NMR Investigation of Asymmetric Conjugate Additions Using Chiral 4-Phenyloxazolidinone as a Mechanistic Probe

Bih-Show Lou, Guigen Li, Feng-Di Lung, and Victor J. Hruby*

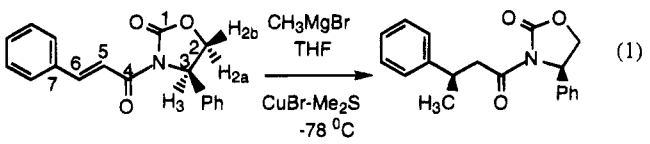
Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received March 16, 1995®

The asymmetric conjugate addition of organocopper(I) reagents to α,β-unsaturated *N*-acyl-4-phenyl-2-oxazolidinones has been studied by ^{1}H- and ^{13}C-NMR spectroscopy using the Evans-type 4-phenyloxazolidinone auxiliary as a mechanistic probe. Three chiral intermediates were observed directly. The two metal methyl groups in the olefin–copper(I) complex **2**, which is crucial for asymmetric induction, were assigned by both chemical shift and kinetic analysis. The dihedral angle of the α- and β-protons of the metallo enolate **3** was measured as 150° which provided valuable information for examining the stereochemical effects of the β position on the chirality of the α center. Enolates **3** and **4** are reversibly temperature dependent. Enolate **3** is the major component at 253 K, while enolate **4** becomes the major component at 293 K. Therefore, temperatures lower than ~253 K are required for high stereoselectivity in the electrophilic bromination of the resulting enolate to build an α-chiral center. The free energy of activation ($\Delta G^{\ddagger}$) and rate constant (k_c) of the equilibrium were measured as 15.0 kcal/mol and 1.4×10^2 s^{-1}, respectively.

Introduction

Asymmetric 1,4-additions of organocopper(I) reagents to α, β-unsaturated N-acyl-4-phenyl-2-oxazolidinones and related reactions have been used for the synthesis of optically pure β-branched carboxylic acids and unusual amino acids.[1,2] The β-branched amino acids have provided new insights into the molecular design of biologically active peptides with improved potency and receptor selectivity and in the study of molecular recognition between peptide ligands and receptors and receptor subtypes.[3] The detailed understanding of these asymmetric syntheses is important for improving reaction conditions so as to obtain high stereoselectivities and yields.



(1)

Studies of the mechanism of conjugate additions with organocuprates have been made, but no definitive mechanism has been generally accepted.[4] Recent NMR spectroscopic investigations of the mechanism for the 1,4-addition of lithium organocuprates to enones and enolates have led to the suggestion that a π-complex of the cuprate at the carbon-carbon double bond with a lithium–carbonyl interaction is formed.[5] Organocopper(I) reagents, very reactive species often used for organic synthesis,[6] have not been studied extensively. They can be prepared from Grignard reagents or lithium reagents with equimolecular amounts of copper(I) bromide in ether, THF, and DMS.[7] They generally provide high regioselectivity and good yields.[8] Recently, Castellino reported the NMR study of an Et_2AlCl complex with *N*-acyloxazolidinone by a "titration" technique.[9] However, the mechanism of asymmetric Michael-type additions of copper(I) reagents to oxazolidinones has not been examined, and much more information needs to be obtained about this important asymmetric reaction. Knowledge about the mechanism and the structure of

* Author to whom reprint requests should be addressed.

® Abstract published in *Advance ACS Abstracts,* July 15, 1995.

(1) (a) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766. (b) Li, G.; Lung, F.-D.; Lou, B.-S.; Hruby, V. J. *Abstracts of Papers*; 207th ACS National Meeting, San Diego, March 13–17, 1994; Part II, ORG 441.

(2) (a) Lander, P. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 8126. (b) For a review on organocopper chemistry see: Lipshutz, B. H.; Saengupta, S. *Org. React. (New York)* **1992**, *41*, 135. (c) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030. (d) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123–26. (e) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397. (f) Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron: Asymmetry* **1993**, *4*, 2315. (g) Li, G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2561. (h) Li, G.; Russell, K. C.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2565. (i) Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 5393. (j) Li, G.; Boteju, L. W.; D. Patel; Hruby, V. J. *Peptides: Chemistry and Biology* **1994**, Hodges, R. S., Smith, J. A., Eds.; ESCOM Publisher: Leiden, 1994; pp 181–183. (k) Lung, F.-D.; Li, G.; Lou, B.-S.; Hruby, V. J. *Synth. Commun.* **1995**, *25*, 57.

