

Figure 1. Pulse voltammetry of 0.001 M $\text{CO}(\text{acac})_3$ in 0.1 M II-acetonitrile, at a 13-cm² Hg electrode.

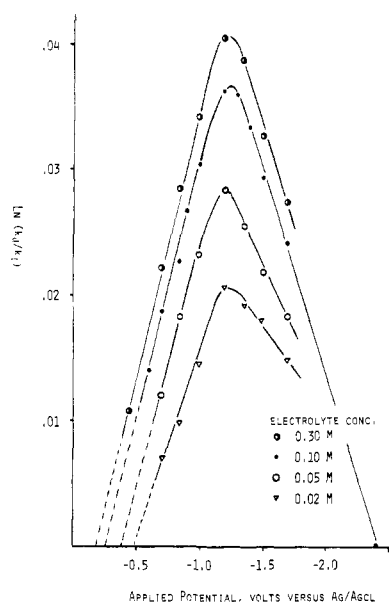


Figure 2. The effect of potential on enantioselectivity.

son of these data. (1) The decrease in selectivity at potentials between -1.20 and -2.4 V corresponds to measurements made under conditions of increasing mass-transport control. Thus, little or no selectivity is associated with mass transport. (2) In the region of pure activation overpotential, ($E > -1.0$ V), $\ln(k_d/k_i)$ increases linearly with decreasing potential. The selectivity must therefore be associated with a potential dependent process at the electrode surface.

Specific adsorption of I is apparently not involved. Zero-time extrapolation of coulometric transients¹³ measured with and without I were found to be the same within experimental error. We conclude that electron transfer per se, under the influence of the chiral double layer, is the selective process.

Several authors have provided quantitative models for the influence of double layer on electrode kinetics.¹⁴⁻¹⁶ In these treatments, only average electrostatic interactions are included. Since enantioselectivity reflects a discrimination

based purely on substrate structure, it must be concluded that interactions with the double layer also have a significant steric component.

Included in Figure 2 is the effect of electrolyte concentration. It was found that, for each concentration, the X intercept at low overpotential corresponded to the potential of zero charge excess (pzc).¹⁹ Since the surface concentration of cations at the pzc cannot be less than their concentration in the bulk solution, it is noteworthy that no selectivity exists at this potential regardless of the electrolyte concentration. It may be inferred that some factor other than the mere presence of asymmetric cations is required for selectivity. We propose that this factor is the orientational ordering of electrolyte dipoles in the Helmholtz plane.¹⁷ An interfacial potential gradient, capable of imposing such order, would be lacking at the pzc but may be quite substantial at other applied potentials.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to Du Pont De Nemours and Co. for a young Faculty Grant, for the support of this work.

References and Notes

- (1) M. M. Baizer, *J. Electrochem. Soc.*, **11**, 215 (1964).
- (2) R. Galli and F. Olivani, *J. Electroanal. Chem.*, **25**, 331 (1970).
- (3) R. Breslow and R. F. Drury, *J. Am. Chem. Soc.*, **96**, 4702 (1974).
- (4) L. Horner and D. Degner, *Tetrahedron Lett.*, 5889 (1968); L. Horner and D. H. Skaletz, *ibid.*, 3679 (1970); L. Horner and R. Schneider, *ibid.*, 3133 (1973); L. Ebersson and L. Horner in "Organic Electrochemistry", M. M. Baizer, Ed., Marcel Dekker, New York, N.Y., 1973 pp 869-893; R. N. Gourley, J. Grimshaw, and P. G. Millar, *Chem. Commun.*, 5889 (1971); E. Kariv et al., *Electrochim. Acta*, **18**, 433 (1973); M. Jubault et al. *C. R. Acad. Sci., Ser. C*, **277**, 583 (1973).
- (5) P. Delahay, "Double Layer and Electrode Kinetics", Wiley, Interscience, New York, N.Y., 1965.
- (6) R. W. Murray and M. Kodama, *Anal. Chem.*, **37**, 1759 (1965).
- (7) F. A. Cotton and R. H. Soderberg, *Inorg. Chem.*, **3**, 1 (1964); F. A. Cotton and R. C. Elder, *ibid.*, **4**, 1145 (1965).
- (8) Control experiments established that the observed rotations were not artifacts of the work-up or analysis. Moreover, when an achiral electrolyte, tetra-*n*-butylammonium perchlorate, was employed, no selectivity could be detected. Optical purities were calculated assuming a molecular rotation of 29,700° at 546 m μ for optically pure I.⁹
- (9) J.-Y. Sun, Ph.D. Thesis, University of North Carolina, 1967.
- (10) Currents were sampled at 200 msec following the application of a given potential.
- (11) The hydrodynamics of turbulent flow (B. G. Levich, "Physicochemical Hydrodynamics", Prentice-Hall, Englewood Cliffs, N.J., 1962, Chapter 3) are probably applicable although the dependence on stirring rate (roughly $\omega^{1/3}$) cannot be simply derived.
- (12) J. P. Brenet, K. Traore "Transfer Coefficients in Electrochemical Kinetics", Academic Press, New York, N.Y., 1971.
- (13) J. H. Christie, R. A. Osteryoung, and F. C. Anson, *J. Electroanal. Chem.*, **13**, 236 (1967).
- (14) A. N. Frumkin, *Z. Phys. Chem., Abt. A*, **164**, 121 (1933).
- (15) W. H. Reinmuth, L. B. Rogers, and L. E. I. Hummelstedt, *J. Am. Chem. Soc.*, **81**, 2947 (1959).
- (16) M. Breiter, M. Kleinerman, and P. Delahay, *J. Am. Chem. Soc.*, **80**, 5111 (1958).
- (17) Evidence for crystalline order of an adsorbed electrolyte has been described: C. M. Elliot and R. W. Murray, *J. Am. Chem. Soc.*, **96**, 3321 (1974).
- (18) On leave from the Department of Synthetic Chemistry, Kumamoto University, Kumamoto, Japan.
- (19) Measured by mercury drop extrusion: F. C. Anson, *Anal. Chem.*, **38**, 54 (1966).

