effect is seen in the 450-nm band and a primarily negative effect is seen in the near-UV region. (The absorption and MCD spectra of P-450 exhibits impurity peaks at 415–420 nm due to the presence of a small amount of P-420 (compare Figure 2).) The visible portions of the model spectra show more fine structure perhaps due to the more symmetrical structure of OEP. Because MCD is a more sensitive measure of the electronic properties of chromophores, the similarity seen in both the shape and intensity of the MCD spectra of the well understood[4] group 5a hyperporphyrins and of reduced + CO P-450 lends credence to the proposal that their absorption spectra result from similar orbital mechanisms. We also note that the MCD spectrum of reduced + CO chloroperoxidase,[20] another protein which exhibits a "450-type" absorption spectrum, and of a reduced + CO model *thiolate* compound[6f] are nearly identical with that of reduced + CO P-450.

The rather different absorption and MCD spectra exhibited by the "normal" porphyrin (OEP)$Sb^{V}(OH)_2Cl$ and by reduced + CO P-420[21] shown in Figure 2 provide an interesting contrast to the spectra of the hyperporphyrins shown in Figure 1. As in the "hyper" spectra (Figure 1), the OEP model is somewhat shifted in wavelength relative to the natural porphyrin and shows more fine structure in the visible region. As discussed by Hanson et al.[4] the "normal" complexes lack the requisite conditions for a charge transfer transition, and thus no mixing is seen with the Soret π–π^* transition. The result is a single unshifted Soret absorption band and an uncomplicated MCD spectrum. (The absorption tail below 360 nm in the P-420 spectrum is due to dithionite.) The MCD of reduced + CO model heme complexes with thiol and imidazole trans to the CO are nearly identical with that of P-420.[6f]

The MCD data presented here provide strong support for the orbital mixing hypothesis of Hanson et al.[4] which has furnished, for the first time, a cogent explanation for the origin of the anomalous Soret spectrum of reduced + CO P-450.

Acknowledgments. We wish to thank Ruth Records for running some of the MCD spectra, Dr. D. A. Haugen and Professor M. J. Coon for helpful discussions concerning the isolation of mammalian $P\text{-}450_{LM_2}$, and the National Institutes of Health (Grants GM 20276, Stanford and AM 16508, Washington) for financial assistance.

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(17) Absorption spectra were recorded on a Cary 17 spectrophotometer at ambient temperatures. To avoid obscuring the 360-nm porphyrin transition, the reduced + CO P-450 spectrum was obtained through use of a minimal amount of sodium dithionite under anaerobic conditions. Such precautions are not necessary for MCD measurements because sodium dithionite shows only an extremely weak MCD effect in the 330-nm region.
(18) MCD measurements on the model complexes were made on a JASCO (Japan Spectroscopy Company) J-40 circular dichroism instrument using a 15 kG electromagnet.[19] The protein MCD spectra have been corrected for natural circular dichroism (MCD_{obsd} = MCD + CD). All data have been normalized and are expressed in the units of molar magnetic ellipticity, $[\theta]_M$, deg cm^2 dmol^{-1} G^{-1}. Measurements were made at ambient temperatures.
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(21) Cytochrome P-420 was obtained from cytochrome P-450 as described in ref 6f.

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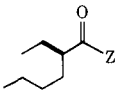
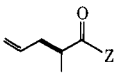
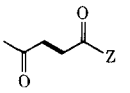
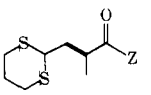
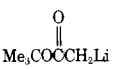
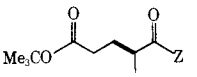
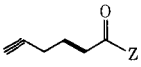
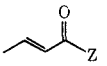
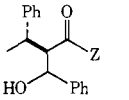
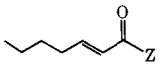
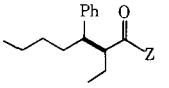
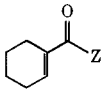
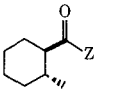
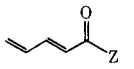
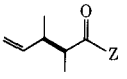
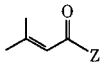
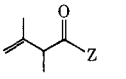
Charge Directed Conjugate Addition. The Addition of Strong Nucleophiles to Unsaturated Acyl Ylides

Sir:

The addition of nucleophilic carbon centers to polarized carbon–carbon multiple bonds constitutes one of the fundamental processes for carbon skeleton construction. Such processes are often hampered by the simultaneous susceptibility of the polarizing moiety to attack by the nucleophile. This factor is especially important in additions to carbonyl-activated olefins where the dominance of conjugate addition over carbonyl addition is usually limited to cases involving relatively weak nucleophiles.[1] The discrete conjugate addition of strong nucleophiles to Michael type acceptors generally requires the use of organocopper reagents.[2] Methods less general in nature involve select donors and acceptors.[3]

