and SbF_5 (^{19}F nmr and X-ray[8]) attacks **1** from the endo side.[9] The hypothetical homotropylium species **3** undergoes ring closure to form **5**. After complexation with the second mole of SbF_5, the excellent stabilization of the anionic portion allows the ring opening to **7**.

The addition of SO_2 to 1,3-dienes can take a concerted pathway as a cheletropic reaction.[10,11] With cyclooctatetraene, however, the lack of a planar diene system probably prevents a concerted SO_2 cycloaddition. There is an analogy to the 1,4 addition of SO_2 to **1** in the formation of the *N*-chlorosulfonyl isocyanate adduct of **1**, a reaction which is also assumed to proceed *via* a homotropylium zwitterion.[12]

The sulfone **4** dissociates quantitatively to **1** and SO_2 in the injection block of a gas chromatograph at 345°.

(8) J. W. Moore, H. W. Baird, and H. B. Miller, *J. Amer. Chem. Soc.*, **90**, 1358 (1968).
(9) R. Huisgen, G. Boche, and H. Huber, *ibid.*, **89**, 3345 (1967).
(10) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(11) W. L. Mock, *J. Amer. Chem. Soc.*, **91**, 5682 (1969); **92**, 3807 (1970).
(12) L. A. Paquette, J. R. Malpass, and T. R. Barton, *ibid.*, **91**, 4714 (1969).

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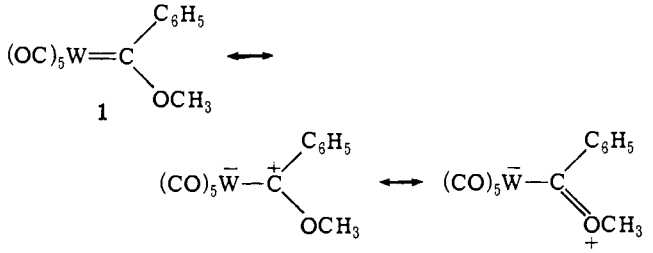
Reaction of Metal–Carbene Complexes with Wittig Reagents. A New Vinyl Ether Synthesis

Sir:

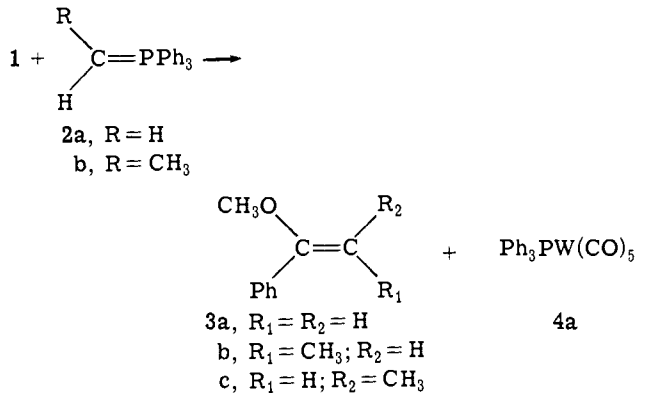
Since stable metal–carbene complexes were first synthesized and characterized by Fischer[1] in 1964, attempts to use these complexes as synthetic carbene or carbenoid sources have met with only limited success. Neither thermal,[2] photochemical,[3] nor pyridine-induced[4] decomposition of metal–carbene complexes in the presence of alkene have led to cyclopropanes. Oxidation of carbene complexes with pyridene *N*-oxide or with cerric ion in the presence of alkenes failed to give cyclopropanes and led only to the corresponding esters.[5,6] The only successful use of a stable metal–carbene complex in cyclopropane synthesis is the recently reported stereospecific reaction of $Ph(CH_3O)CCr(CO)_5$ with *trans*-methyl crotonate which gave a mixture of two cyclopropanes in 60% yield.[3]

