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Enantioselective Synthesis of (*E*)-δ-Stannyl Homoallylic Alcohols via Aldehyde Allylboration Using α-Stannylallylboranes Generated by Allene Hydroboration Followed by a Highly Diastereoselective 1,3-Boratropic Shift

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The asymmetric carbonyl allylation reaction is an important transformation in organic synthesis.[1] Although extensive efforts over the past three decades have provided many useful allylmetal reagents, new developments in this area continue to emerge.[2–6] One disadvantage of the vast majority of prior allylation methods, however, is that homoallylic alcohols with terminal vinyl groups are generated. Several-step manipulations are often required for further carbon−carbon bond formation at this position.[7] Several procedures exist for synthesis of nonracemic α-substituted allylboron reagents, which undergo aldehyde allylboration reactions to give products with substituted olefins,[1] but such reagents typically require multistep syntheses (e.g., involving the Matteson homologation,[8] as in Hall's recent work[5e]) and have not been widely adopted in the literature. An important advance in this area involving the lithiation−borylation of allylic carbamates has recently been achieved by Aggarwal.[9] Olefin cross-metathesis is one method that permits a terminal olefin to be modified directly. However, the efficiency as well as the *E*/*Z* selectivity of cross-metathesis depends on the properties of the olefin metathesis partners.[10] Consequently, olefin metathesis does not provide a general solution to the problem of synthesis of homoallylic alcohols with substituted alkenes. Therefore, a simple method that provides direct access to homoallylic alcohols with functionalized olefins is highly desirable. Toward this end, we have discovered and report herein a direct, one-step, highly enantioselective synthesis of (*E*)-δ-stannyl homoallylic alcohols via an allene hydroboration−aldehyde allylboration sequence.

In connection with an ongoing problem in natural products synthesis, we explored the hydroboration of allenylstannane **1** with diisopinocampheylborane [(^{d}Ipc)$_2$BH]. In principle, hydroboration of **1** could provide allylboranes **2** or **3**, depending on the hydroboration regioselectivity and the rate and equilibrium constant for 1,3-boratropic isomerization in this system.[11] On the basis of the ability of −SnR$_3$ groups to stabilize a β-carbocation,[12] we anticipated that the formation of allylborane intermediate **2** might be thermodynamically favored.[13] If so, (*E*)-δ-stannyl homoallylic alcohols **4** would be available following the reaction of **2** with an aldehyde (Figure 1).

Treatment of allenylstannane **1** at −40 °C with (^{d}Ipc)$_2$BH in diethyl ether, with warming of the solution to −20 °C over 5 h to complete the hydroboration, followed by treatment of the resulting allylborane with hydrocinnamaldehyde at −78 °C provided (*E*)-δ-stannyl homoallylic alcohol **4a** in 64% yield and, remarkably, with >95% ee (Table 1, entry 1). Application of this procedure to a variety of other representative aldehydes (Table 1, entries 2−9) provided homoallylic alcohols **4b**−**h** in 51−78% yield and 92 to >95% ee (absolute configurations were assigned by Mosher ester analysis[14]). The olefin geometry of homoallylic alcohols **4a**−**h** was *E* (J^E = 18.8−19.2 Hz); the corresponding *Z*-olefin isomers as well as the regioisomeric homoallylic alcohols **5** (or dienes accessible by elimination of **5**) were not detected in any of the experiments performed under these conditions.

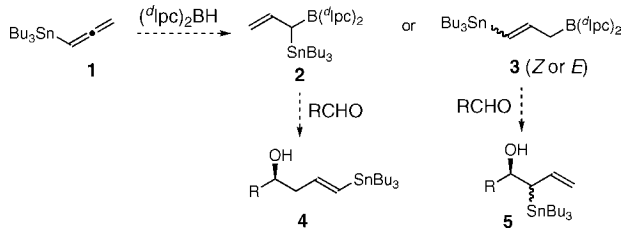
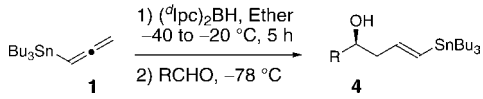


