron compounds to imines are a convenient way of synthesizing homoallylic amines.[1] When the allylboron reagent is terminally substituted ($R^1 \neq H$, Scheme 1a), the product identity and its isomeric purity hinge on how many 1,3-boryl shifts occur before a C–C bond is formed (Scheme 1a); α-addition is observed if the C–B bond relocates once from the Cα to the Cγ carbon atom, and no or two relays means net γ-addition. Rational strategies for the reliable control of boryl isomerizations are therefore much needed.

Catalysts assembled in situ from (pin)B-derived (pin = pinacolato) reagents and an enantiomerically pure aminophenol (e.g., **1a**; Scheme 1b) facilitate additions of allylboronates to imines.[2] These transformations proceed with high α-selectivity (Scheme 1b)[3] because of a pair of γ-selective events: one delivers organoboron intermediate (*Z*)-**i** and the other the homoallylic amide product. However, a preferred approach would involve converting a more easily accessible achiral organoboron reagent into the same type of product by a γ-, diastereo-, and enantioselective route (Scheme 1c).[4,5] One way of achieving this would entail the inclusion of a 1,3-boryl shift in a re-designed pathway. Herein, we describe the implementation of this objective.




***Scheme 1.*** The role of boryl relays and shifts and the challenge of controlling them in the design of a catalytic process.

Our plan was to induce a borotropic shift (**iv**→**v**→(*Z*)-**i**, Scheme 2) that would take place between the γ-selective processes (**ii**→**iii**→**iv** and (*Z*)-**i**→**vi**→**ii**). The driving force would be the lowering of steric strain caused by the tertiary boron-substituted carbon center in **iv** and formation of a more substituted alkene. The question then was: How might the conditions be altered so that **iv** isomerizes to (*Z*)-**i** via **v** faster than it reacts with a phosphinoylimine?

1,3-Borotropic shifts have been examined extensively,[6] and several observations have been attributed to them.[7] Hancock and Kramer have shown[6a,b] that the ease of these isomerizations depends on the electronic attributes of the boron center. For instance, there is <2% rearrangement with the diaminoboryl system **A** at 170 °C after 24 hours (Scheme 3) but (amino)alkyl derivative **B** isomerizes at 150 °C in six hours, and the boryl shift in dialkylboryl compound **D** takes

