Chromium Carbenes as Substrates in Cyclopropanation Reactions: 1,4- vs 1,2-Addition in the Reaction of Sulfur Ylides and α,β-Unsaturated Alkoxychromium(0) Carbenes

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Summary: Pentacarbonyl(methoxystyrylcarbene)-chromium(0) reacts with sulfur ylides to yield cyclopropanes and vinyl ethers derived from the competitive 1,4- vs 1,2-addition of the nucleophile to the α,β-unsaturated complex. Phosphorus ylides give 1,2-addition exclusively, while nitrogen ylides do not react with the above complex.

Chromium(0) carbene complexes were introduced by Fischer as cyclopropanation reagents more than 20 years ago.[1] The use of these complexes and their tungsten and molybdenum analogs in the preparation of cyclopropanes by reaction with olefins has been extensively studied since then.[2] The metal carbene in these processes acts as a carbene source in the formal [2 + 1] cycloaddition with olefins, transferring the carbene ligand to the olefin double bond. To the best of our knowledge, the intermolecular cyclopropanation of a double bond attached to the carbene carbon is unprecedented. This is quite surprising, since α,β-unsaturated carbene complexes exhibit an enhanced reactivity compared with their organic analogs (according to the principle of isolobal relationship,[3] α,β-unsaturated carbene complexes are α,β-unsaturated ester analogs).[4] In our ongoing program devoted to developing the reaction of chromium(0) carbenes and different types of ylides to a synthetically useful level,[5] we devised α,β-unsaturated chromium carbene complexes as activated olefin substrates to effect ylide-mediated cyclopropanations, a reaction well established

for their organic analogs.[6] The idea was to take advantage of the enhanced reactivity of these complexes and to study the competence of 1,2- vs 1,4-addition of carbon ylides, a problem hitherto not raised.[7]

The reaction of pentacarbonyl(methoxystyrylcarbene)-chromium(0) (1) and sulfur ylide **2a** was examined first under a variety of conditions. The results obtained are summarized in Table 1. Depending on the molar ratio of both reagents, three different types of compounds were formed: cyclopropanes **3**, vinylcyclopropanes **4**, and vinyl enol ethers **5** (Figure 1). The product ratio in the different experiments was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude mixtures, and the nature and stereochemical assignation of the different compounds was made by a combination of one- and two-dimensional NMR techniques on the isolated compounds.[8,9] As can be seen in Table 1, vinyl enol ethers **5** are the main products at low temperatures (−78 °C) for a 1:1 molar ratio of reagents (entry A), while almost equimolar amounts of cyclopropane **3** and vinyl enol ethers **5** are obtained at temperatures above −40 °C (entries B–E). Furthermore, vinylcyclopropanes **4** are not formed under these conditions but become the sole cyclopropane products with reagent ratios of carbene complex to ylide of 1:2

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(8) Compounds **3–5** were separated and purified by flash chromatography of those mixtures in which each class of compound predominated. See the supplementary material for detailed experimental procedures, characterizations, and stereochemical assignations of the different compounds.

Table 1. Reaction of Complex 1 with Ylides 2[a]

entry	molar ratio 1:2	temp (°C)	R^1	3:4:5[b]	3a:3b	4a,b:4c,d	(E,E)-5a: (Z,E)-5b
A	1:1	−78	Me	15:0:85	60:40	not formed	77:23
B	1:1	−40	Me	46:0:54	52:48	not formed	72:28
C	1:1	−20	Me	49:0:51	59:41	not formed	74:26
D	1:1	room temp	Me	46:0:54	58:42	not formed	72:28
E	1:1	Δ	Me	39:0:61	54:46	not formed	77:23
F	1:2	room temp	Me	0:64:36	not formed	59:41	75:25
G	1:3	−78	Me	0:21:79	not formed	62:38	76:24
H	1:3	room temp	Me	0:65:35	not formed	63:37	67:33
I	1:3	Δ	Me	0:46:54	not formed	65:35	76:24
J	1:1	room temp	t-Bu	52:0:48	61:39	not formed	88:12