Stephen Mazur,* Katsutoshi Ohkubo¹⁸

Department of Chemistry, University of Chicago
Chicago, Illinois 60637

Received December 20, 1974

Reaction of Ketone Enolates with Copper Dichloride. A Synthesis of 1,4-Diketones

Sir:

Copper-promoted dimerization of carbanions has constituted a convenient method of carbon-carbon bond forma-

Table I. Synthesis of 1,4-Diketones by the Reaction of Ketone Enolates with CuCl₂

Starting ketone	1,4-Diketones (yield, %) ^a
(CH ₃) ₃ CCOCH ₃	(CH ₃) ₃ CCOCH ₂ CH ₂ COC(CH ₃) ₃ ^b (95)
C ₆ H ₅ COCH ₃	C ₆ H ₅ COCH ₂ CH ₂ COC ₆ H ₅ ^c (83)
(CH ₃) ₂ CHCOCH ₃	{ (CH ₃) ₂ CHCOCH ₂ CH ₂ COCH(CH ₃) ₂ ^d (89)
C ₂ H ₅ COC ₂ H ₅	{ (CH ₃) ₂ CHCOCH ₂ CH ₂ COCH ₃ ^d (3)
CH ₃ COC ₂ H ₅	C ₂ H ₅ COCH(CH ₃)CH(CH ₃)COC ₂ H ₅ ^{d,e} (32)
CH ₃ COC ₆ H ₁₃	{ C ₂ H ₅ COCH ₂ CH ₂ COC ₆ H ₁₃ ^f (58)
	{ C ₂ H ₅ COCH ₂ CH(CH ₃)COC ₆ H ₁₃ ^g (12)
	C ₆ H ₁₃ COCH ₂ CH ₂ COC ₆ H ₁₃ ^h (62)
	C ₆ H ₁₃ COCH ₂ CH(CH ₃)COC ₆ H ₁₃ ⁱ (18)
CH ₃ COCH=CH(CH ₃) ₂	(CH ₃) ₂ C=CHCOCH ₂ CH ₂ COCH=CH(CH ₃) ₂ ^j (47)
	+ some minor products ^k

^a The yields are not necessarily optimum since each run was performed only once. The isomeric 1,4-diketones are separated by GLPC. ^b Reference 9. ^c Reference 1. ^d Reference 10. ^e *dl*/meso mixture. ^f Reference 11. ^g NMR (CCl₄ with TMS): δ 0.98 (t, 3 H), 1.04 (d, 3 H), 2.10 (s, 3 H), 2.10–2.80 (m, 5 H). ^h NMR (CDCl₃ with TMS): δ 0.85 (t, 6 H), 0.80–1.90 (m, 16 H), 2.35 (q, 4 H), 2.63 (s, 4 H). ⁱ NMR (CDCl₃ with TMS): δ 0.84 (t, 6 H), 0.90–1.80 (m, 16 H), 2.20 (s, 3 H), 1.95–2.80 (m, 5 H). ^j NMR (CCl₄ with TMS): δ 1.83 (d, 6 H), 2.05 (d, 6 H), 2.55 (s, 4 H), 6.00 (m, 2 H). ^k Unidentified.