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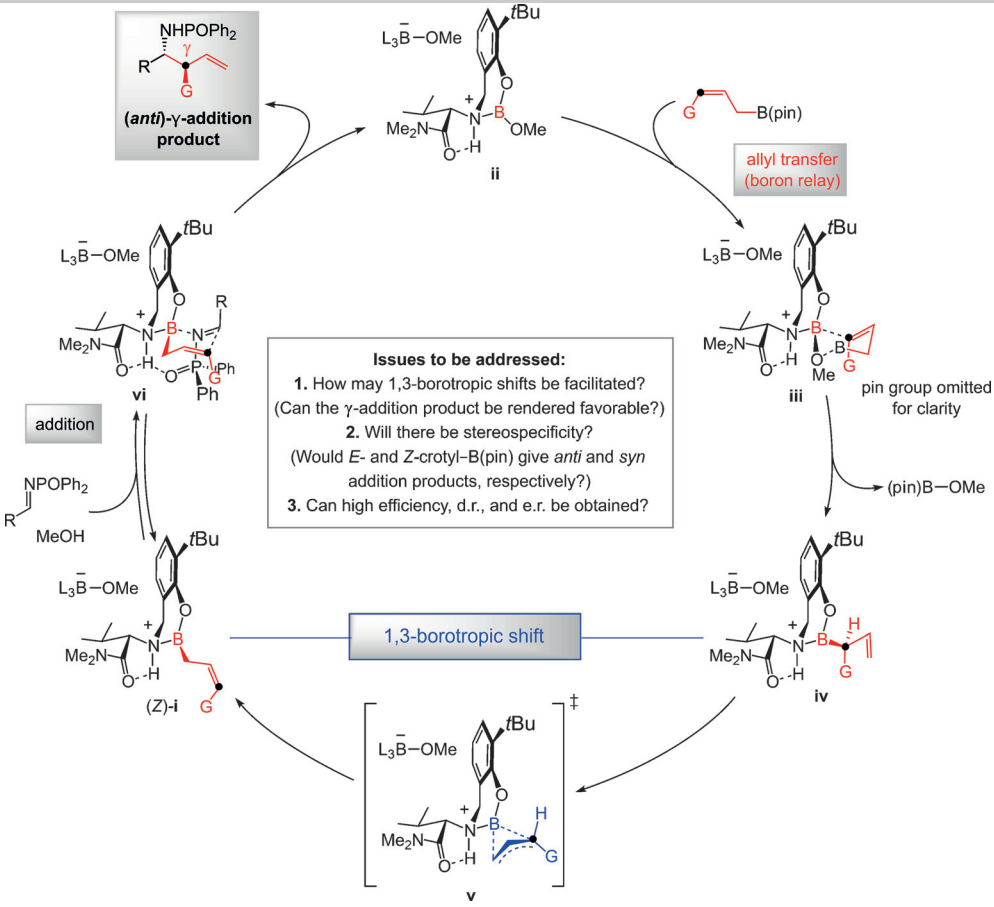
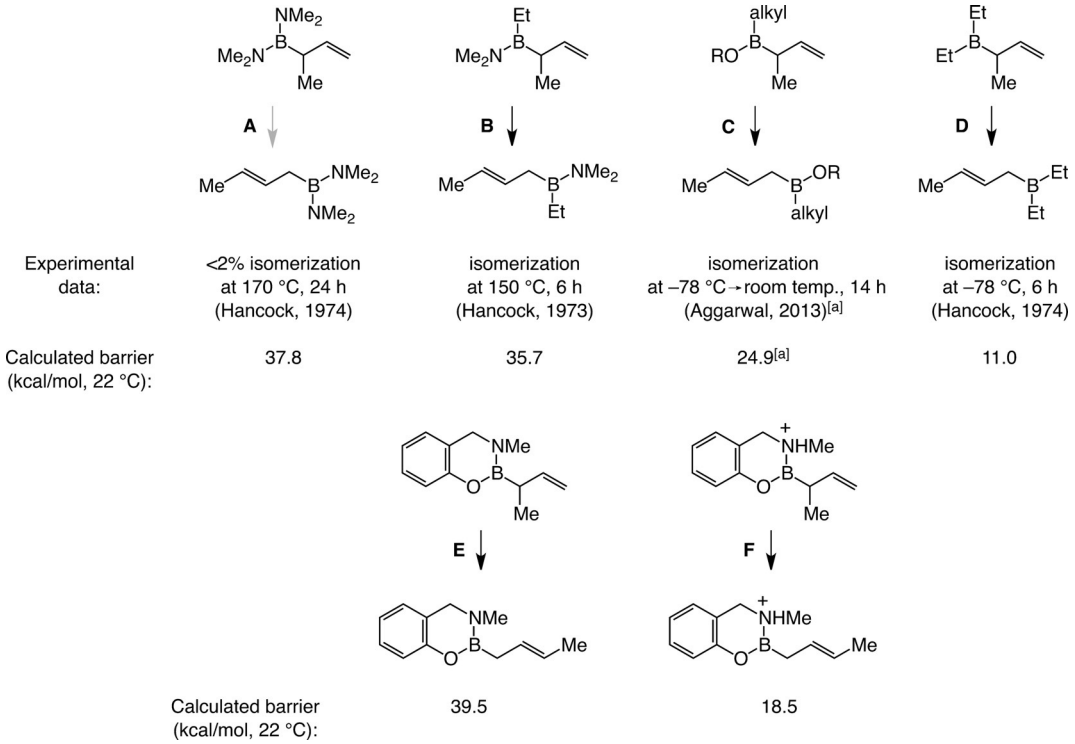



***Scheme 2.*** A 1,3-borotropic shift (**iv**→**v**→(*Z*)-**i**) might give rise to the preferential formation of γ-addition products.




