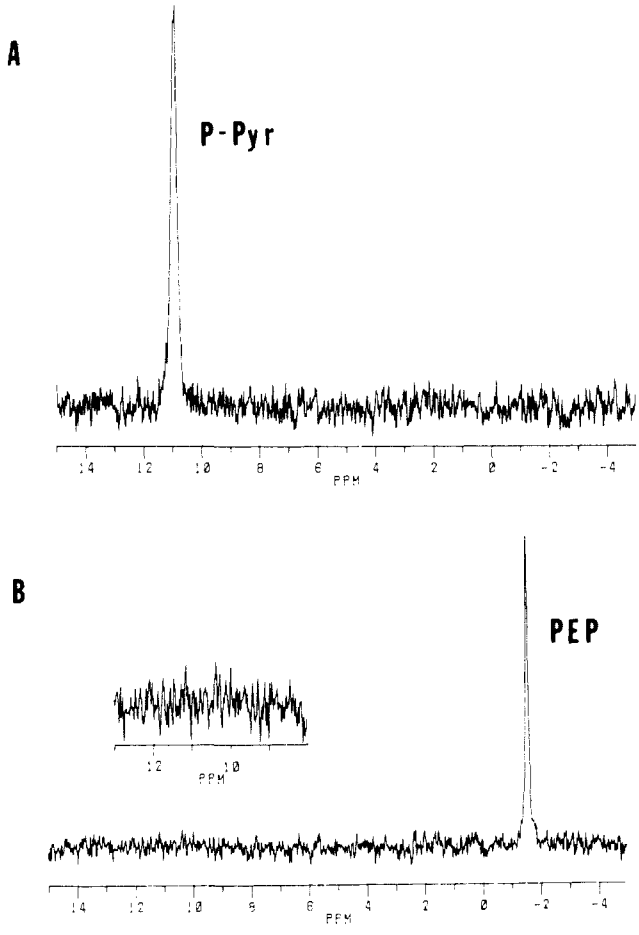

Figure 1. ^{31}P NMR spectra (162.04 MHz, 0.1 M D_3PO_4 external standard, 25 °C, 50% D_2O) of a solution initially containing 20 mM phosphonopyruvate, 10 mM $MgCl_2$, and 50 mM K^+Hepes (pH 8.0) before (A) and after (B) incubation with 0.3 unit/mL of phosphomutase for 1 h.

ergetics of the PEP ⇒ P-pyr conversion. However, opposing the PEP ⇒ P-pyr conversion is the difference in the P–O and P–C bond energies. Although the exact difference in the P–O and P–C bond energies of PEP and P-pyr has not been reported, published values for other systems range from 10–17 kcal/mol in favor of the P–O bond.[14] Relevant to the PEP ⇔ P-pyr rearrangement reaction are the reported thermal rearrangements of diesters of α-ketophosphonates in acid solution to the corresponding vinyl phosphates[15] (Scheme II). Thus, the equilibrium position of the vinyl phosphate ⇔ ketophosphonate interconversion in this system as well as in the PEP ⇔ P-pyr system appears to be dominated by the comparatively higher energy of the P–C bond of the ketophosphonate.

The unexpected equilibrium position for the catalyzed PEP ⇔ P-pyr isomerization reaction has no doubt contributed to the failure of previous attempts[1,8,16] to observe P-pyr formation from PEP in whole cell or cell free systems. Nevertheless, the current results along with those from recent studies of the PEP to AEP pathway[18] (Scheme III) in *T. pyriformis* leave little doubt that the PEP to P-pyr conversion is the key P–C bond-forming step of phosphonate biosynthesis in this organism. It should be recognized, however, that because of the unfavorable position of the PEP ⇔ P-pyr equilibrium that in order for the phosphomutase-catalyzed reaction to serve as the source of P-pyr it must be coupled to a thermodynamically favorable ensuing step in the pathway. In the case of the AEP[6,18] and bialaphos[8] biosynthetic pathways, P-pyr formation is followed by its decarboxylation to produce phosphonoacetaldehyde. Studies carried out in our laboratory on the competing reaction pathways of PEP and P-pyr in *T pyriformis* cellular homogenates suggest that the phosphomutase and α-ketodecarboxylase reactions are coupled in such a way that the P-pyr formed at the phosphomutase active site (where the PEP ⇔ P-pyr equilibrium seems to be more favorable) is shuttled directly into the active site of the decarboxylase.[19]

Ongoing studies in our laboratory are focussed on distinguishing a concerted vs stepwise mechanism for the PEP ⇔ P-pyr rearrangement by determining the stereochemical course of the phosphomutase catalyzed reaction of a chiral P-pyr derivative.

