Direct Irradiation of BNA in Cyclohexane. Solutions of BNA (7.5×10^{-4} M) in cyclohexane were purged with N_2 or O_2 for 20 min and then irradiated at 350 nm (Rayonet) for 12 min. A 50-μL portion of ethanol was added to each sample, and the solutions were analyzed by HPLC. Both samples gave identical products: carbamate (from BNI) (54%), and amide **1** (44%). No additional products could be detected in the oxygen-saturated sample.

Triplet-Sensitized (ITX) Irradiation of BNA in Cyclohexane. A N_2-purged solution of BNA (4.4×10^{-4} M) in cyclohexane containing ITX (1.6×10^{-3} M) was prepared in a Pyrex cell equipped with a magnetic stir bar and a Teflon stopcock. The sample was irradiated (>385 nm) for 105 min, and then 50 μL of ethanol was added. HPLC analysis showed amide **1** (63%), β-naphthamide **2** (25%), and carbamate (from BNI) (5%).

Direct Irradiation of BNA in Solutions Containing Cyclohexene. A solution of BNA (2.3×10^{-3} M) in cyclohexane containing cyclohexene (1 M) was purged with N_2 and irradiated at 350 nm (Rayonet) for 12 min. After addition of ethanol, the products were analyzed by HPLC: carbamate (from BNI) (52%) and aziridine **3** (42%) were detected. Authentic **3** was prepared from β-naphthoyl chloride and cyclohexenimine in 21% yield after recrystallization from cyclohexane/benzene (6/1 (v/v)): white crystals, mp 88-89 °C; IR ($CHCl_3$) 1672, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2-2.3 (m, 8 H), 2.92 (d, 2 H), 7.5-8.5 (m, 8 H); mass spectrum (high resolution), calcd for $C_{17}H_{17}NO$, 251.1310; found, 251.1314.

Direct Irradiation of BNA with *cis*- and *trans*-4-Methyl-2-pentene. A stirred, N_2-saturated solution of BNA (50 mg) in 25 mL of cyclohexane containing 0.67 M of the *trans*-pentene was irradiated at 350 nm (Rayonet) for 2 h. After addition of 0.5 mL of ethanol, the solvent and unreacted olefin were removed by evaporation, and the residue was analyzed by ^1H NMR spectroscopy. The products were ethyl carbamate (from BNI) (53%), *trans*-aziridine **5** (36%), and amide **1** (9%). Adduct **5** was isolated by chromatography on silica gel (Chromatotron), eluting with ether/petroleum ether (1/7 (v/v)) in 22% yield as a viscous oil: ^1H NMR ($CDCl_3$) δ 1.07 (m, 9 H), δ 1.66 (m, 1 H), δ 2.03 (d of d, 1 H), δ 2.80 (m, 1 H), δ 7.5-8.5 (m, 7 H); IR ($CHCl_3$) 1661 cm^{-1}; mass spectrum (high resolution), calcd for $C_{17}H_{19}NO$, 253.14655; found, 253.14689.

The experiment was repeated with *cis*-4-methyl-2-pentene. The ^1H NMR spectrum in this case showed ethyl carbamate (54%), *cis*-aziridine **4** (43%), and amide **1** (2%). The *cis*-aziridine was isolated as above, and after recrystallization from ether gave 18 mg (28%): mp 89-90 °C; IR ($CHCl_3$) 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06, 1.23 (two d, 6 H), 1.53 (d, 3 H), 1.65 (m, 1 H), 2.49 (m, 2 H), 7.5-8.5 (m, 7 H). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.89; H, 7.59; N, 5.50.

Triplet-Sensitized (ITX) Irradiation of BNA with *cis*- and *trans*-4-Methyl-2-pentene. Nitrogen-purged, stirred cyclohexane solutions of BNA (5×10^{-3} to 3×10^{-4} M; see Table III) containing either the *trans*- or *cis*-pentene (0.66 M) and ITX (1.36×10^{-3} M) were irradiated for 4 h (>385 nm) in Pyrex cuvettes. The precipitated β-naphthamide that formed during the irradiation dissolved when 50 μL of ethanol was added to convert BNI to the carbamate. The solutions were analyzed by HPLC; the results are summarized in Table III and on Figure 4.

