J. Am. Chem. Soc. **1992**, *114*, 6686-6692

Theoretical Studies of Heteroatom-Directed Carbometalation. Addition of MeCu, Me_2Cu^-, and MeLi to Substituted Acetylenes

Eiichi Nakamura,*,† Yoshimitsu Miyachi,† Nobuaki Koga,‡ and Keiji Morokuma*,‡

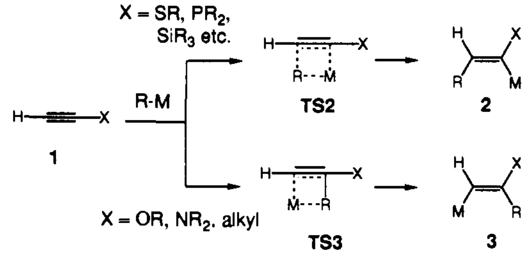
Contribution from the Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan, and Institute for Molecular Science, Myodaiji, Okazaki 444, Japan.

Received January 30, 1992

Abstract: Ab initio theoretical studies of the additions of MeCu, Me_2Cu^-, and MeLi to acetylenes bearing heteroatoms substituents (i.e., OH and SH as well as SiH_3, CH_3, and H) have shown that the calculated and experimental regioselectivities of carbometalation reactions show excellent correlation, indicating that the activation enthalpy plays a decisive role in the regioselection of heteroatom-directed carbometalations. Energy decomposition analysis of the regioisomeric transition states for the MeCu and MeLi additions to the OH- and SH-substituted acetylenes indicates that electrostatic interaction is a dominant contributor to the energy difference between the regioisomeric transition states. On the other hand, the overall interaction energy is dependent on orbital and electrostatic interactions for the MeCu and MeLi additions, respectively.

The synthetic and mechanistic importance of kinetic and thermodynamic stabilization of a negative charge by a neighboring heteroatom is well documented.[1] Kinetic effects of heteroatoms in directing carbometalation across a C–C multiple bond[2,3] (Scheme I) have gained equal importance and have been exploited in organic synthesis, but mechanistic understanding has been lacking. Despite its appearance, the heteroatom-directed carbometalation (1,2-addition) is mechanistically distinct from conjugate additions (1,4-addition).[4,5] In the latter, there is a well-known correlation of the regiochemistry of the reaction to the LUMO coefficient of the acceptor C–C multiple bond, while such correlation is not found in the former (vide infra).

Scheme I



Carbocupration of substituted acetylenes[6] provides the most typical and well-behaved examples of the heteroatom effects.[7] Organocopper reagents undergo cis addition to RS-,[8] R_2P-,[9] or R_3Si-substituted[10] acetylenes (**1**) to give exclusively the vinyl organometallic **2**. On the other hand, the reactions with acetylenes bearing RO and R_2N substituents exclusively afford regioisomer **3**.[11] The contrasting behavior of the second and the third row heteroatoms is particularly striking. The same regioselectivity profile has also been found for carbolithiation reactions of heteroatom-substituted olefins.[12-14]

Intuitive prediction of the product stability (i.e., **2** favored for all heteroatoms) as supported by the molecular orbital calculations (vide infra) does not provide a unified view of the regioselectivity, nor do the frontier molecular orbitals (FMOs) of the starting acetylenes (vide infra). Given the generality of the heteroatom-directing phenomenon and the failure of simple theorems, we were interested in elucidating the origin of the regioselectivity by theoretical methods. To address this issue, we have studied the addition of MeLi, MeCu, and Me_2Cu^- to substituted acetylenes by the ab initio molecular orbital calculations and found that there is an excellent correlation between experimental regioselectivity and the calculated energies of the regioisomeric transition structures (TSs), indicating that activation enthalpy is an important determinant of the regioselectivity. No indicating of chelation between the heteroatom and the metal was found in any TSs, whereas such chelation was found in some products. In addition to the regiochemical information, the calculations also provided implications to the relative reactivities of heteroatom-substituted C–C multiple bonds.

Computational Methods. The geometries of reactants, complexes, and TSs were optimized with the Hartree–Fock method with the assumption of C_s symmetry in all cases.[15] The 3-21G basis set[16] was used for geometry optimizations for all atoms except copper. Further optimization was performed for some transition states at the Hartree–Fock level of theory with the 6-31G* basis set. For the copper atom, the inner-shell (from 1s to 3p) electrons

---

† Tokyo Institute of Technology.

‡ Institute for Molecular Science.

[1] (a) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191 and references therein. Reviews: Gilman, H.; Morton, J. W. *Org. React.* **1954**, *8*, 258. Gschwend, H. W.; Rodrigues, H. R. *Org. React.* **1979**, *26*, 1. (b) For theoretical studies, see: Stork, G.; Polt, R. L.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 8360. See also: Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

[2] Review: Vara Prasad, J. V. N.; Pillai, C. N. *J. Organomet. Chem.* **1983**, *259*, 1. Proximity effects: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. Carbometalation (an organic term) is equivalent to olefin insertion to a carbon–metal bond (an organometallic term).

[3] Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, 1980; pp 133–136. Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: Oxford, 1974; pp 89–108, 204–211.

[4] Theoretical studies: Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 4635. Wong, S. S.; Paddon-Row, M. N.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 8679.

[5] (a) Note that RCu addition to enolate is not a carbocupration reaction: Yamamoto, Y.; Yamada, J.-i.; Uyehara, T. *J. Am. Chem. Soc.* **1987**, *109*, 5820. Addition to acetylenic esters probably involves a carbometalation mechanism: Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1979**, *44*, 1744. (b) For carbocupration in allylation reaction, see: Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

[6] (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) For carbometalation of cyclopropenes, see: Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428. Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297. Nakamura, E. *Synlett* **1991**, 539. Nakamura, E.; Isaka, M. *Organomet. News* **1990**, 194.

[7] Though the term heteroatom conventionally refers to atom such as O, N, S, and P, we have also investigated Si because of its importance in carbanion chemistry.

[8] (a) Normant, J. F.; Alexakis, A.; Commerçon, A.; Cahiez, G.; Villieras, J. *C. R. Acad. Sci. Paris Sér. C* **1977**, *285*, 29. (b) Vermeer, P.; Meijer, J.; de Graaf, C. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 24. (c) Meijer, J.; Westmijze, H.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 102. (d) Alexakis, A.; Cahiez, G.; Normant, J. F.; Villieras, J. *Bull. Soc. Chim. Fr.* **1977**, 693.