(3) (a) Hruby, V. J. *Biopolymers* **1993**, *33*, 1073. (b) Hruby, V. J. *Prog. Brain Res.* **1992**, *92*, 215. (c) Kazmierski, W. M.; Yamamura, H. I.; Hruby, V. J. *J. Am. Chem. Soc.* **1991**, *113*, 2275. (d) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. M. *Biochem. J.* **1990**, *268*, 249. (e) Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptide and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983, Vol. VII, p 267. (f) Hruby, V. J. *Life Sci.* **1982**, *31*, 189. (g) Toth, G.; Russell, K. C.; Landis, G.; Kramer, T. H.; Fang, L.; Knapp, R.; Davis, P.; Burks, T. F.; Yamamura, H. I.; Hruby, V. J. *J. Med. Chem.* **1992**, *35*, 2383. (h) Huang, Z.; He, Y.-B.; Raynor, K.; Tallent, M.; Reisine, T.; Goodman, M. *J. Am. Chem. Soc.* **1992**, *114*, 9390. (i) Hruby, V. J.; Toth, G.; Gehrig, C. A.; Kao, L.-F.; Knapp, R.; Lui, G. K.; Yamamura, H. I.; Kramer, T. H.; Davis, P.; Burks, T. F. *J. Med. Chem.* **1991**, *34*, 1823.

(4) (a) House, H. O. *Acc. Chem Res.* **1976**, *9*, 59. (b) Smith R. A. J.; Hannah, *Tetrahedron* **1979**, *35*, 1183. (c) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Org. Chem.* **1985**, *282*, 133. (d) Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, *60*(1), 57. (e) Bertz, S. H.; Smith, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 8276. (f) Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523.

(5) (a) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116*, 381. (b) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509. (c) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197. (d) Sharma, S.; Oehlschlager A. C. *Tetrahedron*, **1991**, *47*, 1177. (e) Vellekoop, A. S. and Smith R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902.

(6) Review: Normant, J. F. *Synthesis* **1972**, 63 and references cited therein.

(7) (a) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425–434. (b) Carruthers, W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, K. A., Abel, E. W., Eds.; Pergamon: London, 1982, Vol. 7, Chapter 49, p 661.

(8) (a) Normant, J. F.; Cahiez, G.; Bourgain, M.; Chuit, C.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 1656. (b) Koten, G. V.; Noletes, J. G. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, K. A., Abel, E. W., Eds.; Pergamon: London, 1982; Vol. 2, Chapter 14, p 709.

(9) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

0022-3263/95/1960-5509$09.00/0

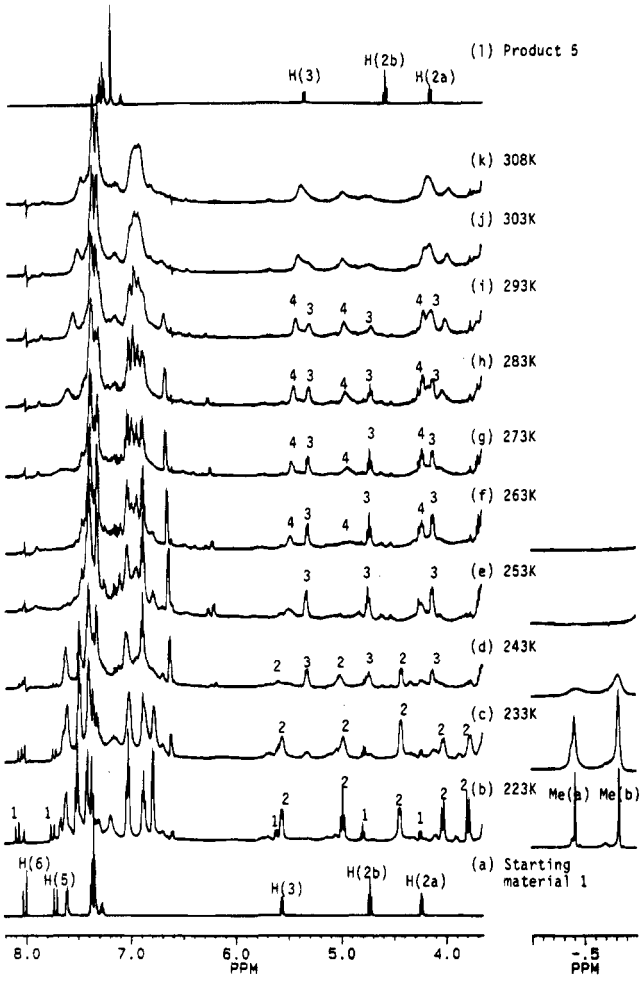
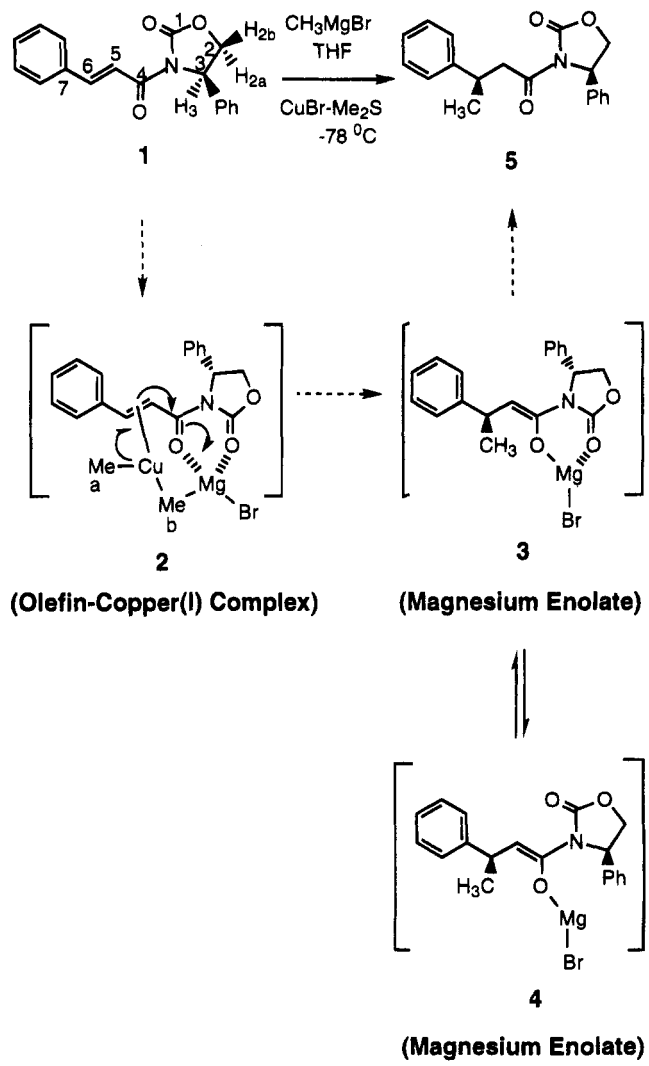