Direct Irradiation of BNA with Ethanol. A N_2-purged cyclohexane solution of BNA (2.35×10^{-3} M) containing ethanol (1 M) was irradiated at 350 nm (Rayonet) for 15 min. The products, analyzed by HPLC, were the ethyl carbamate (from BNI) (54%), hydroxamate **6** (42%), and amide **1** (3%). Hydroxamate **6** was isolated from a preparative-scale experiment (BNA, 100 mg in 35 mL of ethanol irradiated at 350 nm for 90 min) by chromatography on silica gel (Chromatotron). Recrystallization from cyclohexane/$CHCl_3$ yields 10 mg of white crystals (26% based on BNA consumed): mp 124-125 °C; IR ($CHCl_3$) 3405, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H), 4.3 (q, 2 H), 7.5-8.5 (m, 7 H). Anal. Calcd for $C_{12}H_{12}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.36; H, 6.13; N, 6.49.

Direct Irradiation of BNA in α-Methylstyrene. A solution of BNA (5.1×10^{-3} M) in cyclohexane containing the styrene (0.15 M) was purged with nitrogen and irradiated for 20 min at 350 nm. The products, determined by ^1H NMR spectroscopy were carbamate from BNI (54%) and the expected aziridine (40%). The experiment was repeated with (*E*)-deuterio-α-methylstyrene (0.15 M) to determine the stereochemistry of addition. The products were carbamate (55%) and the deuteriated aziridine (40%); only one isomer of the aziridine could be detected. ^1H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 2.56 (s, 1 H), 2.86 (s, 1 H), 7.2-8.25 (m, ArH). The NMR spectrum of the aziridine from the deuteriated styrene was identical except that the absorption in the aziridine at δ 2.86 was reduced to the level of residual hydrogen in the *E* position of the styrene. The aziridine could not be separated from the ethyl carbamate without decomposition. It was converted to *N*-(2-methoxy-2-phenylpropyl)-β-naphthamide for characterization: ^1H NMR ($CDCl_3$) δ 1.66 (s, 3 H), 3.10 (s, 3 H), 3.61 (d of d, 1 H), 3.91 (d of d, 1 H), 6.64 (bs, 1 H), 7.2-8.2 (m, 12 H); mass spectrum (high resolution), Calcd for $C_{21}H_{21}NO_2$, 319.15719; found, 319.15712.

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Do the Organocopper Conjugate Additions to α,β-Unsaturated Esters Proceed in a 1,4- or 1,2-Fashion?

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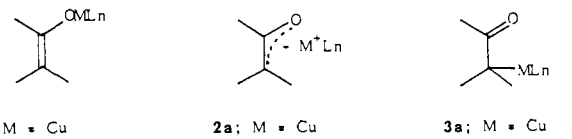
Abstract: The organocopper conjugate addition to methyl tiglate (**4**) and methyl angelate (**6**) followed by protonolysis at −78 °C produced the syn (**8**) and anti (**9**) adducts in the same isomer ratio (73:27). Further, the conjugate addition to **4** and **6** followed by treatment with acetone-d_6 at −78 °C gave the syn (**12**) and anti (**13**) adducts, again in the same isomer ratio (2:1). These results clearly indicate the intermediacy of the copper–oxygen-bonded enolate (**1a**) rather than α-cupriocarbonyl derivative (**3a**).

Conjugate addition reactions of organocopper reagents to α,β-unsaturated carbonyl compounds produce enolate anions, which are protonated or further reacted with electrophiles. This process is now a very important synthetic procedure in modern organic chemistry.[1] Mechanistically, important unanswered questions remain concerning the enolate structure.[2] Most of the literature

Chart I



1a; M = Cu **2a**; M = Cu **3a**; M = Cu

b; M = $SnPh_3$ **b**; M = $SnPh_3$

adopts the copper–oxygen-bonded enolate **1a** (see Chart I) without any convincing evidence. On the other hand, the α-cupriocarbonyl

(1) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980. (c) Normant, J. F. *J. Organomet. Chem. Libr.* **1976**, *1*, 219. (d) Taylor, R. J. K. *Synthesis* **1985**, *364*.