[9] Meijer, J.; Westmijze, H.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 102.

[10] Obayashi, M.; Utimoto, K.; Nozaki, H. *J. Organomet. Chem.* **1979**, *177*, 145. Westmijze, H.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1977**, *21*, 1823.

0002-7863/92/1514-6686$03.00/0

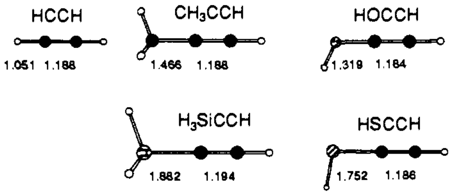


Figure 1. HF/3-21G optimized structures of acetylene and CH_3-, SiH_3-, OH-, and SH-substituted acetylenes (distances in Å).

were replaced by an effective core potential (ECP). The potential parameters employed in our calculations are those given by Hay and Wadt.[17,18] The remaining electrons were described by basis functions of double-ζ quality.[17] In order to obtain better activation energies, energy calculations were also performed at the MP2-(FC)[19]/6-31G*(5D)[20] level on the HF/3-21G optimized geometry (abbreviated as MP2/6-31G*(5D)//HF/3-21G) for the structures involving copper and at the MP2(FC)/6-31G*(6D) level on the HF/3-21G optimized geometry (abbreviated as MP2/6-31G*-(6D)//HF/3-21G) for other structures. To evaluate the role of the metal, the reaction of Me^- with acetylene was also studied with the HF/3-21G optimization. In all cases studied, the energy profiles of the reaction obtained with electron correlation at the MP2/6-31G* level were qualitatively the same as those at the HF/3-21G levels. The regiochemical dependence of the zero-point energies of the TSs as determined for the MeLi addition to the SH-substituted acetylene (ca. 0.4 kcal/mol) was found to be much smaller than the regiochemical dependence of total electron energies, and therefore it was neglected throughout the present studies.

The extremely large number of calculations involved in the present studies necessitated dealing with only monomeric ligand-free MeCu and MeLi.[21] However, some important reference points were also examined for Me_2Cu^- at the HF/3-21G level with two purposes: first, because of the importance of organocuprates in experimental carbocupration chemistry,[22] and second, because the highly basic Me^- ligand on copper may serve as a model of a basic ligand. Use of this model did not change the calculated regiochemistry as reported in the following paragraphs.

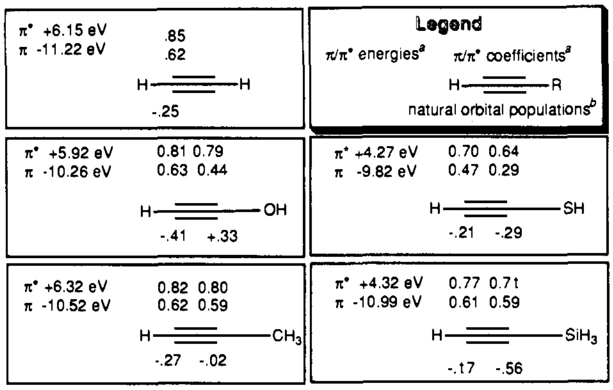


Figure 2. FMO (π and π*) energies, coefficients, and electron populations of acetylenic carbons in substituted acetylenes at the HF/3-21G optimized geometries: (a) FMO energies at the HF/3-21G//HF/3-21G level, and the FMO coefficients at the HF/STO-3G//HF3-21G level; (b) natural orbital population at the HF/3-21G*//HF/3-21G level.

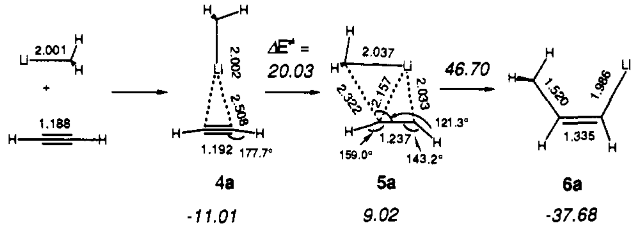


Figure 3. Addition of MeLi to acetylene. Energies (kcal/mol; HF/3-21G) shown under the structures are relative to reactants. Bond lengths are in Å.

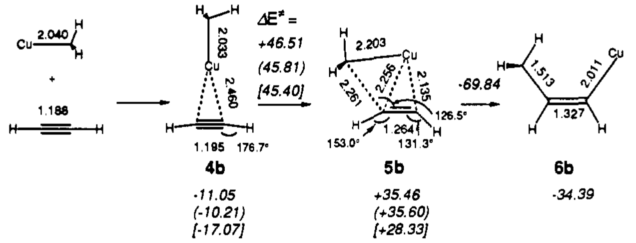


Figure 4. Addition of MeCu to acetylene. Geometries (Å) for reaction of MeCu with acetylene. Energies (kcal/mol; HF/3-21G) shown under the structures are relative to reactants. The HF/6-31G*(5D)//HF/3-21G energies are in parentheses, and the MP2/6-31G*(5D)//HF/3-21G energies are in brackets. Bond lengths are in Å.

To alleviate the obvious deficiency of our model, we evaluated the energies and structures of the TSs by comparing closely related isomers so that any systematic errors inherent to our model may cancel each other. Moreover, such simplification may be justified in the light of the results[23] that reactants and transition structures of the reaction of methyllithium monomer and its dimers with formaldehyde share in common the important features.

Results

FMO and Population Analysis of Substituted Acetylenes. It is widely accepted that 1,4-addition of a nucleophile to an olefin conjugated to an electron-withdrawing group (e.g., carbonyl groups) takes place in such a manner that the nucleophile attacks the olefinic carbon with a larger LUMO coefficient. We started the present studies by investigating if such a simple perturbation concept is applicable to the heteroatom-directed carbometalation reaction.

To investigate the contrasting behavior of the second and the third row heteroatoms (Scheme I), we have chosen the group 16 elements, OH and SH groups, as model substituents for OR and

---

(11) Normant, J.-F.; Alexakis, A.; Commerçon, A.; Cahiez, G.; Villieras, J. *C. R. Acad. Sci. Paris Ser. C* **1974**, *279*, 763. Alexakis, A.; Cahiez, G.; Normant, J.-F.; Villieras, J. *Bull. Soc. Chim. Fr.* **1977**, 693.

