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Construction of Homoallylic Alcohols from Terminal Alkynes and Aldehydes with Installation of *syn*-Stereochemistry

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Supporting Information

ABSTRACT: A cationic rhodium(I) catalyst turns 2-silyl-1-alkenylboronate, readily prepared from a terminal alkyne, into the corresponding allylboronate species, which immediately undergoes nucleophilic addition to an aldehyde to give a *syn*-homoallylic alcohol stereoselectively.

Stereoselective construction of contiguous chiral centers in an acyclic system has been an area of intensive research in organic synthesis. An allylation reaction of carbonyl compounds with allylmetal reagents serves as a powerful tool for stereoselective synthesis of homoallylic alcohols.[1−3] When a six-membered chairlike transition state is assumed, the stereochemical outcome depends on the *E*/*Z* stereochemistry of allylmetal reagents.[4] Thus, the development of stereoselective preparative methods of allylmetal reagents has attracted considerable attention.[5] Recently, we have reported a convenient method for the diastereoselective synthesis of *anti*-homoallylic alcohols using simple 1-alkenylboronates,[6] which are readily prepared by hydroboration of terminal alkynes. Cationic rhodium(I) or iridium(I) complexes catalyze their double bond transposition to generate thermodynamically less stable (*E*)-*2-alkenylboronates*,[7] which spontaneously react with coexisting aldehydes. Although this transformation makes *anti*-homoallylic alcohols accessible from terminal alkynes and aldehydes, in greater demand is a complementary stereoselective method for *syn*-diastereomers, which are generally more difficult to synthesize.[8] Cheng,[8a] Knochel,[8b] and Krische[8f] made use of the presence of a sterically demanding silyl group at the 2-position of allylic systems to gain *syn* stereochemistry. We now report a new synthetic pathway starting from terminal alkynes stereoselectively leading to *syn*-homoallylic alcohols via 2-silyl-1-alkenylboronates, which act as the synthetic equivalent of (*Z*)-*2-alkenylboronates* (Figure 1).

(*Z*)-2-Silyl-1-butenylboronate (*Z*)-**3a** was prepared from but-1-yne (**1a**) and $PhMe_2Si$-Bpin (**2**) by silaboration under the general conditions developed by Suginome and Ito (eq 1).[9]

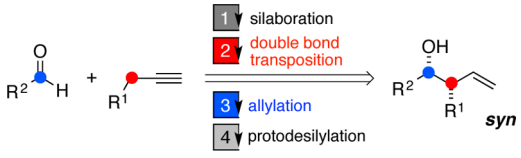
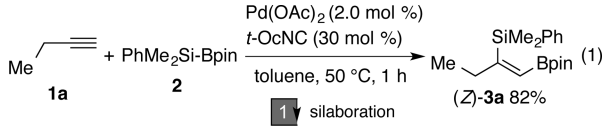
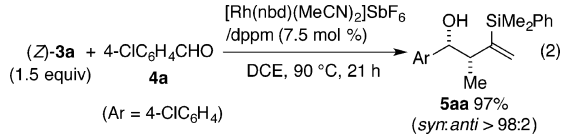


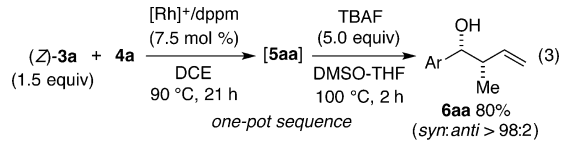
Figure 1. Construction of *syn*-homoallylic alcohols starting from terminal alkynes and aldehydes.



Then, an allylation reaction of aldehydes with (*Z*)-**3a** was examined. A mixture of (*Z*)-**3a** and **4a** in 1,2-dichloroethane (DCE) was heated at 90 °C for 21 h in the presence of a cationic rhodium(I) catalyst[10] generated *in situ* from [Rh(nbd)(MeCN)$_2$]SbF$_6$ and dppm.[11] Chromatographic purification of the reaction mixture furnished *syn*-homoallylic alcohol **5aa** in 97% isolated yield with excellent *syn* selectivity (eq 2). No *anti* isomer was observed within the detection limit of ^{1}H NMR (>98:2).



