3158 *Organometallics* **2003,** *22,* 3158−3163

Addition of Chiral Allenylzinc Reagent to Acetaldehyde: Diastereotopic Cyclic Transition States with a Tetrahedral Zinc Atom Located by ab Initio and Density Functional Theory

Benjamin W. Gung,*,† Xiaowen Xue,† Nina Knatz,† and James A. Marshall*,‡

Department of Chemistry and Biochemistry, Miami University, Oxford, Ohio 45056, and
Department of Chemistry, University of Virginia, P.O. Box 400319,
Charlottesville, Virginia 22904

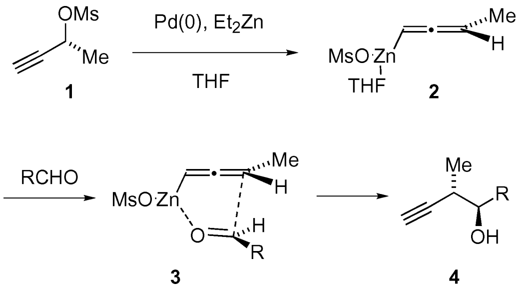
Received March 21, 2003

Transition-state structures for the reaction between the chiral allenylzinc reagent (*M*)-**2** and acetaldehyde are located at the B3LYP/6-31G* and HF/6-31++G** levels of theory. A tetrahedrally coordinated zinc atom in the transition state is found to give energy differences that are most consistent with the observed results. The tetrahedral zinc atom with the coordination of a solvent molecule also allows the staggering of the bonding sp^2 carbons, which avoids the eclipsing of the aldehyde and the allenyl substituents. A fluoride ligand is used to mimic the methanesulfonate anion present in the reaction, and a methyl ether molecule is used to explicitly mimic the solvent molecule THF. The allenyl carbons in the transition states are slightly bent, despite the fact that both the starting allenylzinc reagent and the propargylic product are linear. The transition state for allenylzinc addition to acetaldehyde is "late" in comparison to cyclic transition states of similar type.

Introduction

Organometallic allenes have captured the interest of organic chemists for a long time.[1,2] More recently, allenylmetal reagents with practical utility in organic synthesis have been realized.[3−6] Enantioselective and diastereoselective syntheses of stereotriads commonly found in natural products using allenylmetal reagents have been documented.[7,8]

Several years ago one of us reported that chiral propargylic mesylates (**1**) are converted to allenylzinc reagents (**2**) through treatment with a Pd(0) catalyst in the presence of Et_2Zn.[9] These reagents afford anti homopropargylic alcohols (**4**) upon in situ additions to aldehydes. The predominant formation of anti adducts suggested involvement of a cyclic transition state (**3**) for the addition reaction:



Additions to α-branched aldehydes were highly anti selective (~95:5) and less so for unbranched and conjugated aldehydes (~80:20−90:10). Initially Zweifel[10] and recently one of us[11] and others[6,12] have assumed that additions of allenylmetal reagents of the type $RCH{=}C{=}CHMX_n$ proceed via cyclic transition states (**3**). Evidence to support this assumption is derived solely from stereochemical correlations between the allenyl reagents and the homopropargylic adducts. A problem with the cyclic transition state is the eclipsing of the aldehyde and allenyl substituents. As described later, a totally eclipsed transition state (**12**) was computed when no solvent molecule was considered. Since no theoretical studies involving allenylzinc species have been reported, it is our intention to examine the validity of the cyclic arrangement (**3**) of this reaction.

---

* To whom correspondence should be addressed. E-mail: B.W.G., gungbw@muohio.edu; J.A.M., jam5x@virginia.edu.

† Miami University.

‡ University of Virginia.

(1) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984.

(2) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Permagon Press: Oxford, U.K., 1991; Vol. 2, pp 81−98.

(3) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1992**, *57*, 1242−1252.

(4) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1991**, *56*, 3211−3213.

(5) Wang, K. K.; Wang, Z. G.; Gu, Y. G. *Tetrahedron Lett.* **1993**, *34*, 8391−8394.

(6) Poisson, J.-F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889−1891.

(7) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001−6005.

(8) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556−5559.