***Scheme 3.*** Previous observations and calculations performed in this study (with the ωB97XD/Def2TZVPP functional, solvation in toluene) point to a significant substituent influence on the rate of the borotropic shift (the more π-donating the substituent, the slower the rearrangement). [a] For the experimental observation: alkyl = *n*Bu, R = $C(Me)_2C(Me)_2OLi$. For the calculations: alkyl = Et, R = Me.

place at –78 °C (6 h). Crossover experiments indicate that the rearrangements are intramolecular.[6a,b] Congruent with Hancock's conclusions is the proposal by Aggarwal[7o] and coworkers that an (alkoxy)-alkylboron species (**C**) rearranges at lower temperature (–78→22 °C, 14 h); the energy barrier calculated by us for this transformation supports the suggested scenario (Scheme 3).[8] In the systems more directly relevant to the studies below (**E** and **F**; Scheme 3), the ammonium salt derivative (i.e., **F**) should rearrange more readily. Still, the high α-selectivities in the original studies[2] (see Scheme 1 b) mean that the boron atom within a chiral complex (e.g., **iv**; Scheme 2) is not Lewis acidic enough for swift borotropic shifts.

The idea of deploying a Lewis acidic co-catalyst

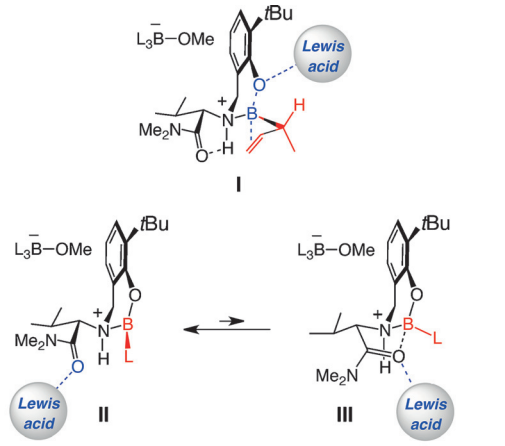
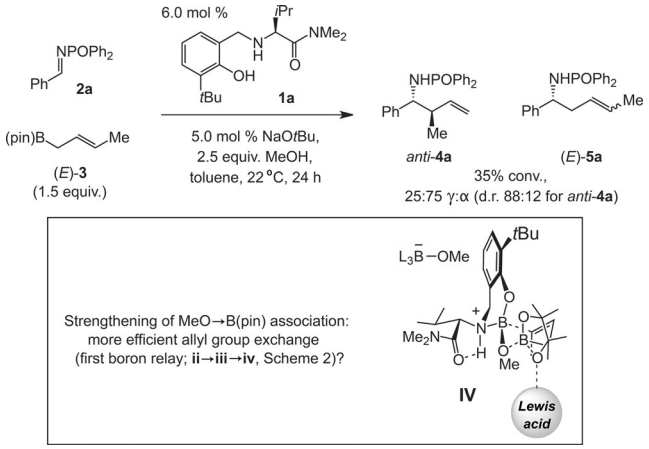



