Published in final edited form as:

J Am Chem Soc. 2010 June 16; 132(23): 7881–7883. doi:10.1021/ja103041u.

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

The asymmetric carbonyl allylation reaction is an important transformation in organic synthesis.¹ Although extensive efforts in the past three decades have provided many useful allyl metal 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 non-racemic 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 homologation⁸ as in Hall's recent work^{5e}) and are not widely adopted in the literature. An important advance in this area involving the lithiation-borylation of allylic carbamates has been recently 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 [$(^d\text{Ipc})_2\text{BH}$]. 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 Based on the ability of $-\text{SnR}_3$ 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 $(^d\text{Ipc})_2\text{BH}$ in diethyl ether with the solution being allowed to warm 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 $>95\%$ e.e. (entry 1, Table 1).

* roush@scripps.edu .

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

Application of this procedure to a variety of other representative aldehydes (entries 1–9, Table 1) provided homoallylic alcohols **4a–h** in 51–78% yield and 92% to >95% e.e. (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 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 experimental conditions. As shown in entry 10 of Table 1, when the hydroboration of **1** was performed at 0 °C followed by addition of aldehydes at –78 °C, the *enantiomeric* homoallylic alcohols, **ent-4a** was obtained in 73% yield and 30% e.e. (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% e.e. and 77% yield. Here again, products with a (*Z*)-vinylstannane unit (e.g. **6** in Scheme 1a) were not detected.

Based on recent work on allenylboronate hydroboration,¹⁵ the reaction of allenylstannane **1** with (d_5 IPC)₂BH is expected to provide (*Z*)- γ -stannylallylborane **3a** as the kinetic product (Scheme 1a). If so, the results in Table 1 (entries 1–9) require 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 aldehydes at –78 °C to give **4** via the usual chair-like 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 have assigned by conversion of **4** to known compounds or by application of the modified Mosher method¹⁴; see SI) is fully consistent with the normal sense of asymmetric induction by the –B(IPC)₂ unit.¹⁶

Support for this analysis is provided by low temperature ¹H-NMR studies of hydroboration of **1** (see SI) which indicates that (*Z*)-**3a** is present at short reaction time, as well as by data from an experiment in which the hydroboration of allenylstannane **1** with (d_5 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 corresponding dienes are 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 ¹H-NMR study of the hydroboration reaction (SI) are consistent with the theses that (i) the kinetic mode of hydroboration of **1** is that depicted in Scheme 1a leading to (*Z*)- γ -stannylallylboronate **3a** (the precursor to **5**), and (ii) that equilibrium constant for the 1,3-borotropic shift is highly displaced in favor of **2a** (and/or **2b**, depending on reaction temperature, *vide supra*).

The data for the experiment summarized in Table 1, entry 10, indicates that when the hydroboration of **1** is performed at 0 °C, (or if the product of the hydroboration at –40 °C to –20 °C is allowed to warm to 0 °C) a rapid and reversible 1,3-borotropic shift occurs that gives a thermodynamic mixture of allylboranes **2a** and **2b**, slightly favoring **2b**. Indeed, when the hydroboration reaction of **1** was monitored at 0 °C, a ca. 1:2 mixture of two α -stannyl allylborane species—**2a** and **2b**—was observed via ¹H-NMR (see 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_5 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 have utilized B3LYP DFT to explore the transition states of the hydroboration, 1,3-borotropic rearrangement and aldehyde allylation steps leading to **4** and *ent*-**4** (SnBu₃ groups were modeled as SnMe₃).¹⁷ As shown in Scheme 1a, hydroboration of **1** proceeds through the lowest energy pathway¹⁷ **TS-1** ($\Delta H^\ddagger = 9.4$ kcal/mol) and gives the (*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 due to severe congestion between the Bu₃Sn 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 so that the hydrogen and methylene positions are closest to the Bu₃Sn group, while in **TS-6** the Bu₃Sn group is next to the hydrogen and large tertiary carbon center (Scheme 1b). The repulsion between the isopinocampheyl and Bu₃Sn 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 provides homoallylic alcohols **4** via **TS-2** with equatorial placement of the α -Bu₃Sn 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 or (*l*Ipc)₂BH at -40 °C (with warming to -20 °C) and then addition of aldehyde **7** at -78 °C provided **4i** and **4j** in 70–75% yield, each with >50:1 diastereoselectivity (¹H-NMR analysis—the alternative minor diastereomers could not be detected in either experiment). Similarly, use of the more elaborated aldehyde **8** as substrate provided **4k** and **4l** in 71–78% yield, both again with >50:1 diastereoselectivity (Table 3). The very high diastereoselectivity of these pairs of double asymmetric reactions attests 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**. Allylborane **2a** is easily generated from the hydroboration of commercially available allenylstannane **1** with (*d*Ipc)₂BH at -40 to -20 °C followed by a kinetically controlled and highly diastereoselective 1,3-borotropic shift of intermediate **3a**. While the 1,3-borotropic shift, 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(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. Compared to 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, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support provided by the National Institutes of Health (GM038436 and GM026782) is gratefully acknowledged. We thank Professor William A. Goddard III of Cal Tech for use of his computational facilities and software for some of these calculations.

