

Published in final edited form as:

J Am Chem Soc. 2006 June 28; 128(25): 8142–8143. doi:10.1021/ja0620639.

Regiochemical Control in the Metal-Catalyzed Transposition of Allylic Silyl Ethers

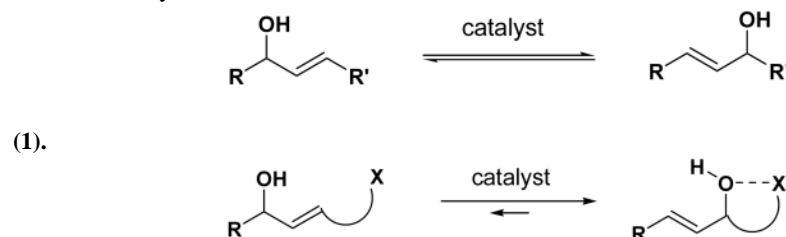
Eric C. Hansen and Daesung Lee*

Department of Chemistry, University of Wisconsin, Madison, WI 53706

Abstract

A novel mode of regiochemical control over the allylic [1,3]-transposition of silyloxy groups catalyzed by Re_2O_7 has been developed. This strategy relies on a *cis*-oriented vinyl boronate, generated from the Alder ene reaction of homoallylic silyl ethers and alkynyl boronates, to trap out the allylic hydroxyl group. The resulting cyclic boronic acids are excellent partners for cross coupling reactions. High chirality transfer is observed for the rearrangement of enantioenriched allylic silyl ethers.

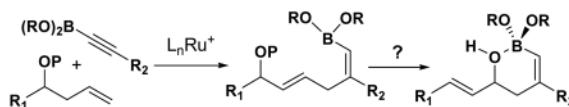
In the context of manipulating synthetic intermediates, the efficient [1,3]-transposition of allylic heteroatom functionalities is an important goal in synthetic chemistry.¹ One of the most direct and atom-economical methods for this transformation is a transition metal-catalyzed rearrangement of an allylic hydroxyl group.² Although the rhenium catalyst-based rearrangement developed by Osborn and coworkers³ is the most efficient method, it generally suffers from low regioselectivity, giving equilibrium mixtures of two isomers (eq 1). Efforts to control the regioselectivity have focused on introducing stereoelectronic biasing elements around the allylic double bond^{2c} such as



conjugation or by taking advantage of the steric environment of the allylic hydroxyl group.^{2a,c,4} To further improve the scope of this rearrangement, we envisioned a new approach where the equilibrium can be shifted toward the desired direction by introducing certain functionality within the molecule that can interact with the [1,3]-transposed hydroxyl group (eq 2).

In search of a suitable platform that allows us to test this concept, we became interested in boron's unique affinity for hydroxyl group. The *cis*-vinyl boronate generated from the ruthenium-catalyzed Alder ene reaction⁵ between homoallylic alcohol derivatives and alkynyl boronates nicely sets the stage for testing the subsequent allylic [1,3]-transposition, after removal of the hydroxyl protecting group (eq 3). Herein we report a successful implementation of a two-step protocol for an efficient synthesis of cyclic vinyl boronic acids via a novel mode

of regiochemical control in the allylic [1,3]-transposition induced by boronate trapping of hydroxyl and silyloxy groups.

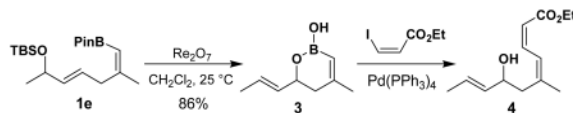


(3).

Having recognized the critical role of the protecting group in the Alder ene reaction as well as in the deprotection step, particularly due to the unstable nature of the boronate both under basic and acidic conditions, we tested several common protecting groups on the substrate homoallylic alcohol (Table 1). First, an ethyl carbonate and an acetate group were used (entries 1 and 2), which gave a good yield of the Alder ene reaction product **1a** and **1b**, respectively. However, deprotection of these protecting groups under typical mildly basic conditions gave only low yield of free alcohol **2**. Again, ethereal protecting group MOM is suitable for the first step but its removal under acidic conditions led to rapid protodeboronation (entry 3). To avoid both basic and acidic aqueous conditions for the deprotection, the Troc (trichloroethoxycarbonyl) protecting group was used. Although the deprotection was nicely accomplished in Zn/AcOH as expected, the first coupling step gave low yield of **1d** probably due to the ionization of the allylic C–O bond with the highly activated Troc group.⁶ A silyl protecting group such as TBS (**1e**) was found to be problematic for its removal in the presence of the boronate functionality (entry 5).

