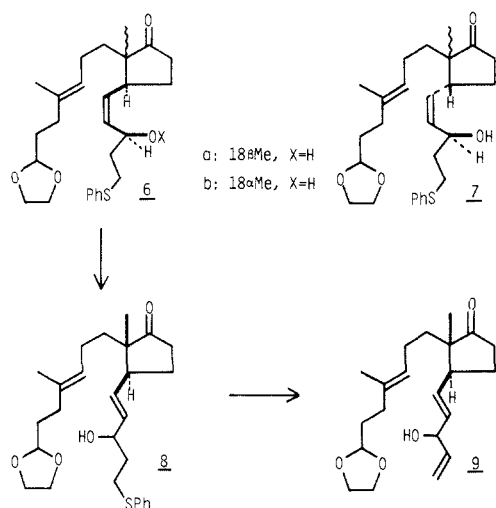


Scheme II



**5a** (3.8 mmol), prepared by applying Noyori's procedure,<sup>15</sup> in ether at  $-70$  °C for 1.5 h, followed by addition of an excess hexamethylphosphoramide at  $-40$  °C, methylation of the resulting enolate with an excess MeI at  $-30$  °C, and hydrolysis of the 1-methoxyisopropyl group (0.1 N HCl/THF) afforded a readily separable mixture of ketones **6a,b**:**7a,b** (94:6)<sup>16</sup> in 64% overall yield. The HPLC analysis of a mixture of **6a** and **6b** revealed two peaks in an 80:20 ratio.<sup>16</sup> The assignment of the major isomer to **6a** is based on our previous results.<sup>9,10</sup> Transformation of **6a** to the dienyl chloride **3b** required three operations: (1) isomerization of the (*Z*)- to the (*E*)-olefin, (2) generation of the (*E,E*)-dienyl chloride, and (3) cyanohydrin ether formations. The (*Z*)-olefin in **6a** was isomerized to the (*E*)-olefin by the double [2,3]-sigmatropic rearrangements<sup>17</sup> (*p*-TolSICI/Et<sub>3</sub>N, P(OMe)<sub>3</sub>/MeOH) to give the alcohol **8** in 85% overall yield. Acetylation of **8** (Ac<sub>2</sub>O/pyridine), oxidative elimination of the terminal phenyl sulfide (NaIO<sub>4</sub>, 160 °C/xylene-pyridine), and methanolysis of the acetyl group (K<sub>2</sub>CO<sub>3</sub>/MeOH) gave **9** in 61% overall yield. The allylic chlorination of **9** (SOCl<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>-pyridine at  $-70$  °C, 83% yield), hydrolysis of the acetal (3 N HCl/THF, 73% yield), and protected cyanohydrin formations of the resulting keto aldehyde **3a** under our standard conditions<sup>8a</sup> gave **3b** in 90% yield (Scheme II).

Cyclization of **3b** with LiN(TMS)<sub>2</sub> in dioxane at 80 °C gave the macrocyclic product **2b** in 75% yield.<sup>18</sup> Acid treatment of **2b**, followed by base treatment of the resulting cyanohydrin gave the diketone **2a**<sup>19</sup> in 65% overall yield from **3b**. The Diels–Alder reaction of **2a** (in xylene at 180 °C, a catalytic amount of methylene blue) was completed within 1 h to give the tetracyclic diketone **1**<sup>19</sup> in 84% yield. None of the diastereomer of **1** could be detected by HPLC and NMR analyses. The <sup>1</sup>H NMR spectral data of the synthetic ( $\pm$ )-**1** were identical with those previously reported.<sup>20</sup> The predictions of stereoselectivity based on calculations are in quantitative agreement with the experimental trends.

This type of stereocontrol might have predictable value in organic synthesis because easy formations of the tricycles take

place under mild condition and even with a less reactive dienophile. Moreover, the ab initio MM2 transition structure models are useful in designing the synthetic key intermediate providing high stereoselectivity.

