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Mechanistic Insight into the Anomalous *syn*-Selectivity Observed during the Addition of Allenylboronates to Aromatic Aldehydes

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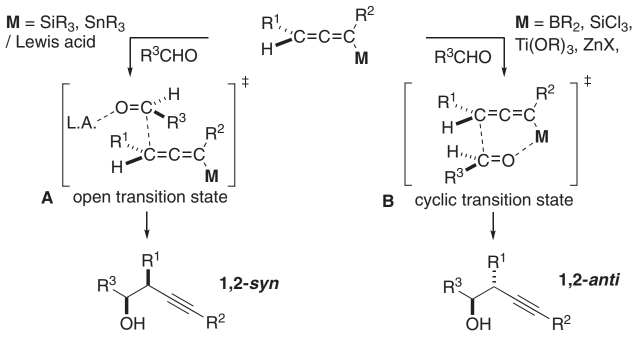
The reaction of enantioenriched allenylboronate **3a** (98% ee) with benzaldehyde gave homopropargylic alcohol *syn*- and *anti*-**4b** with anomalous *syn* addition selectivity (*anti*:*syn* = 29:71) and high ee (98% and 97%, respectively). The stereochemical outcome in terms of the absolute configuration shows that this reaction proceeds through a cyclic transition state. Density functional theoretical (DFT) calculations were carried out to elucidate the mechanism of this anomalous *syn*-selectivity.

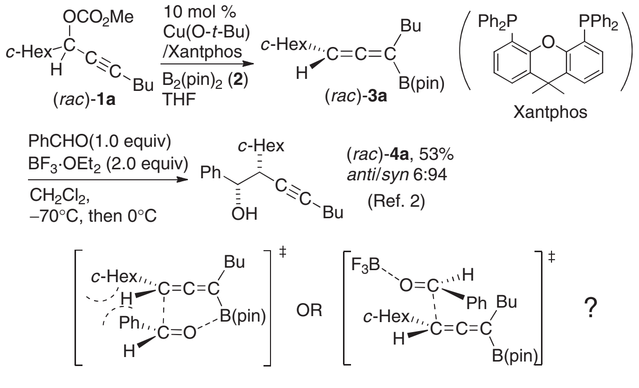
The stereoselective reaction of allenylmetal reagents with carbonyl compounds is the most attractive method available for the synthesis of sterically defined homopropargylic alcohols.[1] The product profiles generated depend mainly on the Lewis acidity of the metal substituents on the allenylmetal reagent used (Scheme 1). For example, non-Lewis acidic allenylmetal reagents, such as allenyl(trialkyl)silanes or allenyl(trialkyl)stannanes, add to aldehydes in the presence of additional Lewis acid catalyst through an acyclic, open structure transition state where the R[1] and R[3] groups adopt an *anti*-periplanar conformation. This results in the corresponding 1,2-*syn*-product (**A**) when γ-monosubstituted allenylmetal reagents are used.[1] On the other hand, allenylmetals that contain a Lewis acidic metal center, such as $-B(OR)_2$, $-SiCl_3$, or $-ZnX$, add to aldehydes through a cyclic transition state, in the presence or absence of an external Lewis acid, leading to the 1,2-*anti*-product (**B**).[2]

During the course of our studies on a copper(I)-catalyzed route to multisubstituted allenylboronates, and their aldehyde addition reactions,[3] we encountered an unusual 1,2-*syn* type product during the addition of an allenylboronate to an aromatic aldehyde (Scheme 2). A cyclic or open transition state can be proposed for this reaction. It seems likely, however, that a cyclic transition state would suffer from steric congestion between the cyclohexyl group and the phenyl group, while an open transition state is uncommon for Lewis acidic allenylmetal reagents such as allenylboronates. Similar anomalous *syn* preferences have been reported previously for Lewis acidic allenylmetal additions to aromatic aldehydes; however, no reports have addressed the origin of this anomalous selectivity in detail.[4]

In this study, we first established that the reaction proceeds through a cyclic transition state. This was achieved by measuring the absolute configuration of the 1,2-*syn*-product obtained from the reaction of the enantioenriched allenylboronate, whose synthesis in high enantiomeric purity we reported for the first time in the previous paper.[3] Density functional theoretical (DFT) calculations along the cyclic transition state pathway were also carried out to investigate the origin of the anomalous *syn*-selectivity.