(9) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812−3813.

(10) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565−4567.

(11) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201−5204.

(12) Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553−6560.

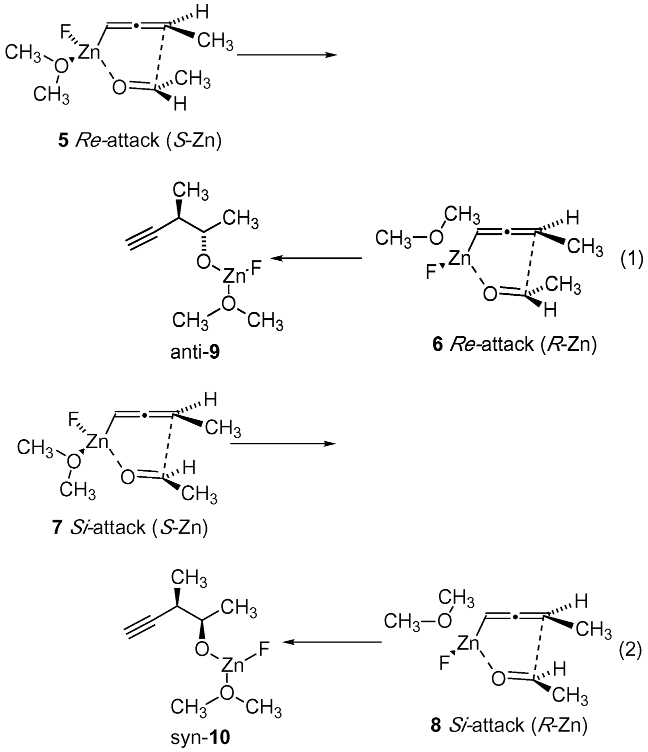
10.1021/om030220w CCC: $25.00

Previous ab initio calculations on the allenyl anion reveal a strong preference for a bent structure.[13] The allenyl anion was found to be ca. 1.3 kcal/mol lower in energy than the propyn-1-yl anion.[14] Another calculation on allenylmagnesium hydride, a model for the corresponding allenyl Grignard reagent, confirms the allenic nature of the reagent.[15] No allenylzinc species has been studied using computational methods at high levels of theory. Since little is known about the nature of the transition state of the allenylzinc additions to aldehydes, and the proposed transition states have not been confirmed, we have initiated an ab initio and density functional theory (DFT) study of this newly developed and highly stereoselective reaction.

Interest in the origins of diastereofacial selectivity has prompted one of us to use ab initio molecular orbital methods to investigate the diastereotopic transition states of synthetically useful reactions.[16,17] The transition states of the allenylzinc reactions with acetaldehyde involve the zinc atom, a third-row element. Although several computational studies of dialkylzinc addition to aldehydes have been reported,[18−23] studies of allenylzinc addition to aldehydes have not appeared. To reach a reasonable convergence and confidence, we have pushed the limit of our computational resources and located four transition states at the B3LYP/6-31G* and HF/6-31++G** levels of theory. These calculations support the proposed cyclic array and provide transition states with a tetrahedrally coordinated zinc atom, which avoid the eclipsing of the aldehyde and allenyl substituents. A more complete picture regarding the origins of stereoselectivity in these additions is presented.

Computational Methods

In our calculations we employed complexes of the allenylzinc and acetaldehyde as starting materials and the zinc alkoxide of the propargyl alcohol as products (eqs 1 and 2). The calculations were carried out using the Gaussian 98 programs[24] on the CRAY SV1 supercomputer at the Ohio Supercomputer Center. Initial molecular structures, generated with the ChemBats3D graphical program, were complexes of acetaldehyde and (M)-1,2-butadienylzinc corresponding to *si* and *re* π-face attack on the aldehyde. Both enantiomers of the zinc atom were considered, leading to the four diastereomeric transition states **5**−**8** and two derived adducts **9** and **10** (eqs 1 and 2).