**Supplementary Material Available:** Preparation of **4**, III, **5b**, and **3b**, experimental and spectral data for IV, VIII, IXa, IXb, III, XI, XIIa, XV, **6a**, **9**, **3a**, **3b**, and **2a**, MM2 calculations, the processes of one-pot conjugate addition–enolate methylation, the cyclization of **3b**, the Diels–Alder reaction of **2a**, and spectral data for **1** and **4** (22 pages). Ordering information is given on any current masthead page.

### Fischer Carbene Mediated Conversions of Enynes to Bi- and Tricyclic Cyclopropane-Containing Carbon Skeletons

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The reaction of Fischer carbene complexes with enyne substrates represents a potentially valuable strategy for the construction of bicyclic (or tricyclic if the carbene is tethered to the enyne) carbon skeletons (cf. **9**, Scheme I) through a coupling of the well-established mode of carbene/alkyne reactions to generate presumed vinylcarbene intermediates (cf. **1**  $\rightarrow$  **2**  $\rightarrow$  **3**)<sup>2</sup> with the less often exploited reaction of carbenes with alkenes to generate cyclopropanes (cf. **3**  $\rightarrow$  **4**  $\rightarrow$  **9**). The latter process of this pair is admittedly suspect of having limitations since intermolecular cyclopropane formation by donor-atom-substituted carbenes (e.g., R(MeO)C=M(CO)<sub>3</sub>) is general only with electron deficient alkenes;<sup>3</sup> simple or electron rich olefins often suffer competitive reactions such as metathesis via presumed metallacyclobutane intermediates (cf. **4**  $\rightarrow$  **8**).<sup>4</sup> Indeed, neither of two previous reports of reaction between carbene complexes and enynes has described the formation of cyclopropane-containing products. In one,<sup>5</sup> the (catalytic) conversion of 2-alkynyl-2'-alkenylbiphenyls to 5-alkenylphenanthrenes proceeded by metathesis which was driven by generation of the aromatic phenanthrene skeleton. In the other,<sup>6</sup> the parent hept-6-en-1-yne produced bicyclic cyclobutanones and simple furans. Carbon monoxide insertion into the vinyl carbene (cf. **3**  $\rightarrow$  **7**) to provide a vinyl ketene (an intermediate which has also been proposed in naphthol formation when aryl-substituted carbenes are reacted with alkynes) followed either by an internal 2 + 2 cycloaddition (cf. **7**  $\rightarrow$  **5**) or by rearrangement (cf. **7**  $\rightarrow$

(1) (a) 3M Graduate Fellow, 1986–1987. (b) Fellow of the Alfred P. Sloan Foundation, 1985–1989. (c) Lando-SOHIO Undergraduate Research Fellow, summer 1986.

(2) For excellent overviews of both synthetic and mechanistic aspects of the chemistry of Fischer and other electrophilic carbenes, see (a) Dotz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 783–811.

(3) (a) Fischer, E. O.; Dotz, K. *Chem. Ber.* **1970**, *103*, 1273. (b) Dotz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 1356.

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(16) TLC: **6a,b** *R*<sub>f</sub> 0.19, **7a,b** *R*<sub>f</sub> 0.34 (55:45 hexane–AcOEt); HPLC: **6a** *R*<sub>t</sub> = 14–15 min, **6b** *R*<sub>t</sub> = 16–18 min, silica gel 60–5  $\mu$ m, 7.5 o.d  $\times$  300 mm, 3.0 mL/min, 6% *i*-PrOH–hexane.








(17) Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 6774.

(18) When the reaction was carried out at 100 °C in dioxane, the tetracyclic product resulting from the transannular Diels–Alder reaction was formed in ca. 10% yield.