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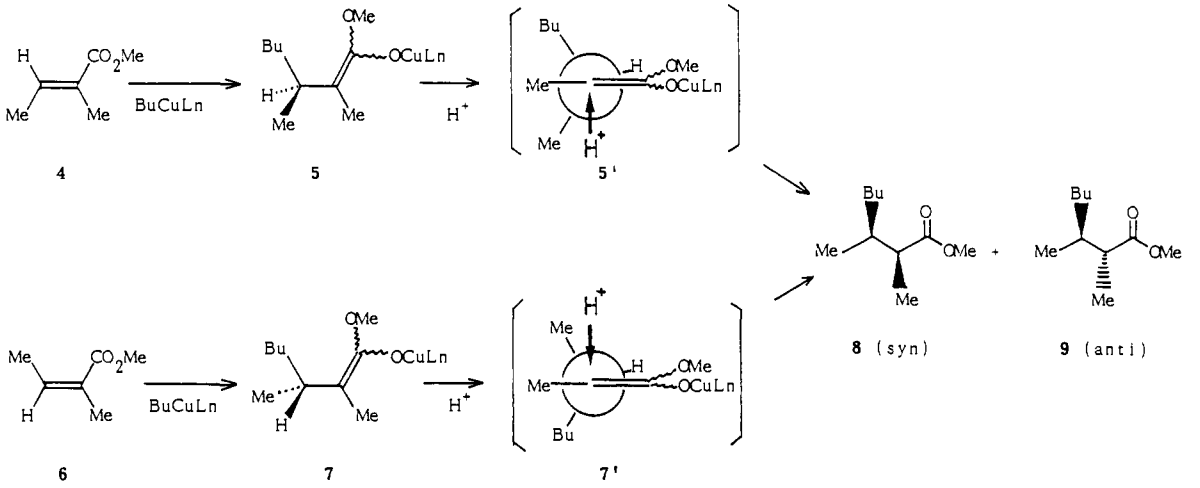
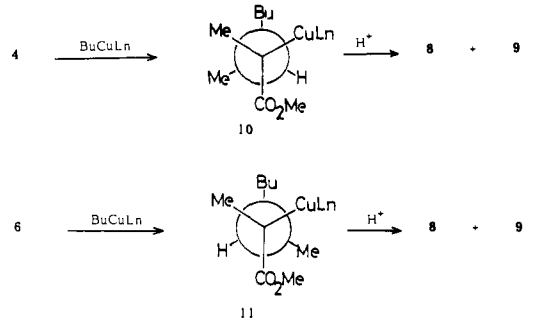
Scheme I



Scheme II



intermediate (**3a**) has been proposed in the conjugate addition to 1-phenyl-3,4-pentadien-2-one.[3] Further, it is believed that the conjugate addition to α,β-acetylenic carbonyl compounds proceeds through the intermediacy of a vinylcopper species,[1,4] i.e., a 1,2-addition. In some of the literature,[1d,5] structure **2a** is utilized to avoid the structural ambiguity. Furthermore, the α-stannyl ketone form **3b** might be involved in the erythro-selective aldol reaction of triphenyltin enolates.[6] Consequently, it is not clear whether organocopper conjugate additions proceed in a 1,4-fashion to give **1a** or in a 1,2-fashion to produce **3a**. We report that this long-standing problem, for the first time, can be solved by a stereochemical probe.

Results and Discussion

Stereochemical Probe. The 1,4-conjugate addition to methyl tiglate (**4**) produces **5**, while the 1,4-conjugate addition to methyl angelate (**6**) gives **7** (Scheme I). The intermediate copper–oxygen-bonded enolates (**5** and **7**) are protonated through the eclipsed conformation[7] (**5′** and **7′**, respectively) as reported previously.[8] The electrophilic attack to **5′** and **7′** from the less hindered side results in predominant formation of **8** (syn) along with minor amounts of **9** (anti). Therefore, the 1,4-addition to **4** and **6** should give the same isomer ratio.