Acknowledgment. This work was supported by a National Institutes of Health Grant GM-28688 and by a Fellowship Award from the Alfred P. Sloan Foundation. We thank Patrick S. Mariano for helpful discussion of this work.

(14) Huheey, J. E. *Inorganic Chemistry*, 3rd Ed.; Harper and Row: New York, 1983; p A-321. Tarr, A. M.; Whittle, E. *Trans. Faraday Soc.* **1964**, *60*, 2039.

(15) Machleidt, H.; Strehlke, G. U. *Angew. Chem., Int. Ed. Engl.* **1964**, 443.

(16) Horiguchi,[17] however, reported that P-pyr was isolated from a *T. pyriformis* cellular homogenate–PEP mixture as a hydrazone derivative by reacting the mixture with 2,4-dinitrophenylhydrazine under acidic conditions. Several attempts to reproduce this result failed. Because appreciable amounts of PEP-derived P-pyr could not possibly be present in the reaction mixture failure to trap the P-pyr under enzyme denaturing conditions is understandable.

(17) Horiguchi, M.; Rosenberg, H. *Biochem. Biphys. Acta* **1975**, *404*, 333.

(18) Barry, R. J.; Bowman, E.; McQueney, M.; Dunaway-Mariano, D. *Biochem. Biophys. Res. Commun.* **1988**, *153*, 177.

(19) We have shown[18] (1) that the conversion of PEP to AEP in the homogenate is significantly more efficient than the conversion of the pathway intermediate, P-pyr to AEP and (2) that the reason for this is that the P-pyr added to the homogenate is rapidly consumed by a competing hydrolysis reaction, while the added PEP is not. The P-pyr generated from PEP via the phosphomutase (as opposed to the "added" P-pyr) is therefore protected from the reaction catalyzed by the crude homogenate. Such protection would be afforded by transfer of the P-pyr formed in the active site of the phosphomutase directly into the active site of the decarboxylase.

First Experimental Evaluation of Hypervalent N–S–N Bond Energy from the Restricted Rotation of Pyrimidine Ring in 10-S-3 Sulfuranes

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Received April 11, 1988

Since the discovery of the unusual structure in trithiapentalenes,[1] i.e., sometimes referred to as "no bond resonance compounds", many examples of the 10-S-3 species have been prepared.[1,2] In these species,[2,3] the bond distances in the three-center four-electron bond (X-S-Y) vary according to the electronegativity of the two ligands.[3b] In connection with these studies, we have shown the presence of ring transformation equilibrium ("bond switching") in sulfur-containing heterocyclic systems via such 10-S-3 sulfuranes, which show susceptibility of the hypervalent bond to the ligand stability.[5]

(1) (a) Arndt, F.; Nachtwey, P.; Pusch, J. *Chem. Ber.* **1925**, *58*, 1633. (b) Bezzi, S.; Mammi, M.; Garbuglio, C. *Nature (London)* **1958**, *182*, 247. (c) Pfister-Guillouzo, G. *Bull. Soc. Chim. Fr.* **1958**, 1316.

(2) (a) Gleiter, R.; Gygax, R. *Top. Curr. Chem.* **1976**, *63*, 49. (b) Lozac'h, N. *Adv. Heterocyclic Chem.* **1971**, *13*, 161. (c) Gleiter, R.; Spanget-Larsen, J. *Top. Curr. Chem.* **1979**, *86*, 139.