References

- (a) Roush, WR. Comprehensive Organic Synthesis. Trost, BM., editor. Vol. 2. Pergamon Press; Oxford: 1991. p. 1 (b) Yamamoto Y, Asao N. Chem. Rev 1993;93:2207. (c) Denmark, SE.; Almstead, NG. Modern Carbonyl Chemistry. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 299 (d) Chemler, SR.; Roush, WR. Modern Carbonyl Chemistry. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 403 (e) Denmark SE, Fu J. Chem. Rev 2003;103:2763. [PubMed: 12914480] (f) Lachance H, Hall DG. Org. React 2008;73:1.
- (a) Kinnaird JWA, Ng PY, Kubota K, Leighton JL. J. Am. Chem. Soc 2002;124:7920. [PubMed: 12095334] (b) Kubota K, Leighton JL. Angew. Chem. Int. Ed 2003;42:946. (c) Hackman BM, Lombardi PJ, Leighton JL. Org. Lett 2004;6:4375. [PubMed: 15524487]
- (a) Burgos CH, Canales E, Matos K, Soderquist JA. J. Am. Chem. Soc 2005;127:8044. [PubMed: 15926828] (b) Canales E, Prasad KG, Soderquist JA. J. Am. Chem. Soc 2005;127:11572. [PubMed: 16104712]
- (a) Kennedy JWJ, Hall DG. J. Am. Chem. Soc 2002;124:11586. [PubMed: 12296710] (b) Ishiyama T, Ahiko T, Miyaura N. J. Am. Chem. Soc 2002;124:12414. [PubMed: 12381174]
- (a) Lachance H, Lu X, Gravel M, Hall DG. J. Am. Chem. Soc 2003;125:10160. [PubMed: 12926924] (b) Kennedy JWJ, Hall DG. J. Org. Chem 2004;69:4412. [PubMed: 15202896] (c) Rauniyar V, Hall DG. J. Am. Chem. Soc 2004;126:4518. [PubMed: 15070360] (d) Rauniyar V, Hall DG. Angew. Chem., Int. Ed 2006;45:2426. (e) Peng F, Hall DG. J. Am. Chem. Soc 2007;129:3070. [PubMed: 17315879] (f) Rauniyar V, Zhai H, Hall DG. J. Am. Chem. Soc 2008;130:8481. [PubMed: 18540580] (g) Rauniyar V, Hall DG. J. Org. Chem 2009;74:4236. [PubMed: 19422213]
- (a) Kim IS, Ngai M-Y, Krische MJ. J. Am. Chem. Soc 2008;130:6340. [PubMed: 18444616] (b) Kim IS, Nagi M-Y, Krische MJ. J. Am. Chem. Soc 2008;130:14891. [PubMed: 18841896] (c) Kim IS, Han SB, Krische MJ. J. Am. Chem. Soc 2009;131:2514. [PubMed: 19191498] (d) Kim IS, Han SB, Krische MJ. Chem. Commun 2009:7278. (e) Bower JE, Kim IS, Patman RL, Krische MJ. Angew. Chem. Int. Ed 2009;48:3.
- For recent examples: (a) Amans D, Bareille L, Bellosta V, Cossy J. J. Org. Chem 2009;74:7665. [PubMed: 19769335] (b) Frein JD, Taylor RE, Sackett DL. Org. Lett 2009;11:3186. [PubMed: 19572566]
- (a) Matteson DS. Chem. Rev 1989;89:1535. (b) Matteson DS. Tetrahedron 1989;45:1859. (c) Matteson DS. Tetrahedron 1998;54:10555.
- (a) Althaus M, Mahmood A, Suarez JR, Thomas SP, Aggarwal VK. J. Am. Chem. Soc 2010;132:4025. [PubMed: 20192266] (b) Binanzer M, Fang GY, Aggarwal VK. Angew. Chem. Int. Ed 2010;49 DOI: 10.1002/anie.201001223.
- Chatterjee AK, Choi T-L, Sanders DP, Grubbs RH. J. Am. Chem. Soc 2003;125:11360. [PubMed: 16220959]
- (a) Hancock KG, Kramer JD. J. Am. Chem. Soc 1973;95:6463. (b) Kramer GW, Brown HC. J. Organomet. Chem 1977;132:9. (c) Hoffmann RW, Zeiss HJ. J. Org. Chem 1981;46:1309. (d) Henriksen U, Snyder JP, Halgren TA. J. Org. Chem 1981;46:3767. (e) Brown HC, Jadhav PK, Bhat KS. J. Am. Chem. Soc 1985;107:2564. (f) Wang KK, Gu YG, Liu C. J. Am. Chem. Soc 1990;112:4424. (g) Gu YG, Wang KK. Tetrahedron Lett 1991;32:3029. (h) Narla G, Brown HC. Tetrahedron Lett 1997;38:219. (i) Fang GY, Aggarwal VK. Angew. Chem. Int. Ed 2007;46:359. (j) Canales E, González AZ, Soderquist JA. Angew. Chem. Int. Ed 2007;46:397. (k) González AZ, Soderquist JA. Org. Lett 2007;9:1081. [PubMed: 17295500]
- (a) Davis DD, Gray CE. J. Org. Chem 1970;35:1303. (b) Jerkunica JM, Traylor TG. J. Am. Chem. Soc 1971;93:6278. (c) Lambert JB, Wang GT, Teramura DH. J. Org. Chem 1988;53:5422.
- Yamamoto Y, Yatagai H, Maruyama K. J. Am. Chem. Soc 1981;103:3229.