Scheme 1. Open and cyclic transition states in the reaction of allenylmetal reagents.

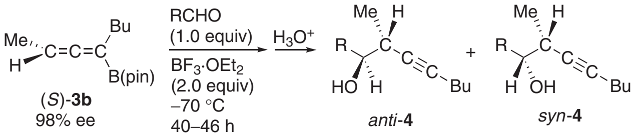


Scheme 2. 1,2-*syn*-Selectivity in a reaction of an allenylboronate with benzaldehyde.

Our first goal was to establish whether the reaction proceeds through an open (Scheme 1, **A**) or a cyclic transition state (Scheme 1, **B**). We have previously reported that the enantioenriched allenylboronate (*S*)-**3b** reacts with isobutyraldehyde to afford the corresponding homopropargylic alcohols *syn*-(3*R*,4*R*)-**4b** and *anti*-(3*S*,4*R*)-**4b** with good 1,2-*anti*-selectivity (Table 1, Entry 1, 89%, *anti*/*syn* = 87:13, 97% ee for *syn*). These reaction conditions included an external Lewis acid; however, it is reasonable to assume a cyclic transition state where the steric repulsion between the *i*-Pr and methyl groups is minimized in the *anti*-periplanar conformation.[2]

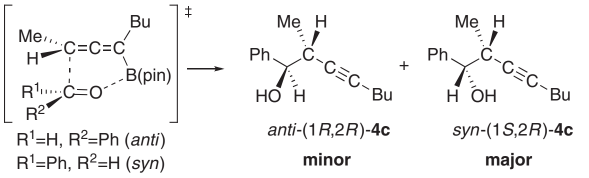
The reaction of (*S*)-**3a** with benzaldehyde gave the corresponding *syn*-(1*S*,2*R*)-**4c** and *anti*-(1*R*,2*R*)-**4c** with a moderate *syn*-selectivity (Table 1, Entry 2, 94%, *anti*/*syn* = 29:71, 97% ee for *syn*).[5,6] The high enantioselectivity was retained even in the absence of Lewis acid, although the diastereoselectivity observed was reduced slightly (Entry 3, 97%, *anti*/*syn* = 37:63, 97% ee for *syn*). The absolute configurations of the products, *syn*-(1*S*,2*R*)-**4c** and *anti*-(1*R*,2*R*)-**4c**, were determined by derivatization as α-methoxy-α-trifluoromethylphenylacetate esters,

Table 1. Reaction of enantioenriched allenylboronate (*S*)-**3b** and aldehydes[a]



Entry	Aldehyde	**4**, Yield/%[b]	*anti*/*syn*[c]	ee/%[d]
1[e]	*i*-PrCHO	**4b**, 89	87:13	96 (*anti*), 97 (*syn*)
2	PhCHO	**4c**, 94	29:71	98 (*anti*), 97 (*syn*)
3[f]	PhCHO	**4c**, 97	37:63	98 (*anti*), 97 (*syn*)
4[g,h]	*p*-MeOC$_6$H$_4$CHO	**4d**, 69	36:64	97 (*anti*), 97 (*syn*)
5[h]	*p*-NCC$_6$H$_4$CHO	**4e**, 78	39:61	98 (*anti*), 97 (*syn*)

[a] Conditions: (*S*)-**3b** (0.21 mmol), CH_2Cl_2 (0.2 mL), benzaldehyde (0.21 mmol), and $BF_3 \cdot OEt_2$.(0.42 mmol) at −70 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR and HPLC analysis. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Data was taken from ref. 3. [f] Reaction carried out at room temperature in the absence of $BF_3 \cdot OEt_2$. [g] Reaction carried out at 0 °C in the absence of $BF_3 \cdot OEt_2$. [h] Yield was determined by ^{1}H NMR.



after isolation from the diastereomeric mixture. The absolute configuration of the *syn*-product indicated that the reaction also proceeded through a cyclic transition state. The electron density of the phenyl ring did have significant impact on the diastereoselectivity. The reaction of an aromatic aldehyde with an electron-donating substituent gave the corresponding homopropargylic alcohols with moderate diastereoselectivity (Entry 4, 69%, *anti*/*syn* = 36:64, 97% ee for *syn*). The reaction of *p*-cyanobenzaldehyde gave the product with a similar diastereoselectivity (Entry 5, 78%, *anti*/*syn* = 39:61, 97% ee for *syn*).