(3) (a) Musher, J. I. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 54. (b) Hayes, R. A.; Martin, J. C. *Organic Sulfur Chemistry: Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier Scientific Publishing Company: Amsterdam, 1985; p 408. (c) Kucsman, A.; Kapovits, I. *Ibid.* p 191.

(4) Angyan, J. G.; Poirier, R. A.; Kucsman, A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1987**, *109*, 2237.

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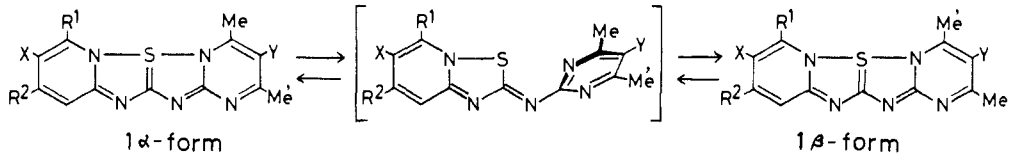
Table I. Kinetic Data for the Restricted Rotation of the Pyrimidine Ring of **1** in $CDCl_3$[a]

compd	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Tc (°C)	$\Delta G_{Tc}^{\ddagger}$ (kcal/mol)
1a	8.6	16.6	17.1 ± 0.9	1.6 ± 2.8	45	16.4
1b	8.5	16.6	18.8 ± 0.8	7.2 ± 2.6	45	16.6
1c	20.8	16.0	19.3 ± 1.0	10.7 ± 3.2	35	16.0
1d	0.3	18.6	20.2 ± 1.0	5.4 ± 2.8	85	18.3
1e[b]					32	15.7

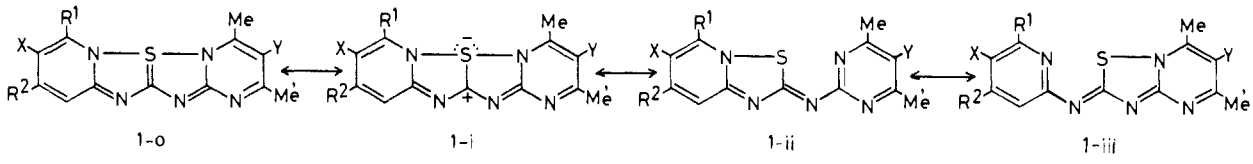
[a] The rate constant (k), $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are calculated at 32 °C. [b] Measurement at low temperature could not be done because of low solubility of **1e** in $CDCl_3$.

Scheme I

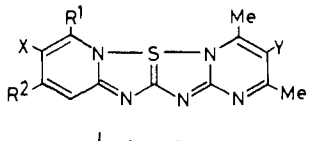


(1)

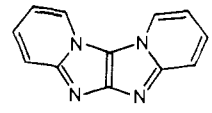
Chart I



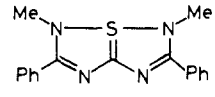
Although there are many theoretical investigations on hypervalent bonding of 10-S-3 sulfuranes,[2,4] the experimental evaluation of the bond energy has been unprecedented to the best of our knowledge. We now report the first experimental evaluation of the energy by the determination of the rotation barrier of the pyrimidine ring of **1**.



	R^1	R^2	X	Y
1a	H	H	H	H
1b	H	Me	H	H
1c	Me	H	H	H
1d	H	H	Cl	H
1e	H	H	H	Br



2



3

Compounds (**1a–d**) were prepared from the corresponding thioureas by oxidation with *N*-bromosuccinimide (NBS) or sulfuryl chloride under the similar conditions developed by Potts.[6,7] Bromination of **1a** with 1 equiv of NBS afforded monobromo derivative **1e** in quantitative yield.[8] In the ^1H NMR spectrum at 32 °C ($CDCl_3$), compound **1a** showed two peaks at δ 2.54 and δ 2.68 (integral ratios 1:1, separated by 13.2 Hz at 90 MHZ) for the two nonequivalent methyls of pyrimidine ring along with a sharp singlet at δ 6.54 for the pyrimidine proton and clearly separated multiplets at δ 6.8–8.4 for pyridine protons.[8]