***Figure 1.*** Possible ways through which a Lewis acid may facilitate borotropic shifts.



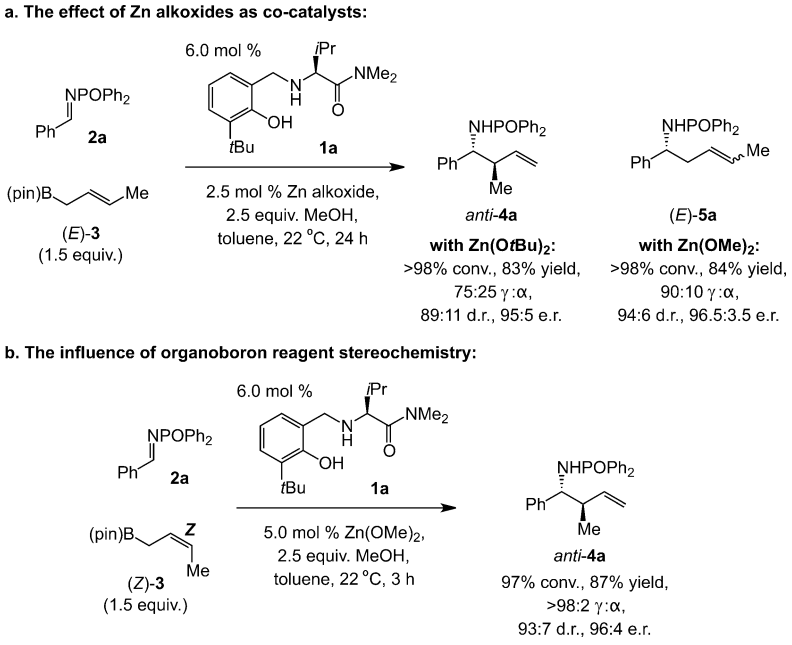

***Scheme 4.*** Possible role of a Lewis acidic co-catalyst in facilitating the initial allyl transfer.

was based on the following reasoning: First, as illustrated in **I** (Figure 1), by coordination to the aryloxy arm of the chiral complex, the Lewis acidity of the boron center and thus the rate of isomerization could be enhanced (i.e., **iv**→**v**→(*Z*)-**i**; Scheme 2). Second, association of the amide carbonyl group with a Lewis acid (**II**, Figure 1) could disrupt its coordination with the boron atom (**III**), facilitating allyl exchange (L = OMe) and/or a 1,3-borotropic shift (L = allylic group). DFT calculations[8] suggested that complex **III** (without the Lewis acid) is favored, although the reaction most probably proceeds via **II** (and/or the complex without a bound Lewis acid).

Our initial foray uncovered another problem (Scheme 4): Under the previous conditions,[2] reaction of *E*-configured crotyl–B(pin) ((*E*)-**3**) with imine **2a** resulted in only 35% conversion after 24 h [γ/α = 25:75; 88:12 diastereomeric ratio (d.r.) for the γ-product]. We surmised that the low rate might be due to the fact that the methyl substituent [vs. a terminal olefin in Scheme 1b or with allyl–B(pin)] causes the chiral allylboron intermediate to be generated inefficiently because of steric factors (i.e., **ii**→**iii**→**iv**; Scheme 2). We wondered if coordination of the same Lewis acidic co-catalyst to the B(pin) moiety[9] might strengthen chelation of its boron center with the methoxy unit of the chiral complex to accelerate allyl transfer as well (Scheme 4).

