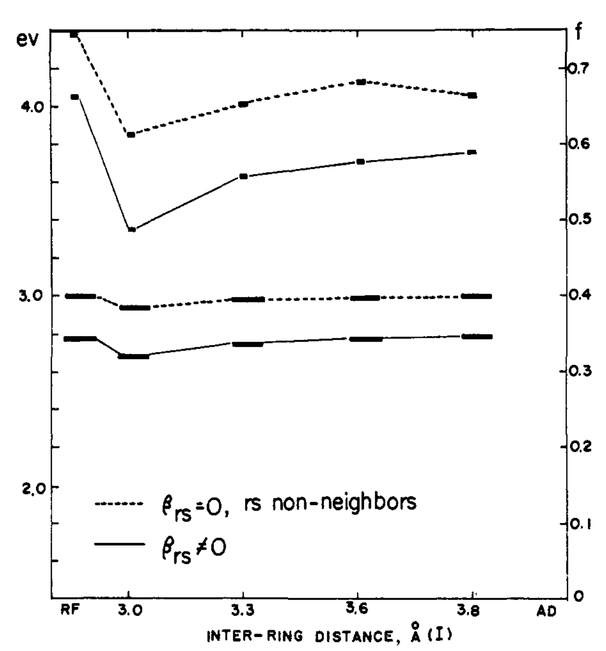


Figure 2. The lowest singlet ($\pi \rightarrow \pi^*$) transition energies (eV) and oscillator strengths ($f$) as a function of the inter-ring distance (Å) between the flavin (RF) and adenine (AD) moieties of FAD (Model I).

several other models in preliminary calculations did not produce strikingly different spectroscopic quantities. Miles and Urry[13] proposed an FAD stacking model almost identical with model II, based on their circular dichroic data and our calculated transition energies and moments of 6,7-dimethylisoalloxazine.[14,15] The agreement of the observed energies and rotational strengths with those of our calculated data was found to be excellent.[13] The lowest triplet states are also localized in the flavin moiety in all three models. However, sensitive variations of the triplet-state energies with different models were displayed in the calculations. Experimental confirmation of this prediction is attempted.

Most of the flavoenzymes have redox potentials considerably higher than that of free riboflavin ($E_0' = -0.186$ V). FAD in aqueous solution has an $E_0'$ of $-0.195$ V. Since FAD in aqueous solution assumes the stacked form, it appears that the internal complex of FAD cannot be catalytically important in flavoenzyme reactions with $E_0'$ higher than $-0.186$ V. We calculated the ionization potentials and electron affinities of all three models on the basis of Koopmans' theorem.[16] Model I is predicted to be a better electron acceptor than II and III, model I yielding an ionization potential and electron affinity higher than those of 6,7-dimethylisoalloxazine. Model II or III, therefore, is consistent with the more negative $E_0'$ of FAD relative to riboflavin.

In conclusion, it is emphasized that all valence electron calculations of FAD are practically impossible. The calculation of the present model is already complex. The estimations of stabilities of the complex models calculated here are not meaningful due to inadequate representation of the dispersion forces in the SCF MO scheme. In spite of the complexity of the system and crudeness of the method, conclusions drawn in this communication are qualitatively significant in view of reasonable agreement between the predicted and experimental quantities discussed above. More detailed accounts of the present work and its extension will be published elsewhere.[17]

---

[13] D. W. Miles and D. W. Urry, *Biochemistry*, **7**, 2791 (1968).

[14] P.-S. Song, *Ann. N. Y. Acad. Sci.*, in press.

[15] P.-S. Song, *Intern. J. Quantum Chem.*, in press.

[16] T. Koopmans, *Physica*, **1**, 104 (1934).

[17] "International Conference on Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry," Jerusalem, Israel, March 31–April 5, 1969, to be published.

**Pill-Soon Song**
*Department of Chemistry, Texas Technological College*
*Lubbock, Texas 79409*

*Received January 22, 1969*

---

## A New Stereospecific Synthesis of Trisubstituted and Tetrasubstituted Olefins. The Conjugate Addition of Dialkylcopper–Lithium Reagents to α,β-Acetylenic Esters[1]