(12) For oxygen-substituted olefins, see: Hill, C. M.; Senter, G. W.; Haynes, L.; Hill, M. E. *J. Am. Chem. Soc.* **1954**, *76*, 4538. Pattison, F. L. M.; Dear, R. E. A. *Can. J. Chem.* **1963**, *41*, 2600. Stähle, M.; Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1730. Fujisawa, T.; Kurita, Y.; Kawashima, M.; Sato, T. *Chem. Lett.* **1982**, 1641.

(13) (a) For sulfur-substitued olefins, cf.: Seebach, D.; Bürstinghaus, R.; Gröbel, B.-T.; Kolb, M. *Justus Liebigs Ann. Chem.* **1977**, 830. (b) Selenium activation: Kauffmann, T.; Ahlers, H.; Tilhard, H.-J.; Woltermann, A. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 710.

(14) For silicon-substituted olefins, see: Chan, T. H.; Chang, E. *J. Org. Chem.* **1974**, *39*, 3264. Utimoto, K.; Imi, K.; Shiragami, H.; Fujikura, S.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 2101. Lehmkuhl, H.; Hauschild, K.; Bellenbaum, M. *Chem. Ber.* **1984**, *117*, 383.

(15) The GAUSSIAN 82 and 86 program were used: Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whitesides, R. A.; Schlegel, H. B.; Pople, J. A. GAUSSIAN 82, Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA. Natural orbital analysis was carried out with the SPARTAN program (Hehre, W. J./Asahi Chemical Industry).

(16) (a) 3-21G basis set: Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939. (b) 6-31G *basis* set: Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(17) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270, 284. For ECP parameters, see: Goddard, W. A., III; Kahn, L. R. *J. Chem. Phys.* **1972**, *56*, 2685. Melius, C. F.; Goddard, W. A., III *Phys. Rev. A* **1974**, *10*, 1528.

(18) The procedure on which the code was based is described in the following: Davidson, E. R.; McMurchie, L. E. *J. Comp. Phys.* **1981**, *44*, 289. The computational implementation is due to Martin, L. R.

(19) Binkley, J. S.; Pople, J. A.; Seeger, R. *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1.

(20) In specifying the level of calculation, the basis set for Cu, which is always DZ with ECP, will not be shown.

(21) We have recently located some C_1 TSs of the addition of $(MeLi)_2$ to acetylenes, which share the salient features of the monomeric TSs and also supported the present conclusion: unpublished results.

(22) (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 5869. (b) Incorporation of a lithium atom will be the next step toward a more realistic model.

(23) (a) Kaufmann, E.; Schleyer, P. v. R.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) See also: Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946.

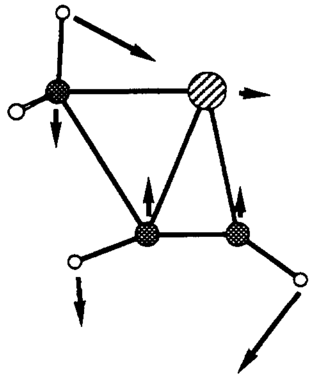


Figure 5. Motion in the normal mode of imaginary frequency at the TS of the MeLi addition to acetylene.

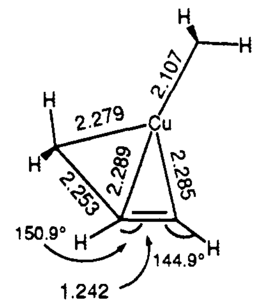


Figure 6. Transition structure of the addition of Me_2Cu^- to acetylene in Å.

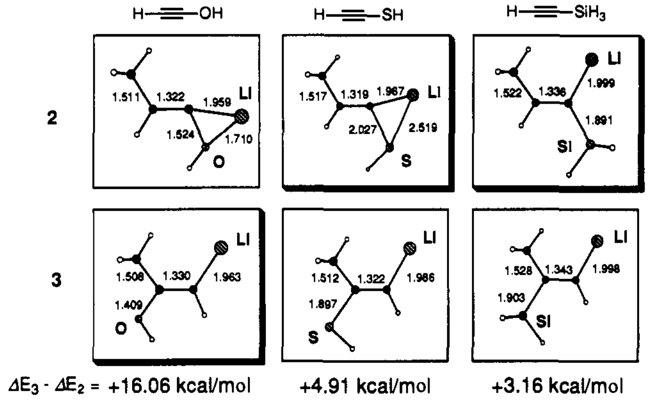


Figure 7. Regioisomeric products of the addition of MeLi to OH-, SH-, and SiH_3-substituted acetylenes in Å. The energy differences shown at the bottom are at the HF/3-21G//HF/3-21G level.

SR groups. Electronically less characteristic group 14 elements, CH_3 and SiH_3 groups, were also investigated.[7]

Structures of the starting acetylenes were optimized with C_s symmetry at the HF/3-21G level (Figure 1). The frontier orbital coefficients obtained at the HF/STO-3G, 3-21G, and 6-31G* levels on the HF/3-21G optimized geometry were not correlated well to the experimental regioselectivity (Figure 2). On the other hand, electron population (natural orbital analysis)[24] was in accord with the observed selectivity, implying that the regioselectivity may be controlled by electrostatic interactions rather than FMO interactions.

Reaction Pathway of the Addition of Me–Metals to Acetylene. The additions of MeLi (Figure 3) and MeCu (Figure 4) to the parent acetylene were found to proceed through two stages, via the π-complex[25] (**4a**,**b**) and transition structure (**5a**,**b**)[26–28] to the product (**6a**,**b**). Both reactions are highly exothermic (34.4 and 37.7 kcal/mol respectively at the HF/3-21G//HF/3-21G level), and much more so than the additions to ethylene.[26] The TSs of the MeLi and MeCu additions (**5a** and **5b**) are quite similar to each other, and both are relatively "early", as judged by the lengths of the forming Me–C bond. However, it is quite asynchronous in the sense that the metal–C bond is nearly formed while the Me–C bond formation is still in the early stage. Between the TSs **5a** for MeLi and **5b** for MeCu, the latter may be considered "later": especially noteworthy is that the stretching of the C–C triple bond in the TS of the MeCu addition is already advanced 55% toward the product, while only 35% with MeLi. The reaction coordinate, i.e., the normal mode of the single imaginary frequency of the TS of the MeLi addition (Figure 5), suggests that the metal–C bond breaking is beginning to take place at the TS. In these TSs, the metal is placed quite close to the acetylene carbons, suggesting that metal–olefin interaction is an important factor of the overall character of the reaction. Such features are also found for the addition of MeLi and MeCu[29] to ethylene[26] and to cyclopropene[29] and are quite similar to the reactions of other organometallics such as Me–ZrL_n and H–$ZrCp_2$.[30]