Having allylic alcohol **2** in hand, we next tried the allylic [1,3]-transposition. The rearrangement was found to be very efficient to give an excellent yield of the singly allylic [1,3]-transposed product in <5 min using either Ph₃SiOREO₃⁷ or Re₂O₇ at room temperature. Surprisingly, the identity of the rearranged product is not the expected vinyl boronate with the transposed hydroxyl group but instead the cyclic vinyl boronic acid **3**.⁸ Despite the efficient allylic transposition, the significance of this overall transformation was compromised by unacceptably low yields for the three-step sequence caused by the protecting group incompatibility in the first two steps.

At this juncture, we turned our attention to the possibility of direct rearrangement of the protected form of hydroxyl functionality. Based on examples of the allylic [1,3]-transposition of silyl ethers^{3b,9} in combination with their efficient preparation, we chose **1e** as the model substrate for the rearrangement. Gratifyingly, treatment of **1e** with Re₂O₇ (CH₂Cl₂, 25 °C, 2 h) provided silyl group-free product, which was identical to vinyl boronic acid **3**, the structure of which was confirmed after conversion to **4** via Suzuki coupling (eq 4).¹⁰



(4).

Encouraged by this observation, a variety of *cis*-vinyl boronates were synthesized via the Alder-ene reaction in order to test the generality of the rearrangement (Table 2). Substrates **5a–d** were obtained in good yield and moderate selectivity for the *Z*-isomer.¹¹ Under typical conditions (Re₂O₇; CH₂Cl₂ or Et₂O, 25 °C), these substrates provided the rearrangement products **6a–d** in excellent yields.¹² Unexpectedly, products **5e** and **5f** were not obtained from the Alder-ene reaction. Instead, the reaction directly lead to the [1,3]-transposed products **6e** and **6f** in 43% and 54% yields respectively (entries 5 and 6).^{10,13} This tandem Alder ene reaction followed

by allylic transposition is probably due to the activated nature of the benzylic silyl ether toward the cationic ruthenium catalyst employed.⁶

The rearrangement of **5d** renders the important issue of chirality transfer during the reaction (entry 4). Because the assessment of the diastereomeric ratio of **6d**¹⁴ was not trivial, enantioenriched substrates **5b** and **5c** were tested. Interestingly, when the rearrangement was performed in CH₂Cl₂, significant loss of stereochemical information was observed for **6b** and **6c** (Table 3). However, when the reaction was run in ether, the stereochemical integrity was preserved.¹⁵ The efficiency of chirality transfer from **5b** to **6b** and **5c** to **6c** was determined by analysis of the Mosher ester derivatives after conversion to **7b** and **7c**.

The cyclic vinyl boronic acids **6a–f** were found to be excellent coupling partners in Suzuki couplings.^{14,16} Compounds **6a–c** and **6e–f** underwent coupling with *cis*-ethyl- β -iodoacrylate to give the corresponding coupled products **7a–c** and **7e–f**, representative examples of which are illustrated in Scheme 1.

In conclusion, we have developed a highly efficient protocol for the synthesis of cyclic vinyl boronic acid. This novel mode of regiochemical control in the allylic [1,3]-transposition was achieved by using the oxygen affinity of a *cis*-oriented vinyl boronate to trap out the hydroxyl and silyloxy group. Application of this consecutive Alder ene reaction followed by allylic transposition to natural products synthesis is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

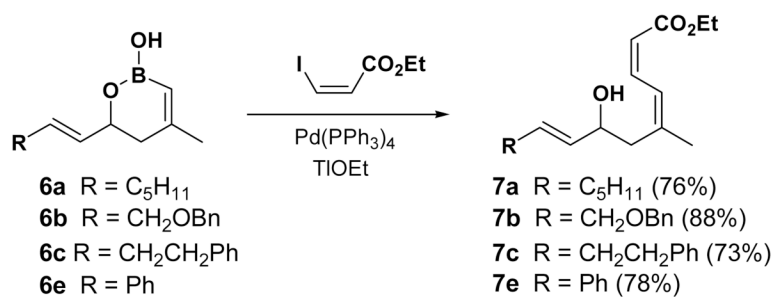
Acknowledgements

We thank NIH (CA106673) for financial support of this work as well as the NSF and NIH for NMR and Mass Spectrometry instrumentation. E. C. H. thanks Abbott Laboratories for an Abbott fellowship. D. L. is a fellow of the Alfred P. Sloan foundation.