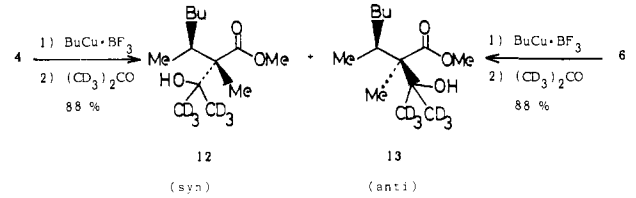
On the other hand, the 1,2-addition to **4** produces **10**, while the 1,2-addition to **6** gives **11** (Scheme II). The α-cuprio ester intermediates **10** and **11** are diastereomeric in comparison with the enantiomeric intermediates **5** and **7**. Therefore, protonolysis of the C–Cu bond of **10** and **11** must give a different isomer ratio regardless of the mode of the electrophilic cleavage (backside or frontside attack). Consequently, investigation of the isomer ratio in the conjugate addition to **4** and **6** should provide an answer to the problem.

Table I. Isomer Ratio of the Conjugate Addition[a]

entry	ester	BuCuLn[b]	condition[c]	**8**(syn): **9**(anti)[d]	total yield, %
1	**4**	$BuCu{\cdot}BF_3$	A	66:34	93
2	**6**	$BuCu{\cdot}BF_3$	A	66:34	90
3	**4**	$BuCu{\cdot}BF_3$	B	73:27	85
4	**6**	$BuCu{\cdot}BF_3$	B	73:27	85
5	**6**	$Bu_2CuLi{\cdot}BF_3$	B	75:25	22[e]
6	**4**	$BuCu{\cdot}BF_3$	C	73:27	88
7	**6**	$BuCu{\cdot}BF_3$	C	73:27	87

[a] All reactions were carried out on 1-mmol scale as described previously.[9] [b] Three equivalents of the reagents was used. [c] (A) The addition was carried out at −78 °C and then the reaction was quenched at 0 °C. (b) The addition was carried out at −78 °C and then the reaction was quenched at −78 °C. (c) The addition was carried out at −78 °C and then Ph_3SnCl (3 equiv) was added. After 30 min, the reaction was quenched at this temperature. [d] By 400-MHz ^1H NMR. [e] A major product was the 1,2-adduct (ketone).[9]

Scheme III



Isomer Ratio. The results are summarized in Table I. The **8**/**9** ratio was identical irrespective of the starting materials (entries 1 and 2). Protonolysis at −78 °C again produced the same isomer ratio (entries 3 and 4). The cuprate·BF_3 reagent did not give the conjugate adduct as the major product[9] (entry 5). The reaction with Bu_2CuLi itself gave the ketone as reported previously;[9] use of the copper·BF_3 reagent[10] was essential for the conjugate addition. The conjugate addition followed by treatment with Ph_3SnCl again gave the same isomer ratio (entries 6 and 7). This

(2) An unanswered question is whether the process is a 1,2-addition to the ene double bond (carbocupration) or a 1,4-addition to the enoate. Another important problem is the "composition" of the enolate: is the enolate a Li enolate or a Cu enolate? For the latter problem, see ref 5b and the following reference: Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141. We deal with the former problem.

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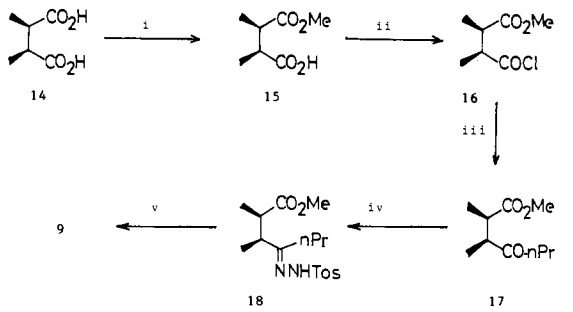
Scheme IV[a]