The activation energy of the addition of MeLi to acetylene (20.0 kcal/mol at the HF/3-21G level) is slightly lower than that of the MeLi addition to ethylene (23.6 kcal/mol), and the reaction is more exothermic than the ethylene reaction (by 18.9 kcal/mol). The activating energy of 46.5 kcal/mol for the MeCu addition at the HF/3-21G level is unrealistically high and was not much improved at the correlated MP2/6-31G*//HF/3-21G level (45.4 kcal/mol). It is thus likely to be a direct result of the deficiency of our monomeric, ligand-free model.

The TS of the addition of Me_2Cu^- was found to be qualitatively similar to that of the MeCu addition, in spite of the presence of a powerful Me^- ligand on the metal (Figure 6), suggesting insensitivity of the TS to the presence of a basic ligand. On the other hand, we could not find a stationary point corresponding to a π-complex between Me_2Cu^- and acetylene (at the HF/3-21G level).

In order to evaluate the effects of the metal atom, the TS of methyl anion addition to aceytlene was also determined at the HF/3-21G level (structure not shown). The TS was found to be much earlier with the forming Me–C bond as long as 2.53 Å, and the attack angle of the incoming Me anion was 125.9°. This angle falls in the same range (116° to 132°) observed for the Me–metal additions (cf. Figures 3, 4, 6, and 8). This stands in contrast to the observation in the carbonyl additions; namely, inclusion of metal (Li) makes the angle smaller[21a] due to coordination of the metal to the oxygen nonbonding orbital. The effects of metal complexation thus must be considered differently for the addition

---

(24) (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Mulliken population analysis led to quite irrational results.

(25) (a) For olefin and acetylene π-complexes of Cu(I) salts, see: Edwards, D. A.; Richards, R. *J. Organomet. Chem.* **1975**, *86*, 407. X-ray crystal structures: Budzelaar, P. H.; Timmermans, P. J. J. A.; Mackor, A.; Spek, A. L.; Duisenberg, A. J. M. *Acta Cryst. Sect. C* **1987**, *43*, 2298. Andersson, S.; Håkansson, M.; Jagner, S.; Nilsson, M.; Urso, F. *Acta Chem. Scand. A* **1986**, *40*, 194. Andersson, S.; Håkansson, M.; Jagner, S.; Nilsson, M.; Ullenius, C.; Urso, F. *Acta Chem. Scand. A* **1986**, *40*, 58. Håkansson, M.; Jagner, S. *J. Organomet. Chem.* **1989**, *361*, 269. (b) NMR studies on the complexation of cuprates with α,β-unsaturated esters: Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523. Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, *60*, 57. (c) For evidence of π-complexation with main group organometallics, see: Hata, G. *J. Chem. Soc., Chem. Commun.* **1968**, 7. Denis, J. S.; Oliver, J. P. *Dolzine*, T. W.; Smart, J. B. *J. Organomet. Chem.* **1974**, *71*, 315. Albright, M. J.; Denis, J. N.; Oliver, J. P. *J. Organomet. Chem.* **1977**, *125*, 1. Gropen, O.; Haaland, A.; Defrees, D. *Acta Chem. Scand., Sect. A* **1985**, *39*, 367.

(26) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821.

(27) For the four-centered transition state of carbolithiation, see: Dolzine, T. W.; Oliver, J. P. *J. Organomet. Chem.* **1974**, *78*, 165. Review: Hill, E. A. *J. Organomet. Chem.* **1975**, *91*, 123. For a stereochemical test, see: Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. See also: Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720.

(28) Kammermeier, B. O. T.; Klumpp, G. W.; Kolthof, K.; Vos, M. *Tetrahedron Lett.* **1991**, *32*, 3111. Cf.: Bartlett, P. D.; Goebel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 7425.

(29) Unpublished results.

(30) Kuribayashi, H.; Koga, N.; Morokuma, K. 38th Symposium on Organometallic Chemistry, Japan, Kyoto, 1991; abstract A 208. Endo, J.; Koga, N.; Morokuma, K. 38th Symposium on Organometallic Chemistry, Japan, Kyoto, 1991; abstract PA221.

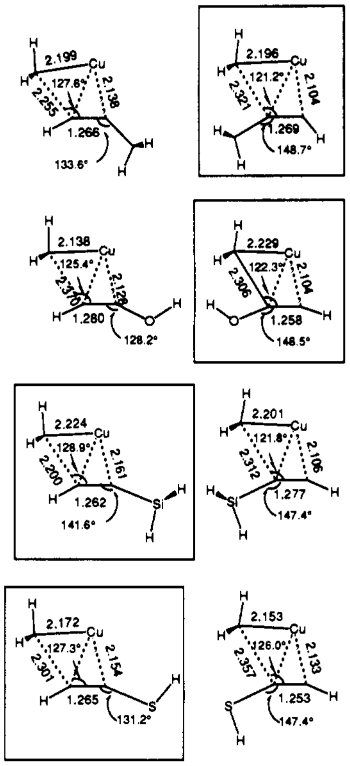


Figure 8. Regioisomeric transition structures of the addition of MeCu to CH_3-, SiH_3-, OH-, and SH-substituted acetylenes in Å. Experimentally observed isomers are shown in boxes.

to a C—C multiple bond and to a C=O bond.[31]

Regioselective Addition of Me-Metals to Substituted Acetylenes. The reaction course of carbometalation was investigated for OH- and SH-substituted acetylenes as well as for CH_3- and SiH_3-substituted acetylenes. As for the parent acetylene, these reactions were also found to go through two stages. In both MeCu and MeLi series, the substituents were found to only slightly affect the structures (see Supplement) and the energies (Table I, columns 2 and 9) of the π-complexes.