Figure 1

Table 1. Synthesis of δ-Stannyl Homoallylic Alcohols **4** via Hydroboration of **1** at −40 to −20 °C (via Kinetically Controlled Allylborane Isomerization)[a]



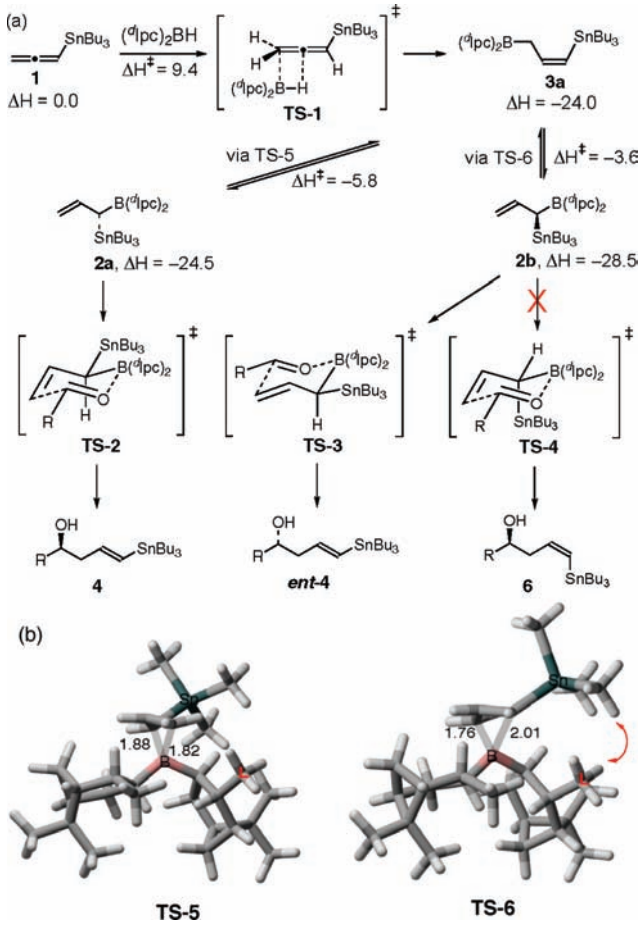
entry	RCHO	product	yield	% ee[b]
1	Ph(CH$_2$)$_2$CHO	**4a**	64%	>95
2	PhCH$_2$CHO	**4b**	67%	>95
3	PhCHO	**4c**	78%	93
4	BnO(CH$_2$)$_2$CHO	**4d**	68%	>95
5	BnOCH$_2$CHO	**4e**	71%	>95
6	PhCH=CHCHO	**4f**	73%	>95
7	CyCHO	**4g**	55%	92
8	*t*-BuCHO	**4h**	51%	94
9[c]	Ph(CH$_2$)$_2$CHO	*ent*-**4a**	71%	94
10[d]	Ph(CH$_2$)$_2$CHO	*ent*-**4a**	73%	30

[a] Reactions were performed by treatment of **1** with (^{d}Ipc)$_2$BH (0.7 equiv) in Et$_2$O at −40 °C and warming to −20 °C over 5 h followed by the addition of RCHO (0.5 equiv) at −78 °C. The mixture was then allowed to stir at −78 °C for 8 h. The reactions were subjected to a standard workup (NaHCO$_3$, H$_2$O$_2$) at 0 °C prior to product isolation. [b] Determined by Mosher ester analysis. [c] (^{l}Ipc)$_2$BH was used. [d] This reaction was performed by treatment of **1** with (^{d}Ipc)$_2$BH (0.7 equiv) in Et$_2$O at 0 °C followed by addition of RCHO (0.5 equiv) at −78 °C.

The enantioselectivity of this sequence proved to be highly dependent on the experimental conditions. As shown in entry 10 of Table 1, when the hydroboration of **1** was performed at 0 °C with subsequent addition of hydrocinnamaldehyde at −78 °C, the *enantiomeric* homoallylic alcohol *ent*-**4a** was obtained in 73% yield and 30% ee (as measured by Mosher ester analysis[14]). Similarly, when the hydroboration step was carried out at −40 °C and the solution was then allowed to warm to 0 °C, addition of hydrocinnamaldehyde at −78 °C provided *ent*-**4a** in 30% ee and 77% yield. Here again, products with a (*Z*)-vinylstannane unit (e.g., **6** in Scheme 1a) were not detected.