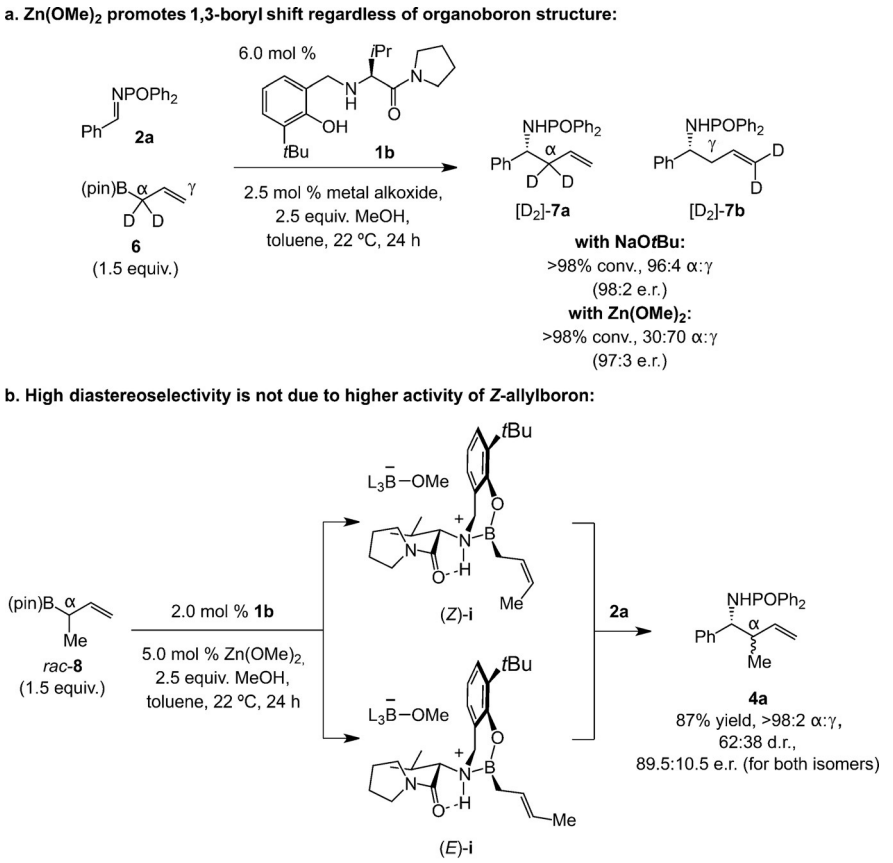
Several Lewis acidic metal salts were screened,[8] resulting in the discovery that with 2.5 mol% $Zn(OtBu)_2$ (Scheme 5a) not only may efficiency be improved substantially (>98% vs. 35% conv. with NaO*t*Bu; Scheme 4), but also the α-addition product was generated predominantly (γ/α = 25:75) in 89:11 d.r. and 95:5 enantiomeric ratio (e.r.). The catalyst's *tert*-butyl substituent meant that a diminutive co-catalyst could be better. Indeed, with the smaller $Zn(OMe)_2$, the γ/α ratio (90:10) and the diastereo- and enantioselectivity were higher still (94:6 d.r. and 96.5:3.5 e.r.).[10] The transformation with the *Z*-configured organoboron reagent proceeded to 97% conversion in three hours (vs. 24 h with (*E*)-**3**), furnishing the same diastereomer as with the *E* isomer in >98% γ-selectivity, 93:7 d.r., and 96:4 e.r. (Scheme 5b). Control experiments indicated that (*E*)- and (*Z*)-**3** do not undergo isomerization.

The data in Scheme 6 offer further insight.[11] Reaction with deuterium-labeled allyl–B(pin) **6** led to high α-selectivity when NaO*t*Bu was present (96:4 [$D_2$]-**7a**/[$D_2$]-**7b**; Scheme 6a) but with $Zn(OMe)_2$, the γ-product was formed preferentially (γ/α = 70:30). The impact of the co-catalyst thus extends to the unsubstituted organoboron system. The γ/α ratio is lower (than with (*E*)- or (*Z*)-**3**; Scheme 5), likely because the less hindered chiral allylboron intermediate (see




