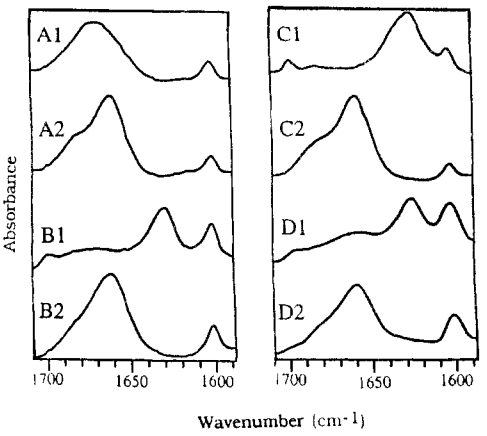

Figure 1. FTIR of resin-bound peptides in DCM and 2 M LiBr/THF. A1: Peptide A in DCM. A2: Peptide A in 2 M LiBr/THF. B1: Peptide B in DCM. B2: Peptide B in 2 M LiBr/THF. C1: Peptide C in DCM. C2: Peptide C in 2 M LiBr/THF. D1: Peptide D in DCM. D2: Peptide D in 2 M LiBr/THF. Peptide D: Boc-(amyloid β1-41)-resin, fully protected.[14,15] The band at 1601 cm^{-1} is due to polystyrene.

swelling of the Kaiser oxime resin was very different from that of the three peptide-resins tested (Table I).[20] THF was very effective in swelling the oxime resin but was a poor solvent for swelling peptide-resins. The peptide-resins differed from each other in their swelling behavior. Peptide A[21] swelled effectively in all of the solvents tested; this behavior was typical of most of the peptide-resins we have analyzed. In contrast, peptides B[22] and C[23] were slightly swollen in DCM and DMF but had a much larger volume in 2 M LiBr/THF. In all cases, peptide-resins reached their greatest volume in 2 M LiBr/THF.

Resin-bound peptides were suspended in solvent and analyzed by FTIR[24] to determine the structural basis for the swelling of peptide-resins (Figure 1). A monomeric amide in DCM absorbs at ca. 1680 cm^{-1}. The presence of a band at 1630 cm^{-1} is indicative of strongly hydrogen bonded β-sheet structure; an additional weak band at ca. 1695 cm^{-1} is indicative of antiparallel β-sheet.[25] Peptide A did not assume β-sheet structure in DCM or in 2 M LiBr/THF (Figure 1; A1, A2). Peptides B, C, and D were aggregated antiparallel β-sheets in DCM (Figure 1; B1, C1, D1). Aggregation was disrupted in 2 M LiBr/THF, as evidenced by the disappearance of the band at 1630 cm^{-1} (Figure 1; B2, C2, D2). The observed amide I band in 2 M LiBr/THF (1660 cm^{-1}) probably represents a lithium-amide complex.[6]

Most peptides can be cleaved from the Kaiser oxime resin in >90% yield[26] using *N*-hydroxypiperidine[27] (HO-Pip) or amino acid tetra-*n*-butylammonium salts.[18] Peptide A, which does not aggregate, was cleaved in high yield in both DCM[18] and in 2 M LiBr/THF (Table II). However, cleavages of peptides B and D, which form β-sheet aggregates in DCM, proceeded in very low yields. Cleavage yields improved dramatically when 2 M LiBr/THF was used as the solvent. The yield for cleavage of peptide C was high in DCM, but was improved in 2 M LiBr/THF.

The principles illustrated here should be applicable to other reactions in solid-phase peptide synthesis. New solvent systems can be evaluated using FTIR and simple swelling measurements in order to minimize aggregation and increase chemical yields. Our results indicate that 2 M LiBr/THF is a powerful solvent for resin-bound peptides. While couplings to unaggregated resin-bound peptides seem to be slower in this solvent system than in dimethyl formamide (DMF),[28] it may serve as a last resort for coupling to certain resin-bound peptides which aggregate strongly in DMF. For our fragment-coupling strategy, this solvent system may prove invaluable for the solvation of protected fragments which are sparingly soluble in organic solvents.[29]

Acknowledgment. We would like to thank Professor Dieter Seebach for sharing his results with us prior to publication. Financial support for this work from the Camille and Henry Dreyfus Foundation (New Faculty Award), the Whitaker Health Sciences Fund, the National Institutes of Health (AG08470-01), Merck & Co. (Faculty Development Grant), and the Procter and Gamble Co. (University Exploratory Research Program) is gratefully acknowledged.