Figure 1. ^{1}H NMR (500 MHz) spectra (δ −1 to 8.5 vs solvent peak of THF at δ 3.58) of (4*R*)-4-phenyl-3-[phenyl-2(*E*)-propenoyl]-2-oxazolidinone (starting material **1**) (a), temperature dynamic ^{1}H NMR spectra for its solution with $Me_2CuMgBr$ at (b) T = 223 K, (c) 233 K, (d) 243 K, (e) 253 K, (f) 263 K, (g) 273 K, (h) 283 K, (i) 293 K, (j) 303 K, (k) 308 K, and (l) the final product **5**. Three intermediates are observed. Labelled as H(1)−H(6) in spectra a and l are for assignments of the ^{1}H chemical shifts. Labelled as 1−4 in spectra b−k are for the resonances of the starting material **1** and the key intermediates **2**−**4** (Scheme 1). The spectrum obtained at T = 223 K is assigned to the olefin−copper(I) complex **2**. Enolate **3** is formed when the Michael addition is completed at T = 253 K, and the other enolate, **4**, becomes the major component at T = 293 K. Some important chemical shifts and coupling constants of the ^{1}H NMR data, which correspond to the intermediates **2**−**4**, the starting material **1**, and the final product **5** are summarized in Table 1. See text for details.

intermediates in this reaction will be helpful for the design of highly stereoselective syntheses. Since the methods used in these advanced syntheses are difficult, and the short-lived intermediates along the reaction path make structural determination very challenging, it is important to establish good approximate descriptions of the structures for the transition states. This was the objective of this study.

NMR spectroscopy is the single most useful tool for characterization of compounds and for studying their behavior in solution. In addition, dynamic NMR spectroscopy provides a powerful method for the elucidation of mechanism and of conformational interchange. In the present study, the organocopper(I) reagent $Me_2CuMgBr$[10] was prepared by the reaction of Grignard reagent with the dimethyl sulfide complex of cuprous bromide in a

Scheme 1



mixture of DMS and THF. We investigated the structures of intermediates from conjugate addition of this organocopper(I) reagent to (4*R*)-4-phenyl-3-[phenyl-2(*E*)-propenoyl]-2-oxazolidinone (and others) by ^{1}H and ^{13}C NMR spectroscopy in the temperature range from 213 to 318 K. Using this chiral 4-phenyloxazolidinone as a mechanism probe, three intermediates were observed which provide critical insights into the mechanism of the reaction.

Results

Assignment of ^{1}H NMR. Figure 1 shows the temperature dynamic ^{1}H NMR spectra for (4*R*)-4-phenyl-3-[phenyl-2(*E*)-propenoyl]-2-oxazolidinone (starting material **1** in Scheme 1), its solution with $Me_2CuMgBr$ (Figure 1b−k), and the final product **5** (Scheme 1). Some important chemical shifts and coupling constants in the ^{1}H NMR data, which correspond to intermediates **2**−**4** (Scheme 1), are summarized in Table 1. In these spectra, most of the signals at high field ($<\delta$ 3.5) could not be evaluated due to overlap with the signals from the

(10) Organocopper reagents are shown as monomers in this paper for simplicity. However, this does not rule out the possibility that higher-order complexes are present in solution. (a) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197. (b) Lipshutz, B. H.; Kozlowski J. A.; Breneman, C. M. *Tetrahedron Lett.* **1985**, *26*, 5911.