On the other hand, the calculated energies of the products of MeLi addition (columns 13-15) indicate that OH, SH, and SiH_3 substituents stabilize the regioisomer **2** and that a methyl group destabilizes **2**. The product structures are accordingly affected by the heteroatoms (Figure 7). Thus, the OH and SH groups stabilize regioisomer **2** by internal coordination as indicated by the structures in Figure 7.[32] This is in line with the intuitive prediction based on the heteroatom stabilization of α-anions. Thus, the experimental regioselectivity[6-14] is unrelated to the product stability.

The structures of the regioisomeric TSs of the MeCu additions of OH- and SH-substituted acetylenes as well as those for CH_3- and SiH_3-substituted acetylenes are shown in Figure 8 (for the MeLi additions, see supplementary material), and the energies of MeCu and MeLi additions are summarized in Table I. The absolute magnitudes of the activation energies ($\Delta E^\ddagger = \Delta E_{TS} - \Delta E_{\pi\text{-complex}}$) do vary as the substituents are changed (columns 3, 4, 10, and 11). In addition, when two regioisomeric TSs are compared, their *relative* energies ($\Delta\Delta E^\ddagger = \Delta E_2{}^\ddagger - \Delta E_3{}^\ddagger$) were found to be highly dependent on the substituent. For all substituents examined, the latter (column 5) successfully reproduced the general trend of the experimental selectivity reported for

Table I. Addition of MeCu and MeLi to Substituted Acetylenes[a]

	MeCu addition							MeLi addition				product		
≡-X (1)	π-complex[b] $\Delta E_{\pi\text{-complex}}$	TS2 $\Delta E_2{}^\ddagger$	TS3 $\Delta E_3{}^\ddagger$	$\Delta\Delta E^\ddagger$ ($\Delta E_2{}^\ddagger - \Delta E_3{}^\ddagger$)	expt $\Delta\Delta G^{\ddagger c}$ ($\Delta G_2{}^\ddagger - \Delta G_3{}^\ddagger$)	2 ΔE_2	3 ΔE_3	π-complex[b] $\Delta E_{\pi\text{-complex}}$	TS2 $\Delta E_2{}^\ddagger$	TS3 $\Delta E_3{}^\ddagger$	$\Delta\Delta E^\ddagger$ ($\Delta E_2{}^\ddagger - \Delta E_3{}^\ddagger$)	2 ΔE_2	3 ΔE_3	$\Delta\Delta E$ ($\Delta E_2 - \Delta E_3$)
X = H	−11.05	46.51				−30.36		−11.01	20.03				−37.67	
	(−17.07)	(45.40)												
X = OH	−10.37	47.68	42.78	4.91	>2			−11.57	25.84	16.31	9.53	−65.60	−49.54	−16.06
	(−15.99)	(40.13)	(36.07)	(4.06)				(−16.30)	(19.40)	(5.86)	(13.55)			
											[13.56][d]			
for Me_2Cu^-				6.89										
X = SH	−9.28	42.29	49.95	−7.66	<−2			−9.70	17.45	23.18	−5.73	−50.75	−45.85	−4.91
	(−15.88)	(38.11)	(41.23)	(−3.13)				(−14.84)	(10.53)	(11.56)	(−1.03)			
											[−0.51][d]			
for Me_2Cu^-				−4.31										
X = CH_3	−12.52	53.47	52.20	1.27	>2	−27.78	−29.49	−12.88	28.18	25.52	2.06	−31.14	−32.73	1.59
	(−19.30)	(50.45)	(48.68)	(1.77)										
X = SiH_3	−11.79	47.02	54.31	−7.29	<−2			−12.07	19.07	27.21	−8.14	−31.69	−28.53	−3.16
	(−18.65)	(44.57)	(51.70)	(−7.13)										

[a] All calculations were performed with C_s symmetry. Energies (kcal/mol) are at the HF/3-21G//HF/3-21G level, and values in parentheses are for MP2/6-31G*(5D)//HF/3-21G for MeCu addition and MP2/6-31G*(6D)//HF/3-21G for MeLi addition. [b] A π-complex such as **4**. π-Complexes between Me_2Cu^- and the acetylenes could not be located at the HF/3-21G level. Energies relative to reactants. $\Delta E^\ddagger$ refers to the energy difference between the π-complex and the TS. [c] Experimental regioselectivity observed for $RCu{\cdot}MgBr_2$ (ref 6a). [d] MP2/6-31G*(6D)//HF/6-31G*(6D).

---

[31] For the suggested importance of π-complexation in the stereoselective reactions of organocopper reagents, see: Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091. Nakamura, E. *Synlett* **1991**, 539. Dorigo, A. E.; Morokuma, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1884.

[32] Cf.: Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

Table II. Energy Decomposition Analysis of the Carbocupration Reaction[a]

	HCCOH		HCCSH	
	TS2	TS3	TS2	TS3
ΔE_{TS}	37.3	32.4	33.7	40.7
DEF(A)	48.9	42.4	37.4	37.8
DEF(M)	4.5	12.6	7.0	7.9
DEF	53.4	55.0	44.4	45.8
INT	−16.1	−22.6	−10.8	−5.1
ES	−28.8	−46.2	−37.8	−33.3
EX	94.0	114.1	106.3	110.4
$CTPLX_{A \to M}$	−36.1	−42.9	−32.9	−34.8
$CTPLX_{M \to A}$	−45.5	−46.9	−47.8	−46.5
R	0.2	−0.7	1.5	−0.9

[a] See text for definition of terms.

$RCu \cdot MgBr_2$ ($\Delta\Delta G^‡$, column 6).[6a] The calculations of the MeLi additions (column 12) also showed the same trend.

As is evident from the TSs in Figure 8, substituents do not affect the gross structures of the TSs, wherein the metal and the heteroatom are located away from each other and do not have direct mutual interactions. Therefore, the calculated regioselectivity does not originate from direct metal–heteroatom coordination. In order to investigate the role of d-orbitals on heteroatoms, optimization of the MeLi reactions with the OH- and SH-substituted acetylenes was carried out with the HF/6-31G* level, and the optimization at this level changed the TSs (see Supplement) or their relative energies only a little (Table I column 12, at the MP2/6-31G*(6D)//HF/6-31G*(6D) level), indicating the unimportance of d-orbitals on the heteroatoms. Thus, the effect of the heteroatoms on the energies of the TSs must be due to their electronegativity rather than the stabilization by its d-orbitals.[32] In all cases studied, inclusion of electron correlation at the MP2(FC) level did not affect the calculated regioselectivity (cf. Table I, energies in parentheses).