(20) Swelling measurements in Table I were made by washing a sample of resin (ca. 0.5 g) with the solvent and suspending the resin in the solvent in a glass column (i.d. 1.0 cm) above a glass frit. The resin was allowed to settle until all excess liquid had drained through the frit. The height of the resin was measured, and the procedure was repeated twice. The same sample of resin was used for all solvents.

(21) The sequence of the protected resin-bound peptide A is derived from the N-terminal region (residues 1-9) of the amyloid-β protein.

(22) The sequence of the protected resin-bound peptide B is derived from the consensus 16 amino acid repeating sequence of two bacterial ice nucleation proteins. (Warren, G.; Corotto, L.; Wolber, P. *Nucl. Acids Res.* **1986**, *14*, 8047.)

(23) The sequence of the protected resin-bound peptide C is derived from the C-terminal region (residues 34-42) of the amyloid-β protein.

(24) FTIR measurements were made using a Mattson Cygnus 100V spectrometer. Peptide-resins were swollen and suspended in solvent. A drop of this suspension was placed between the windows of a solution cell (AgCl windows for DCM; CaF_2 windows for 2 M LiBr/THF.).

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(26) Cleavage yields were determined by amino acid analysis (Waters Picotag) of the resin before and after cleavage. Cleavage products of peptides A, B, and C have been purified and fully characterized.

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(28) The tetrapeptide LMVG was prepared on the Kaiser oxime resin. Boc-amino acids were activated as the preformed symmetric anhydride in THF. Couplings were carried out in 2 M LiBr/THF (1 h) with yields of 60-80%, compared with 95-100% for couplings in DCM. Current efforts include optimization of coupling time to allow quantitative coupling.

(29) We have had some success using 1 M LiBr/THF as solvent for gel permeation (Waters Ultrastyragel 1000-Å column) purification of protected peptides which, due to their insolubility, cannot be easily purified by existing methods.

Alkyne Insertion Reactions of Metal-Carbenes Derived from Enynyl α-Diazo Ketones [$R'CN_2COCR_2CH_2C{\equiv}C(CH_2)_{n-2}CH{=}CH_2$]

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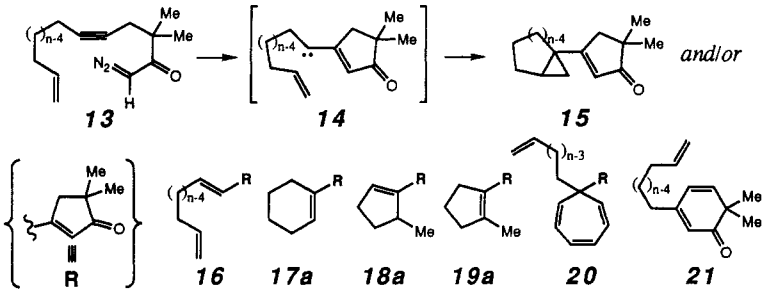
Summary: The title substrates react with a variety of metal catalysts to give metal-dependent product arrays (including tricyclic cyclopropanes and others formally arising from the vinylogous α-keto carbene **3** shown in Scheme I) of both synthetic and mechanistic interest.

Stoichiometric quantities of Fischer carbene complexes [e.g., $(CO)_5Cr{=}C(R)(OMe)$] react both inter- and intra-

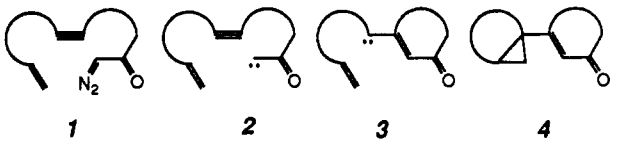
Table I. Metal-Induced Reactions[a] of Enynyl α-Diazo Ketones 13a and 13b



entry	13–21	n	M cat.	mol %	temp, °C	time, h	% yield[b] 15	16	17	18	19	20	21[11]
1	a	5	$Rh_2(OAc)_4$	14	80	1	18	28	–	–	–	–	–
2	a	5	$Rh_2(OAc)_4$	6	23	14	30	9[c]	–	–	–	14	2
3	a	5	$Pd(acac)_2$	14	80	7	87	3	–	–	–	–	–
4	a	5	$Cu(acac)_2$	15	80	12	29	7	–	–	–	–	–
5	a	5	$Rh(acac)(=)_2$	26	80	10	36	–	25	<4	<4	–	–
6	a	5	$Rh_6(CO)_{16}$	17	80	12	59	–	<1	–	15	–	–
7	a	5	$Pd(PPh_3)_4$	2.5	60	12	13	60	–	–	–	–	–
8	a	5	$Co_2(CO)_8$	100	60	12	51	–	–	–	10	–	–
9	b	6	$Pd(acac)_2$	8	80	12	21	8	–	–	–	–	–
10	b	6	$Rh_2(OAc)_4$	10	23	20	9	10[d]	–	–	–	6	8