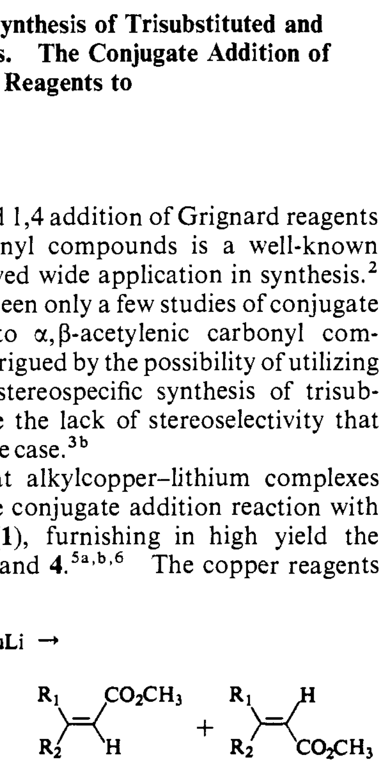
*Sir:*

The copper-catalyzed 1,4 addition of Grignard reagents to α,β-ethylenic carbonyl compounds is a well-known reaction that has received wide application in synthesis.[2] In contrast there have been only a few studies of conjugate addition as applied to α,β-acetylenic carbonyl compounds.[3] We were intrigued by the possibility of utilizing this reaction for the stereospecific synthesis of trisubstituted olefins, despite the lack of stereoselectivity that had been reported in one case.[3b]

We have found that alkylcopper–lithium complexes (2)[2b,4] undergo a facile conjugate addition reaction with α,β-acetylenic esters (1), furnishing in high yield the ethylenic esters 3[5a,b,6] and 4.[5a,b,6] The copper reagents

$R_1C\equiv CCO_2CH_3$ + $(R_2)_2CuLi$ →

1 2



3 4

---

[1] For a different new stereospecific synthesis of trisubstituted olefins, see E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967).

[2] (a) J. Munch-Petersen, *Bull. Soc. Chim. Fr.*, 471 (1966), and references therein; (b) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (c) H. O. House and W. T. Fischer, Jr., *ibid.*, **33**, 949 (1968).

[3] (a) I. Iwai and T. Konotsune, *Yakugaku Zasshi*, **82**, 601 (1962); *Chem. Abstr.*, **58**, 1392*a* (1963); (b) G. Boularand and R. Vessière, *Bull. Soc. Chim. Fr.*, 1706 (1967); (c) C. Bretting, J. Munch-Petersen, P. M. Jørgensen, and S. Refn, *Acta Chem. Scand.*, **14**, 151 (1960), and references cited therein.

[4] E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **90**, 5615 (1968).

[5] (a) The assigned structure is entirely consistent with nmr and ir data; (b) a satisfactory carbon–hydrogen combustion analysis was obtained on this compound.

[6] The stereochemistry of the pure isomeric esters 3 and 4 ($R_1$ = $n$-$C_7H_{15}$; $R_2$ = $CH_3$) is evident from their nmr spectra. The resonance of $R_2$ ($CH_3$) (in $CCl_4$ solution expressed as parts per million shifts downfield (δ) from tetramethylsilane as internal standard) appears at 1.85 (d, $J$ = 1.3 Hz) in 3 and at 2.15 (d, $J$ = 1.3 Hz) in 4. Unequivocal evidence of the stereochemistry of 4 was obtained by reduction with aluminum hydride to the corresponding alcohol, 3-methyl-*trans*-2-decen-1-ol, which proved to be identical (nmr, ir, and glpc) with the alcohol obtained from 2-decyn-1-ol by the sequence: lithum aluminum hydride–sodium methoxide reduction, iodination, and methylation with dimethylcopper–lithium (see ref 1).

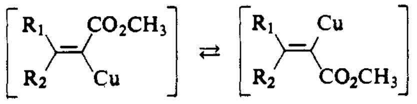
**Table I.** Stereochemistry and Yields of Conjugate Addition Products

| $R_1$ | $R_2$ | Solvent | Temp, °C | Approx time to completion | Addition,[a] *cis*:*trans* | Yield,[b] % |
|---|---|---|---|---|---|---|
| $n$-$C_7H_{15}$ | $CH_3$ | THF | −78 | 3 hr | 99.8:0.2 | 95 |
| $CH_3$ | $n$-$C_7H_{15}$ | THF | −78 | 3 hr | 99.5:0.5 | 90 |
| $n$-$C_7H_{15}$ | $CH_3$ | THF, $Et_2O$ | 0 | <5 min | 39:61 | (90) |
| $n$-$C_7H_{15}$ | $CH_3$ | Toluene | −78 | <5 min | 92:8 | (50) |

[a] Products were analyzed on an F & M Model 810 or 5750 research chromatograph using the following columns: 16 ft × 0.125 in. 10% LAC-728 on 80–100 mesh Diatoport S; 6 ft × 0.125 in. 10% Carbowax 20M on 80–100 mesh Diatoport S; 3 ft × 0.125 in. 5% SE-30 on 80–100 mesh Gas Chrom Q. [b] Isolated yield; glpc yield in parentheses.

are generated *in situ* from the alkyllithium (2 equiv) and cuprous iodide (1 equiv) at 0°, and reaction with the ester is complete within a few hours at low temperatures.[7] The stereochemistry of the products is highly dependent upon the reaction temperature and the nature of the solvent. Some of our results are summarized in Table I.