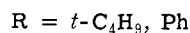
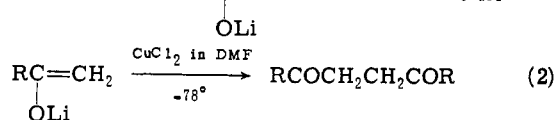
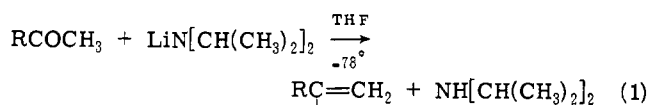
Table II. Synthesis of Unsymmetrical 1,4-Diketones and γ-Ketoesters by Cross Coupling Reactions

Cross coupling (mole ratio) ^a	Products ^b (yield, %)
CH ₃ COCH ₃ + CH ₃ COC ₆ H ₁₃ (3:1)	CH ₃ COCH ₂ CH ₂ COC ₆ H ₁₃ ^c (73)
	CH ₃ COCH ₂ CH(CH ₃)COC ₆ H ₁₃ ^d (4)
	C ₆ H ₁₃ COCH ₂ CH ₂ COC ₆ H ₁₃ (8)
	CH ₃ COCH ₂ CH ₂ COCH ₃ ^e
(CH ₃) ₃ CCOCH ₃ + CH ₃ COC ₆ H ₁₃ (3:1)	(CH ₃) ₃ CCOCH ₂ CH ₂ COC ₆ H ₁₃ ^f (60)
	(CH ₃) ₃ CCOCH ₂ CH ₂ COC(CH ₃) ₃ ^e
(CH ₃) ₃ CCOCH ₃ + CH ₃ CO ₂ CH ₃ (1:3.5)	(CH ₃) ₃ CCOCH ₂ CH ₂ CO ₂ CH ₃ ^g (70)
	CH ₃ COCH ₂ CH ₂ CO ₂ CH ₃ ^e
CH ₃ COCH ₃ + CH ₃ CO ₂ C(CH ₃) ₃ (3.5:1)	CH ₃ COCH ₂ CH ₂ CO ₂ C(CH ₃) ₃ ^h (65)
	(CH ₃) ₃ COCH ₂ CH ₂ CO ₂ C(CH ₃) ₃ ⁱ (28)
	CH ₃ COCH ₂ CH ₂ COCH ₃ ^e

^a No attempt has been made to optimize the reaction conditions. ^b Yields are based upon the smaller amount of the starting material. The products are separated by GLPC. ^c Reference 12. ^d NMR (CDCl₃ with TMS): δ 0.85 (t, 3 H), 0.90–1.90 (m, 8 H), 2.10 (s, 3 H), 2.19 (s, 3 H), 2.50–3.00 (m, 3 H). ^e Yields are comparable to those of the major cross coupling products. ^f NMR (CCl₄ with TMS): δ 1.15 (s, 9 H), 2.78 (t, 2 H), 3.12 (t, 2 H), 7.15–8.05 (m, 5 H). ^g Reference 13. ^h NMR (CCl₄ with TMS): δ 1.38 (s, 9 H), 2.08 (s, 3 H), 2.42 (t, 2 H), 2.47 (t, 2 H). ⁱ Reference 2.

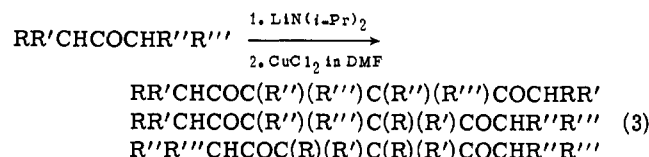
tion in organic syntheses. Successful dimerization of carbanions which are stabilized by sulfonyl,¹ phosphoryl,¹ imidoyl,¹ and alkoxy-carbonyl² by copper salts have been reported. Nevertheless, there are few examples¹ of the copper-promoted dimerization of ketone enolates, which should become an attractive entry into 1,4-diketone derivatives. Recently, we have reported³ the regiospecific coupling of silyl enol ethers by Ag₂O producing 1,4-diketones, in which the use of aprotic polar solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoric amide (HMPA) is crucial.