[a] Reactions were carried out in benzene at [13] = 0.01–0.06 M under N_2; 13a was stable to these conditions in the absence of catalyst. [b] Material purified by MPLC or HPLC on SiO_2. A "–" entry means none of that product was observed. [c] Plus ≈1% of *Z*-16a. [d] Plus ≈3% of *Z*-16b.

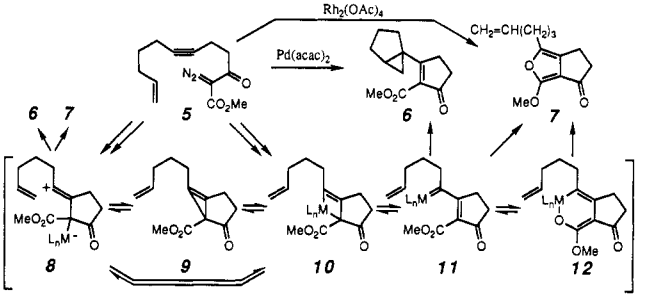
Scheme I



molecularly with enynes in synthetically useful and mechanistically interesting manners.[2] We have begun to investigate conceptually related processes which utilize *catalytic* quantities of metal species with the goal of discovering synthetically and/or mechanistically analogous and/or complementary transformations and now report some of the initial observations.[3]

α-Diazo carbonyl compounds are recognized precursors to carbenoid species when exposed to many metal complexes or salts.[4] Moreover, much is known about the reactions of such species with alkenes, in both inter- and intramolecular contexts, to generate, e.g., cyclopropanes, dihydrofurans, and CH-insertion products. In Scheme I is outlined a reaction manifold formalism which identifies a possible pathway for the reaction of an α-diazo ketone

Scheme II



bearing an appropriately tethered enyne unit (1) such that the alkyne is predisposed for preferential reaction with the carbenoid center in the initially generated, reactive intermediate 2. Carbenoid/alkyne "metathesis" within 2 could give a functional equivalent of the vinyl carbenoid 3, which might then give cyclopropane 4 and/or any of a variety of other carbene-derived products.

That such an alkyne-incorporation process is feasible was demonstrated[3,5] by the reaction of the α-diazo-β-keto ester 5[6a] with $Pd(acac)_2$ (9 mol %, PhH, 80 °C) to give the cyclopropane 6 in 78% yield as the only isolated product (Scheme II). That this general process is susceptible to dramatic metal dependencies was first suggested by exposure of 5 to $Rh_2(OAc)_4$ (2.5 mol %, PhH, 80 °C) to give the fused furan 7, which presumably arises from trapping of a carbenoid carbon by the ester carbonyl oxygen, in 65% yield. The divergent outcome of these two reactions demands that a metallated species is involved in the product determining step. Although we cannot yet say with cer-

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1985–89. (b) Rohm & Haas Graduate Fellow, 1989–90. (c) NSF-REU, summer 1989. (d) 3M Graduate Fellow, 1986–87.

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(6) (a) Prepared from $EEOCH_2C{\equiv}CH$ with (i) *n*-BuLi, $Br(CH_2)_{n-2}CH{=}CH_2$ (*n* = 5, for 5 and 13a and *n* = 6 for 13b); (ii) H_3O^+; (iii) *n*-BuLi, TsCl; (iv) $LiCH_2COCHLiCO_2CH_3$; (v) TsN_3, Et_3N. (b) Prepared by i–iii; (2v) $Me_2LiCCO_2CH_3$; (v) KOH, H_2O; (vi) ClCOCOCl; (vii) CH_2N_2.