Finally, we also investigated the cuprate reagent, Me_2Cu^-. The transition structures to the additions to OH- and SH-substituted acetylenes display features similar to those of the MeCu additions (see Supplement), and the calculated $\Delta\Delta E^‡$ (Table I, column 5) also reproduced the experimental regiochemical trend.

Discussion

The foregoing computational results indicated that the regiochemical analysis at the transition state level reproduces the experimental selectivity. It was particularly pleasing that the calculations reproduced the contrasting effect of OR and SR groups for both MeCu and MeLi additions. The successful TS analysis strongly suggests that a common basic principle operates for both metals. We therefore carried out energy decomposition analysis (EDA)[33] of the TS energies with the Kitaura–Morokuma scheme to decipher the nature of this basic principle. The analysis for the OH- and SH-substituted acetylenes revealed two factors. (1) The TS energies of the MeLi additions are dominantly controlled by electrostatic interactions between MeLi and the acetylene, while those of the MeCu additions were controlled by orbital interactions. (2) On the other hand, as to the *difference* in the energy of two regioisomeric TSs, electrostatic interaction is a dominant controlling factor, though orbital interactions may sometime provide small perturbations. Details are described below.

Table III. Energy Decomposition Analysis of the Carbolithiation Reaction[a]

	HCCOH		HCCSH	
	TS2	TS3	TS2	TS3
ΔE_{TS}	14.3	4.7	7.8	13.5
DEF(A)	24.4	30.2	18.0	20.6
DEF(M)	3.6	6.4	3.7	4.7
DEF	28.0	36.6	21.7	25.3
INT	−13.7	−31.9	−14.0	−11.8
ES	−51.5	−73.1	−54.5	−49.6
EX	91.8	108.0	92.5	91.6
$CTPLX_{A \to M}$	−19.6	−25.6	−17.6	−18.8
$CTPLX_{M \to A}$	−39.2	−48.2	−39.5	−39.6
R	4.9	7.1	5.0	4.6

[a] See text for definition of terms.

Table IV. Energy Decomposition Analysis of the Carbocupration Reaction at Equi-EX Points[a]

	HCCOH		HCCSH	
	TS2	TS3	TS2	TS3
ΔE_{TS}	37.3	32.9	33.8	40.9
DEF	53.4	55.0	44.4	45.8
INT	−16.1	−22.1	−10.6	−4.9
ES	−28.8	−42.0	−34.8	−30.6
EX	94.0	94.0	94.0	94.0
$CTPLX_{A \to M}$	−36.1	−34.8	−28.8	−28.6
$CTPLX_{M \to A}$	−45.5	−38.1	−41.8	−38.4
R	0.2	−1.3	0.8	−1.3

[a] See text for definition of terms. The data after appropriate equalization of the EX term for all reactions.

The EDA procedure will be described briefly in this paragraph, while the details of the theory[33] and an application to a closely related investigation[4] have been described elsewhere. With this procedure, the acetylene component (A) and the Me–metal (M) in the TS are considered separately, and the energy of the transition state relative to the reactants, ΔE_{TS}, is formally divided into two parts, deformation energy (DEF) and interaction energy (INT) (eq 1). The former is the sum of the deformation energy

$$\Delta E_{TS} = DEF + INT \qquad (1)$$

of A and M components, the energy required to deform them from their equilibrium geometry to those of the transition state. The latter consists of electrostatic (ES), exchange (EX), $CTPLX_{(A \to M)}$ and $CTPLX_{(M \to A)}$, and residual (R) terms (eq 2). The

$$INT = ES + EX + CTPLX_{(A \to M)} + CTPLX_{(M \to A)} + R \qquad (2)$$

$CTPLX_{(A \to M)}$ and $CTPLX_{(M \to A)}$ terms represent "donative orbital interaction" from A to M and M to A, respectively. The DEF and EX terms generally come out as positive (i.e., repulsive) and the ES and CTPLX terms as negative (i.e., attractive). The results of EDA for the reactions of MeCu and MeLi with OH- and SH-substituted acetylenes are summarized in Tables II and III, respectively. Energies are those determined at the HF/3-21G level of theory.[34]

Comparison of these two tables reveals that, in the MeCu series (Table II), the CTPLX terms mainly contribute to the attractive interaction of two fragments (i.e., the sum of CTPLX energy components is more negative than the ES energy), whereas the ES term is the major contributor in the MeLi reaction (Table III). The small magnitude of the $CTPLX_{(A \to M)}$ terms is characteristic for the MeLi addition, while this term is quite negative for the MeCu reaction. Given the importance of metal–acetylene interaction inferred by the structures (vide supra), these EDA results coincide with the conventional wisdom that electrostatic interaction is important for the hard lithium atom and the orbital interaction is vital for the soft copper metal to interact with a C–C multiple bond.

The exact location of the TS on the reaction coordinate is different for each reaction pathway, and the absolute magnitudes of the EDA terms are accordingly different for each pathway. In order to make a fair comparison of ES and CTPLX contributions (both attractive) for various regioisomers, we therefore set the EX term (repulsive) constant for each series of reactions by adjusting the distance between A and M,[4,35] and the results

---

(33) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* **1976**, *10*, 325. Morokuma, K. *Acc. Chem. Soc.* **1977**, *10*, 294.

(34) For the unimportance of the basis set in the EDA analyses, see ref 33.

(35) Sakaki, S.; Kitaura, K.; Morokuma, K. *Inorg. Chem.* **1983**, *21*, 760.

Table V. Energy Decomposition Analysis of the Carbolithiation Reaction at Equi-EX Points[a]

	HCCOH		HCCSH	
	TS2	**TS3**	**TS2**	**TS3**
ΔE_{TS}	14.3	5.0	7.8	13.5
DEF	28.0	36.6	21.7	25.3
INT	−13.7	−31.6	−14.0	−11.8
ES	−51.5	−64.3	−54.1	−49.7
EX	91.8	91.8	91.8	91.8
$CTPLX_{A\to M}$	−19.6	−23.0	−17.5	−18.8
$CTPLX_{M\to A}$	−39.2	−41.7	−39.1	−39.7
R	4.9	5.7	5.0	4.6

[a] See text for definition of terms. The data after appropriate equalization of the EX term for all reactions.