[a] All experiments were carried out in MeCN as solvent, except for those at −78 °C, which were performed in THF/MeCN mixtures. Compound ratios were determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures, prior to purification. All experiments were repeated at least twice, and the values in the table are the average of those for the two experiments. [b] Almost quantitative yields in organic material were obtained in all cases. Small amounts (<10%) of methyl cinnamate were obtained together with compounds 3–5 when 1:1 molar ratios were used.[8]
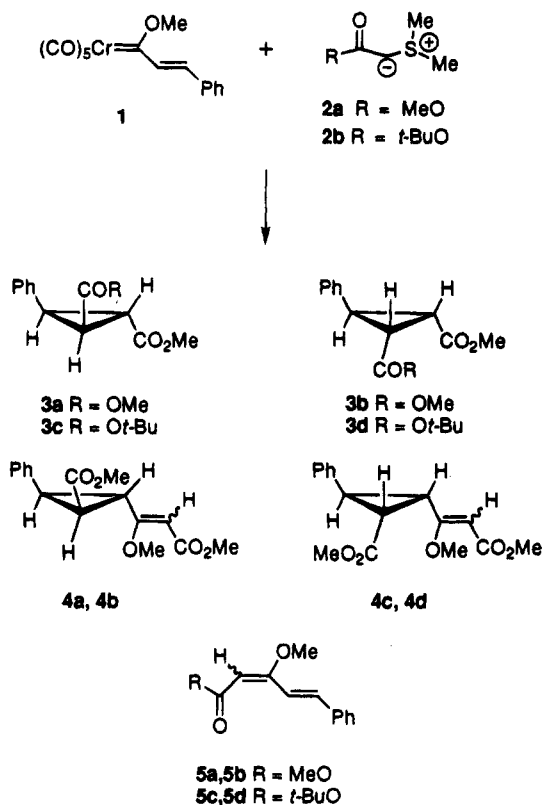

Figure 1.

or higher (entries G–J). Compounds 4 are formed with an excess of ylide, independent of the speed of reagent addition. Additionally, the *cis:trans* ratio of vinyl ether

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(9) The following experimental procedure for the preparation of cyclopropane 6 and furan 7 is representative: Complex 1 (338 mg, 1 mmol) was dissolved in degassed MeCN (15 mL) and placed in a test tube which was sealed with a rubber septum, evacuated, and purged with argon (three times). Ylide 2c (180 mg, 1 mmol) dissolved in degassed MeCN (15 mL) was added, and the resulting solution was stirred for 1.5 h at room temperature. The solvent was removed under reduced pressure, and the resulting brown residue was dissolved in MeOAc, filtered through a short path of Celite, diluted with one volume of pentane, and air-oxidized in an open flask under direct sunlight (10–12 h). Filtration through Celite of the dark brown precipitate and solvent removal gave a mixture of compounds 6 and 7, which were separated by flash chromatography (hexane–EtOAc mixtures). Cyclopropane 6 (101 mg, 36%, colorless oil) and furan 7 (78 mg, 28%, pale yellow oil) were obtained as analytically pure materials.