A comparison of UV spectrum of **1a** with related compound **2** is informative to support the similarity of the molecular frame.[9] The characteristic spectral shape of **1a** is very similar to that of **2** in phosphate-buffered solution. On the basis of the UV and the other spectral features, **1a** is considered to be a planar 18π electron system like **2** because the structure of **2** is established to be planar by X-ray structural analysis,[9b] and also **3** is shown to be a planar molecule by X-ray analysis.[10] Hence the pyrimidino part in **1a** should be coplanar to the pyridothiadiazolo part so that the N, S, and N atoms should arrange linearly to form a typical hypervalent bond of 10-S-3 sulfurane.

The two methyl peaks of **1a** coalesced at 45 °C, but the heteroaromatic peaks remained unchanged over the temperature range of spectral measurements (28–58 °C). Line-shape analysis[11] of the methyl group afforded kinetic parameters as k = 8.6 s^{-1} and $\Delta G^{\ddagger}$ = 16.6 kcal/mol at 32 °C (Table I).

The coalescence process can only be explained by the rotation of the pyrimidine ring as shown in eq 1 in Scheme I. Therefore the sum of the energy of hypervalent bond and resonance stabilization of the 18π electron in the sulfurane system may be estimated on the basis of the kinetic data of the restricted rotation of the pyrimidine ring. The rotation of the pyrimidine ring in **1d** is much slower than in **1a–c**, i.e., k = 0.3 s^{-1} and $\Delta G^{\ddagger}$ = 18.6 kcal/mol at 32 °C (over temperature range 50–90 °C; the two methyls are separated by 23.1 Hz at 40 °C), and that of the bromopyrimidine ring in **1e** is the fastest of the present system, i.e., $\Delta G_{Tc}^{\ddagger}$ = 15.7 kcal/mol as estimated at the coalescence temperature (32 °C) (the two methyls are separated by 13.4 Hz at −20 °C).[11,12]

(5) (a) Akiba, K-y.; Kobayashi, T.; Arai, S. *J. Am. Chem. Soc.* **1979**, *101*, 5857. (b) Yamamoto, Y.; Akiba, K-y. *J. Am. Chem. Soc.* **1984**, *106*, 2713. (c) Akiba, K-y.; Kashiwagi, K.; Ohyama, Y.; Yamamoto, Y.; Ohkata, K. *J. Am. Chem. Soc.* **1985**, *107*, 2721.

(6) (a) Potts, K. T.; Kane, J. *J. Org. Chem.* **1974**, *39*, 3783. (b) Harris, R. L. N. *Aust. J. Chem.* **1972**, *25*, 993.

(7) Analytical and spectral data for all new compounds were fully compatible with the given assignments.

(8) **1a** (2,4-dimethylpyrido[1″,2″:2′3′][1,2,4]thiadiazolo[5′,1′:5,1][1,2,4]-thiadiazolo[2,3-*a*]pyrimidine-6-S^{IV}): mp 234–235 °C; ^1H NMR (δ, $CDCl_3$) 2.54 (s, 3 H), 2.68 (s, 3 H), 6.54 (s, 1 H), 6.89 (ddd, J = 8.1, 6.2, 1.8 Hz, 1 H), 7.53 (dd, J = 8.6, 1.8 Hz, 1 H), 7.63 (ddd, J = 8.6, 8.1, 1.5 Hz, 1 H), 8.31 (dd, J = 6.2, 1.5 Hz, 1 H); **1b**: mp 235–236 °C; **1c**: mp 265 °C; **1d**: mp >300 °C; **1e**: mp 263–265 °C; **1f**: mp 246–247 °C.

(9) (a) **1a**: UV, λ_{max} (ϵ_{max}, $CHCl_3$) 266 (12 100), 322 nm (12 600); (H_2O: pH 7 phosphate buffer) 235 (16 600) 246 (sh, 16 000), 287 (15 000), 338 nm (17 200). (b) **2**: UV, λ_{max} (ϵ_{max}, H_2O: pH 7 phosphate buffer) 233 (26 700), 255 (sh, 25 800), 260 (26 700), 284 (11 200), 296 (9300), 338 (18 200), 354 nm (16 300); see, in: Groziak, M. P.; Wilson, S. R.; Clauson, G. L.; Leonard, N. J. *J. Am. Chem. Soc.* **1986**, *108*, 8002. Cruickshank, K. A.; Sumoto, K.; Leonard, N. J. *Tetrahedron Lett.* **1985**, *26*, 2723.