[a] (i) $(CH_3CO)_2O$, reflux; MeOH, reflux; yield 95%; (ii) $SOCl_2$, 20 °C; yield 97%; (iii) Pr_2CuLi, −78 °C; yield 82%; (iv) $TosNHNH_2$–MeOH, 20 °C; yield 80%; (v) $NaBH_3CH$–DMF–sulfolane–H^+, 110 °C; yield 70%.

result clearly indicates that the triphenyltin enolate takes the structure **1b**.[11]

Consequently, the protonolysis experiments clarify that the ultimate destination of copper in the conjugate addition to enoates is the oxygen atom rather than the α-carbon atom, which is in marked contrast to the conjugate addition to ynoates[4] and allenic ketones.[3]

However, we may wonder whether protonation occurs initially at the oxygen–copper bond to produce an enol and whether the stereodetermining step is protonation of the enol rather than the enolate. Although existence of such a process does not influence the above conclusion, trapping of the intermediate with acetone-d_6 instead of proton was examined to avoid the unnecessary complexity.

The conjugate addition to **4** followed by trapping with $(CD_3)_2CO$ at −78 °C produced **12** and **13** in a 2:1 ratio (Scheme III). The same isomer ratio was obtained starting from **6**. In conclusion, it is now unambiguous that the ultimate destination of copper in the enolate system is the oxygen atom. However, the possibility of initial 1,2-addition followed by rapid migration of copper from C to O in the enolate intermediate is not ruled out by the present experiments. Further, the generality of the present results, that is, the applicability to α-enones and other organocopper reagents, remains to be established.[12]

Structure Determination. The stereochemistry of **8** and **9** was determined by comparison with an authentic material prepared independently.[8] Treatment of *meso*-2,3-dimethylsuccinic acid (**14**) with acetic anhydride followed by refluxing in dry methanol gave **15**, as described in the literature.[13] Conversion to acid chloride (**16**) followed by treatment with di-*n*-propylcuprate[14] produced ketone **17** in 82% yield. The tosylhydrazone **18** was prepared with tosylhydrazine in MeOH–H_2O according to the usual procedure.[15] Reduction with $NaBH_3CN$[15] gave the anti isomer (**9**) (Scheme IV).

Experimental Section

General information concerning instrumentation and materials has been described previously.[9] Methyl tiglate and *meso*-2,3-dimethylsuccinic acid were purchased from Tokyo Kasei Co. Ltd. Methyl angelate was prepared according to the literature procedure: bp 125 °C (760 mmHg) (Kugelrohr) (lit.[16] bp 127–128 °C); ^1H NMR (CCl_4) δ 1.84 (d, *J* = 2 Hz, 3 H), 1.97 (dd, *J* = 2, 7 Hz, 3 H), 3.72 (s, 3 H), 6.05 (quartet-d, *J* = 7, 2 Hz, 1 H).

Methyl 2,3-dimethylheptanoate: bp 85 °C (25 mmHg) (Kugelrohr); IR (NaCl) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ of **8**, 0.889 (d, *J* = 7 Hz, 3 H), 0.900 (t, *J* = 7 Hz, 3 H), *1.113* (d, *J* = 7 Hz, 3 H), 1.3–1.4 (m, 6 H), 1.7–1.8 (m, 1 H), 2.367 (quintet, *J* = 6 Hz, 1 H), 3.661 (s, 3 H); δ of **9**, 0.856 (d, *J* = 7 Hz, 3 H), 0.941 (t, *J* = 7 Hz, 3 H), *1.067* (d, *J* = 7 Hz, 3 H), 1.3–1.4 (m, 6 H), 1.7–1.8 (m, 1 H), 2.389 (quintet, *J* = 6 Hz, 1 H), 3.665 (s, 3 H); mass spectrum, *m/e* 182 (M^+). The isomer ratio was determined by the area ratio of the signals at δ 1.113 and 1.067.