5 *Re*-attack (*S*-Zn)

anti-**9**

6 *Re*-attack (*R*-Zn)

7 *Si*-attack (*S*-Zn)

syn-**10**

8 *Si*-attack (*R*-Zn)

Structural optimizations for the starting materials and products were determined by means of the 3-21G split-valence basis set. The transition-state structures were initially located at the HF/3-21G level of theory by using the keyword opt=qst3 with input parameters for the starting material, the product, and an initial transition-state guess.[24] Successive optimization continued at the HF/6-31G* and the B3LYP/6-31G* levels of theory using keywords opt=(ts, calcfc). The B3LYP/6-31G* method (density functional theory) was chosen for its ability to include electron correlation.[25,26] The transition structures (**5**−**8**) were fully optimized without any constraint and characterized by vibration frequency calculations at the HF/6-31++G** and B3LYP/6-31G* levels of theory. Only one imaginary frequency was found for each structure. Relative energies of transition states are tabulated in Table 2. Single-point calculations were performed at the B3LYP/6-31++G**//HF/6-31++G** and the B3LYP/6-311G(3df)//HF/6-31++G** levels. No corrections were made on basis set superposition errors, because all discussions are based on relative energies.[27,28] No attempt was made to give absolute complex formation energies or activation barriers.

Results and Discussion

Although various levels of calculations involving organozinc compounds have been reported, we were

---

[13] Reich, M. J.; Holladay, J. E.; Walker, T. G.; Thompson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 9769−9780.

[14] Ikuta, S. *Theochem-J. Mol. Struct.* **1998**, *434*, 121−128.

[15] Lambert, C.; Schleyer, P. v. R.; Wurthwein, E. U. *J. Org. Chem.* **1993**, *58*, 6377−6389.

[16] Gung, B. W.; Xue, X. W.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692−10697.

[17] Gung, B. W.; Xue, X. W. *Tetrahedron: Asymmetry* **2001**, *12*, 2955−2959.

[18] Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335.

[19] Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128−133.

[20] Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998−9006.

[21] Vazquez, J.; Pericas, M. A.; Maseras, F.; Lledos, A. *J. Org. Chem.* **2000**, *65*, 7303−7309.

[22] Rasmussen, T.; Norrby, P. O. *J. Am. Chem. Soc.* **2001**, *123*, 2464−2465.

[23] Weston, J. *Organometallics* **2001**, *20*, 713−720.

[24] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

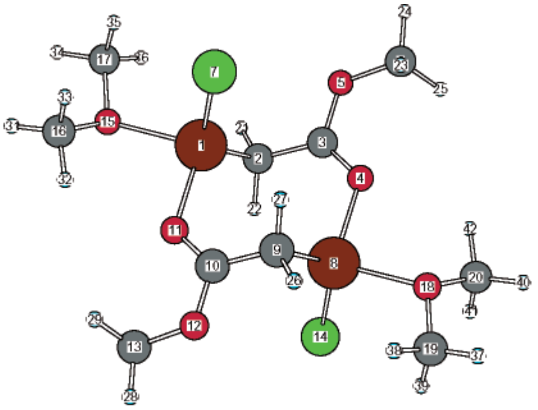
[25] *Density Functional Methods in Chemistry*, Labanowski, J. K., Andzelm, J. W., Eds.; Springer-Verlag: New York, 1991.

[26] Parr, R. G.; Yang, W. T. *Annu. Rev. Phys. Chem.* **1995**, *46*, 701−728.

[27] Frisch, M. J.; Trucks, G. W.; Cheeseman, J. R. *Theor. Comput. Chem.* **1996**, *4*, 679−707.

[28] Schwenke, D. W.; Truhlar, D. G. *J. Chem. Phys.* **1985**, *82*, 2418−2426.

Table 1. Comparison of Gaussian 98 Computed Structure Parameters with Those from the X-ray Analysis of the Crystal Structure of Reformatsky Reagent 11: Selected Bond Distances (Å) and Angles (deg)



11

	HF/3-21G*	HF/6-31G*	B3LYP/ 6-31G*	exptl
Zn(1)−O(11)	1.91	2.03	2.01	2.02
Zn(1)−C(2)	2.05	2.08	2.02	1.98
Zn(1)−O(15)	1.96	2.13	2.12	2.05
Cl(7)−Zn(1)−C(2)	115.9	124.0	126.3	127.6
O(11)−Zn(1)−O(15)	101.5	95.8	93.9	93.2
O(15)−Zn(1)−C(2)	113.5	110.0	109.3	106.9
O(11)−Zn(1)−C(2)	110.6	109.8	110.0	111.2
Zn(1)−O(11)−C(10)	135.8	127.9	122.7	123.0