Rather than viewing metal–carbene complexes as carbenoid sources, we have now centered our attention on the M^-–C^+ ylide nature of the metal–carbene bond in developing new approaches to the use of metal–carbene complexes in synthesis. Nucleophiles such as amines[7] and thiols[8] attack the electropositive carbene carbon atom to give substitution products. Here



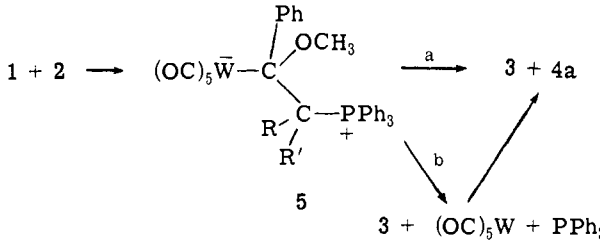
we report the reaction of a carbon nucleophile with a metal–carbene complex which leads to the removal of the carbene ligand from the metal in a synthetically useful way.

Phenylmethoxycarbenepentacarbonyltungsten(0) undergoes facile reactions with Wittig reagents to give enol ethers in high yields. Addition of methylidenetriphenylphosphorane (**2a**) to a solution of **1** in ether



at room temperature resulted in a rapid reaction giving methyl 1-phenylvinyl ether and pentacarbonyltriphenylphosphinetungsten(0) (**4a**, 40% yield). **3a** was identified by comparison of its ir and nmr spectra and gas chromatographic retention time with those of an authentic sample[9] and by conversion to acetophenone on treatment with dilute hydrochloric acid (82% yield from **1**). **4a** was identified by comparison of its infrared and mass spectra and its R_f on thin-layer chromatography with those of an authentic sample.[10] Similarly ethylidenetriphenylphosphorane (**2b**) reacted with **1** in diethyl ether to give **4a** (47% yield) and an approximately 1:1 mixture of methyl *cis*- and *trans*-1-phenylpropenyl ether **3b** and **3c**.[11] The vinyl ethers **3b** and **3c** were converted to propiophenone (98% yield from **1**) by treatment with dilute hydrochloric acid.

The reaction can be envisioned as proceeding *via* nucleophilic attack by the phosphorane carbon atom upon the electron-deficient carbene carbon atom to form a betaine-like intermediate **5** which subsequently frag-



(1) E. O. Fischer and A. Maasböl, *Angew. Chem., Int. Ed. Engl.*, **3**, 580 (1964); E. O. Fischer and A. Maasböl, *Chem. Ber.*, **100**, 2445 (1967).
(2) E. O. Fischer, B. Heckel, K. H. Dötz, J. Müller, and H. Werner, *J. Organometal. Chem.*, **16**, P29 (1969).
(3) E. O. Fischer and K. H. Dötz, *Chem. Ber.*, **102**, 1273 (1970).
(4) E. O. Fischer and A. Maasböl, *J. Organometal. Chem.*, **12**, P15 (1968).
(5) C. P. Casey, R. Boggs, and T. J. Burkhardt, unpublished results.
(6) F. A. Cotton and C. M. Lukehart, *J. Amer. Chem. Soc.*, **93**, 2672 (1971).
(7) J. A. Connor and E. O. Fischer, *Chem. Commun.*, 1024 (1970).
(8) E. O. Fischer and V. Keiner, *Angew. Chem., Int. Ed. Engl.*, **6**, 961 (1967).
(9) V. H. Lüssi, *Makromol. Chem.*, **103**, 68 (1967); S. Winstein and L. L. Ingraham, *J. Amer. Chem. Soc.*, **77**, 1738 (1955).
(10) T. A. Magee, C. N. Matthews, T. S. Wang, and J. H. Wotiz, *ibid.*, **83**, 3200 (1961).
(11) R. C. Fahey and C. Schubert, *ibid.*, **87**, 5172 (1965).