(19) Macrocyclic **2a**: NMR (CDCl<sub>3</sub>, 500 MHz) 0.86 (s, 18-Me), 1.48 (d, *J* = 0.6 Hz, 19-Me). Tricyclic **1**: NMR (CDCl<sub>3</sub>, 90 MHz) 0.95 (s, 18-Me, lit.<sup>20</sup> 0.94), 0.99 (s, 19-Me, lit. 0.99), 5.62 (br s, C(6,7)-olefin, lit. 5.57); CMR (CDCl<sub>3</sub>, 22.5 MHz) 219.92, 212.15, 130.23, 127.09, 49.87, 48.44, 44.13, 43.74 (2  $\times$  C), 36.49, 36.29, 35.90, 34.66, 33.81, 31.92, 21.67, 21.28, 20.37, 13.97.

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Table I. Intermolecular Reactions of (MeO)(Me)C=Cr(CO)<sub>5</sub> (10) with Enynes (11)<sup>g</sup>

enynes (11)	product no., yield, <sup>a</sup> (E:Z ratio) <sup>a,9</sup>			
	cyclopropane 12 <sup>f</sup>	cyclobutanone 13	diene 14	furan 15
 <b>11a</b>	<b>12a</b> R <sup>1</sup> = H R <sup>2</sup> = H n = 1 69% (5 <sup>10b</sup> :1 <sup>10b</sup> )	b	b	b
 <b>11b<sup>10a</sup></b>	<b>12b</b> R <sup>1</sup> = Me R <sup>2</sup> = H n = 1 22% (3 <sup>10a,b</sup> :2 <sup>10b</sup> )	<b>13b</b> R <sup>1</sup> = Me R <sup>2</sup> = H R <sup>3</sup> = H 30% (2 <sup>10b</sup> :1 <sup>10b</sup> )	b	b
 <b>11c<sup>10a</sup></b>	<b>12c<sup>10b</sup></b> R <sup>1</sup> = H R <sup>2</sup> = Me n = 1 2% (1:trace) <sup>c</sup>	<b>13c<sup>10b</sup></b> R <sup>1</sup> = H R <sup>2</sup> = Me R <sup>3</sup> = H 6% (1:trace) <sup>c</sup>	<b>14</b> 30% (2 <sup>10a,b</sup> :1 <sup>10b</sup> )	<b>15c<sup>e,10b</sup></b> R <sup>2</sup> = Me R <sup>3</sup> = H n = 1 7%
 <b>11d<sup>10a</sup></b>	b	<b>13d<sup>d,10b</sup></b> R <sup>1</sup> = H R <sup>2</sup> = Me R <sup>3</sup> = Me 7% (1:0)	<b>14</b> 23% (3.6:1)	<b>15d<sup>10b</sup></b> R <sup>2</sup> = Me R <sup>3</sup> = Me n = 1 8%
 <b>11e<sup>10a</sup></b>	<b>12e</b> R <sup>1</sup> = H R <sup>2</sup> = E n = 1 64% (4 <sup>10b</sup> :1)	b	b	b
 <b>11f<sup>10a</sup></b>	<b>12f</b> R <sup>1</sup> = H R <sup>2</sup> = H n = 2 46% (1:10 <sup>10b</sup> )	b	b	<b>15f<sup>e,10b</sup></b> R <sup>2</sup> = H R <sup>3</sup> = H n = 2 20%
 <b>11g<sup>10a</sup></b>	b	b	b	<b>15g<sup>e</sup></b> R <sup>2</sup> = H R <sup>3</sup> = H n = 3 20%

<sup>a</sup>Yields and product ratios refer to masses after MPLC or HPLC separation unless otherwise noted. <sup>b</sup>None observed (i.e., <2%). <sup>c</sup>Ratio estimated from <sup>1</sup>H NMR analysis of a mixture. <sup>d</sup>It is possible that this structure is instead a "crossed" bicyclo[3.1.1]heptanone. <sup>e</sup>Facile air oxidation to a methyl Z-2-substituted-4-oxo-pentenoate observed. <sup>f</sup>The hydrolysis ketones corresponding to **12a**, **12b**, **12e**, and **12f** gave satisfactory combustion data. <sup>g</sup>E = CO<sub>2</sub>Me.