Table 1. ^{1}H NMR Chemical Shifts (δ) and Coupling Constants (Hz) for (1) Starting Material, (5) Final Product, (2) Copper(I) Complex, and (3 and 4) Magnesium Enolates[a]

position	1	2	3	4	5
H(2a)	4.24 (3.8, 8.7)	4.44 (3.3, 9.0)	4.13 (2.5, 8.2)	4.22 (8.2, 5.5)	4.15 (3.7, 8.9)
H(2b)	4.73 (8.5)	4.99 (3.3, 9.0)	4.74 (6.6, 9.0)	4.96	4.58 (8.8)
H(3)	5.61 (3.8, 8.7)	5.56 (3.3, 9.0)	5.32 (3.0, 6.0)	5.47	5.35 (3.9, 9.2)
H(5)	7.72 (15.8)	3.79 (11.4)	6.64 (6.5)		3.29
H(6)	8.01 (15.8)	4.03 (11.4)			3.15 (9.7)

[a] See eq 1 for ^{1}H positions and ref 4f to compare the assignments.

solvent (THF, ethyl ether). Fortunately, the chemical shifts of the three protons on the chiral 4-phenyloxazolidinone, H(2a), H(2b), and H(3), are found between δ 3.50 and 6.00, which is an otherwise clean area, and provided sufficient information to show the intermediates during the temperature changes.

By comparison with starting material **1** in Figure 1a and the final product **5** in Figure 1l, the ^{1}H NMR spectrum at 223 K in Figure 1b demonstrates that no Michael addition has occurred at this temperature. Only a small amount of **1** is left, and one major component, **2** (Scheme 1), has been formed. Four significant changes were observed for the process **1** → **2** (Scheme 1):

(i) Sharp signals at δ −0.83 and −0.41 in Figure 1b were assigned to the two cuprate methyl groups in **2**, while no signal was found in this region for $Me_2CuMgBr$ itself under the same conditions.

(ii) A large chemical shift for the olefinic hydrogens was observed. H(5) and H(6) began in **1** at δ 7.72 and 8.01 (Figure 1a) and were shifted to δ 3.79 and 4.03 (Figure 1b) for **2**, respectively. These hydrogens appeared as doublets, and their coupling constants, $^3J_{H(5)H(6)}$, decreased from 15.8 Hz for **1** to 11.4 Hz for **2**.

(iii) The signals assigned to H(2a) and H(2b) were shifted downfield from δ 4.24 and 4.73 (Figure 1a), respectively, to δ 4.44 and 4.99 (Figure 1b), but H(3) was shifted slightly upfield from δ 5.56 to 5.61.

(iv) The phenyl protons in the oxazolidinone ring, which overlapped with the phenyl protons in C(6) (Figure 1a), were shifted upfield, and therefore, the two groups of aromatic protons were separated (Figure 1b).

As the temperature was increased, the three 4-phenyloxazolidinone proton signals were changed dramatically. The signals at δ 4.44, 4.99, and 5.56 for **2** (Scheme 1) began to broaden at 233 K (Figure 1c), and the intensities began to decrease at 243 K (Figure 1d) and disappeared at 253 K (Figure 1e), while those at δ 4.13, 4.74, and 5.32 for enolate **3** (Scheme 1) started to grow. This was accompanied by the disappearance of the signals from the cuprate methyls at δ −0.83 and −0.41 and H(5) and H(6) at δ 3.79 and 4.03 and the appearance of a new doublet at δ 6.64 with a coupling constant of 6.5 Hz for **3** H(5). These changes indicated that the Michael addition was complete at 253 K and that the enolate **3** from conjugate addition of the organocopper(I) reagent had been formed.

As the temperature was further increased (Figure 1f–h), a new set of 4-phenyloxazolidinone signals at δ 4.22, 4.96, and 5.47 for the nonchelated enolate **4** (Scheme 1) started to grow. The relative signal intensities of **3** (δ 4.13, 4.74, and 5.32) and of **4** (δ 4.22, 4.96, and 5.47) depended on the change in temperature. Intermediates **3** and **4** are interconvertable depending on the temperature; **3** is the major component at 253 K (Figure 1e), while **4** becomes dominant at 283 K (Figure 1h). When the temperature reached 293 K, the two sets of signals began to broaden significantly as coalescence was approached. The signals for H(3) at δ 5.32 and 5.47 and H(2a) at δ 4.13 and 4.22 in **3** and **4** coalesce with each other at 308 K (Figure 1k). When the temperature was decreased back to 253 K, **3** predominated again. This dynamic process was also observed in the aromatic region (δ 6.80–7.20). The exchange between **3** and **4** also was observed in the aromatic protons.