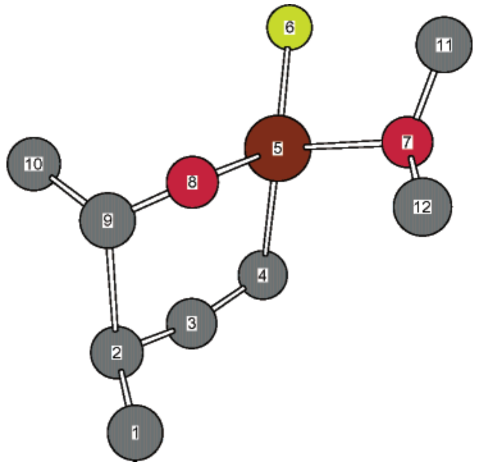
Table 2. Relative Transition-State Energies for Allenylzinc (2) Addition to CH_3CHO (kcal/mol)

	transition state			
	anti (*S*-Zn), **5**	anti (*R*-Zn), **6**	syn (*S*-Zn), **7**	syn (*R*-Zn), **8**
HF/6-31G*	0.0	0.36	1.23	1.96
HF/6-31++G**	0.0	0.12	1.10	1.96
B3LYP/6-31G*	0.0	0.56	1.54	1.63
B3LYP/6-31++G**[a]	0.0	0.32	1.42	1.64
B3LYP/6-311G(3df)[a]	0.0	0.47	1.36	1.68

[a] Single-point calculations.

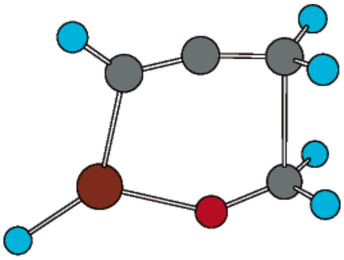
uncertain about the quality of the reported methods. We decided to calibrate the quality of the ab initio and DFT methods on the zinc atom by a series of calculations on a known organozinc compound. The crystal structure of a famous organometallic reagent, the Reformatsky reagent (**11**; Table 1), has many similarities to the organozinc reagent in question.[29] The zinc atom is tetrahedral, and THF solvent molecules are among the ligands. Similarly to the approximations made in the following calculations, the THF solvent molecules are substituted with dimethyl ether molecules to reduce computational cost. The B3LYP/6-31G* method performs most satisfactorily and gives a structure (**11**) that closely resembles the X-ray structure. A comparison of the calculated structural parameters to the reported data for the X-ray analysis of the crystal structure is listed in Table 1.

Table 3. Comparisons of Structural Parameters Calculated at B3LYP/6-31G* and HF/6-31++G Levels of Theory for the Most Favorable Transition State 5**



structural param	B3LYP/6-31G*	HF/6-31++G**
Bond Lengths (Å)		
C(9)═O(8)	**1.28**	**1.27**
C(2)═C(3)	**1.37**	**1.37**
C(3)═C(4)	**1.27**	**1.25**
C(2)- - -C(9)$_{\text{incipient}}$	**2.10**	**2.09**
C(2)−C(1)	1.52	1.52
Zn(5)−C(4)	2.05	2.15
O(8)−Zn(5)	1.95	1.98
F(6)−Zn(5)	1.80	1.82
O(7)−Zn(5)	2.12	2.17
C(10)−C(9)	1.52	1.51
C(11)−O(7)	1.44	1.42
Bond Angles (deg)		
C(2)−C(9)−O(8)	**112.0**	**112.4**
C(4)−C(3)−C(2)	**161.2**	**165.6**
C(3)−C(2)−C(1)	119.6	119.3
C(9)−C(2)−C(3)	96.0	96.1
Zn(5)−C(4)−C(3)	108.5	105.8
O(8)−Zn(5)−C(4)	98.6	96.2
Dihedral Angles (deg)		
C(3)−C(2)−C(9)−O(8)	**−37.8**	**−34.0**