**6**) apparently intercepted any potential precursors for cyclopropane formation. Particularly relevant is the reaction of (CO)<sub>5</sub>W=C-(OMe)CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub> with a series of alkynes which generated, for the first time, bicyclic cyclopropanes arising, in that case, from bimolecular insertion of the alkyne into the tungsten-carbene bond (cf. **1** → **3**) and subsequent cyclopropanation of the olefin originally bound to the carbene moiety.<sup>7</sup> We were interested in the additional molecular complexity that would accompany formation of products like **9** which contain a higher density of sp<sup>3</sup>-hybridized atoms (and their attendant stereochemical features) rather than those flatter frameworks which arise from the much more thoroughly studied union of Fischer carbenes with alkynes, diynes, and nitriles to generate phenols and naphthols, phenols and cyclohexadienones, and pyridines, respectively.<sup>2b</sup> Herein are reported our initial observations of the reaction of carbene complexes with enyne-containing substrates.

The results of intermolecular reactions between pentacarbonyl(1-methoxyethylidene)chromium (**10**) and a series of simple enyne substrates **11** are summarized in Table I. Reaction<sup>8</sup> of **11a** with **10** demonstrates the feasibility of the overall method

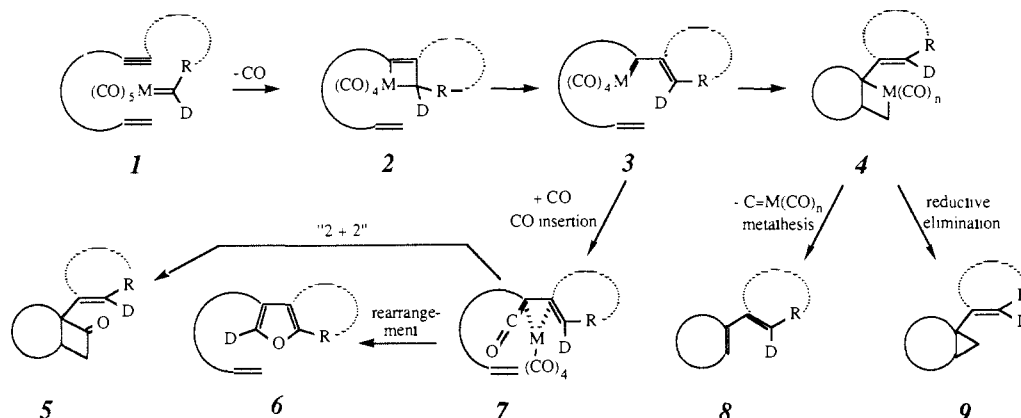
for synthesis of bicyclic cyclopropanes (bicyclo[3.1.0]hexanes, **12** [*n* = 1]). (*E*)- and (*Z*)-Enol ethers **12a**<sup>9</sup> were isolated in 69% yield, and no evidence of cyclobutanone formation was obtained. These and all other enol ethers described here could be easily hydrolyzed to the corresponding ketones and occasionally did so spontaneously. In fact, several reactions were carried out in CDCl<sub>3</sub>, and ketone formation was observed directly by NMR assay of the reaction progress. Addition of substituents to the alkene (substrates **11b–e**) led to varying amounts of competing reaction pathways. The methallylated enyne **11b** formed comparable amounts of cyclopropanes **12b** and cyclobutanones **13b**. The dienes **14** from metathesis became the major products with the crotyl- and prenyl-containing substrates **11c** and **11d**, and the furans **15c** and **15d** were observed as well. These results are consistent with the notion that additional substitution of the alkene inhibits (in both kinetic and thermodynamic senses) its ability to form η<sup>2</sup>-complexes with electron-deficient metal species like **3**, thereby providing time for competing ketene then cyclobutanone<sup>6</sup> and/or furan<sup>6</sup> formation. The metathesis products **14** presumably arise via an intermediate like **4** which is common to formation of products like both **8** and **9**. Metathesis is apparently promoted

(7) Rudler, H.; Parlier, A.; Platzler, N.; Fontanille, M.; Soum, A. *J. Organomet. Chem.* **1985**, *287*, C8.