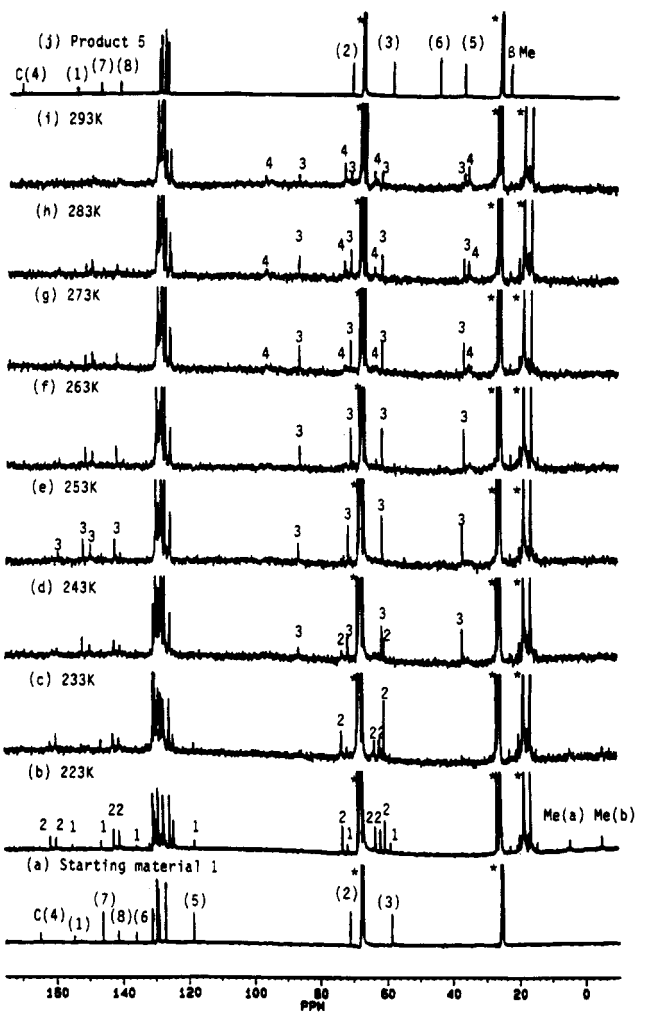


Figure 2. ^{1}H-decoupled ^{13}C NMR (125.67 MHz) spectra (δ -10 to 175) of (4*R*)-4-phenyl-3-[phenyl-2(*E*)-propenoyl]-2-oxazolidinone (starting material **1**) (a), temperature dynamic ^{13}C NMR spectra for its solution with $Me_2CuMgBr$ at (b) T = 223 K, (c) 233 K, (d) 243 K, (e) 253 K, (f) 263 K, (g) 273 K, (h) 283 K, (i) 293 K, and (j) the final product **5**. Intermediates **2**–**4** are also observed in the ^{13}C NMR spectra. Labelled as C(1)–(8) in spectra (a) and (j) are for assignments of the ^{13}C chemical shifts. Labelled as 1–4 in spectra (b)–(i) are for the resonances of the starting material **1** and the key intermediates **2**–**4** (Scheme 1). Labelled as * are the solvent peaks. The important ^{13}C NMR chemical shifts, which correspond to the intermediates **2**–**4**, the starting material **1**, and the final product **5**, are summarized in Table 2. See text for details.

Assignment of ^{13}C NMR. The ^{13}C NMR spectra are shown in Figure 2, and the important chemical shifts are

summarized in Table 2. The ^{13}C NMR data are consistent with the ^{1}H NMR and fully support the observation that at least three intermediates were formed during the Michael addition.

When the ^{1}H and ^{13}C NMR spectra in the temperature range of 233−243 K are compared, different time scales seem to appear. From the disappearance of the cuprate methyl resonances, the ^{1}H NMR spectral time scale appears to be slower than ^{13}C. This "apparent difference" is due to signal-to-noise and line-width differences for the different spectra. They in fact use the same time scale. The spectra measurements were taken in the sequence ^{1}H, ^{13}C, ^{1}H to verify the stability of the time scale. The first and second ^{1}H spectra match very well. The ^{13}C NMR spectrum for starting material **1** is shown in Figure 2a and could be characterized by the following signals:

carbon type	chemical shift (δ)
carbonyl C(1)	154.9
carbonyl C(4)	164.8
olefinic carbon C(5)	118.5
olefinic carbon C(6)	135.9
oxazolidinone carbon C(2)	70.9
oxazolidinone carbon C(3)	58.6

By comparison with **1** in Figure 2a, the ^{13}C NMR spectrum at 223 K (Figure 2b) clearly demonstrated the existence of intermediate **2**. The corresponding signals for **2** in Figure 2b were as follows:

carbon type	chemical shift (ppm)
carbonyl C(1)	159.7
carbonyl C(4)	161.4
olefinic carbon C(5)	61.6
olefinic carbon C(6)	63.0
oxazolidinone carbon C(2)	72.7
oxazolidinone carbon C(3)	60.1

Note from the previous two data sets that the olefinic carbons C(5) and C(6) shifted upfield remarkably [$\Delta\delta$ = 56.9 ppm for C(5) and $\Delta\delta$ = 72.9 ppm for C(6)], while C(1) and C(4) remained more or less the same. In addition, the signals at δ 2.2 and −3.0 from the cuprate methyl groups of the complex **2** began to broaden at 233 K (Figure 2c) and were hardly observable at 243 K (Figure 2d) when the Michael addition had started.