On the basis of recent work on allenylboronate hydroboration,[15] the reaction of allenylstannane **1** with (^{d}Ipc)$_2$BH would be expected

Scheme 1. Hydroboration of **1** and Allylborane Isomerization Pathways



to provide (*Z*)-γ-stannylallylborane **3a** as the kinetic product (Scheme 1a). If this is the case, the results in Table 1 (entries 1−9) indicate that **3a** undergoes a kinetically controlled and highly diastereoselective 1,3-boratropic shift at temperatures below −20 °C to give α-stannylallylborane **2a**, which then reacts with the aldehyde at −78 °C to give **4** via the usual chairlike transition state, **TS-2**. The *E* olefin geometry of **4** dictates that the α-stannyl unit occupies a pseudoequatorial position in **TS-2**. The absolute configuration of the hydroxyl group of **4** [which we assigned by conversion of **4** to known compounds or by application of the modified Mosher method,[14] as described in the Supporting Information (SI)] is fully consistent with the normal sense of asymmetric induction by the $-B(Ipc)_2$ unit.[16]

Support for this analysis was provided by the results of a low-temperature ^{1}H NMR study of the hydroboration of **1** (see the SI), which showed that (*Z*)-**3a** was present at short reaction times, as well as by data from an experiment in which the hydroboration of allenylstannane **1** with $(^d Ipc)_2BH$ was performed at −40 °C for 2 h before addition of hydrocinnamaldehyde at −78 °C. Small amounts (<5%) of *syn*-β-hydroxyallylstannane **5a** were isolated along with recovered allenylstannane **1** and homoallylic alcohol **4a** as the major product (the allene hydroboration was not complete under these conditions). Because neither β-hydroxyallylstannanes **5** nor the corresponding dienes were observed in any experiments in which the hydroboration solution was allowed to warm to −20 °C prior to addition of the aldehyde, the results of the −40 °C hydroboration experiment and the low temperature ^{1}H NMR study of the hydroboration reaction (see the SI) are consistent with the following three theses: (i) the kinetic mode of hydroboration of **1** is that depicted in Scheme 1a, leading to (*Z*)-γ-stannylallylborane **3a** (the precursor to **5**); (ii) the 1,3-boratropic shift of **3a** at temperatures below −20 °C is highly diastereoselective for **2a**; and (iii) the equilibrium constant for the 1,3-boratropic shift is highly displaced in favor of **2a** [and/or **2b**, depending on the reaction temperature (see above)].

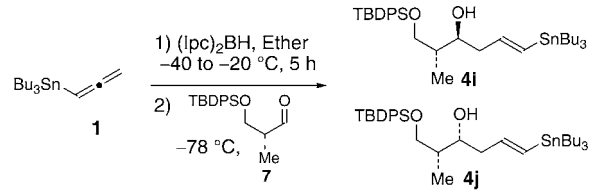
The data for the experiment summarized in entry 10 of Table 1 indicate that when the hydroboration of **1** was performed at 0 °C (or when the product of the hydroboration at −40 to −20 °C was allowed to warm to 0 °C), a rapid and reversible 1,3-boratropic shift occurred that gave a thermodynamic mixture of allylboranes **2a** and **2b**, slightly favoring **2b**. Indeed, when the hydroboration reaction of **1** was monitored at 0 °C, a ∼1:2 mixture of two α-stannyl allylborane species (**2a** and **2b**) was observed via ^{1}H NMR spectroscopy (see the SI). Allylborane **2a** reacts with aldehydes via **TS-2** to give **4**, and **2b** reacts via **TS-3** to give *ent*-**4**. These data indicate that pseudoequatorial placement of the α-stannyl unit in **TS-3** overrides the enantiofacial selectivity of the $(^d Ipc)_2B-$ group, which, if dominant, would have dictated the formation of (*Z*)-δ-stannyl homoallylic alcohols **6** via **TS-4**. That is, the stereodirecting influences of the α-stannylboryl stereocenter and that of the $(^d Ipc)_2B-$ group are mismatched in **2b**, with the α-stannylboryl stereocenter being the more dominant of the two.