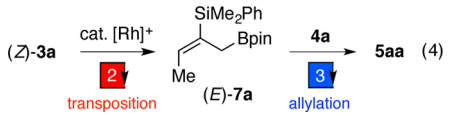
When tetrabutylammonium fluoride (TBAF) was directly added to the reaction mixture, protodesilylation of **5aa** ensued to form simple *syn*-crotylated product **6aa** in 80% isolated yield (eq 3).[8f] Thus, the reactions of eqs 1 and 3 are combined in sequence to provide a stereoselective pathway to *syn*-homoallylic alcohols starting from terminal alkynes and aldehydes.



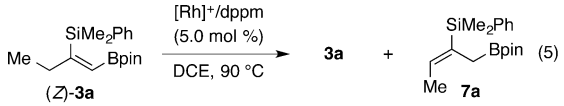
The following pathway consisting of two steps, i.e., double bond transposition and allylation, accounts for the formation of the homoallylic alcohol **5aa** from (*Z*)-2-silyl-1-alkenylboronate (*Z*)-**3a** and aldehyde **4a** (eq 4). The rhodium(I) catalyst promotes double bond transposition of (*Z*)-**3a** at 90 °C, generating 2-silyl-2-alkenylboronate **7a**,[8a,12] which spontaneously adds to the aldehyde **4a** through a six-membered chairlike transition state at that temperature to produce **5aa**. The *syn* stereochemistry observed with **5aa** suggests the stereoselective generation of the *E* isomer of **7a**.

Received: March 3, 2014
Published: April 15, 2014

   dx.doi.org/10.1021/ja502169d | *J. Am. Chem. Soc.* 2014, 136, 6223−6226



The control experiments were carried out to confirm this mechanistic scenario; (*Z*)-2-silyl-1-alkenylboronate (*Z*)-**3a** was treated with a catalytic amount of the rhodium(I) complex in the absence of aldehyde **4a**, and the double bond transposition was monitored by ^{1}H NMR (eq 5). The *E*/*Z* ratio of the

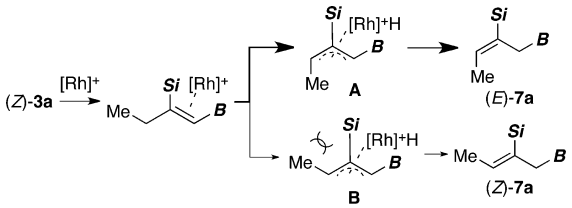


time	3a/7a	*E*/*Z* of 7a
1 h	63:37	>98:2
3 h	**3:97**	>98:2
10 h	4:96	>98:2

resulting 2-silyl-2-alkenylboronate **7a** was constantly >98:2 during the early stage of transposition, suggesting that (*E*)-**7a** was kinetically favored over (*Z*)-**7a**. After 3 h, the (*E*)-**7a**:**3a** ratio became steady in favor of (*E*)-**7a** (ca. 97:3). Thus, unlike the case of simple 1-alkenylboronates, (*E*)-**7a** is thermodynamically far more stable than **3a**. The steric repulsion between the boryl group and other substituents in its vicinity would be smallest with (*E*)-**7a** among the possible four isomers (*E*)/(*Z*)-**3a** and (*E*)/(*Z*)-**7a**. This unidirectional double bond transposition of **3a** stands in marked contrast to the result of its palladium-catalyzed isomerization reaction reported by Ohmura and Suginome.[13]

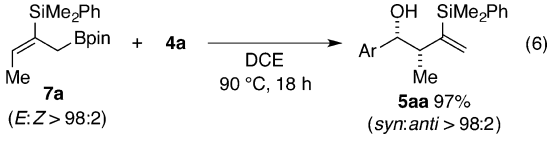
We propose a mechanism depicted in Scheme 1 for the double bond transposition. It initiates with coordination of the

Scheme 1. Proposed Pathway for Double Bond Transposition



double bond of (*Z*)-**3a** to the cationic rhodium(I) center, which is followed by oxidative addition of the allylic C−H bond. For the resulting π-allyl hydridorhodium intermediate, **A** would be more stable than **B** due to the repulsive influence of the silyl group. Reductive elimination gives rise to (*E*)-**7a**, which is the most energetically stable isomer (vide supra). Thus, we assume that (*E*)-**7a** is favored by both kinetics and thermodynamics.

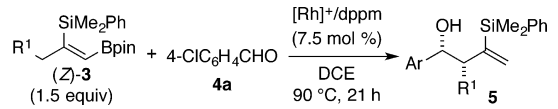
The isolated (*E*)-**7a** was reacted with the aldehyde **4a** in the absence of the rhodium(I) catalyst in DCE at 90 °C for 18 h (eq 6). The *syn*-homoallylic alcohol **5aa** was formed in 97%



isolated yield with a *syn*/*anti* ratio of >98:2 in agreement with the reported result.[8a] This experiment suggested that the allylation step proceeded without participation of the rhodium(I) catalyst.