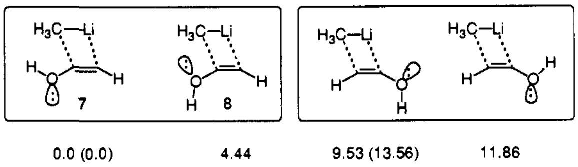


Figure 9. Conformation dependence of the activation energies for the two regioisomeric TSs of the MeLi addition to OH-substituted acetylene. Energy differences (kcal/mol) are at the HF/3-21G//HF/3-21G level (MP2/6-31G*//HF/6-31G*).

of the analysis at such Equi-EX points are shown in Tables IV and V. For the MeCu reaction (Table IV), comparison of each pair of ES and CTPLX terms for OH- and SH-substituted acetylenes reveals that given the nearly equal DEF terms for each regioisomeric pair the ES term is a single dominant factor that determines the calculated regiochemistry ($\Delta\Delta E^{\ddagger}$). Similarly, comparison for the MeLi reaction (Table V) leads to the same conclusion. This analysis thus leads to the conclusion that *the electrostatic term consistently and predominantly contributes to the difference of the activation energies between the regioisomeric TSs irrespective of the metal or the substituent.*[36]

The importance of the electrostatic interaction in determining the regioselectivity is in good accord with the prediction based on natural orbital population (Figure 2).[37]

There are two possible C_s conformations in each regioisomeric series of the TSs and the MeLi addition to OH-substituted acetylene (Figure 9), and we found smaller but intriguing perturbation of the TS energy depending on the orientation of the O–H bond. Thus, TS **7** whose lone pair is pointing downward is favored over **8** by ca. 4 kcal/mol at the HF/3-21G//HF/3-21G level. This is likely due to the enhanced electron donation from the oxygen lone pair to the carbon to be attached to lithium (for **7**) and to the electron repulsion between the oxygen lone pair and the incoming methyl anion (for **8**).[38] For the alternative regioisomeric TSs, on the other hand, much less energy difference (ca. 2 kcal/mol) was found. For the MeLi addition to SH-substituted acetylene and for Me–Cu additions in general, a much smaller conformational dependency was observed.

For the additions to SH-substituted acetylenes, conformational effect was variable depending on the regioisomer, the metal, and the level of theory, yet the magnitude of such variation was minimal, varying within a range of 0.5 kcal/mol at MP2/6-31G*//HF/6-31G* level. All energies in Table I are based on the lower energy conformers in each regioisomeric pathway.

Besides the regiochemistry-directing effects, heteroatoms also affect the reaction rate of carbometalation reactions. Although quantitative data are scarce, there is a clear tendency that a heteroatom accelerates carbometalation of olefins and acetylenes, while an alkyl group retards the reaction. For instance, 1,2-alkylacetylenes have never been reported to be carbocuprated, while 1-alkyl-2-alkoxy- and 1-alkyl-2-alkylthioacetylenes are good acceptors of organocopper reagents.[6a] We also found that alkyl groups on a cyclopropene show a large deceleration effect.[6b,39]

In this respect, the activation energies summarized in Table I also gives us insights to the reaction rate. Methyl substitution raises the activation energies of both regioisomers by several kilocalories per mole, and by taking this as a standard, OH, SH, and SiH_3 substituents uniformly lower the activation energies of the experimentally observed pathway by as much as 10 kcal/mol. The calculated energy fluctuation is well over the range expected from simple steric effects and must be electronic in origin. Interestingly, the calculations indicate that the most electron-rich OH-substituted acetylene is the most reactive toward a methyl–metal compound in the gas phase. It is notable that the activation energies of the reaction path leading to the experimentally unobservable isomers are uniformly higher than that of the addition to the parent acetylene. This trend is consistent with mismatching of the polarization between the substituted acetylene and the Me–metal.

On finishing this section, it may be appropriate to consider the validity of the present models for the studies of regioselectivities. There is an obvious deficiency in the monomeric Me–metal models, and in order to overcome this problem, we relied on a protocol to evaluate the energies only in a relative sense. Thus, the energy of one TS was compared with that of its closely related TS for the same metal. Such treatment may be meaningless if the substituents have a direct interaction with the metal in the TS, since the magnitude of such interaction would depend heavily on the exact relative geometry of the metal and the substituent. However, as has been described above, the metal and the heteroatom are always located far away from each other and have no direct mutual interactions. In our preliminary studies, we found that such features of the TSs (and energy profiles) are also shared by the TSs of the addition of dimeric MeLi to acetylenes.[21] Successful reproduction of the regiochemistry and elucidation of the background principle add to the credibility and the practical utility of the present theoretical model.

Conclusion. The present theoretical studies have led to the following conclusions for the heteroatom-directed carbometalation reactions. (1) The regiochemistry of carbocupration and carbolithiation can be correctly evaluated by the gas-phase activation energies obtained by theoretical calculations using a simple, monomeric model organometallic.[21] The conclusion remains unaffected by the level of theory. (2) The EDA of the OH- and SH-substituted acetylene reactions indicates that electrostatic interaction may be a dominant contributor to *the energy difference* between the regioisomeric transition states, whereas *the total interaction energy* is largely controlled by the orbital interactions in the MeCu additions and by the electrostatic interactions in the MeLi additions. Thus, a heteroatom substituent controls the regiochemistry of carbometalation mainly by affecting electron population of the acetylene fragment in the transition state. (3) In this respect, the observed correlation of the experimental re-

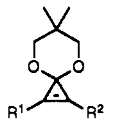
---

(36) EDA was also carried out for the reaction of methyl- and silylacetylenes (see supplementary material). Unlike the Group 16 substituents, differential contributions of various terms are subtle, and the DEF and EX terms are important for regiocontrol, suggesting that steric factors may be significant for these substituents.

(37) Natural orbital population of the deformed acetylene fragments (A) in the TSs led to the same conclusion.

(38) TS7 (and presumably **8**) has two imaginary frequencies. The smaller of them corresponds to the C–O bond rotation and the true transition state of the MeLi addition reaction must be lower in energy than those of **7** and **8**.