ments to form enol ether.[12] Two modes of fragmentation of the intermediate **5** have been considered. The first is a concerted cis elimination of the phosphine–tungsten complex from the intermediate **5** leading directly to **3** and **4a** (path a) in analogy with the direct formation of triphenylphosphine oxide in reactions of Wittig reagents with aldehydes. A second possible fragmentation pathway is an elimination from **5** giving vinyl ether, coordinately unsaturated $W(CO)_5$, and triphenylphosphine (path b). $W(CO)_5$ and PPh_3 could subsequently react to form **4a**. To distinguish between these two processes we have carried out the reaction of **1** and **2a** in the presence of tri-*p*-tolylphosphine which could compete with PPh_3 for capture of the coordinately unsaturated $W(CO)_5$ produced in pathway b. When equimolar amounts of **1** and $P(PhCH_3)_3$ were treated with an equivalent amount of **2a** in ether, a mixture of **4a** and pentacarbonyltri-*p*-tolylphosphinetungsten(0) (**4b**) was isolated in 42% yield by preparative thick-layer chromatography. Analysis of this mixture by nmr indicated a 1.8:1 ratio of **4a**:**4b**. In a control experiment it was demonstrated that $P(PhCH_3)_3$ does not react with **4a** under the reaction conditions. The greater amount of **4a** formed may be due to reaction of PPh_3 and $W(CO)_5$ within the initial solvent cage.

The reactions of metal–carbene complexes with other carbon nucleophiles are currently under investigation in an attempt to find synthetically useful ways of releasing the carbene ligand from metal–carbene complexes.

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(12) Reaction of isopropylidenetriphenylphosphorane with **1** did not lead to the formation of vinyl ethers. A possible explanation is that the increased steric crowding due to the additional methyl group in the isopropylidenephosphorane prevents the formation of the initial adduct **5**. The products of this reaction are currently under investigation.

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Active-Site Specific Inhibitors of Elastase

Sir:

Destruction of elastin and other fibrous connective tissue proteins associated with pulmonary emphysema and some inflammatory diseases has been shown to be caused by elastase and related neutral proteases.[1,2] Numerous site specific inhibitors of the homologous enzymes chymotrypsin and trypsin and for the related serine protease subtilisin BPN′ have been reported[3] and peptide chloromethyl ketones in particular have proven to be invaluable in the elucidation of the extended substrate binding sites of chymotrypsin and subtilisin by X-ray crystallography.[4] Although several stoichiometric inhibitors of elastase are known, reagents which resemble normal substrates have thus far proved inactive.[5,6] We wish to report the design and synthesis of a series of substrate-related peptide chloromethyl ketone inhibitors for the elastase from porcine pancreas, which has proven valuable in the study of the binding sites and biological function of elastolytic enzymes.

Benzyloxycarbonyl-L-alanyl chloromethyl ketone (Z-AlaCH_2Cl)[7] was prepared by reaction of an ether solution of Z-AlaCHN_2[8] with anhydrous HCl. Deblocking of Z-AlaCH_2Cl was accomplished at room temperature using HBr in acetic acid. The resultant low melting crystalline hydrobromide was coupled with a variety of blocked peptide acids using a mixed anhydride procedure[9] to obtain the compounds listed in Table I. The inhibitors were designed to partially resemble the normal elastase substrate elastin, a cross-linked polypeptide containing a high content of alanine, proline, and glycine, and to incorporate features found in the more reactive peptide substrates for this enzyme.[10]

Table I. Inhibition of Porcine Pancreatic Elastase (5×10^{-6} *M* with Peptide Chloromethyl Ketones in 5% Methanol at 30.0°