Trapping with Acetone-d_6. The conjugate addition to **4** and **6** was carried out similarly[9] at −78 °C, and then 1.4 equiv of acetone-d_6 was added. After 30 min, the reaction was quenched at −78 °C. The adducts (**12** and **13**) were isolated through a column of silica gel by using hexane–ether (10:1) as an eluant: IR (NaCl) 3460, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ of **12**, 0.886 (t, *J* = 7 Hz, 3 H), 0.990 (d, *J* = 7 Hz, 3 H), *1.076* (s, 3 H), 1.10 1.40 (m, 7 H), 1.65 (m, 1 H), 3.661 (s, 3 H); δ of **13**, 0.812 (d, *J* = 7 Hz, 3 H), 0.896 (t, *J* = 7 Hz, 3 H), *1.099* (s, 3 H), 1.10–1.40 (m, 7 H), 1.65 (m, 1 H), 3.665 (s, 3 H); mass spectrum, *m/e* 236 (M^+). The stereochemistry was not determined unambiguously but was assigned by analogy with the ^1H NMR chemical shifts; generally the triplet and singlet signals of the syn isomers (**8** and **12**) appeared at higher field than those of anti isomers (**9** and **13**). The isomer ratio was determined by the area ratio of the signals at δ 1.076 and 1.099.

Structure Determination. Reflux of **14** in acetic anhydride for 4 h, removal of the solvent, and then reflux in dry methanol for 3 h gave **15**: bp 65 °C (1 mmHg); ^1H NMR (CCl_4) δ 1.15 (d, *J* = 7 Hz, 3 H), 1.17 (d, *J* = 7 Hz, 3 H), 2.70–3.00 (m, 2 H), 3.67 (s, 3 H), 12.1 (s, 1 H). Treatment of **15** with thionyl chloride at room temperature overnight produced **16**; bp 42 °C (1 mmHg); ^1H NMR (CCl_4) δ 1.17 (d, *J* = 7 Hz, 3 H), 1.27 (d, *J* = 7 Hz, 3 H), 2.96 (quintet, *J* = 7 Hz, 1 H), 3.25 (quintet, *J* = 7 Hz, 1 H), 3.73 (s, 3 H). The reaction of **16** with dipropylcuprate according to the reported procedure gave **17**: bp 100 °C (1 mmHg) (Kugelrohr); ^1H NMR (CCl_4) δ 0.90 (t, *J* = 7 Hz, 3 H), 0.956 (d, *J* = 7 Hz, 3 H), 1.13 (d, *J* = 7 Hz, 3 H), 1.40–1.70 (m, 2 H), 2.44 (t, *J* = 7 Hz, 2 H), 2.60–2.80 (m, 2 H), 3.66 (s, 3 H). Tosylhydrazone (**18**) was prepared according to the literature procedure.[15] Without further purification, the white precipitate was reduced with $NaBH_3CN$ in DMF–sulfolane.[15] ^1H NMR of **18** (acetone-d_6) δ 0.94 (t, *J* = 7 Hz, 3 H), 1.09 (d, *J* = 7 Hz, 3 H), 1.13 (d, *J* = 7 Hz, 3 H), 1.30–1.60 (m, 4 H), 1.80 (s, 3 H), 1.90–2.10 (m, 2 H), 3.64 (s, 3 H), 7.32–7.80 (aromatic H, 4 H). The reduction product was compared with **8** and **9**.

(11) Certain tin enolates exist as the α-tin structure (**3b**). See ref 6.
(12) A referee pointed out the possibility of the boron enolate intermediate instead of the copper enolate. This possibility is ruled out by the following experiment. The lithium enolate of cyclohexanone was treated with 1 equiv of BF_3·OEt_2 at −78 °C, and then benzaldehyde was added. The aldol product was not obtained and the starting materials were recovered. Therefore, an enolate such as >C=C—O—BF_2 does not react with an aldehyde, indicating that the −BF_2 type enolate is not involved in the present system.
(13) (a) Noller, C. R.; Pannell, C. E. *J. Am. Chem. Soc.* **1955**, *77*, 1862. (b) Allinger, N. L. *Ibid.* **1959**, *81*, 232.
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