When the temperature was increased (Figure 2c−e), the intensities of the ^{13}C signals from the enolate **3** were enhanced, but those from **2** were decreased. At 253 K (Figure 2e), the signals for **3** were characterized by the following signals:

carbon type	chemical shift (ppm)
carbonyl C(1)	151.7
carbonyl C(4)	159.0
olefinic carbon C(5)	85.8
olefinic carbon C(6)	36.5
oxazolidinone carbon C(2)	70.9
oxazolidinone carbon C(3)	60.9

The large chemical shift of C(6) ($\Delta\delta$ = 26.5 ppm) for **3**, by comparison with **2**, was caused by the addition of a methyl group to C(6) to change the hybridization from sp^2 to sp^3, and thus the chemical shift was shifted upfield from δ 63.0 to 36.5. The chemical shift of C(5) was shifted downfield from δ 61.6 to 85.8, implying that C(5) has partial double bond character. When the temperature was further increased, four new peaks were observed, indicating the appearance of **4** (Figure 2g−i):

Table 2. ^{13}C Chemical Shifts (ppm) for (1) Starting Material, (5) Final Product, (2) Copper(I) Complex, and (3 and 4) Magnesium Enolates[a]

position	1	2	3	4	5
C1	154.9	159.7	149.5	154.9	154.5
C2	70.9	72.7	70.9	72.9	70.8
C3	58.6	60.1	60.9	63.4	58.3
C4	164.8	161.4	151.7	N/A	171.6
C5	118.5	61.6	85.8	96.0	36.6
C6	135.9	63.0	36.5	35.1	44.1
C7	145.8	142.2	142.1	N/A	147.2
C8	141.3	140.6	140.0	N/A	141.3

[a] See eq 1 for ^{13}C position and ref 4f, 5a, and 9 to compare the assignments.

carbon type	chemical shift (ppm)
olefinic carbon C(5)	96.0
olefinic carbon C(6)	35.1
oxazolidinone carbon C(2)	72.9
oxazolidinone carbon C(3)	63.4

These observations are in good agreement with the ^{1}H NMR spectra in that **3** is the major component at lower temperatures (~253 K) and **4** is the dominant intermediate at higher temperatures (~293 K).

Discussion

Olefin−Copper(I) Complex 2. On the basis of the NMR spectra, it is clear that $Me_2CuMgBr$ does not add its methyl group to (4*R*)-4-phenyl-3-[phenyl-2(*E*)-propenoyl]-2-oxazolidinone (**1**, Scheme 1) in THF-d_8 at 213 K. Instead, it forms a rather stable π-complex, which is characterized by a bond between the copper(I) moiety and the π-system of the double bond and an interaction of the magnesium with the carbonyl oxygen atom. The chemical shifts at δ 61.5 [C(5)] and 63.0 [C(6)] in the ^{13}C NMR spectrum are within the established δ 50−70 range for complexed olefin carbons.[4c] The large upfield shifts of C(5) ($\Delta\delta$ = 56.9) and C(6) ($\Delta\delta$ = 72.9) of the π-complex (**2**, Scheme 1), as compared with that of **1**, are consistent with the Dewar−Chatt−Duncanson model for olefin−transition metal π-complexes.[11] The back-donation of electrons by filled copper d-orbitals to an olefin π^*-orbital results in strong shielding of the olefinic carbons. Much larger perturbations are observed for the olefinic C(5) and C(6) rather than for the carbonyl carbons C(1) and C(4) or the aromatic carbons, suggesting that the cuprate ion interacts with the carbon−carbon double bond through coordination of the copper to the olefin π-bond of **2** (see Scheme 1).

For the ^{1}H NMR spectra, the chemical shifts of H(5) and H(6) for **1** in Figure 1a (Scheme 1) are observed at fairly low field (δ 7.72 and 8.01, respectively), whereas olefinic protons are normally observed in the range δ 4.5−7.5.[12] The unusual downfield chemical shifts for H(5) and H(6) are due to deshielding from the carbonyl groups at C(1) and C(4). However, after the two carbonyl groups at C(1) and C(4) rotate from *trans* to *cis* in **2** (Scheme 1), the deshielding effect for H(5) from the 4-phenyl carbonyl group C(1) disappears. In addition, the electron-with-

(11) Chatt, J.; Duncanson, J. A. *J. Chem. Soc.* **1953**, 2939.
(12) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometeric Identification of Organic Compounds*, 5th ed.; John Wiley & Sons: New York, **1991**; p 176.

drawing effect of the copper shifted the H(5) further upfield to δ 4.03 ppm (Figure 1b). A similar change for the α-H chemical shifts has been observed in $AlMe_2Cl$ and $TiCl_4$ with chiral imide derivatives.[13] The upfield shift of H(6) in Figure 1b was mainly induced by copper coordination which interfered with the deshielding from the carbonyl group C(4).

The structure of **2** in Scheme 1 also is well supported by the NMR signals for the cuprate methyl groups. For olefin−copper(I) complex **2**, both of the ^1H and the ^{13}C NMR spectra (Figures 1b and 2b) show two nonequivalent methyl signals. This evidence reflects that **2** has two methyl groups in different environments. The proton signal at the higher field of δ −0.8 is assigned to Me(b) (Scheme 1, **2**) because Me(b) binds with the two electropositive metals Mg and Cu, causing a large electronic inductive effect and a shift to higher field compared to Me(a), which binds only with Cu. In addition, the strong falloff of the Me(a) signal at higher temperatures implies that it is Me(a) which adds to C(6). All this fits perfectly with the structure **2** proposed in Scheme 1.