(8) Tabulated reactions were typically conducted at [carbene] = ~0.07 M in benzene at 80 °C under N<sub>2</sub> for 2 h in the presence of 1.5 equiv of enyne.

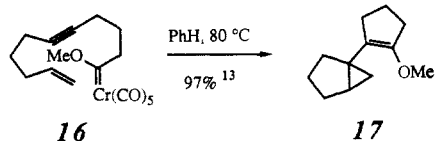
(9) (*E*)- and (*Z*)-Enol ethers were assigned on the basis of <sup>13</sup>C NMR analysis: Strobel, M. P.; Andrieu, C. G.; Paquer, D.; Vazeux, M.; Pham, C. *C. Nouv. J. Chim.* **1980**, *4*, 101.

Scheme 1



when it is possible to generate a new, electron-deficient carbene which bears one<sup>5</sup> or more stabilizing donor alkyl groups (i.e., Me versus H). Consistent with this is that substrate **11e**, containing a crotonate ester moiety, gave cyclopropanes **12e** as the only observed product; metathesis would have required generation of an unstable, carbomethoxy-bearing Fischer carbene. Enynes **11f** and **11g** are one- and two-carbon homologs of **11a** and should form bicyclic products more slowly. The former gave the bicyclo[4.1.0]heptanes **12f** as the dominant adducts, although the competition product, furan **15f**, was also observed. The latter produced furan **15g** as the only identifiable product; cyclization to the bicyclo[5.1.0]octane skeleton is now slowed to the point where other processes compete exclusively.

Covalent attachment of the carbene center to the enyne moiety (see dashed bond in **1**) provides an opportunity for formation of three rings during the reaction course. Carbene **16**<sup>10b</sup> was syn-



thesized<sup>11</sup> to test this possibility. Warming **16**<sup>12</sup> provided the labile tricyclic enol ether **17**<sup>10a</sup> in excellent yield.<sup>13</sup> Thus, the viability of this potentially powerful tricyclization operation has been clearly demonstrated. Studies to delineate stereochemical,<sup>14</sup> mechanistic,

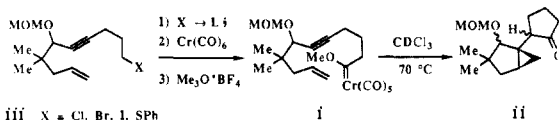
(10) This compound was characterized by <sup>1</sup>H NMR, IR, and (a) combustion and/or (b) HRMS analysis.

(11) Metal-halogen exchange between *t*-BuLi (2 equiv) and 1-iododec-9-en-4-yne (made in five steps from pent-4-yn-1-ol and 1-bromopent-4-ene) at -78 °C in the presence of Cr(CO)<sub>6</sub>, warming to 0 °C, and methylation (Vedejs, E. *Organic Syntheses*; Wiley: New York, 1987; p 140) provided **16** in 57% yield.

(12) Sealed tube in benzene under argon at 80 °C for 5 h.

(13) Filtration of the reaction mixture through florisil provided tricycle **17** in 97% yield as the sole species observable by <sup>1</sup>H NMR analysis. MPLC on florisil gave analytically pure **17** in 63% yield. Purification on silica gel was accompanied both by partial hydrolysis to the ketone and by rearrangement to less substituted enol ethers.