Now we found that the CuCl₂-promoted dimerization of ketone enolates is realized by the use of cosolvent DMF at –78°, leading to the desired 1,4-diketones in satisfactory yields. Lithium enolates of pinacolone and acetophenone, prepared according to eq 1, were treated with CuCl₂ in DMF at –78° to produce the corresponding 1,4-diketones in high yields (eq 2). In the CuCl₂ promoted coupling of ke-



tones having two different enolizable hydrogens (RR'CHCOCHR''R'''), a mixture of 1,4-diketones was yielded with the less crowded 1,4-diketone predominating

(eq 3). Some results are summarized in Table I. The prod-

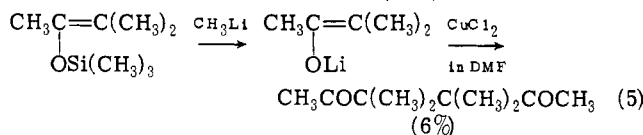
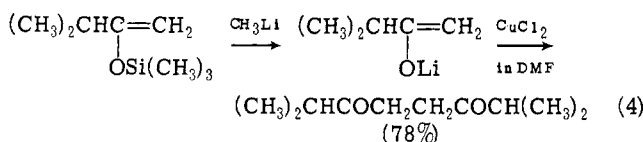


uct yields and selectivities in the reaction depend upon alkyl substitution at the α-carbon of the ketone. Increasing alkyl substitution at the coupling site results in a remarkable reduction in the yield of the coupling product.⁴ The reaction with methyl ketones (CH₃COCHR') furnishes 1,4-diketones (RR'CHCOCH₂CH₂COCHR') arising from coupling at the methyl group in high selectivities (80–90%) and in good yields (60–90%) together with other isomeric 1,4-diketones as minor products. The highly selective coupling at the methyl group of methyl ketone (CH₃COCHR') may be due to kinetically controlled deprotonation⁵ of the ketone by lithium diisopropylamide and steric hindrance in the transition state of ketone enolate coupling. The present coupling reaction of ketones provides a general and convenient route to the symmetrical 1,4-diketone of RCOCH₂CH₂COR, which has been otherwise prepared with rather great difficulty.

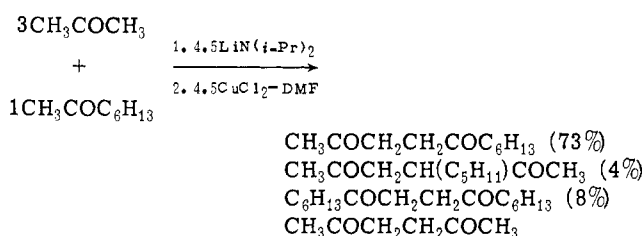
A typical experimental procedure is as follows; a solution of diisopropylamine (5 mmol) in dry THF (5 ml) is treated with *n*-butyllithium (15% hexane solution, 5 mmol) at –78°, and after 15 min 3-methylbutan-2-one (4.5 mmol) is added dropwise with stirring. After 15 min, anhydrous CuCl₂ (5 mmol) in DMF (5 ml) is added all at once at the same temperature. The dark green solution is stirred for an

additional 30 min and then allowed to reach room temperature. The reaction mixture becomes dark brown and homogeneous. Acid work-up produces 2,7-dimethyloctan-3,6-dione (89%) with 3,3,6-trimethylheptan-2,5-dione (3%).

As might have been expected, coupling of lithium enolates, which were regioselectively generated from silyl enol ethers and methyllithium,⁶ by CuCl₂ in DMF at -78° produced the corresponding 1,4-diketones regioselectively³ according to eq 4 and 5.



Next, the present method is successfully applicable to some cross couplings of two different methyl ketones and of methyl ketone with acetate, leading to unsymmetrical 1,4-diketones (RCOCH₂CH₂COR') and γ -ketocarboesters (RCOCH₂CH₂CO₂R'), respectively (Table II). For instance, addition of CuCl₂ in DMF to a 1:3 mixture of lithium enolates of 2-octanone and acetone at -78°, prepared by addition of a 1:3 mixture of 2-octanone and acetone into lithium diisopropylamide in THF according to the above procedure, produced undecan-2,5-dione in 73% yield (based upon the starting 2-octanone) together with 3-pentylhexan-2,5-dione (4%), hexadecan-7,11-dione (8%), and hexan-2,5-dione. Besides the readily available starting materials



and the manipulative simplicity, the high selectivity and good yield render this reaction most straightforward and useful in the preparation of undecan-2,5-dione, a precursor of dihydrojasmonone.⁷

Cross coupling of ketone enolate with ester enolate by CuCl₂ was carried out as follows. First, a mixture of ketone enolate and ester enolate was prepared by the sequential additions of ketone and ester (after 15 min) to lithium diisopropylamide in THF at -78°. Then, the mixture was treated with CuCl₂ in DMF at the same temperature. By this procedure, condensation product⁸ is almost completely excluded, resulting in the formation of coupling products. We are currently exploring the full scope of the coupling reaction of ketone enolates by CuCl₂ in aprotic polar solvents.