Inhibitor P_4 P_3 P_2 P_1	pH	Inhibitor concn $\times 10^4$, *M*	k_{obsd}[a] $\times 10^4$, sec^{-1}	k_{obsd}/I,[c] M^{-1} sec^{-1}
Ac- Ala-Gly-AlaCH_2Cl	6.5	5.0	2.3[b]	0.47
Ac- Ala-Ala-AlaCH_2Cl	6.5	5.0	13[c]	2.6
	5.0	5.0	2.6[d]	0.53
Z- Gly-Leu-AlaCH_2Cl	5.0	5.0	5.0[b]	1.0
Ac-Ala-Ala-Ala-AlaCH_2Cl	5.0	0.5	4.9[d]	9.8
Ac-Ala-Ala-Phe-AlaCH_2Cl	5.0	0.5	4.2[d]	8.4
Ac-Ala-Ala-Pro-AlaCH_2Cl	5.0	0.5	19[c]	38

[a] These values have a maximum spread of ±5%. [b] Average of two determinations. [c] Average of five determinations. [d] Average of three determinations.

Inhibition experiments were performed by adding a stock solution of elastase to a freshly prepared[11] solution of inhibitor in a 0.1 *M* acetate (pH 5.0) or 0.1 *M* phosphate (pH 6.5) buffer containing 10% (v/v) methanol. Residual enzyme activity was measured using a spectrophotometric assay for measuring the hydrolysis rate of BOC-Ala-ONP.[12] Good first-order kinetics were observed to at least 2 half-lives for all compounds. The data were processed using a least-squares computer

(1) C. Mittman, Ed., "Pulmonary Emphysema and Proteolysis," Academic Press, New York, N. Y., 1972.
(2) A. Janoff and R. S. Basch, *Proc. Soc. Exp. Biol. Med.*, **136**, 1045 (1971); A. Janoff and J. Blondin, *ibid.*, **136**, 1050 (1971); A. Janoff and J. Scherer, *J. Exp. Med.*, **128**, 1137 (1968).
(3) E. Shaw in "The Enzymes," 3rd ed, Vol. I, P. D. Boyer, Ed., Academic Press, New York, N. Y., 1970, Chapter 2.
(4) J. C. Powers and P. E. Wilcox, *J. Amer. Chem. Soc.*, **92**, 1782 (1970); D. M. Segal, J. C. Powers, G. H. Cohen, D. R. Davies, and P. E. Wilcox, *Biochemistry*, **10**, 3728 (1971); D. M. Segal, G. H. Cohen, D. R. Davies, J. C. Powers, and P. E. Wilcox, *Cold Spring Harbor Symp. Quant. Biol.*, **36**, 85 (1972); J. Kraut, J. Robertus, J. J. Birktoft, R. A. Alden, P. E. Wilcox, and J. C. Powers, *ibid.*, **36**, 117 (1972); J. D. Robertus, R. A. Alden, J. J. Birktoft, J. Kraut, J. C. Powers, and P. E. Wilcox, *Biochemistry*, **11**, 2439 (1972).
(5) W. E. Brown and F. Wold, *Science*, **174**, 608 (1971); L. Visser, D. S. Sigman, and E. R. Blout, *Biochemistry*, **10**, 735 (1971).
(6) H. Kaplan, V. B. Symonds, H. Dugas, and D. R. Whitaker, *Can. J. Biochem.*, **48**, 649 (1970).
(7) All new compounds have been fully characterized (combustion analysis, ir, nmr, mass spectra).
(8) B. Penke, J. Czombos, L. Balaspiri, J. Petres, and K. Kovacs, *Helv. Chim. Acta*, **53**, 67 (1970).
(9) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **89**, 5012 (1967).
(10) P. Geneste and M. L. Bender, *Proc. Nat. Acad. Sci.*, **64**, 683 (1969); R. C. Thompson and E. R. Blout, *ibid.*, **67**, 1734 (1970); D. Atlas, S. Levit, I. Schechter, and A. Berger, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **11**, 281 (1970).
(11) A slow hydrolysis of the chloro ketones occurred upon standing in 10% (v/v) methanol–water as measured by a decreased k_{obsd} with aged chloro ketone solutions.
(12) L. Visser and E. R. Blout, *Biochim. Biophys. Acta*, **268**, 257 (1972).