References

1. For epoxidation/reduction, see: (a) Wharton PS, Bohlen DH. *J Org Chem* 1961;26:3615–3616. (b) Nicolaou KC, Duggan ME, Ladduwahetty T. *Tetrahedron Lett* 1984;25:2069–2072. For [3,3]-sigmatropic rearrangements, see: (c) Overman LE. *Angew Chem Int Ed* 1984;23:579–586. (d) Lutz RP. *Chem Rev* 1984;84:205–247. For [2,3]-sigmatropic rearrangements, see: (e) Evans DA, Andrews GC. *Acc Chem Res* 1974;7:147–155. (f) Reich HJ. *J Org Chem* 1975;40:2570–2572.
2. (a) Takai K, Nozaki H, Oshima K, Okazoe T, Matsubara S. *Bull Chem Soc Jpn* 1985;58:844–849. (b) Narasaka K, Kusama H, Hayashi Y. *Tetrahedron* 1992;48:2059–2068. (c) Gordon MS, Jensen JH, Espenson JH, Jacob J. *Organometallics* 1998;17:1835–1840. (d) Bellemin-Laponnaz S, Le Ny JP, Dedieu A. *Chem Eur J* 1999;5:57–64. For a review, see: Le Ny JP, Bellemin-Laponnaz S. *C R Chimie* 2002;217–224.
3. (a) Bellemin-Laponnaz S, Gisie H, Le Ny JP, Osborn JA. *Angew Chem Int Ed* 1997;36:976–978. (b) Bellemin-Laponnaz S, Gisie H, Le Ny JP, Osborn JA. *Tetrahedron Lett* 2000;41:1549–1552.
4. Morrill C, Grubbs RH. *J Am Chem Soc* 2005;127:2842–2843. [PubMed: 15740106]
5. Hansen EC, Lee D. *J Am Chem Soc* 2005;127:3252–3253. [PubMed: 15755122] For a review of ruthenium-catalyzed reactions, see: Trost BM, Federiksen MU, Rudd MT. *Angew Chem Int Ed* 2005;44:6630–6666.
6. For π -allylruthenium complex formation from allylic carbonates or chlorides, see: Pregosin PS, Fernandez I, Breher F, Hermatschweiler R. *Organometallics* 2006;25:1440–1447.
7. The more soluble catalyst Ph₃SiOReO₃ gave lower conversion in the current reaction. For synthesis and structure of this catalyst, see: Schoop T, Roesky HW, Noltemeyer M, Schmidt HG. *Organometallics* 1993;12:571–574.

8. For related compounds, see: (a) Falck JR, Bondlela M, Venkataraman SK, Srinivas D. *J Org Chem* 2001;66:7148–7150. [PubMed: 11597243] (b) Micalizio GC, Schreiber SL. *Angew Chem Int Ed* 2002;41:3272–3276. (c) Jean Zhou Q, Worm K, Dolle RE. *J Org Chem* 2004;69:5147–5149. [PubMed: 15255755]
9. Herrmann WA, Wojtczak WA, Artus GRJ, Kuhn FE, Mattner MR. *Inorg Chem* 1997;36:465–471.
10. The cyclic boronic acids could be identified by crude ^1H NMR but complete characterization was only achieved after derivitization via Suzuki coupling.
11. Higher *Z/E* ratios had been observed previously for alkenes with no branching substituents in the homoallylic position (ref 5).
12. The *E*-isomer could be recovered as a mixture of allylic silyl ethers regioisomers.
13. Complete racemization of **6e** was observed.
14. **6d** represents the C4–C16 subunit of (-)-zampanolide and (-)-dactylolide. Details of its use in total synthesis will be reported in a future article.
15. Chirality transfer has been observed for cyclic allylic alcohols, see: Troste BM, Toste FD. *J Am Chem Soc* 2000;122:11262–11263. Acyclic allylic alcohols require low temperatures (-78 °C) for chirality transfer (ref 4).
16. (a) Frank SA, Chen H, Kunz RK, Schnaderbeck MJ, Roush WR. *Org Lett* 2000;2:2691–2694. [PubMed: 10990429] For a review, see: (a) Miyaoura N, Suzuki A. *Chem Rev* 1995;95:2457–2483.