(39) The reaction rate depends critically on the number of alkyl substituents on the olefin. An unsubstituted cyclopropenone acetal (i: R^1, R^2 = H) reacts extremely rapidly with dialkyl cuprates at −78 °C, monosubstituted compound i (R^1 = H, R^2 = alkyl) reacts only slowly, and a disubstituted compound (R^1, R^2 = alkyl) is totally unreactive: unpublished results by Dr. M. Isaka at Tokyo Institute.



gioselectivity with the electron population obtained by natural orbital analysis may be of some use in predicting the regioselectivity of carbometalation reactions. In the light of the data presented above, the carbometalation reaction may be viewed to involve both an electrophilic attack of the metal and a nucleophilic attack of the alkyl group taking place simultaneously. It may thus be qualitatively stated that polarization of the acetylene group directed by mesomeric electron donation from oxygen or nitrogen group and inductive influence of the sulfur or silicon group determines the regiochemistry of the carbometalation reaction. In addition, it is very likely that the same principle operates for the heteroatom-substituted olefin.[12–14] (4) Success of the present theoretical analysis suggests that simple monomeric metal models may be useful for the understanding and designing[6b] of carbometalation reactions. The deficiency of the metal environment may be cancelled by judicious setup of reference models for comparative evaluation.

Acknowledgment. We thank Drs. M. Isaka and B. H. Lipshutz for helpful discussions and M. Nakamura for some computational work. Financial support from the Ministry of Education, Science and Culture and the Asahi Glass Foundation is gratefully acknowledged. A generous allotment of computer time from the Institute for Molecular Science is deeply appreciated.

Supplementary Material Available: Listings of optimized geometries (*Z*-matrices) of π-complexes, TSs, and products and the EDA data for MeCu and MeLi additions to CH_3- and SiH_3-substituted acetylenes (34 pages). Ordering information is given on any current masthead page.

On the Mechanism of the Zirconium-Catalyzed Carbomagnesation Reaction. Efficient and Selective Catalytic Carbomagnesation with Higher Alkyls of Magnesium

Amir H. Hoveyda,* James P. Morken, Ahmad F. Houri, and Zhongmin Xu

Contribution from the Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167. *Received January 31, 1992*

Abstract: In zirconium-catalyzed carbomagnesation of alkenes, the dramatic enhancement in reactivity and selectivity induced by an internal Lewis base is such that higher order alkylmagnesium halides, normally significantly less reactive than EtMgCl, may be used efficiently. In reactions with *n*-BuMgCl, two secondary carbon stereogenic centers are formed with excellent levels of stereocontrol (**4**, >95%). Experimental data are presented which demonstrate that the observed levels of selectivity and reactivity are not simply the result of regioselective insertion of the alkene into the zirconacyclopropane. A general mechanism scheme for carbomagnesation of bicyclic substrates **1** is presented. Noteworthy mechanistic issues are the following: (1) Excess alkylmagnesium halide is required for high levels of regioselectivity and substrate reactivity. We suggest that the influence of the Grignard reagent stems from generation of the zirconate complex **12** (R = H, Me, or Et), which may be more susceptible to ligand exchange than its zirconacyclopropane precursor **7**. Subsequent formation of the zirconocene complex of the reacting alkene would then lead to the high levels of reactivity and selectivity observed in reactions where excess alkylmagnesium halide is present. (2) Deuterium labeling experiments demonstrate that the resident Lewis base strictly controls and reverses the mode of metallacyclopentane cleavage. The heteroatom binds and delivers magnesium to initiate a highly regioselective metallacyclopentane cleavage, effecting a Mg–Zr exchange with inversion of configuration.

Recent studies from these laboratories have demonstrated that Cp_2ZrCl_2 effectively catalyzes the addition of EtMgCl to unactivated alkenes with excellent levels of regio- and stereocontrol.[1] Internal Lewis bases were shown to enhance significantly the utility of the catalytic carbon–carbon bond-forming reaction. Herein, we report the results of our studies on the mechanism of the zirconium-catalyzed carbomagnesation of cyclic homoallylic alcohols and ethers. Alkenes **1** were selected as initial mechanistic probes for their rigid structure and olefin substitution pattern (to study regioselectivity; terminal alkenes invariably afford a primary C–Mg bond). Our work employs variations in reaction efficiency and selectivity (both regio and stereo) to shed light on several of the salient features of the reaction pathway. We find that, although metallacyclopentanes are likely intermediates,[2] simple insertion of the reacting alkene into the zirconacyclopropane does not account for the reported levels of selectivity and reactivity.[1]

In connection to our mechanistic studies, we have explored catalytic carbomagnesations with longer chain alkylmagnesium halides. We find that the enhancement in reactivity and selectivity induced by an internal Lewis base is such that these alkylmagnesium halides, normally significantly less reactive than EtMgCl,[3] can also be used in the metal-catalyzed process. Whereas reactions of *exo*-5-norbornen-2-ol with *n*-PrMgCl and *n*-BuMgCl yield ≤15% of the two exo alkyl isomers nonselectively, *endo*-5-norbornen-2-ol (5 equiv of *n*-alkylMgCl, 10 mol % Cp_2ZrCl_2, 25 °C) affords **2** or **4** in >99% regioselectivity and >85% yield (Tables I and II).[4] Noteworthy is the fact that with *n*-BuMgCl, as is shown in Table II, two secondary carbon stereogenic centers are formed with excellent stereocontrol (**4**, >95%).[5] When the hydroxyl group is protected as its MEM ether,[6] or with

---

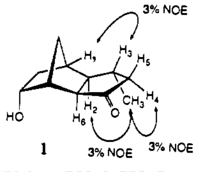
[1] (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079–5080. (b) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950–8952.

[2] Zirconacycles have been suggested as intermediates in carbomagnesation. See: (a) Reference 1. (b) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268. (c) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268–6270. (d) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797–6800.

[3] Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285* 43–51.

[4] All compounds reported herein gave ^1H NMR, ^{13}C NMR, IR and combustion analysis data/high-resolution mass spectra consistent with the structures given.

[5] The stereochemical outcome of the carbomagnesation with higher alkyls of magnesium was determined through NOE difference experiments on the tricyclic ketone I, derived from reaction of **1a** with $Cp_2Zr(n\text{-}Pr)_2$ and 200 mol % *n*-PrMgCl, followed by CO quench (see the Experimental Section for further details). Irradiation of H_1 leads to 3% enhancement of H_3, and H_6 shows a 2.0 Hz *W*-coupling with H_4 (and not H_5); irradiation of CH_3 results in 3% enhancement of H_4 and H_2, but none of H_5.



1

[6] Abbreviation: MEM = $CH_3OCH_2CH_2OCH_2$.

0002-7863/92/1514-6692$03.00/0