***Scheme 5.*** The influence of $Zn(OMe)_2$ and the crotyl–B(pin) stereochemistry on efficiency and selectivity.

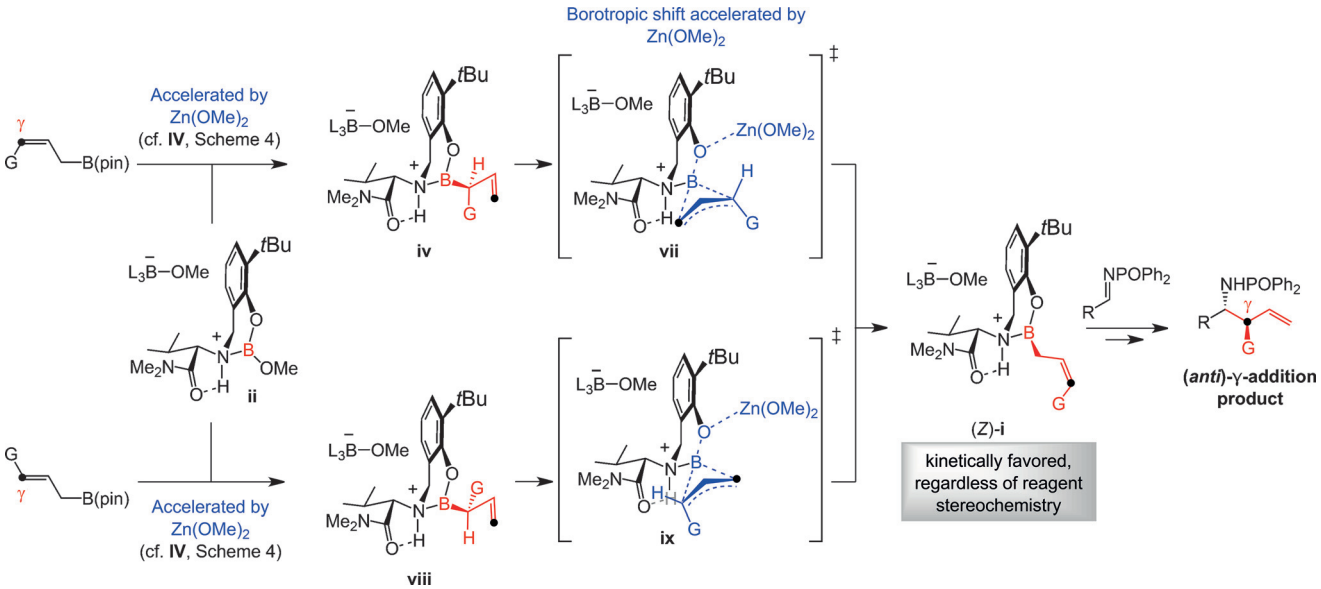
  




***Scheme 6.*** Experiments indicating that a) $Zn(OMe)_2$ promotes the borotropic shift and that b) formation of the *anti* diastereomer with the *E* and *Z* organoboron reagent is due to a kinetic preference for the formation of the chiral *Z*-crotylboron intermediate.

**iv**, G = H) reacts faster with the imine, competing more easily with a borotropic shift. There is no steric or electronic impetus for isomerization (see above). Furthermore, with *rac*-**8**, the product from α-addition was formed exclusively in 62:38 d.r. (Scheme 6b), indicating that conversion into (*E*)-**i** and (*Z*)-**i** is probably followed by an eventual γ-addition to the imine **2a**.[12] The predominant formation of the *anti* diastereomer in the reaction with *E*- or *Z*-configured crotyl–B(pin) ((*E*)-**3** or (*Z*)-**3**; Scheme 5) must therefore originate from a kinetic preference for isomerization to afford the chiral *Z*-allylboron intermediate ((*Z*)-**i**; Scheme 2).

The routes in Scheme 7 account for the kinetically controlled stereoselective Lewis acid promoted 1,3-borotropic shifts. With the higher-energy *Z*-configured reagent, complex **iv** is produced faster than isomeric **viii**, which is generated from the corresponding *E* isomer. In either instance, regardless of the stereochemistry of the initial allylboronate, isomerization proceeds via transition states wherein the substituent (G) is oriented away from the chiral complex (see **vii** and **ix**; Scheme 7). Allylboron intermediate (*Z*)-**i**[13] and the *anti* diastereomer of the γ-addition product are hence favored. That is, diastereoselectivities are high not because the *Z* and *E* isomers rapidly interconvert, and the former reacts faster (i.e., Curtin–Hammett kinetics are not operative). Moreover, regardless of the crotyl–B(pin) stereochemistry, product identity does not originate from the *E* and *Z* chiral allylboron isomers reacting via different transition structures to give the same stereoisomer.[4f]



