

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

Ming Chen, Daniel H. Ess, and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458

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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 allylmatal 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^{5c}) 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)₂BH]. 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 –SnR₃ 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)₂BH 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 analysis¹⁴). 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

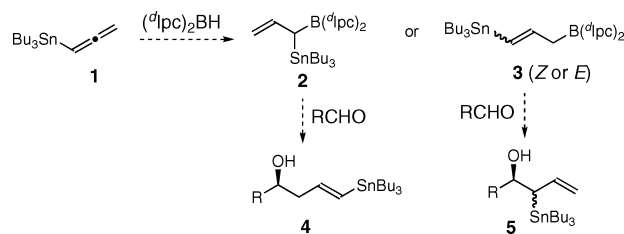


Figure 1

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	<i>t</i> -BuCHO	4h	51%	94
9 ^c	Ph(CH ₂) ₂ CHO	<i>ent</i> - 4a	71%	94
10 ^d	Ph(CH ₂) ₂ CHO	<i>ent</i> - 4a	73%	30

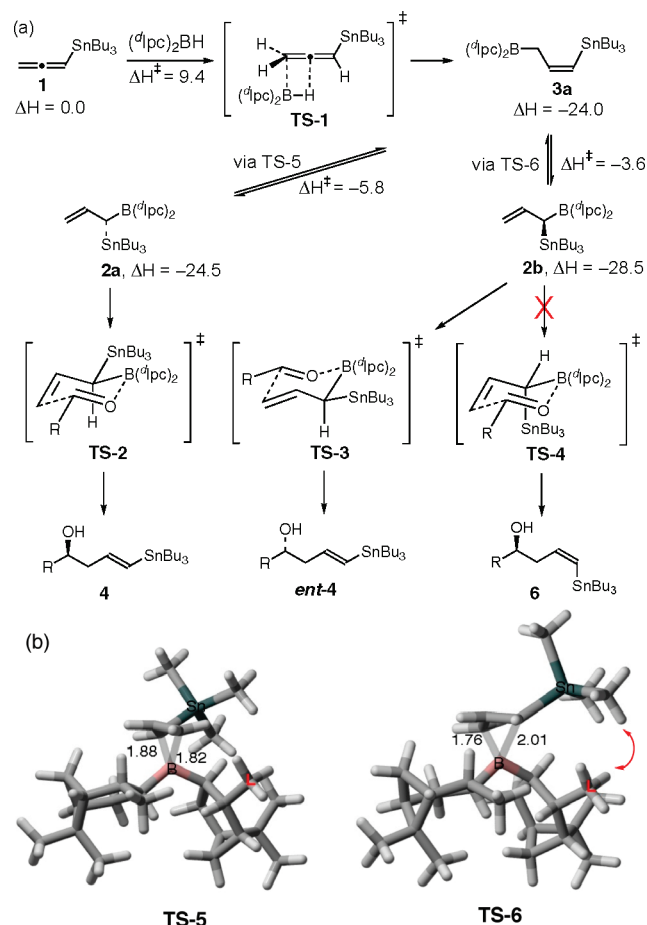
^a Reactions were performed by treatment of **1** with (*d*Ipc)₂BH (0.7 equiv) in Et₂O at –40 °C and warming to –20 °C over 5 h followed by the addition of RCHO (0.5 equiv) at –78 °C. The mixture was then allowed to stir at –78 °C for 8 h. The reactions were subjected to a standard workup (NaHCO₃, H₂O₂) at 0 °C prior to product isolation.

^b Determined by Mosher ester analysis. ^c (*Ipc*)₂BH was used. ^d This reaction was performed by treatment of **1** with (*d*Ipc)₂BH (0.7 equiv) in Et₂O at 0 °C followed by addition of RCHO (0.5 equiv) at –78 °C.

by elimination of **5**) were not detected in any of the experiments performed under these conditions.

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 analysis¹⁴). 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)₂BH 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-borotropic 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 $-\text{B}(\text{Ipc})_2$ unit.¹⁶

Support for this analysis was provided by the results of a low-temperature ^1H 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 $(^d\text{Ipc})_2\text{BH}$ 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 ^1H 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-borotropic shift of **3a** at temperatures below -20 °C is highly diastereoselective for **2a**; and (iii) the equilibrium constant for the 1,3-borotropic 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-borotropic 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 $\sim 1:2$ mixture of two α -stannyl allylborane species (**2a** and **2b**) was observed via ^1H 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 $(^d\text{Ipc})_2\text{B}-$ 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 $(^d\text{Ipc})_2\text{B}-$ 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-borotropic 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 pathway¹⁷ for hydroboration of **1** proceeds through **TS-1** ($\Delta H^\ddagger = 9.4$ 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-borotropic shift transition states lead from **3a** to either **2a** or **2b**. **TS-5** ($\Delta H^\ddagger = -5.8$ kcal/mol) is favored over **TS-6** ($\Delta H^\ddagger = -3.6$ 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, allylboration 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 $(^d\text{Ipc})_2\text{BH}$ and $(^l\text{Ipc})_2\text{BH}$ 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 ^1H 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-borotropic 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 lpc) ₂ BH	4i:4j	70%	>50:1
2	(^l lpc) ₂ BH	4i:4j	75%	1: >50

entry	borane	products	yield	d.s.
1	(^d lpc) ₂ BH	4k:4l	71%	>50:1
2	(^l lpc) ₂ BH	4k:4l	78%	1: >50

Allylborane **2a** is easily generated from the hydroboration of commercially available allenylstannane **1** with (^dlpc)₂BH at −40 to −20 °C followed by a kinetically controlled and highly diastereoselective 1,3-borotropic shift of intermediate **3a**. While 1,3-borotropic shifts, including examples that occur with 1,3-stereochemical transfer, are well-known,^{3a,11} the discovery of the highly diastereoselective 1,3-borotropic shift of **3a** to **2a** was totally unexpected. To the best of our knowledge, the asymmetric induction due to the asymmetry of the −B(lpc)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 allylmatal 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 -stannylallylboration ($\Delta H^\ddagger = 12.7$ kcal/mol). Hydroboration TSs that directly give **2a** or **2b** are 6–10 kcal/mol higher in energy because of severe congestion between the Bu₃Sn and lpc 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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