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

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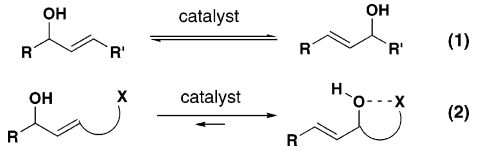
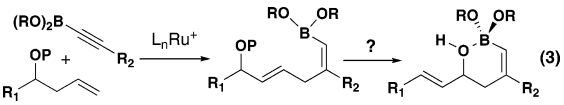
In the context of manipulating synthetic intermediates, the efficient [1,3]-transposition of allylic heteroatom functionalities is an important goal in synthetic chemistry.[1] One of the most direct and atom-economical methods for this transformation is a transition-metal-catalyzed rearrangement of an allylic hydroxyl group.[2] Although the rhenium catalyst-based rearrangement developed by Osborn and co-workers[3] 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).

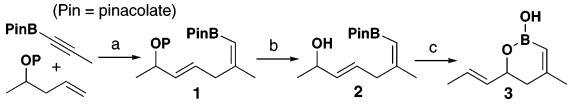


In search of a suitable platform that allows us to test this concept, we became interested in boron's unique affinity for hydroxyl group. The *cis*-vinyl boronate generated from the ruthenium-catalyzed Alder-ene reaction[5] between homoallylic alcohol derivatives and alkynyl boronates nicely sets the 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.



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 products **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 (trichloroethyloxycarbonyl) 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).

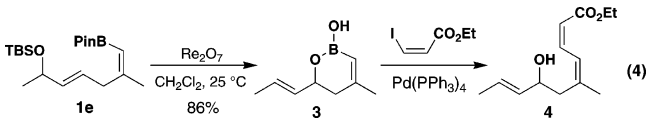
Table 1. Protecting Group Effect for Alder-ene Reaction of Borylated Alkynes−Deprotection−Allylic Transposition



entry	P =	yield **1** (%)	b: deprotection	yield **2** (%)	yield **3** (%)[d]
1	CO_2Et (**a**)	68	K_2CO_3/MeOH	25	17
2	Ac (**b**)	70	LiOH/MeOH	30	20
3	CH_2OMe (**c**)	67	HF/pyr	0[e]	0
4	$CO_2CH_2CCl_3$ (**d**)	33	Zn/AcOH	95	31
5	TBS (**e**)	77	TBAF	0[f]	0

[a] With 10 mol % of $RuCp(CH_3CN)_3PF_6$ at 25 °C. [b] Deprotection conditions. [c] $Ph_3SiOReO_3$ or Re_2O_7 in CH_2Cl_2, 25 °C. [d] Three-step yield. [e] Protodeboronation was observed. [f] Decomposition was observed.

At this juncture, we turned our attention to the possibility of direct rearrangement of the protected form of hydroxyl functionality. On the basis of 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 Re_2O_7 (CH_2Cl_2, 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]



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 (Re_2O_7; CH_2Cl_2 or Et_2O, 25 °C), these substrates provided the rearrangement products **6a**−**d** in excellent yields.[12] Unexpectedly, products **5e** and **5f** were not obtained from

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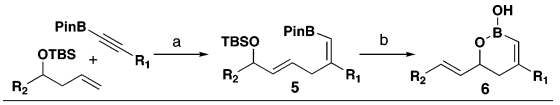
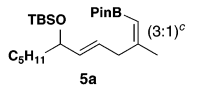
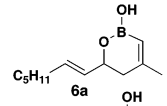
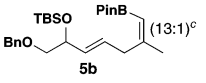
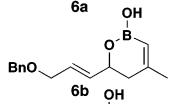
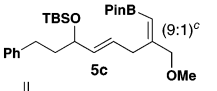
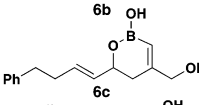
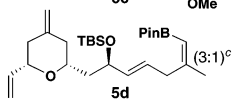
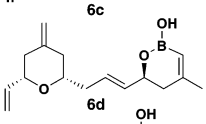
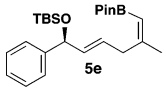
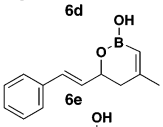
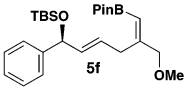
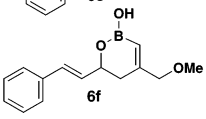
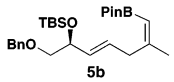
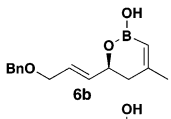
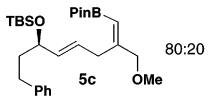
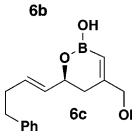
Table 2. Allylic [1,3]-Transposition of Silyl Ethers



entry	yield **5** (%)	yield **6** (%)
1	 (3:1)[c]	77		57
2	 (13:1)[c]	60		82
3	 (9:1)[c]	82		86
4	 (3:1)[c]	45		65
5		—		43[e] (88)[d]
6		—		54[e] (90)[d]

[a] With 5 mol % of $RuCp(CH_3CN)_3PF_6$ in acetone at 25 °C. [b] With 2.5 mol % of Re_2O_7 in CH_2Cl_2 or ether at 25 °C. [c] Mixtures of boronate stereoisomers. [d] Based on recovered starting material. [e] Racemic mixture.

Table 3. Chirality Transfer for Allylic [1,3]-Transposition

substrate	e.r.	product	solvent	yield (%)	e.r.
 **5b**	99:1	 **6b**	CH_2Cl_2	68	84:16
			Et_2O	72	99:1
 **5c**	80:20	 **6c**	CH_2Cl_2	64	50:50
			Et_2O	70	80:20

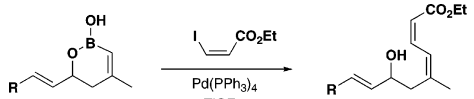
the Alder-ene reaction. Instead, the reaction directly lead to the [1,3]-transposed products **6e** and **6f** in 43 and 54% yields, respectively (entries 5 and 6).[10,13] This tandem Alder-ene reaction followed by allylic transposition is probably due to the activated nature of the benzylic silyl ether 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 CH_2Cl_2, 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

Scheme 1. Suzuki Coupling of Cyclic Vinyl Boronic Acids



6a R = C_5H_{11}
6b R = CH_2OBn
6c R = CH_2CH_2Ph
6e R = Ph

7a R = C_5H_{11} (76%)
7b R = CH_2OBn (88%)
7c R = CH_2CH_2Ph (73%)
7e R = Ph (78%)

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.

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Supporting Information Available: General procedures and characterization of represented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Herrmann, W. A.; Wojtczak, W. A.; Artus, G. R. J.; Kuhn, F. E.; Mattner, M. R. *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 ether 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, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **2000**, *122*, 11262−11263. Acyclic allylic alcohols require low temperatures (−78 °C) for chirality transfer (ref 4).

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