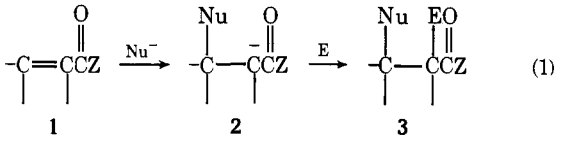
It seemed plausible that discrete conjugate addition reactions might be possible in unsaturated carbonyl-deactivated systems such as **1** (Z = X^-) where additions would result in the formation of stable but reactive dianionic adducts **2** (Z = X^-). Dianions of this type are well known.[4] In such systems, direct 1,4-addition might be expected to predominate over carbonyl addition owing to the marked resistance of charge-

Table I. Reactions of **1a** with Nucleophiles and Electrophiles

	Phosphorane	Nucleophile[a]	Electrophile[b]	Product[c]	Yield (%)[d]
1		MeLi	*n*-BuI		83
2		CH_2=CHLi	MeI		90
3			H_2O		70[e]
4			MeI		97
5			MeI		72
6		$Me_3SiC{\equiv}CCH_2Li$	H_2O		80[f]
7		PhLi	PhCHO		92[g]
8		PhLi	EtI		78[h]
9		MeLi	H_2O		85[i]
10		MeLi	MeI		84[h,j]
11		MeLi	MeI		82

[a] Typically, solutions in **1a** in THF were treated with a slight excess of nucleophile at −78 °C and allowed to warm at 25 °C. [b] A slight excess of electrophile was added to adduct **2** at −78 °C followed by warming to 25 °C. [c] Products were in general purified by preparative TLC (silica gel, EtOAc:CH_2Cl_2) and were characterized by the usual analytical techniques including satisfactory elemental analysis. [d] Yields are of pure, isolated materials. [e] The ketone was formed by hydrolysis of the enol ether during workup. [f] The trimethylsilyl group was removed by treatment with methanolic NaOH. [g] Product appears to be a single isomer of undefined stereochemistry. [h] A mixture of stereoisomers. [i] Shown to be the trans isomer by comparison with an authentic sample prepared from *trans*-2-methylcyclohexanecarboxylic acid. [j] Product identical with the one obtained upon treatment of the crotonyl ylide (entry 7) with vinyllithium followed by methyl iodide.

deactivated carbonyl systems to attack by even strong nucleophiles.[5] We now wish to report some results of our efforts to explore this concept through the scheme shown in eq 1.



(1)

1a, Z = −C(PPh$_3$)COOEt

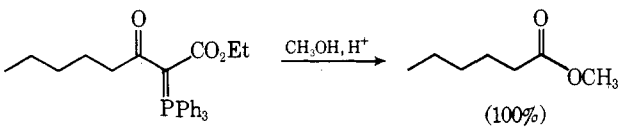
Our initial efforts have centered on neutral unsaturated acyl systems in which an anionic center present in an adjacent ylide system (**1**, = $^-$X-Y$^+$) has rendered the carbonyl unit resistant to attack by nucleophiles. It has previously been shown that acylphosphoranes possess this property as well as the ability to stabilize the new carbanionic center in **2**.[6] We have now found that unsaturated acyl derivatives of carboethoxymethylenetriphenylphosphorane, **1a**, Z = −C(PPh$_3$)COOEt, readily undergo direct conjugate addition reactions with a wide variety of carbanionic nucleophiles to give anionic adducts (**2a**) which are readily alkylated by alkyl halides.[7] These acyl ylides are in general readily prepared from acyl chlorides and Ph$_3$P=CHCO$_2$Et, are exceptionally stable, easily chromatographed and often crystalline.[8] Results of the addition of nucleophiles to these unsaturated acyl derivatives with subsequent utilization of the highly nucleophilic adduct are shown in Table I.

It can be seen that the addition step is tolerant of considerable variation in both the structure and reactivity of the nucleophilic donor. The more potent nucleophiles such as the alkyllithium reagents undergo rapid addition at −78 °C. Structural units corresponding to acyl equivalents (entries 3 and 4) are likewise useful as Michael-type donors.[9] Of special interest is the ability to effect the addition of functionalized nucleophiles (entries 4 and 5) which are not successfully introduced in a conjugate manner through their cuprates.[10] While *tert*-butyl 2-lithioacetate readily undergoes addition (entry 5), nucleophiles of lower reactivity such as the lithium enolate of acetophenone and propynyllithium do not. A further advantage enjoyed by these charge-protected carbonyl systems is illustrated in entry 6 where silyl group removal under highly alkaline conditions leaves the carbonyl system unaffected.