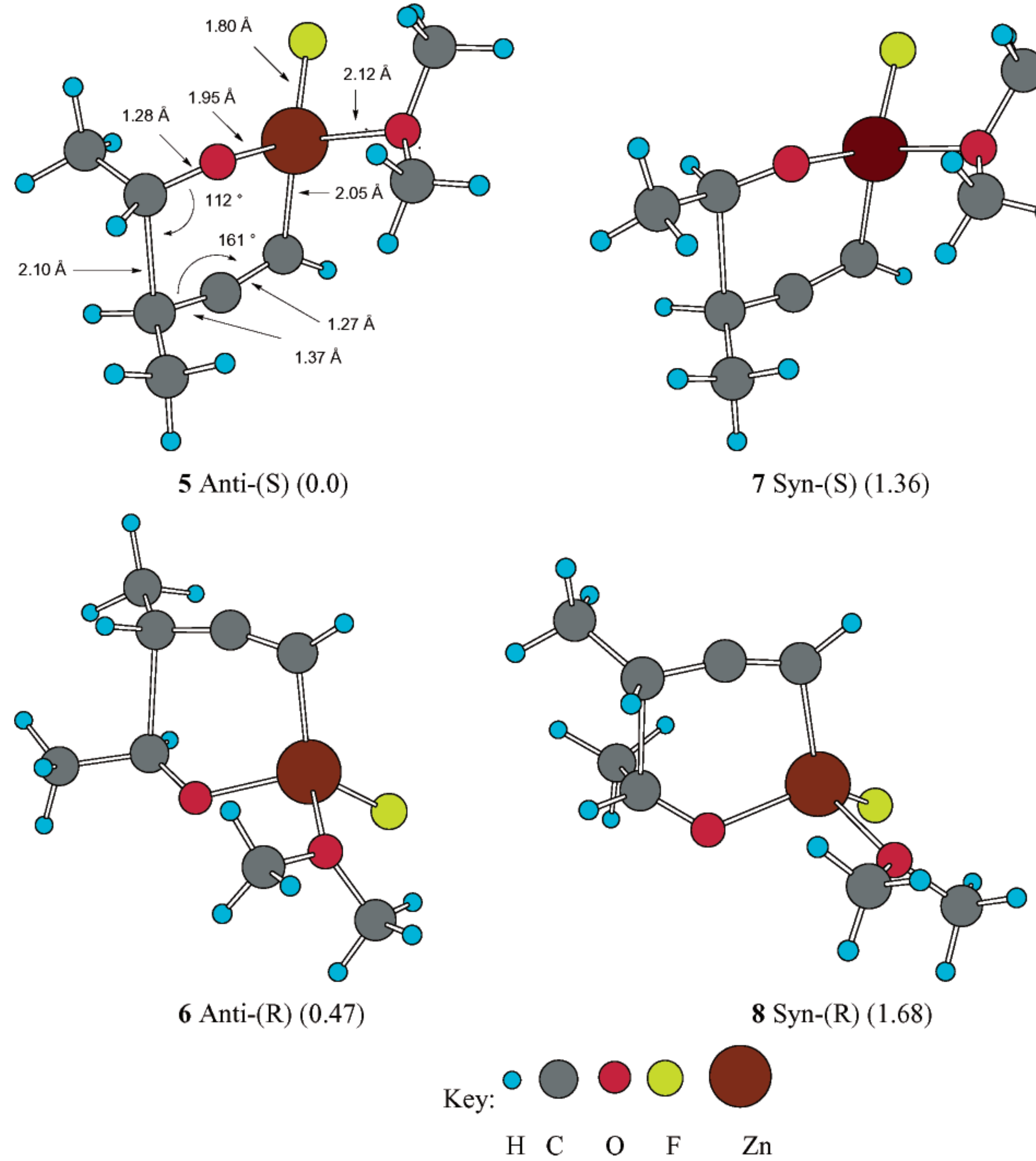
Initially, structure **12** for the addition of the simple allenylzinc to formaldehyde was studied. For these calculations the zinc atom was assumed to be trigonally coordinated and the other ligand in addition to the allenyl unit was a hydride. The minimized structure contained a bent-allenyl array, similar to that previously reported for the allenyl anion.[13] Eclipsed hydrogen substituents on the two bonding sp^2 carbons were obtained in this gas-phase model. The electrostatic attraction between the trigonal zinc atom and the aldehyde oxygen atom appear to dominate and render the repulsion among the eclipsed C−H bonds less



12

---

(29) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; Vanderkerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403−1407.