To gain information regarding the structure and energy levels of the cyclic transition state, DFT calculations (B3PW91/6-31G+(d,p)) were performed using model compounds, as shown in Figure 1.[7,8] Gibbs free energies (298.15 K, 1.00 atm) of four different transition states ($\mathbf{TS_{anti1}}$, $\mathbf{TS_{anti2}}$, $\mathbf{TS_{syn1}}$, and $\mathbf{TS_{syn2}}$) that correspond to the possible reaction pathways with CH_3CHO were calculated, and the energy values were compared. In the most stable transition state ($\mathbf{TS_{anti1}}$, 0.0 kcal mol^{-1}), the 5-methyl group of the allenylboronate and the aldehyde methyl group adopted a *gauche*-conformation (Table 2, Entry 1). The second most stable transition state was $\mathbf{TS_{syn1}}$ (0.87 kcal mol^{-1}). The other transition states examined were found to have much higher energies ($\mathbf{TS_{anti2}}$, 3.59 kcal mol^{-1}; $\mathbf{TS_{syn2}}$ 5.41 kcal mol^{-1}) and were therefore omitted from consideration. In the two stable transition states ($\mathbf{TS_{anti1}}$ and $\mathbf{TS_{syn1}}$), the R groups of the aldehyde are in a pseudo-equatorial conformation, while in the unstable transition states ($\mathbf{TS_{anti2}}$ and $\mathbf{TS_{syn2}}$) the R groups adopt a pseudo-axial position. The calculation for CH_3CHO reaction is consistent with the experimental result (Table 1, Entry 1). In the reaction of benzaldehyde, the most stable transition state calculated using the B3PW91 DFT method was also found to be $\mathbf{TS_{anti1}}$, with an energy difference between $\mathbf{TS_{anti1}}$ and $\mathbf{TS_{syn1}}$ of 0.31 kcal mol^{-1}. One possible factor in the anomalous 1,2-*syn*-selectivity preference may be stabilization due to a CH/π interaction between the alkyl group and the phenyl group. The allenylboronate methyl group was found to be in close proximity with the benzaldehyde phenyl ring in the lowest energy transition state. The B3PW91 method has been shown to be unable to identify weak interaction energies, such as CH/π interactions.[9,10] We therefore evaluated the two transition states, $\mathbf{TS_{anti1}}$ and $\mathbf{TS_{syn1}}$, for the reaction of benzaldehyde using the alternative method, M06-2X. This method has been shown to model CH/π

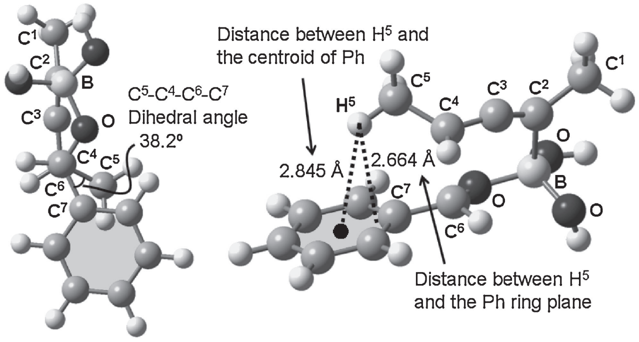
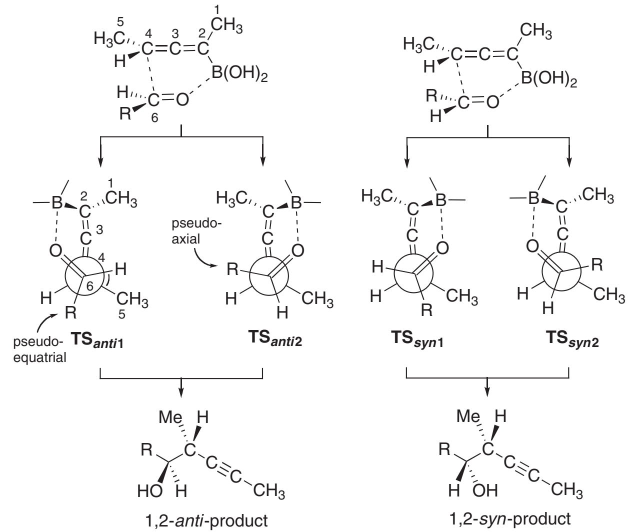


Figure 1. Three-dimensional structure of $\mathbf{TS_{syn1}}$ for R = Ph.