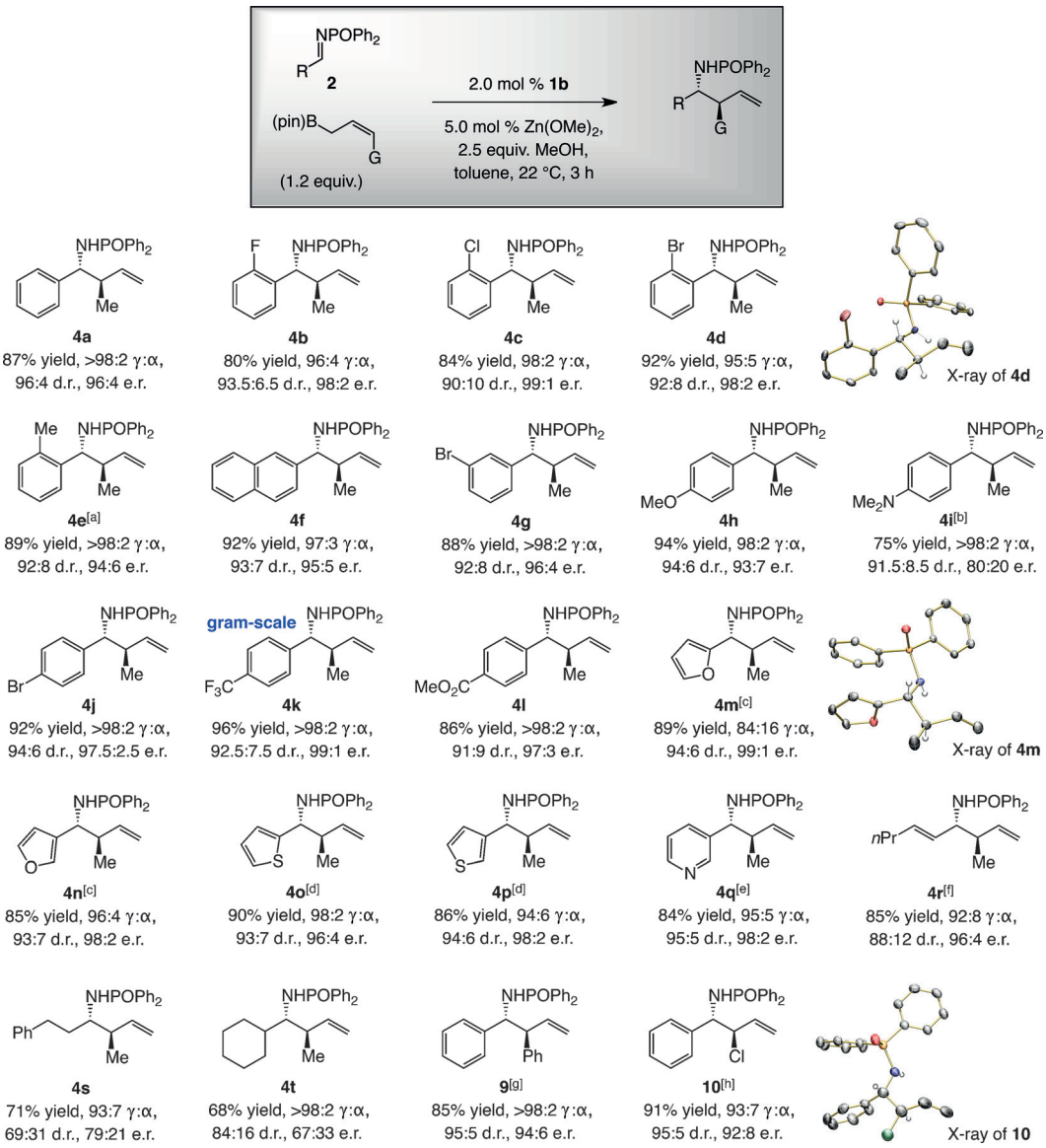

***Scheme 7.*** Rationale for the preferential generation of the *Z*-configured crotylboryl intermediate ((*Z*)-**i**), irrespective of the reagent stereochemistry.