5 Anti-(S) (0.0)

7 Syn-(S) (1.36)

6 Anti-(R) (0.47)

8 Syn-(R) (1.68)

Figure 1. Perspective views from the side of the cyclic transition states for the (*M*)-1,2-butadienylzinc additions to acetaldehyde calculated at the B3LYP/6-31G* level of theory. The relative energies are given in parentheses (kcal/mol) and are calculated at the B3LYP/6-311G(3df)//HF/6-31++G** level.

important. The result was a totally eclipsed transition state. We then considered modifications to this simplified model. Since the reaction of interest was performed in THF, and zinc atoms prefer a tetrahedral coordination in solution,[30] we decided to model the solvent effect with an explicitly coordinated dimethyl ether ligand as illustrated in eqs 1 and 2. The methanesulfonate anion of the actual reaction was replaced with a fluoride anion to simplify the calculations. When these modifications were incorporated into the (*M*)-1,2-butadienylzinc/acetaldehyde system, the calculated relative energies for the diastereomeric transition states were in good agreement with the diastereoisomer ratios observed for additions to unbranched aldehydes (Table 2). The large basis sets (6-31++G** and 6-311G(3df)) had insignificant effects on the relative energies of the four transition states.

To examine the basis set effect, the four transition states (**5**−**8**) located at the HF/6-31G* level were subjected to further optimization at the HF/6-31++G** level of theory. All four transition states converged at the HF/6-31++G** level. The relative energy differences among the three methods are small, and the order of transition state stability remains unchanged (Table 2). Selected structural parameters for transition state **5** are listed in Table 3 for a comparison between the B3LYP/

---

[30] Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; Wiley: New York, 1999.