(10) Iwasaki, F.; Akiba, K-y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2581.

(11) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228. (b) *Dynamic Nuclear* Magnetic *Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Ed.; Academic Press: 1975. (c) Binsch, G. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L. Eds.; John Wiley & Sons, Inc.: 1968; Vol. 3, p 97.

(12) Since **1e** was precipitated at lower temperature from $CDCl_3$; the precise line-shape analysis could not be carried out.

(13) Partial support of this research is acknowledged from a Grant-in-Aid for Special Project Research (no. 62215026) administered by the Ministry of Education, Science, and Culture of the Japanese Government.

Pyrimidine is more electronegative than pyridine hence S–N(pyrimidine) bond should be slightly longer and weaker than S–N(pyridine) bond according to the character of hypervalent bond.[3b] This trend is slightly enhanced by the electron-donating character of a methyl group (**1c**), and the rate is accelerated. On the other hand, the chlorine atom (**1d**) on the pyridine ring withdraws an electron to make the S–N(pyrimidine) bond shorter and stronger to recover the balance of the bond, hence the rate is decelerated. Again the bromine atom on the pyrimidine ring (**1e**) withdraws an electron to weaken the S–N(pyrimidine) bond more than that of **1a**. Monomethylpyrimidine derivative (**1f**: Me′ = H in **1a**) shows two kinds of the methyl signal between −48 °C and 35 °C, the ratio being 1.0:1.32 at 35 °C, and these coalesce at 45 °C.[8]

These can be visualized by difference of contribution of "no bond" resonance structures. As the electron-withdrawing property of the pyrimidino part increases compared to the pyridino part, the contribution of resonance structure (**1**-ii) will increase relative to **1**-iii, and therefore the S–N(pyrimidine) bond will be weakened. This is consistent with the (weak and polarizable) character of the hypervalent N–S–N bond which was predicted by the theoretical and structural analyses.[2,3]

A Diastereoselective Synthesis of (*E*)-Alkene-1,3-diols via the Reaction of 3-Borolenes with Aldehydes

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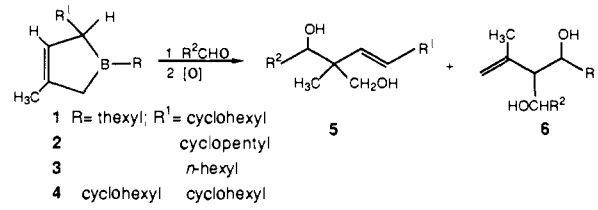
The development of new methods for acyclic stereocontrol is of major current importance in synthetic organic chemistry.[1] Topographical considerations have suggested that the bis-allylic 3-borolenes[2] might serve as templates for diastereoselective carbon–carbon bond-forming reactions in syntheses of acyclic compounds.[3] We now report an investigation of the reaction of 3-borolenes with aldehydes to provide stereodefined (*E*)-alkene-1,3-diols.[4] Specifically, the use of borolenes derived from isopropenyl acetylene (2-methyl-1-butene-3-yne) allows for extension of a carbon chain by one isoprene unit.

For our initial study the cyclohexyl-substituted borolene **1** derived from isopropenyl acetylene[5] was treated in THF with propanal, and the resultant organoboron intermediate was oxidized with alkaline hydrogen peroxide. ^{1}H NMR examination of the crude product mixture revealed the presence of the two regioisomeric diols **5a** and **6a** in a 98:2 ratio. As shown in Table I, the regioselectivity in the reactions of the thexyl-substituted borolenes **1–3** with aldehydes depends on the nature of the carbonyl compound used. Also, increasing amounts of the diols **6** are observed when the alkyl group R^1 at C_2 in **1** is sterically less hindered than cyclohexyl. This is especially evident in the case



of the *n*-hexyl substituted borolene **3** which reacts with aldehydes in an essentially nonregioselective manner. Although the reaction of the cyclopentyl-substituted borolene **2** with propanal is less regioselective as compared to the cyclohexyl analogue, its reaction with *trans*-crotonaldehyde still furnishes mainly the corresponding diol **5f**.