References and Notes

- (1) The reaction of sodium enolate of acetophenone with CuCl₂ gives 1,4-diphenyl-1,4-butanedione in low yield: T. Kauffmann et al., *Angew. Chem., Int. Ed. Engl.*, **7**, 540 (1968).
- (2) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 4605 (1971).
- (3) Y. Ito, T. Konoike, and T. Saegusa, *J. Am. Chem. Soc.*, **97**, 649 (1975).
- (4) The CuCl₂-promoted coupling of phenyl isopropyl ketone produced 1,4-diphenyl-2,2,3,3-tetramethyl-1,4-butanedione only in 2% yield.
- (5) H. O. House, "Modern Synthetic Reactions", 2nd ed, Benjamin, Menlo Park, Calif., 1972.
- (6) (a) G. Stork and P. H. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462, 4468 (1968); (b) H. O. House, L. J. Czuda, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
- (7) T. Ho, *Synth. Commun.*, **4**, 265 (1974).
- (8) M. W. Rathke, *J. Am. Chem. Soc.*, **92**, 3222 (1970).

- (9) M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Am. Chem. Soc.*, **70**, 1269 (1948).
- (10) C. Chassin, E. A. Schmidt, and H. M. R. Hoffmann, *J. Am. Chem. Soc.*, **96**, 606 (1974).
- (11) E. Blaise, *C. R. Acad. Sci.*, **158**, 506 (1914).
- (12) T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).
- (13) G. A. Hill, V. Salvin, and W. T. O'Brien, Jr., *J. Am. Chem. Soc.*, **59**, 2385 (1937).

Yoshihiko Ito, Toshiro Konoike, Takeo Saegusa*

Department of Synthetic Chemistry
Faculty of Engineering, Kyoto University
Kyoto 606, Japan

Received January 20, 1975

An Immuno-electrode

Sir:

Proteins in aqueous solutions are polyelectrolytes and have a net electrical charge polarity and magnitude of which depends on the isoelectric point of the protein and on the ionic composition of the solution. If the protein is an antibody which can complex with a corresponding antigen, which also can have a net electrical charge, the electrical charge of the resulting complex will be different from that of the antibody or the antigen alone.¹

If the antibody is covalently attached to the surface of a thin layer of a hydrophobic polymer which, in turn, is deposited on a metallic conductor, then the surface charge of the polymer-solution interface will depend on the net charge of the immobilized antibody. When corresponding antigen is present in the solution and the binding site of the antibody has not been destroyed during immobilization, the immunochemical reaction will take place at the interface with a resulting change of the surface charge. This change can be measured potentiometrically against a reference electrode immersed in the same solution, using an electrometer amplifier.

It is known² that the reaction between immobilized antibody and free antigen, or vice versa, is an equilibrium process. The potential difference between the reference electrode and an electrode with immobilized antibody or antigen (thereafter called immuno-electrode) should, therefore, depend on concentration of the free immunochemical counterpart. The concept applies equally to the case when antigen is bound to the membrane and antibody is free.

In order to test this idea, Concanavalin A (Con A) was covalently attached to the surface of an approximately 5 μ thick, dense poly(vinyl chloride) membrane deposited on platinum wire. Although Concanavalin A is not a true antibody, it complexes certain polysaccharides³ in the same way true antibodies do. This reaction has been used extensively as a model immunochemical system. Yeast mannan reacts with Concanavalin A, forming a strong complex³ which is soluble between pH 2 and 4 and insoluble between pH 5 and 7. Various other polysaccharides such as, for example, agar or amyloses do not bind to Con A.

Dependence of potential of Con A immuno-electrode on concentration of yeast mannan measured against silver-silver chloride reference electrode is shown in Figure 1. Similar dependence is obtained when poly(vinyl chloride) coated platinum wire *without* Concanavalin A is used instead of a Con A immuno-electrode. This indicates that there is a considerable nonspecific adsorption of polysaccharides at the polymer surface. In order to separate the effect of adsorption from specific immunochemical interaction, the following experiments were carried out. First, the reference electrode was replaced with another Con A immuno-electrode