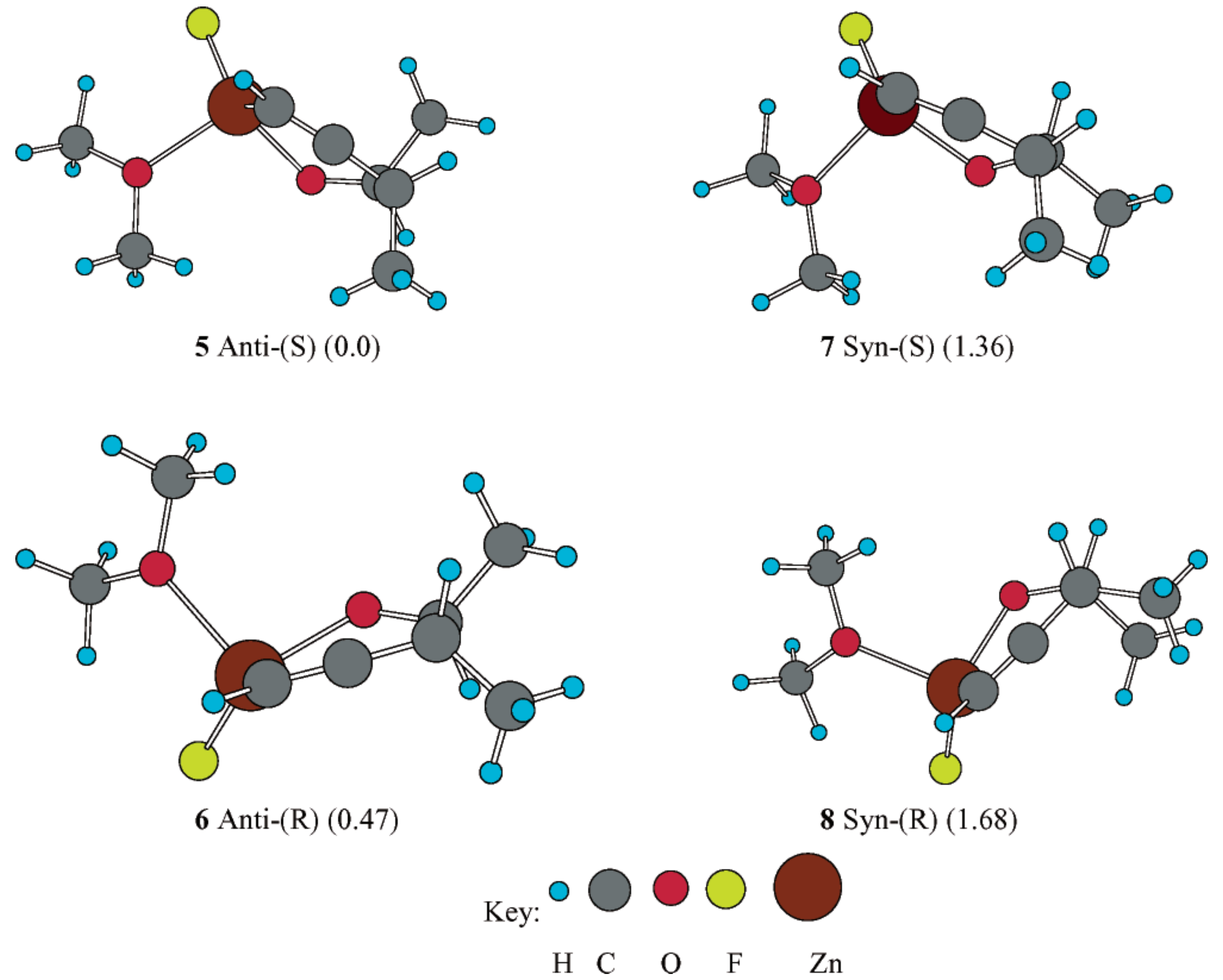


Figure 2. Perspective views from the top of the allenyl sp^2 carbon to the acetaldehyde sp^2 carbon for transition states calculated at the B3LYP/6-31G* level of theory. The relative energies are calculated at the B3LYP/6-311G(3df)//HF/6-31++G** level (kcal/mol).

6-31G* and HF/6-31++G** methods. Key bond lengths and angles are similar for these two structures. However, the allenyl bond angle in the transition state using the B3LYP/6-31G* method (162°) is slightly more bent than that predicted by the HF/6-31++G** method (165.6°). The dihedral angle (C(3)−C(2)−C(9)−O(8)), which can be used as a measure of the degree of eclipsing between the aldehyde and allenyl substituents, indicates a slightly less eclipsed conformation for the B3LYP structure (−37.8°) than for the Hartree−Fock structure (−34°). Thus, the coordination of a solvent molecule to the zinc atom allows the substituents on the bonding sp^2 carbon to be substantially staggered. This can be observed visually through the structures shown in Figures 1 and 2.

The four calculated transition states are shown in ChemBats3D graphics in Figures 1 and 2. These structures are optimized at the B3LYP/6-31G* level. The same order of relative energies, anti-*S* < anti-*R* < syn-*S* < syn-*R*, was found. The descriptors for the transition states have the following meanings. The transition state is labeled by the product stereochemistry it leads to, either anti or syn. The configuration of the tetrahedral zinc atom is indicated by *R* or *S*. Thus, both the anti-*S* (**5**) and the anti-*R* (**6**) transition states lead to a product with anti stereochemistry and both the syn-*S* (**7**) and the syn-*R* (**8**) transition states lead to a product with syn stereochemistry. The anti-*S* transition state **5** is the most favored and the anti-*R* (**6**) only slightly less so. These two account for the major anti product.[11] The syn-*S* transition state **7** is slightly more than 1 kcal/mol higher in energy than the anti state at all levels of theory, consistent with the observation that additions to unbranched aldehydes proceed with anti:syn ratios of ca. 80:20.[9]