As compared to organolithium Grignard reagents which preferentially add to the carbonyl function by 1,2-addition, organocuprates preferentially add to α,β-unsaturated carbonyl compounds almost exclusively by 1,4-addition.[14] The structure of the olefin−copper(I) complex in Scheme 1 suggests that the formation of intermediate **2** favors 1,4-addition over 1,2-addition. The NMR data have confirmed that the Michael-type asymmetric 1,4-conjugate addition reaction of organocopper(I) reagents to 3(2*E*)-(1-oxoprop-2-eneyl-3-phenyl)-2-oxazolidinone goes though an intermediate olefin−copper(I) complex.

Magnesium Enolates 3 and 4. Above 253 K, the enolate resulting from conjugate addition of the organocupper(I) reagent is formed. Both the ^1H and the ^{13}C NMR spectra are best interpreted in terms of two enolate conformers (**3** and **4** in Scheme 1), where the relative population of these two enolates displays significant temperature dependence. From the NMR studies, it is difficult to determine with certainty the structures of the two enolates. However, on the basis of many earlier studies of 1,4-addition of Grignard reagents to conjugated carbonyl systems,[14c] and a strong tendency for magnesium to form three- or four-center electron pair bonds through bridging,[15] the Michael-type addition should produce a magnesium enolate that contains a Mg−O bond and a Mg···O chelation (see Scheme 1, **3**). At higher temperatures, the Mg···O bond is dissociated and provides the thermodynamically stable intermediate **4** (Scheme 1). Alternatively, **4** could be an *E*-enolate. However, there are at least two reasons which make the *E*-enolate an unlikely candidate: (a) it requires much higher energy to rotate the C=C from **3** to *E*-enolate than from **3** to the nonchelated *Z*-enolate **4**. (b) If an *E*-enolate was the case, we should see some percentage of the *E*-enolate when the temperature is decreased. However, we saw no evidence of that. The interchange between **3** and **4** is slow and can be monitored by ^1H NMR spectroscopy. Enolate **3** has high facial selectivity and predominates at 253 K, whereas enolate **4** has low facial selectivity and becomes dominant at 283 K. *Therefore, temperatures lower than ~253 K are required for high stereoselectivity in the electrophilic bromination of the resulting enolate to build an α-chiral center.*[2]

Coupling Constants. The coupling constant $^3J_{H(5)H(6)}$ is 15.8 Hz in **1**, which is typical for a *trans* three-bond $^1H-^1H$ in a substituted olefin. When **2** was formed, the $^3J_{H(5)H(6)}$ decreased to 11.4 Hz which is close to a typical *cis* three-bond $^1H-^1H$ coupling constant in C=C (12.3 Hz).[16] Nevertheless, considering the sterically crowded environment, the smaller **2** coupling constant may be explained by increased carbon π-electron density due to metal−olefin coordination. $^1H-^1H$ couplings through three bonds have been extensively studied and are of tremendous importance for the assignment of structure. This analysis, based on valence bond theoretical study by Karplus,[17] predicts the vicinal $^3J_{HH}$ coupling constants through a C−C bond should be as a function of dihedral angle:[16] $J = A\cos^2\theta - C$, where $A = 8.5$ Hz when the dihedral angle θ is 0−90° or $A = 9.5$ Hz when θ is 90−180° and $C = -0.3$ Hz. Because other factors such as the electronegativity of substitutents, hybridization at carbon, bond angles, and length also affect vincinal couplings, the constants in the Karplus relation must be adjusted using model compounds. Using this Karplus relationship, the angle between H(5) and H(6) for **3** can be established as either 150 or 25°. Considering the allylic steric effect, the 150° angle is the more likely, a conclusion which is further supported by the asymmetric synthesis results.[2k,18] Knowledge of this angle is useful in the study of stereochemical effects of the β position on the chirality of the α center.[2f-k]

Dynamic Processes. Without the presence of an organometal (e.g., $Me_2CuMgBr$), neither **1** nor **2** shows rotation of the C−N bond on the ^1H NMR time scale at room temperature. This is simply due to the double-bond character of the C−N (see Figure 1a and 1).[18a] The addition of an organometallic to the solution causes the ^1H NMR spectrum in Figure 1i to show two sets of oxazolidinone signals [H(2a), H(2b), and H(3)]. This is consistent with the presence of the two intermediates **3** and **4** in solution. As the temperature increases to 308 K, these two signals are merged. The free energy of activation ($\Delta G^{\ddagger}$) and rate constant (k_c) of the exchange processes at 308 K were calculated according to eqs 2 and 3,[19] where $\Delta\nu$ is the difference of chemical shifts of two

$$k_c = \pi/2\Delta\nu\ (s^{-1}) \quad (2)$$

$$\Delta G^{\ddagger} = 4.57T_c[9.97 + \log(T_c/\Delta\nu)]\ (\text{cal/mol}) \quad (3)$$

sites in the absence of exchange (here $\Delta\nu$ is approximated

(13) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trere, A. *J. Org. Chem.* **1993**, *58*, 5615.

(14) (a) House, H. O.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949. (b) Normant, J. F. *Lab. Chim. Org.* **1971**, *11*, 44. (c) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice Hall: New York, 1954. (d) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, C79.