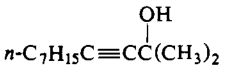
When the reaction is conducted at −78° in tetrahydrofuran, *cis* addition takes place exclusively, and the ester **3** is obtained in very high yield with stereochemical purity greater than 99%. At 0° the reaction is faster, but isomer **4** is also found. This loss in stereospecificity at higher temperatures probably results from the equilibration of the "enolates" **5a** and **5b** which is very slow at −78° but becomes rapid at −20°, giving mixtures of **3** and **4** after isolation.



**5a** **5b**

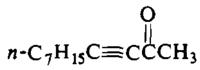
The nature of the solvent influences the stereoselectivity of the reaction. In tetrahydrofuran, addition is exclusively *cis*, and the enolate **5a** retains its stereochemical integrity at −78°. In diethyl ether, addition is predominantly *cis*, but the enolates **5a** and **5b** equilibrate at a significant rate even at −78°; addition of a complexing agent such as tetramethylethylenediamine retards this equilibration considerably. In toluene as solvent some conjugate addition takes place, but the stereoselectivity is less than in ether solvents, and the yield is lower.

In contrast to the conjugate addition reactions of Grignard reagents with enone systems in which only catalytic amounts of copper(I) salts are required, the use of less than 0.5 equiv of cuprous iodide per equivalent of alkyllithium with α,β-acetylenic esters gives predominantly products resulting from 1,2 addition. For example, the alcohol **6**,[5a,b,8a] the ketone **7**,[5a,b,8b] and the products **8**[5a,8c] of conjugate addition on the ketone **7** are formed by the reaction of **1** ($R_1$ = $n$-$C_7H_{15}$) with methyllithium–cuprous iodide (1:0.25) in tetrahydrofuran at −78°.



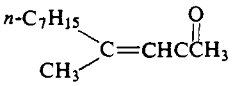
$n$-$C_7H_{15}C{\equiv}CC(OH)(CH_3)_2$

**6**



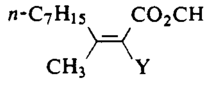
$n$-$C_7H_{15}C{\equiv}CC(=O)CH_3$

**7**

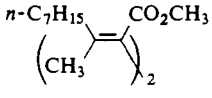


**8**

The enolates **5a** and **5b** are extremely useful intermediates for further reaction. In preliminary experiments we have found that oxidation of **5a** with dry oxygen at −78° in the presence of a large excess of dimethylcopper–lithium allows the isolation of compound **9** (Y = $CH_3$)[5a] in fair yield.[9] This product can be considered the result of formal *cis* addition of *two* methyl groups across the triple bond. Similar oxidation in the absence of excess copper reagent furnishes considerable amounts of the dimer **10**.[5a,9] The iodide **9** (Y = I)[5a,b] is produced in high yield when the enolate **5a** is treated with excess iodine at −78°. Thus, a variety of tetrasubstituted olefins are available stereospecifically.



**9**



**10**

The conjugate addition of dialkylcopper–lithium reagents to acetylenic esters provides a stereospecific synthesis of trisubstituted olefins complementing the method described by us previously;[1] in the conjugate addition alkyl and hydrogen add across the triple bond in a *cis* manner, while in the earlier method *trans* addition took place. We are currently investigating the application of this reaction to the synthesis of natural products and are studying a number of further reactions of the organocopper intermediates which lead stereospecifically to various tetrasubstituted olefins.

**Acknowledgment.** This work was supported by the National Science Foundation and the National Institutes of Health.

---

[7] All reactions were conducted under an atmosphere of dry nitrogen with rigorous exclusion of air and water. Aliquots were removed with syringes precooled to −78°, and reactions were quenched in methanol at −78°.

[8] Compared by glpc, tlc, and nmr with an authentic sample prepared (a) from **1** ($R_1$ = $n$-$C_7H_{15}$) and methyllithium, (b) from $n$-$C_7H_{15}C{\equiv}CAg$ and acetyl chloride, (c) by the reaction of **7** with dimethylcopper–lithium.

[9] G. M. Whitesides, J. SanFilippo, Jr., C. P. Casey, and E. J. Panek, *J. Am. Chem. Soc.*, **89**, 5302 (1967).

**E. J. Corey, John A. Katzenellenbogen**
*Department of Chemistry, Harvard University*
*Cambridge, Massachusetts 02138*

*Received December 12, 1968*