(14) The first carbene-induced cyclization examined in our laboratory was the intramolecular annulation of the chiral enyne **i**. An initial 3 mg sample of **i** was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and then warmed



in CDCl<sub>3</sub> to ~70 °C for ~15 min. Formation of two diastereometric ketones of constitution **ii** was observed by <sup>1</sup>H NMR analysis. These were isolated by HPLC, and the <sup>1</sup>H NMR spectrum of each clearly indicated their epimeric nature at the stereogenic carbon atom adjacent to the ketone carbonyl. This means, of course, that a single diastereomeric relationship was established among the methoxymethoxylated and cyclopropyl carbons by the cyclopropanation event. The relative configuration of these centers has not been established because, despite numerous attempts, we have never been able to successfully repeat the metallation of **iii**, immediate precursors to carbene **i**. Nonetheless, this result portends some interesting and potentially useful stereochemical features for this class of cyclizations.

and additional synthetic features of this process are in progress.

**Acknowledgment.** This investigation was supported by grants CA-24056 and GM-38854 awarded by the DHHS and by an award from the Alfred P. Sloan Foundation.

**Supplementary Material Available:** Spectral data for compounds (*E*)-**12a**, (*Z*)-**12a**, **11b**, (*E*)-**12b**, (*Z*)-**12b**, (*E*)-**13b**, (*Z*)-**13b**, **11c**, (*E*)-**12c**, (*E*)-**13c**, (*E*)-**14**, (*Z*)-**14**, **15c**, **11d**, (*E*)-**13d**, **15d**, **11e**, (*E*)-**12e**, (*Z*)-**12e**, **11f**, (*Z*)-**12f**, **15f**, **11g**, **15g**, **16**, **17**, **i**, and **ii** (16 pages). Ordering information is given on any current masthead page.

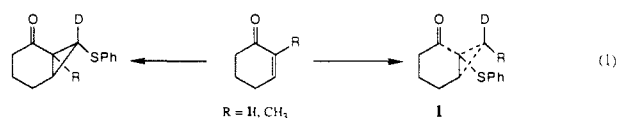
### Lithiothioacetals as Carbenoids. Highly Selective One-Flask Conversion of Cyclohex-2-en-1-ones to Lithium Bicyclo[1.1.0]butan-2-olate Intermediates

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The formation of several carbon-carbon bonds in one flask is a desirable process in organic chemistry.<sup>1</sup> Herein we disclose unusual and synthetically promising reactions in which enones undergo novel types of cyclopropanation (eq 1). During the conversion of 2-cyclohexenones to **1**, a profound annulative rearrangement occurs, while three new C-C bonds (marked by dashed lines in **1**) and one new C-D bond are being formed.



The development of these remarkable reactions was made possible by the recent observation that lithio derivatives of phenyl thioacetals behave as selective carbenoids if another anionic site is positioned in the same molecule.<sup>2</sup> Subsequent elaboration of this principle has engendered synthetically useful and mechanistically interesting chemistry.<sup>3</sup> We now show that the manifold properties of the phenylthio group allow efficient production of homoenolates in the form of highly strained bicyclo[1.1.0]butan-2-olate derivatives which can lead to selective rearrangements.

In 1983, Cohen and Yu reported that the conjugate adduct of 2-cyclohexenone and tris(phenylthio)methyl lithium,<sup>4</sup> when treated

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(2) Cohen, T.; Ritter, R. H.; Ouellette, D. *J. Am. Chem. Soc.* **1982**, *104*, 7142.

(3) (a) Cohen, T.; Ouellette, D.; Senaratne, K. P. A.; Yu, L.-C. *Tetrahedron Lett.* **1981**, *22*, 3377. (b) Cohen, T.; Yu, L.-C. *J. Am. Chem. Soc.* **1983**, *105*, 2811. (c) Cohen, T.; Yu, L.-C. *J. Org. Chem.* **1984**, *49*, 605. (d) Ritter, R. H.; Cohen, T. *J. Am. Chem. Soc.* **1986**, *108*, 3718.