We utilized B3LYP density functional theory (DFT) to explore the transition states (TSs) of the hydroboration, 1,3-boratropic rearrangement, and aldehyde allylation steps leading to **4** and *ent*-**4** (with $SnBu_3$ groups modeled as $SnMe_3$).[17] As shown in Scheme 1a, the lowest energy pathway[17] for hydroboration of **1** proceeds through **TS-1** ($\Delta H^‡ = 9.4$ kcal/mol) and gives (*Z*)-δ-stannylallylborane **3a** ($\Delta H = -24.0$ kcal/mol) as the kinetic product. These DFT calculations indicate that hydroboration transition states that lead directly to **2a** and **2b** are substantially higher in energy because of severe congestion between the Bu_3Sn and Ipc groups.[18] Two possible concerted diastereomeric 1,3-boratropic shift transition states lead from **3a** to either **2a** or **2b**. **TS-5** ($\Delta H^‡ = -5.8$ kcal/mol) is favored over **TS-6** ($\Delta H^‡ = -3.6$ kcal/mol) by 2.2 kcal/mol because the right-hand isopinocampheyl group is oriented to place the hydrogen and methylene positions closest to the Bu_3Sn group, while in **TS-6** the Bu_3Sn group is next to the hydrogen and large tertiary carbon center (Scheme 1b). The repulsion between the isopinocampheyl and Bu_3Sn groups in **TS-6** results in an asynchronous TS with partial bond lengths of 1.76 and 2.01 Å, in contrast to the nearly synchronous partial bond lengths in **TS-5** (1.88 and 1.82 Å). Finally, allylborations of **2a** with aldehyde substrates provide homoallylic alcohols **4** via **TS-2** with pseudoequatorial placement of the α-Bu_3Sn group.

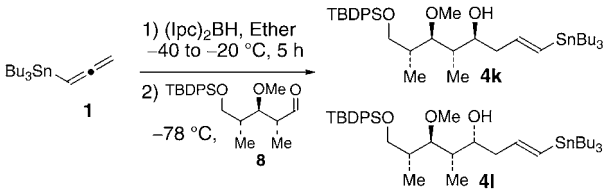
Double asymmetric allylboration reactions of **2a** with chiral aldehydes **7** and **8** are shown in Table 2. Hydroboration of allenylstannane **1** with either $(^d Ipc)_2BH$ and $(^l Ipc)_2BH$ at −40 °C (with warming to −20 °C) followed by addition of aldehyde **7** at −78 °C provided **4i** and **4j**, respectively, in 70−75% yield with >50:1 diastereoselectivity, as determined by ^{1}H NMR analysis (the alternative minor diastereomers could not be detected in either experiment). Similarly, use of the more elaborated aldehyde **8** as the substrate provided **4k** and **4l**, respectively, in 71−78% yield, again with >50:1 diastereoselectivity (Table 2). The very high diastereoselectivities of these pairs of double asymmetric reactions attest to the enantioselectivity of reagent **2a** and the remarkable, highly diastereoselective 1,3-boratropic shift that is involved in the generation of **2a**.

In conclusion, we have developed a highly enantioselective synthesis of (*E*)-δ-stannyl homoallylic alcohols via aldehyde allylboration reactions of the double-chiral allylborane reagent **2a**.