The calculated allenyl bond angle ($\angle_{C=C=C}$) is ca. 162° in all three B3LYP transition states and is 165° for the HF/6-31++G** structure **7**. These results for the allenylzinc species are similar to previous ab initio calculations for allenyllithium.[13] The bond distance between the two bonding sp^2 carbons averages 2.1 Å. A computational study on the transition state for dialkylzinc additions to aldehydes yielded bond lengths of 2.25−2.28 Å.[18] Other cyclic transition states that may or may not be relevant to this study also showed considerably longer incipient bonds. The two incipient bonds in a Diels−Alder cycloaddition of isoprene and maleic anhydride are 2.23 and 2.33 Å.[31] This Diels−Alder transition state was calculated at the B3LYP/6-31G* level of theory and supported by experimental kinetic isotope effects. Recent calculations on the allylboration of aldehydes led to a predicted bond distance of 2.25 Å for the bonding sp^2 carbons.[16] The relatively shorter bonding distance calculated for the allenylzinc addition is suggestive of a "late" or more productlike transition state.[32]

To highlight the staggering of the aldehyde and allenyl substituents and the steric interactions between the allenyl methyl and the aldehydic methyl groups, the transition-state structures in Figure 2 are displayed in a Newman projection orientation in which the axis of observation is the incipient $C(sp^2)-C(sp^2)$ bond. It is of interest to note that in the lower energy anti transition state **5** the Zn atom is coordinated syn to the CH_3 substituent of the aldehyde, resulting in a nearly anti orientation of the allenyl and aldehyde methyl substituents. This is unusual, in light of the fact that Lewis acids coordinate preferentially syn to the aldehyde hydrogen of benzaldehyde.[33,34] Steric repulsions between the allenyl and aldehyde methyl substituents cause **5** to be favored over **6**. This preference would not alter the diastereoselectivity of the addition. However, the more nearly eclipsed relationship of these substituents in transition states **7** and **8** would disfavor the syn adducts in accord with the anti preference of the additions. As expected, this preference is greater with α-branched aldehydes. It is interesting to also note that in the lower energy syn transition state **7** the Zn atom is coordinated anti to the CH_3 substituent, opposite of that in transition state **5**. Structures **5** and **7** each have an *S*-Zn atom. Thus, it appears that the chirality of the zinc atom has a small influence on the transition-state energy. Although this influence is small relative to the steric effect, it is conceivable that one may manipulate the ligand to achieve a cooperative effect with the allene asymmetry and to maximize the stereoselectivity in these reactions.

Conclusions

In conclusion, ab initio and density functional theory calculations at the B3LYP/6-31G* and HF/6-31++G** levels support the proposed cyclic transition state for chiral allenylzinc additions to aldehydes. A tetrahedrally coordinated zinc atom in the transition state is found to give energy differences that are most consistent with the observed results. The tetrahedral zinc atom with the coordination of a solvent molecule allows the staggering of the bonding sp^2 carbons, which alleviates the steric repulsion from eclipsing of the aldehyde and the allenyl substituents. The allenyl array has a "bent" ($\angle_{C=C=C}$ = ca. 162°) geometry in the transition state, which is consistent with previously reported structures for allenyl anions. A relatively "late" transition state is proposed for this reaction on the basis of comparisons to ab initio transition states for dialkylzinc additions, Diels–Alder cycloaddition, and allylboration reactions. This study suggests that steric interactions between the aldehyde and allene substituents control the diastereoselectivity of the reaction. However, this study also highlights a tetrahedrally coordinated zinc atom and suggests the possibility of using ligand effect to maximize the stereoselectivity in these reactions. The results of this study contribute to a better understanding of the experimental observations.

Acknowledgment. This research is supported in part by grants from the National Institutes of Health (No. GM60263 to B.W.G. and No. CA90383 to J.A.M.). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society. We are grateful for access to the computing resources provided by the Ohio Supercomputer Center (Grant No. POS0076-9).

Supporting Information Available: Listings giving internal coordinates of the transition states **5**–**8**, including bond lengths, bond angles, and dihedral angles. This material is available free of charge via the Internet at http://pubs.acs.org.

OM030220W

---

(31) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984–9985.

(32) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369–3372.

(33) Reetz, M. T.; Hullmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405–2408.

(34) Gung, B. W. *Tetrahedron Lett.* **1991**, *32*, 2867–2870.