Table 2. DFT calculations of the free energy differences ($\Delta\Delta G^‡$) of possible transition state models[a]



Entry	R	Method	Free energy difference/kcal mol^{-1}			
			$\mathbf{TS_{anti1}}$	$\mathbf{TS_{anti2}}$	$\mathbf{TS_{syn1}}$	$\mathbf{TS_{syn2}}$
1	CH_3	B3PW91	0	3.59	0.87	5.41
2	CH_3	M06-2X	0	—	2.19	—
3	Ph	B3PW91	0	6.65	0.31	6.27
4	Ph	M06-2X	0	—	−0.69	—

[a] All calculations were carried out with the B3PW91/6-31+G(d,p) or M06-2X/6-31+G(d,p) methods at 298.15 K, 1.00 atm in CH_2Cl_2 (polarizable continuum model, PCM).

interactions with some degree of accuracy.[11] In these calculations, **TS**$_{\textbf{anti1}}$ remained the most stable transition state for the reaction of CH_3CHO (Entry 2). However, in the reaction of benzaldehyde, the **TS**$_{\textbf{syn1}}$ was found to be more stable than **TS**$_{\textbf{anti1}}$ by $-0.69\,\text{kcal mol}^{-1}$ (Entry 4).

The transition state structure calculated using the M06-2X method incorporated the possibility of attractive interactions between the CH bond and the benzene ring (Figure 1). The distances between the hydrogen atom and the plane, and the centroid, of the benzene ring were found to be 2.664 and 2.845 Å, respectively. These values are less than the sum of the van der Waals radii of H and C atoms (2.9 Å), suggesting the presence of CH/π interactions between the allenylmetal CH bond and the benzaldehyde phenyl ring in **TS**$_{\textbf{syn1}}$. No such interactions were found to be present in **TS**$_{\textbf{anti1}}$ for the reaction of benzaldehyde. The transition state structure **TS**$_{\textbf{syn1}}$ featured a small dihedral angle for C^5–C^4–C^6–C^7 (38.2°), allowing the two groups to be in close proximity. This facilitates the formation of CH/π interactions.

In summary, we have shown experimentally that the anomalous 1,2-*syn*-selectivity of the addition reaction of allenylboronates with aromatic aldehydes originates from a cyclic transition state, even in the presence of external Lewis acid. DFT calculations revealed that CH/π interactions weakly stabilize the transition state for the 1,2-*syn*-product. This study provides compelling evidence for a mechanism that explains the anomalous 1,2-*syn*-selectivity of allenylboronates. However, clarification of the role of these CH/π interactions warrants detailed studies that employ improved basis sets and high level calculations, such as the coupled cluster singles and doubles (CCSD) method, as well as further investigation of the role of the external Lewis acid, $BF_3{\cdot}OEt_2$.[12]

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5 A representative procedure for the reaction of allenylboronate with aldehydes: to a solution of allenylboronate (*S*)-**3b** (50 mg, 0.21 mmol) in CH_2Cl_2 (0.2 mL), benzaldehyde (21.6 µL, 0.21 mmol) was added dropwise at −78 °C, followed by addition of $BF_3{\cdot}OEt_2$ (50 µL, 0.42 mmol). After the reaction was complete (46 h), aqueous $NaHCO_3$ was added and the mixture was allowed to warm to room temperature. The reaction mixture was then extracted with ether and the combined organic phases were dried over $MgSO_4$ and filtered. After the removal of solvents in vacuo, the residue was purified by column chromatography (SiO_2, hexane/diethyl ether = 100:0 to 70:30) to give an *anti*/*syn* mixture of **4c**.

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8 All calculations were carried out using the Gaussian 09W program package. The DFT method was employed, using B3PW91 and M06-2X. All transition state geometries were calculated with the 6-31+G(d,p) basis set. The solvent effect was considered using the PCM model method with $\varepsilon = 8.93$ (CH_2Cl_2). Zero-point energy corrections were obtained from frequency calculations without scaling. The presence of one imaginary frequency was checked for all transition state structures.

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