Table 2. Double Asymmetric Stannyl Allylboration Reactions with Aldehydes **7** and **8**



entry	borane	products	yield	d.s.
1	(^{d}Ipc)$_2$BH	**4i:4j**	70%	>50:1
2	(^{l}Ipc)$_2$BH	**4i:4j**	75%	1: >50



entry	borane	products	yield	d.s.
1	(^{d}Ipc)$_2$BH	**4k:4l**	71%	>50:1
2	(^{l}Ipc)$_2$BH	**4k:4l**	78%	1: >50

Allylborane **2a** is easily generated from the hydroboration of commercially available allenylstannane **1** with (^{d}Ipc)$_2$BH at −40 to −20 °C followed by a kinetically controlled and highly diastereoselective 1,3-boratropic shift of intermediate **3a**. While 1,3-boratropic shifts, including examples that occur with 1,3-stereochemical transfer, are well-known,[3a,11] the discovery of the highly diastereoselective 1,3-boratropic shift of **3a** to **2a** was totally unexpected. To the best of our knowledge, the asymmetric induction due to the asymmetry of the −B(Ipc)$_2$ group (or any other chiral dialkylboryl unit) in the conversion of **3a** to **2a** has not been previously documented in the literature.[3a,11] Subsequent allylboration reactions of reagent **2a** with aldehydes provide homoallylic alcohols **4** in good yields and with excellent enantioselectivities. In comparison with conventional allylmetal chemistry, which typically provides homoallylic alcohols with a terminal olefin unit, this stannylallylboration reaction is exceptionally valuable in that it provides homoallylic alcohols with a functionalized olefin unit that is suitable for use in subsequent C−C bond formations (numerous examples of which are documented in the literature).[19] Applications of this methodology in the synthesis of natural products will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds; *xyz* coordinates and absolute energies of transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 1. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 299. (d) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 403. (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (f) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1.

(2) (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (c) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375.

(3) (a) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (b) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572.

(4) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414.

(5) (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (b) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412. (c) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (d) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (e) Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070. (f) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (g) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.

(6) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Nagi, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (d) Kim, I. S.; Han, S. B.; Krische, M. J. *Chem. Commun.* **2009**, 7278. (e) Bower, J. E.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3.

(7) For recent examples, see: (a) Amans, D.; Bareille, L.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2009**, *74*, 7665. (b) Frein, J. D.; Taylor, R. E.; Sackett, D. L. *Org. Lett.* **2009**, *11*, 3186.

(8) (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (b) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (c) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.

(9) (a) Althaus, M.; Mahmood, A.; Suarez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025. (b) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* [Online early access]. DOI: 10.1002/anie.201001223. Published Online: May 5, 2010.

(10) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(11) (a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6463. (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9. (c) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309. (d) Henriksen, U.; Snyder, J. P.; Halgren, T. A. *J. Org. Chem.* **1981**, *46*, 3767. (e) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564. (f) Wang, K. K.; Gu, Y. G.; Liu, C. *J. Am. Chem. Soc.* **1990**, *112*, 4424. (g) Gu, Y. G.; Wang, K. K. *Tetrahedron Lett.* **1991**, *32*, 3029. (h) Narla, G.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 219. (i) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 359. (j) Canales, E.; González, A. Z.; Soderquist, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 397. (k) González, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081.

(12) (a) Davis, D. D.; Gray, C. E. *J. Org. Chem.* **1970**, *35*, 1303. (b) Jerkunica, J. M.; Traylor, T. G. *J. Am. Chem. Soc.* **1971**, *93*, 6278. (c) Lambert, J. B.; Wang, G. T.; Teramura, D. H. *J. Org. Chem.* **1988**, *53*, 5422.

(13) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229.

(14) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(15) (a) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686. (b) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644. (c) González, A. Z.; Román, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269. (d) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602. (e) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174. (f) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *J. Org. Chem.* **2009**, *74*, 8626. (g) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *Org. Lett.* **2009**, *11*, 5538.

(16) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

(17) (a) *Jaguar*, version 7.5; Schrödinger, LLC: New York, 2008. (b) All of the B3LYP/LACVP** stationary points were confirmed to be minima or first-order saddle points by full calculation of the Hessian. Standard enthalpy corrections were applied at 298 K.

(18) **TS-1** is 3.3 kcal/mol lower than the TS that gives the corresponding (*E*)-δ-stannylallylborane ($\Delta H^{\ddagger}$ = 12.7 kcal/mol). Hydroboration TSs that directly give **2a** or **2b** are 6−10 kcal/mol higher in energy because of severe congestion between the Bu$_3$Sn and Ipc groups. See the SI for details.

(19) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777. (d) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445.

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