14. (a) Dale JA, Mosher HS. *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 HC, Narla G. *J. Org. Chem* 1995;60:4686. (b) Flamme EM, Roush WR. *J. Am. Chem. Soc* 2002;124:13644. [PubMed: 12431072] (c) González AZ, Román JG, Alicea E, Canales E, Soderquist JA. *J. Am. Chem. Soc* 2009;131:1269. [PubMed: 19117388] (d) Chen M, Handa M, Roush WR. *J. Am. Chem. Soc* 2009;131:14602. [PubMed: 19778012] (e) Kister J, DeBaillie AC, Lira R, Roush WR. *J. Am. Chem. Soc* 2009;131:14174. [PubMed: 19775159] (f) Ess DH, Kister J, Chen M, Roush WR. *J. Org. Chem* 2009;74:8626. [PubMed: 19824624] (g) Ess DH, Kister J, Chen M, Roush WR. *Org. Lett* 2009;11:5538. [PubMed: 19899749]
16. (a) Brown HC, Jadhav PK. *J. Am. Chem. Soc* 1983;105:2092. (b) Brown HC, Bhat KS. *J. Am. Chem. Soc* 1986;108:293.
17. Jaguar. version 7.5. Schrodinger, LLC; New York, NY: 2008. (b) All 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 -stannyl-allylborane ($\Delta H^\ddagger = 12.7$ kcal/mol). Hydroboration TSs that directly give **7** or **8** are 6–10 kcal/mol higher in energy due to severe congestion between the Bu₃Sn and Ipc groups. See supporting information for details.
19. (a) Stille JK. *Angew. Chem., Int. Ed. Engl* 1986;25:508. (b) Farina V, Krishnamurthy V, Scott WJ. *Org. React* 1997;50:1. (c) Oppolzer W, Radinov RN. *Tetrahedron Lett* 1991;32:5777. (d) Marshall JA, Eidam P. *Org. Lett* 2004;6:445. [PubMed: 14748614]

Figure 1.

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

Table 1

Synthesis of δ -Stannyl Homoallylic Alcohols **4** via Hydroboration of **1** at -40°C to -20°C (via Kinetically Controlled Allylborane Isomerization)^a vs. at 0°C (Thermodynamically Controlled Allylborane Isomerization)

entry	RCHO	product	yield	%e.e. ^b
1	$\text{Ph}(\text{CH}_2)_2\text{CHO}$	4a	64%	>95
2	PhCH_2CHO	4b	67%	>95
3	PhCHO	4c	78%	93
4	$\text{BnO}(\text{CH}_2)_2\text{CHO}$	4d	68%	>95
5	BnOCH_2CHO	4e	71%	>95
6	$\text{PhCH}=\text{CHCHO}$	4f	73%	>95
7	CyCHO	4g	55%	92
8	$t\text{-BuCHO}$	4h	51%	94
9 ^c	$\text{Ph}(\text{CH}_2)_2\text{CHO}$	<i>ent</i> - 4a	71%	94
10 ^d	$\text{Ph}(\text{CH}_2)_2\text{CHO}$	<i>ent</i> - 4a	73%	30

(a) Reactions were performed by treating **1** with $(^d\text{Ipc})_2\text{BH}$ (0.7 equiv.) in Et_2O at -40°C and warmed 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_2O_2) at 0°C prior to product isolation.

(b) Determined by Mosher ester analysis.

(c) $(^d\text{Ipc})_2\text{BH}$ was used.

(d) This reaction was performed by treating **1** with $(^d\text{Ipc})_2\text{BH}$ (0.7 equiv.) in Et_2O at 0°C followed by addition of RCHO (0.5 equiv.) at -78°C .

Table 2Double 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