Scheme 1.
Suzuki Coupling of Cyclic Vinyl Boronic Acids

Table 1
Protecting Group Effect for Alder Ene Reaction of Borylated Alkynes–Deprotection–Allylic Transposition

(Pin = pinacolate)

entry	P =	yield 1 (%)	b: deprotection	yield 2 (%)	yield 3 (%) ^d
1	CO ₂ Et (a)	68	K ₂ CO ₃ /MeOH	25	17
2	Ac (b)	70	LiOH/MeOH	30	20
3	CH ₂ OMe (c)	67	HF/pyr	— ^e	—
4	CO ₂ CH ₂ CCl ₃ (d)	33	Zn/AcOH	95	31
5	TBS (e)	77	TBAF	— ^f	—

^aWith 10 mol % of RuCp(CH₃CN)₃PF₆ at 25 °C.

^bDeprotection conditions.

^cPh₃SiOReO₃ or Re₂O₇ in CH₂Cl₂, 25 °C.

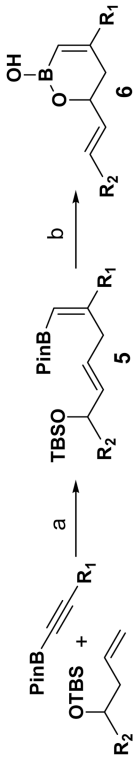
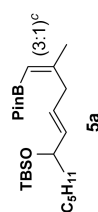
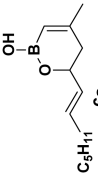
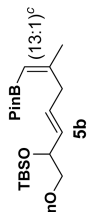
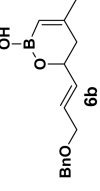
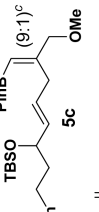
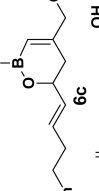
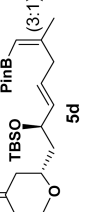
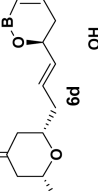
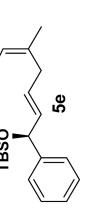
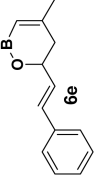
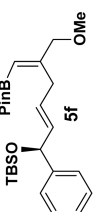
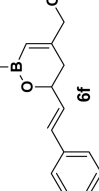
^dThree-step yield.

^eProtodeboronation was observed.

^fDecomposition was observed.

Table 2

Allylic [1,3]-Transposition of Silyl Ethers

entry			yield 6 (%)	
	yield 5 (%)			
1	 5a	77	 6a	57
2	 5b	60	 6b	82
3	 5c	82	 6c	86
4	 5d	45 ^c	 6d	65
5	 5e	—	 6e	43 ^e (88) ^d
6	 5f	—	 6f	54 ^e (90) ^d

^aWith 5 mol % of RuCp(CH₃CN)₃PF₆ in acetone at 25 °C.

^bWith 2.5 mol% Re₂O₇ in CH₂Cl₂ or ether at 25 °C.

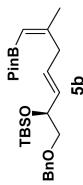
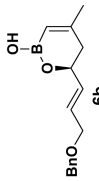
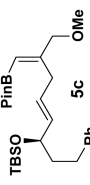
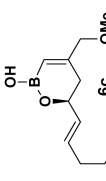
^cMixtures of boronate stereoisomers.

^dBased on recovered starting material.

^eRacemic mixture.

Table 3

Chirality Transfer for Allylic [1,3]-Transposition

substrate	e.r.	product	solvent	yield (%)	e.r.
 5b	99:1	 6b	CH ₂ Cl ₂ Et ₂ O	68 72	84:16 99:1
 5c	80:20	 6c	CH ₂ Cl ₂ Et ₂ O	64 70	50:50 80:20