The catalytic protocol has considerable scope (Scheme 8).[11] Reactions were often complete with 2.0 mol% aminophenol **1b** and 5.0 mol% $Zn(OMe)_2$ within three hours at ambient temperature. Aryl-substituted imines with various electronic attributes were converted into the desired products efficiently and selectively (**4a**–**4l**). Similar results were obtained with heterocyclic moieties, including those containing an oxygen (**4m**, **4n**), sulfur (**4o**, **4p**), or nitrogen substituent (**4q**). Additions to α,β-unsaturated aldimines needed more forcing conditions (**4r**). Transformations with alkyl-substituted imines were equally efficient and considerably γ-selective but less diastereo- and enantioselective. This may be attributed to the diminished rates of addition to the more electron-rich aliphatic substrates, allowing for alternative (uncatalyzed) pathways with different kinetic attributes (i.e., different turnover-limiting steps) to become competitive; related arguments may apply to the reaction leading to *para*-dimethylaminoaryl-substituted **4i**. Other than the processes with commercially available crotyl–B(pin) reagent (*Z*)-**3**, the synthesis of **9** and especially that of chloro-substituted **10**[14] underscore the method's reach and versatility.

Reactions are scalable (see **4k**, Scheme 8), and the ligands and organoboron reagents are easy to access and manipulate. In most cases, the phosphinoyl group renders the substrates and products crystalline and isolable without chromatography, and it is removable under mild conditions at low cost.[2a] These characteristics compare favorably to the alternative strategies.[4] Homoallylic amines are precursors to an array of important enantiomerically enriched N-containing molecules, including β-amino acids.[15,16]

The concepts elucidated here should find applications in the design of other efficient catalytic and stereoselective processes.




***Scheme 8.*** Products obtained from γ-, diastereo-, and enantioselective additions of different organoboron reagents (>98% *E* for phenyl-substituted allylboronate and >98% *Z* for the Cl-substituted reagent) to various aldimines. [a] **1b** (5.0 mol%). [b] Reaction time: 24 h. [c] 5 h. [d] 4 h. [e] With **1b** (10 mol%) and $Zn(OMe)_2$ after 8 h. [f] With **1b** (12.5 mol%) and $Zn(OMe)_2$ (7.5 mol%). [g] At 50°C, 6 h. [h] **1b** (10 mol%) and $Zn(OMe)_2$, 24 h. See the Supporting Information for details.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**Keywords:** boron · borotropic shift · diastereoselective synthesis · enantioselective catalysis · homoallylic amines


  

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*Angew. Chem.* **2016**, *128*, 4779 – 4784

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[10] Allylzinc reagents are likely not involved because such highly nucleophilic entities would not survive the reaction conditions, demonstrated previously to be acidic (see Ref. [2a]).

[11] Catalyst screening indicated that aminophenol **1b** generally delivers somewhat higher enantioselectivity than **1a**.

[12] Initial isomerization of *rac*-**8** to (*E*)- and (*Z*)-**3** (prior to the first γ-addition to generate the chiral allylboron **iii**) is unlikely, as in that case, *anti*-**4a** would be formed with high diastereoselectivity. The stronger propensity of an aminophenol-based allylboron reagent to undergo a 1,3-borotropic shift is almost certainly due to its more Lewis acidic boron atom.

[13] Attempts to observe (*Z*)-**i** through NMR spectroscopy were unsuccessful, as only a minute fraction of the aminophenol present is converted into the active catalyst.

[14] The chloro-substituted allylboron reagent was prepared by catalytic *Z*-selective cross-metathesis; see: M. J. Koh, T. T. Nguyen, H. Zhang, R. R. Schrock, A. H. Hoveyda, *Nature* **2016**, DOI: 10.1038/nature17396.

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