(15) (a) O'Neill, M. E.; Wade, K. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, K. A., Abel, E. W., Eds.; Pergamom: London, 1982; Vol. 1, Chapter 1, p 1. (b) Pinkus, G. A.; Wu, A.-B. *J. Org. Chem.* **1975**, *40*, 2816. (c) Elschenbroich, C.; Salzer, A. *Organometallics*; 1st ed.; VCH Verlagsgesellschaft: Weinheim, New York, 1989; p 38.

(16) Yoder, C. H.; Schaeffer, C. D. *Introduction to Multinuclear NMR*; The Benjamin/Cummings Publishing Company, Inc.: California, 1987; p 154.

(17) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870. Garblish, E. W. *J. Am. Chem. Soc.* **1964**, *86*, 5561.

(18) (a) Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron Lett.* **1994**, *35*, 2301. (b) Li, G.; Patel, D.; Hruby, V. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 13057.

(19) (a) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press, Inc.: London, New York, 1982. (b) Jiao, D.; Russell, K.; Hruby, V. J. *Tetrahedron* **1993**, *49*, 3511.

by the difference of chemical shift at 273 K). $\Delta G^{\ddagger}$ for the rotation of C(4)−N in the exchange between **3** and **4** is ~15.0 kcal/mol, and k_c is 1.4×10^2 s^{-1}.

Conclusions

The Evans-type 4-phenyloxazolidinones are useful chiral auxiliaries to probe the mechanism of Michael-type addition reactions and probably can be extended for studies of other important asymmetric reactions, e.g., the aldol condensation reaction. The mechanism for the reaction studied here is proposed in Scheme 1. Three intermediates, the copper(I) π-complex **2** and the magnesium enolates **3** and **4**, are observed directly by both ^1H and ^{13}C NMR spectroscopy. NMR data confirmed that the Michael-type conjugate addition goes through a chelated conformation state and that only two methyl groups are asymmetrically attached to the copper(I) π-complex (**2**).

Experimental Section

Materials and Methods. All the samples were prepared in vessels sealed with an air-tight rubber septum, and the reactions were performed under the protection of positive N_2 pressure. A representative procedure is described as follows. A mixture containing copper(I) bromide−dimethyl sulfide complex (0.23 g, 1.1 mmol, 1.1 equiv), dimethyl sulfide (1.3 mL), and THF-d_8 (2.2 mL) was cooled to −78 °C to form an opaque mixture. Then a 3 M solution of methylmagnesium bromide in ethyl ether (0.49 mL, 1.4 mmol, 1.4 equiv) was added to yield a yellow slurry that was stirred at −78 °C for 10 min, at 0 °C for another 10 min, and then recooled to −78 °C. This yellow mixture was transferred via a Teflon cannula to a precooled (−78 °C) slurry of (4*R*)-4-phenyl-3-[phenyl-2(*E*)-propenoyl]-2-oxazolidinone (0.29 g, 1.0 mmol) in THF-d_8 (4.6 mL, an additional 1.0 mL was used for washing). The reaction mixture was stirred at −78 °C for 30 min. About 0.5 mL of the resulting solution was transferred by a precooled syringe to an NMR tube that was filled with nitrogen, sealed with a rubber septum, and immersed in a cooling bath at −78 °C. The whole reaction process was monitored inside the NMR probe in the temperature range from 213 to 318 K.

The rest of the mixture was brought to −10 °C and stirred for 45 min and then at 0 °C for additional 1 h to complete the Michael addition (the color of the reaction changed from brown/yellow to green during this period). The reaction was quenched by adding 1 N HCl (15 mL) slowly at 0 °C, and the two layers were separated. The inorganic phase was extracted three times with ethyl acetate. The combined organic layer was washed with distilled water and saturated solutions of NH_4Cl and $NaHCO_3$, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was evaluated by ^1H-NMR prior to and after silica gel chromatography with ethyl acetate and hexane (3:7).

NMR Spectroscopy. Variable temperature ^1H and ^{13}C NMR spectra were measured on a Brucker AM 500 MHz (125.76 MHz for ^{13}C) spectrometer. The temperature was controlled by a Brucker BVT-1000 temperature control unit in 1° steps. Regulation above room temperature required dry compressed air (or N_2). The air flow rate can be adjusted and held constant by means of a flow rate valve. Lower temperatures were achieved with a flow of cold nitrogen gas obtained by heating liquid nitrogen inside a Dewar. The temperature range for the 5 mm probe arm used in this experiment was −150 to +180 °C, and the temperature control at the sample was ±0.5 °C. Each measurement was performed after 20 min for temperature equilibrium, followed by Z and Z^2 shim refinement, and then 160 scans for ^1H and 1000 scans for ^{13}C spectrum were obtained. In these experiments, the first measurement was made at the lowest temperature, and then the temperature was increased in 10 K increments. Proton NMR spectra were taken before and after ^{13}C NMR spectra to make sure that the system did not change while the ^{13}C NMR spectra were acquired. All chemical shifts were referenced to the residual THF solvent peak, which was assumed to be δ 3.58 for ^1H NMR and δ 67.4 for ^{13}C NMR at all temperatures.

Acknowledgment. This research was supported in part by grants from the U.S. Public Health Service AM-17420 and the NIDA grant DA 06284. The authors thank Dr. R. B. Bates and Dr. R. Polt for their discussions and careful reading of the manuscript.

JO950511H