Additions are successful with a variety of substituted acceptors (entries 7–10). It is interesting to note that the diene system of entry 10 suffers exclusive β-carbon addition as opposed to the terminal additions observed in similar systems with Gilman reagents.[11] We have encountered difficulty only in the case of β,β-disubstituon (entry 11) where γ-proton abstraction predominates. This substitution pattern is often observed to interfere with Michael-type additions.[1b]

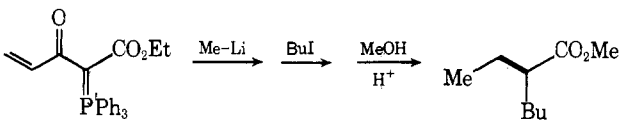
In all cases observed to date involving additions of organolithium derivatives, the resulting adducts (**2a**) undergo facile alkylation with common alkyl halides. Methylations with methyl iodide occur rapidly at 0 °C and *n*-alkyl iodides are consumed within 0.5 h at room temperature.[12] This high reactivity is in sharp contrast with the low reactivity of enolates generated through the use of Gilman reagents.[13]

While the acylphosphorane moiety in **3a** is highly resistant to attack by nucleophiles, the phosphonium salts resulting from treatment of these ylides with mineral acids are readily cleaved by nucleophilic solvents.[14] The acyl ylides **3a** obtained from the conjugate addition–alkylation process are readily converted into simple esters merely by heating in the presence of the desired alcohol containing an equivalent amount of concentrated hydrochloric acid. An example of this highly efficient conversion is shown in eq 2.[15]



(2)

An overall transformation may be envisioned involving sequentially: derivatization of unsaturated carboxylic acids, β-alkylation by charge directed conjugate addition, α-alkylation of the resulting anionic adducts with electrophiles, followed by terminal manipulation of the control element Z. The potential utility of such a sequence is enhanced by the ability to conduct high yield "one pot" conversions without the isolation of intermediates as illustrated in eq 3.



(3)

Preliminary experiments have shown that the principle of charge-directed conjugage addition is applicable to a number of systems where carbonyl interaction with an adjacent charge center suppresses 1,2-carbonyl addition. These studies will be detailed in future reports.

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(8) For example, using a modification of a reported procedure (S. T. D. Gough and S. Tripett, *J. Chem. Soc.*, 2333 (1962) treatment of 2 equiv of carboethyxymethylenetriphenylphosphorane with 1 equiv of crotonyl chloride for 15 min in benzene at 0 °C gave the corresponding ylide in 86% isolated yield. In the preparation of the acroyl derivative, lower yields result owing to polymerization. This derivative is conveniently prepared in high yield from 2-chloroacetyl chloride as above followed by treatment of the β-chloro ylide with sodium methoxide in methanol at 25 °C.
(9) Cuprates from α-methoxyvinyllithium (entry 3) have recently been shown useful for the introduction of the acetyl unit in a conjugate manner: C. G. Chavdarian and C. H. Heathcock, *J. Am. Chem. Soc.*, **97**, 3822 (1975); R. K. Boeckman, Jr., and K. J. Bruza, *J. Chem. Soc., Chem. Commun.*, 519 (1975).
(10) While cuprate derivatives of dithiane are not useful for conjugate additions, it has been reported that cuprates from substituted phenylthioacetals are successfully employed in this manner: see T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).
(11) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1611 (1973).
(12) Separate experiments have shown that these same anions, prepared by deprotonation of the corresponding saturated acyl ylides with BuLi, are readily alkylated by a variety of alkyl bromides (unpublished results with D. Majumdar).
(13) R. D. Boeckman, Jr., *J. Org. Chem.*, **38**, 4450 (1973).
(14) P. A. Chopard, R. J. G. Searle, and F. H. Devitt, *J. Org. Chem.*, **30**, 1015 (1965).
(15) In a typical procedure a solution of **3a** in the appropriate alcohol was treated with 1.05 equiv of concentrated hydrochloric acid and heated at reflux for 5 h followed by removal of excess alcohol by distillation, addition of water, and extraction of the ester with pentane. Yields were determined by GLC after workup.

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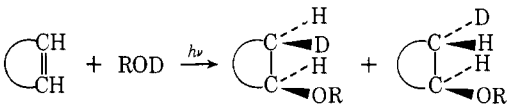
Stereochemistry and Mechanism of the Photochemical Addition of Methanol to Cycloheptenones

Sir:

The photochemical addition of alcohols to cycloalkenes (C_6–C_8) has been extensively investigated.[1] The reaction proceeds via carbocations formed by protonation of the double bond in a highly strained "trans" intermediate.[1,2] The additions are *not* stereospecific, since mixtures of cis and trans adducts are formed.



Cycloheptenones and cyclooctenones undergo a formally similar photoaddition of alcohols and other nucleophiles.[3] We have investigated their stereochemistry for the first time, and wish to report that *these additions are stereospecific.* Our results have important mechanistic consequences.

Irradiation[4] of **1**[5] in furan (0.05 M, 8 h) gave an 83% yield[6] of the trans adducts **2a** and **2b**.[7,8] We infer from this result that **1** photoisomerizes to **1t** which is trapped by the furan.[9] Irradiation of **1** in methanol (0.05 M, 6.5 h) gave ether **3** as the sole product,[8] in 61% (73%) yield.[6] In the NMR spectrum of **3**, H_6 appeared as a doublet of quartets (δ 3.68) showing that one of