Other 2-silyl-1-alkenylboronates **3** having a variety of R^1 substituents were prepared from the corresponding terminal alkynes also by the regio- and stereoselective silaboration reaction[9a] and were subjected to the allylation reaction of **4a** (Table 1). As with the case of **3a** (R^1 = methyl), 2-silyl-1-

Table 1. Rh(I)-Catalyzed Reaction of (*Z*)-2-Silyl-1-alkenylboronates (*Z*)-3b−j with 4-Chlorobenzaldehyde (4a)[a]



entry	3	R^1	5	yield (%)[b]	*syn*/*anti*[c]
1	**3b**	Et	**5ba**	92	>98:2
2	**3c**	*n*-Bu	**5ca**	99	97:3
3	**3d**	cyclopentyl	**5da**	83	>98:2
4	**3e**	*i*-Pr	**5ea**	95[d]	>98:2
5	**3f**	Ph	**5fa**	96	>98:2
6	**3g**	$TBSO(CH_2)_3$	**5ga**	96	>98:2
7	**3h**	$BzO(CH_2)_3$	**5ha**	98	>98:2
8	**3i**	$BnO(CH_2)_3$	**5ia**	98	97:3
9	**3j**	$(Phth)N(CH_2)_3$	**5ja**	99	>98:2

[a] **4a** (0.10 mmol), (*Z*)-**3** (0.15 mmol), $[Rh(nbd)(MeCN)_2]SbF_6$ (7.5 mol %), and dppm (7.5 mol %) in DCE (2 mL) at 90 °C for 21 h unless otherwise noted. [b] Isolated yields (average of two runs). [c] Determined by ^{1}H NMR of desilylated products or **5**. [d] Using **3e** (0.30 mmol), $[Rh(nbd)(MeCN)_2]SbF_6$ (10 mol %), and dppm (10 mol %).

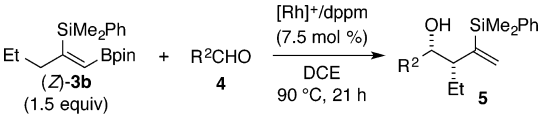
alkenylboronates **3b**−**f** having ethyl, butyl, cyclopentyl, isopropyl, and phenyl groups all exhibited excellent diastereoselectivities (≥97:3) to give the corresponding *syn*-adducts **5ba**−**fa** in yields ranging from 83% to 99% (entries 1−5). Functional groups such as siloxy, benzoyloxy, benzyloxy, and *N*-phthalimidoyl groups were tolerated in the alkyl chain (entries 6−9). The products **5** were readily desilylated by treatment with TBAF to afford the corresponding homoallylic alcohols **6**.

The reaction was highly general also with respect to aldehydes (Table 2). An electronically and sterically diverse array of aromatic aldehydes **4b**−**f** gave the homoallylic alcohols **5bb**−**bf** in high yield with diastereoselectivities over 95:5 (entries 1−5). Of note was that not only aromatic aldehydes but also aliphatic ones **4g**−**i** successfully participated in the reaction with (*Z*)-**3b** to exhibit excellent diastereoselectivities (entries 6−8).

We finally carried out the two reactions, i.e., the silaboration and the allylation, in sequence in one pot (Scheme 2). First, terminal alkynes **1** (1.5−2.3 equiv) were treated with $PhMe_2Si$-Bpin (**2**, 1.5 equiv) in the presence of $Pt(PPh_3)_4$ (3.0 mol %) at 110 °C in toluene for 4 h.[9a] After the reaction mixture was cooled, toluene and an excess amount of terminal alkynes **1** were removed under reduced pressure. Then, 4-chlorobenzaldehyde (**4a**, 1.0 equiv), $[Rh(nbd)(MeCN)_2]SbF_6$, dppm, and DCE were added to the residue, and the reaction mixture was further stirred at 90 °C for 21 h. Chromatographic purification afforded the corresponding homoallylic alcohols **5** in excellent yields and diastereoselectivities in both cases. This one-pot procedure minimizes generation of waste solvents.