tainty whether species 8 or 11 are involved in either or both of the Rh(II) and Pd(II) reactions [or whether the metal remains at the 2-position (e.g., 8)[7] or actually migrates to the distal carbon (e.g., 10/11) of the alkyne], at the very least these reactions do not both proceed via nonmetal-mediated rearrangements (e.g., of the cyclopropene 9[5,8a,b]). We hypothesize that the strain in 9[9] is a key factor in the success of these polycyclizations; 9 either is never formed or is readily reconverted[8b-e] into species like 8, 10, and 11. An attractive intermediate by which to rationalize formation of furan 7 is the rhodacycle 12.[10]

Reactions of the α-diazo ketones 13[6b] were examined next using a variety of metal catalysts (Table I). Once again the product array was quite dependent upon the specific catalyst, but products 15–20 can be simplistically viewed as arising by pathways diverging from the vinylogous α-keto carbene 14.[11] To rule out the possibility that any of the non-cyclopropanes 16–21 arose via secondary, metal-catalyzed,[12a-c] or thermal[12d] isomerizations of the strained vinylcyclopropane, control experiments with pure 15a and each of the catalysts under conditions listed in the table (both in the absence and presence of added ethyl diazoacetate) gave no indication of consumption of 15a.

The question of the degree and nature of association of the metal atom with the alkyne carbons in these reactions is a mechanistically significant issue, and additional studies to probe this point are in progress.

Acknowledgment. This investigation was supported by Grant GM-38854 awarded by the DHHS and by an award from the Alfred P. Sloan Foundation.

Supplementary Material Available: Spectral and characterization data for compounds 5–7, 13a/b, 15a/b, *E*- and *Z*-16a/b, 17a–19a, 20a/b, and 21a/b (5 pages). Ordering information is given on any current masthead page.

(7) (a) The Doyle mechanism[4e,7b] for Rh(II)-catalyzed diazocarbonyl/olefin cyclopropanation involving an electrophilic attack of the carbene carbon on the alkene with no prior complexation of the olefin and metal has a vinylogue which may be be envisioned to proceed via species 8. (b) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

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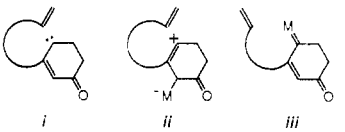
(11) Likewise, the products 21 (along with several polycyclic cyclohexenones from the $Rh_2(OAc)_4$-catalyzed decomposition of 13—submitted manuscript) could arise via the free carbene i (an isomer of 14) or the metal complexes ii and/or iii.



i *ii* *iii*

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A Complex Induced Proximity Effect in the Anionic Fries Rearrangement of *o*-Iodophenyl Benzoates: Synthesis of Dihydro-*O*-methylsterigmatocystin and Other Xanthones

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Summary: The success of an anionic Fries rearrangement, used to synthesise dihydro-*O*-methylsterigmatocystin and other xanthones, is dependent on the presence of a remote methoxyl substituent.

The anionic Fries rearrangement of *o*-bromophenyl esters initiated by lithium–bromine exchange proceeds in moderate yield to the ortho rearranged product only, by an intramolecular pathway.[1] Our current concern with the development of versatile synthetic routes to xanthones in general and the *Aspergillus* mycotoxins in particular[2] led us to reexamine this reaction in spite of the very poor yield of *o*-hydroxybenzophenone (7%) obtained[1] in the rearrangement of *o*-bromophenyl benzoate.

Eighteen benzoates (Table I) prepared from the *o*-iodophenols[2] (or *o*-bromophenols) were rearranged by treatment with *n*-butyllithium or *sec*-butyllithium (entries 11 and 16) at −100 °C followed by warming to −70 °C. After 2 h at that temperature the reaction mixtures were quenched with aqueous ammonium chloride and the products were isolated.

The intramolecular nature[3] of the reaction makes it obligatory that a benzoxetane intermediate is formed by 4-*exo*-*trig* attack of the lithiated carbon atom at the ester carbonyl group. The experimental results compiled in Table I suggest that a juxtaposition of the reacting centers suitable[4] for such a nucleophilic addition is favored by methoxyl substitution at specific sites, in particular by the presence of a methoxyl group at the R_1 position ortho to the ester carbonyl. The dramatic divergence observed in

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(3) We have confirmed this by a "crossover" experiment. An equimolar mixture of benzoates (entries 2 and 7) rearranged under the standard conditions provided only the products of the intramolecular reaction pathway (i.e. the benzophenones in entries 2 and 7). No trace of a crossover product was detected.

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