Condensation of **1** with aldehydes is not only regioselective but also highly diastereoselective. Thus, GLC analysis of the crude mixtures of diols **5a–c** derived from various aldehydes indicated the presence of only one (>98%) out of the two possible diastereomeric diols. Single-crystal X-ray analysis established that the diols possess the relative configuration shown in **5a–c** (only one enantiomer is shown). To ascertain whether both diastereomeric diols if formed would indeed have been identifiable by GLC, **5a–c** were oxidized chemoselectively to the corresponding hydroxy ketones with Ag_2CO_3 on Celite.[6] Reduction of the hydroxy ketones with $LiAlH_4$ afforded mixtures of diastereomeric diols which could indeed be separated by GLC.[7]

The results obtained in the present study do not permit a definitive explanation of the regiochemistries and diastereoselectivities observed in the above carbon–carbon bond formation reactions to be made. However, as mentioned earlier, we have established that the regiochemistry is governed not only by the size of the 2-alkyl group on the borolene and by the nature of the aldehyde used but also, and very importantly, by the size of the alkyl group on boron. Thus, when the thexyl group on boron in **1** was replaced by the sterically less demanding cyclohexyl group and the resultant borolene **4** was reacted with propanal, a 54:46 ratio of the isomeric diols **5a** and **6a** was obtained. Hence, two regiochemically different pathways must be available by which borolenes react with aldehydes.

The preferential formation of diol **5** from the reaction of borolene **1** with various aldehydes may be envisioned to proceed via an initial anti coplanar complexation[8] of the carbonyl group syn to the R^1 group of the borolene giving **7a** or **7b**, respectively, in which the bulky thexyl group and the R^1 group are positioned away from each other. This allows the aldehyde to occupy a pseudoaxial position which is necessary for interaction with the p-orbitals of the borolene in the transition state for the subsequent reaction. Carbon–carbon bond formation between the trigonal centers of the aldehyde and the borolene should then, because of steric hindrance by the large cyclohexyl group (R^1), occur preferentially at the methyl-substituted carbon of the double bond.

The diastereoselectivity observed for the reaction may be rationalized by considering structure **7b**, where the H of the aldehyde is positioned between the C-5 of the borolene and the thexyl group. Rotation about the C=O axis of the aldehyde occurs in the direction that requires the least motion of the atoms involved for overlap of the p-orbitals participating in bond formation, as depicted in **8**.[9] This places the R^2 group over the trigonal centers

(1) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. Nógrádi, M. *Stereoselective Synthesis*; VCH Verlagsgesellschaft: Weinheim, Federal Republic of Germany, 1987.

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(5) Shoup, T. M.; Zweifel, G. In *Organometallic Syntheses*; King, R. B., Eisch, J. J., Eds.; Elsevier: New York, 1986; Vol. 3.

(6) Oxidation of the diols **5a–h** with Ag_2CO_3 on Celite resulted in the nearly selective oxidation of the secondary hydroxyl groups. McKillop, A.; Young, D. W. *Synthesis* **1979**, 402.

(7) GLC examination of the diols **5d–h** coupled with the results of the oxidation–reduction procedure revealed that they were at least 96% diastereomerically pure. On the other hand, the diols **6** shown in Table I are diastereomeric mixtures whose stereochemistries have not yet been established.

(8) It has been shown that boron–carbonyl complexes adopt the anti coplanar structure. Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

(9) A similar mechanistic scheme has been proposed for the reaction of chiral allenylboronic esters with aldehydes. Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483. Yamamoto, H.; Maruoka, K.; Furuta, K. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Verlagsgesellschaft: Weinheim, Federal Republic or Germany, 1987; p 13.

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