dx.doi.org/10.1021/ja502169d | J. Am. Chem. Soc. 2014, 136, 6223−6226

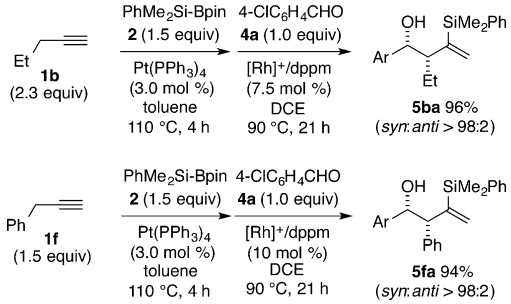
Table 2. Allylation Reaction of Aldehyde 4b–i with (*Z*)-2-Silyl-1-pentenylboronates (*Z*)-3b[a]



entry	4	R^2	5	yield (%)[b]	*syn*/*anti*[c]
1	**4b**	Ph	**5bb**	99	>98:2
2	**4c**	4-$MeO_2CC_6H_4$	**5bc**	99	>95:5
3	**4d**	4-MeC(O)C_6H_4	**5bd**	87	96:4
4	**4e**	3-$MeOC_6H_4$	**5be**	89	>98:2
5	**4f**	2-MeC_6H_4	**5bf**	95	>98:2
6	**4g**	*i*-Bu	**5bg**	72	97:3
7	**4h**	$PhCH_2CH_2$	**5bh**	79	>98:2
8	**4i**	Cy	**5bi**	80	>98:2

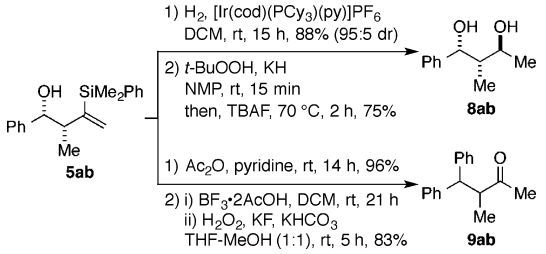
[a]**4** (0.10 mmol), (*Z*)-**3b** (0.15 mmol), $[Rh(nbd)(MeCN)_2]SbF_6$ (7.5 mol %), and dppm (7.5 mol %) in DCE (2 mL) at 90 °C for 21 h. [b]Isolated yields (average of two runs). [c]Determined by ^1H NMR of desilylated products or **5**.

Scheme 2. A One-Pot Reaction via Silaboration/Double Bond Transposition/Allylation Reaction



The silyl group of the homoallylic alcohols could be further used for other synthetic purposes than protodesilylation, as illustrated in Scheme 3. The 1,3-diol **8ab** with three contiguous

Scheme 3. Synthetic Derivatizations of Silyl-Substituted Homoallylic Alcohol 5ab



stereocenters could be synthesized[14] by diastereoselective hydrogenation of the double bond using Crabtree's catalyst (95:5 dr)[15] followed by the modified Fleming–Tamao oxidation of the carbon–silicon bond.[16] Furthermore, the acetylated derivative of **5ab** underwent silicon-to-carbon 1,4-phenyl migration from silicon to carbon upon treatment with BF_3·2AcOH.[17] Subsequent oxidation gave the ketone **9ab**.

In summary, we have developed a new synthetic method of homoallylic alcohols from terminal alkynes and aldehydes with *syn* stereochemistry installed. Accessibility of starting materials is one of the most important criteria for synthetically useful organic reactions. This transformation utilizes terminal alkynes as starting materials, which are among the most easily accessible starting materials, even from commercial sources, presenting better chances of application for various synthetic purposes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for the new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Honorary Professor Jiro Tsuji (Tokyo Institute of Technology) in celebration of his 88th birthday (Beiju). This work was supported by MEXT (Grant-in-Aid for Scientific Research on Innovative Areas Nos. 22105005 and 24106718, Young Scientists (A) No. 23685019, Scientific Research (B) No. 23350041) and JST (ACT-C).

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(10) $[Ir(cod)_2]BF_4/PCy_3$ exhibited no activity toward the double bond transposition of 2-silyl-1-alkenylboronates.

(11) Other cationic rhodium(I) complexes such as $[Rh(nbd)_2]SbF_6$, $[Rh(bpy)(cod)]SbF_6$, and $[Rh(cod)_2]$BARF failed to catalyze the double bond transposition of (*Z*)-**3b**, which was recovered. The use of diphosphine ligands such as dppe, dppp, dppf, and xantphos was not effective either.

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