Scheme 1
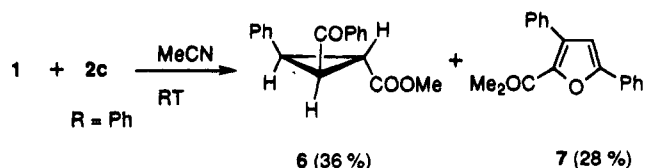
isomers 5 and cyclopropane isomers remains essentially unaltered with the reaction conditions.[10] The relative ratio of cyclopropane and vinyl ethers also remains unchanged when complex 1 is reacted with the more bulky ylide 2b, although the stereochemical outcome for both compounds is slightly different.
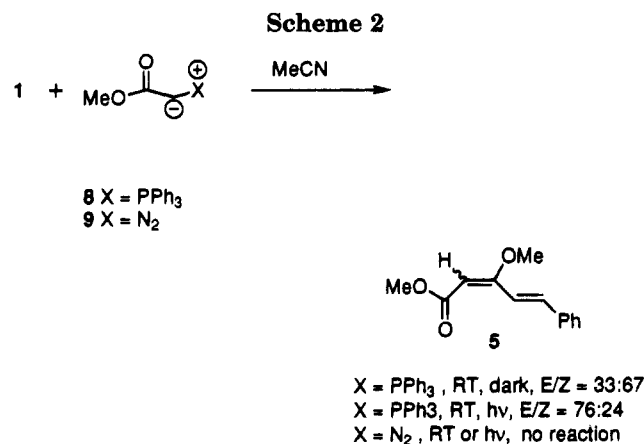
The stereochemistry of the olefin double bond of the starting complex is transferred unchanged to the cyclopropane products 3 and 4, placing a *trans* relationship between the phenyl and the ester or enol ether functionalities, respectively, in their cyclopropane rings. The last chiral center arising from the ylide is formed with low selectivity. A similar result is obtained for vinyl ethers 5, which are obtained as E/Z mixtures in the newly formed double bond but retain the stereochemistry of the former double bond.

With these results in hand the reaction of complex 1 and ylide 2c was next examined in MeCN at room temperature. In this case cyclopropane 6 is obtained as a single isomer together with a new compound, furan 7 (Scheme 1). Vinyl ethers analogous to 5 are detected as traces (<5%) in the crude mixtures, while vinylcyclopropanes of type 4 are not formed, even when there is an excess of the ylide (molar ratios 1:2c up to 1:3). Ylide 2c clearly shows the influence of the stabilization of the ylide in both the regio- and stereochemistry of these reactions.

The enhanced reactivity of complex 1 with respect to methyl cinnamate is also clear. Thus, when equimolar amounts of methyl cinnamate and ylide 2a are reacted over 48 h, only 34% of transformation into the corresponding cyclopropane mixture is obtained. Compare these results with the reaction of ylide 2a and complex 1, which is completed within minutes.

The strong influence of the nature of the ylide is exemplified by the reactions of complex 1 and phosphorus and nitrogen ylides 8 and 9. Ylide 8 forms exclusively the mixture of vinyl ethers 5, under both thermal and photochemical conditions. However, the E/Z selectivity of these reactions is strongly influenced by the reaction conditions, being totally opposite under thermal and photochemical conditions (Scheme 2). Differences in the E:Z ratio probably arise from isomerization of the newly formed double bond under the different conditions used. To confirm this hypothesis, the crude reaction mixture resulting from the thermal reaction of complex 1 and ylide 8 in the dark (E:Z ratio 33:67) was irradiated prior to oxidation. The E:Z ratio of the resulting mixture was 70:30, nearly equal to that obtained under photochemical conditions (76:24). Furthermore, heating (boiling acetonitrile) of the mixture of olefins obtained at room temperature in the dark resulted again in isomerization to form a 60:40 mixture of E and Z isomers. Clearly, both light and temperature are in-

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(10) Vinylcyclopropanes 4 are formed as mixtures of four isomeric products, as two pairs of E/Z isomers in the olefin double bond having identical configuration at the cyclopropane ring, as determined by spectroscopic analysis of separated isomeric compounds.

Scheme 2

$$1 + MeO-\overset{O}{\underset{}{C}}-\overset{\oplus}{X} \xrightarrow{MeCN}$$

8 X = PPh$_3$
9 X = N$_2$

5

X = PPh$_3$, RT, dark, E/Z = 33:67
X = PPh3, RT, hv, E/Z = 76:24
X = N$_2$, RT or hv, no reaction

fluencing the *E/Z* outcome of the reaction. On the other hand, no ketene-derived products, namely captodative allenes, are formed by working under photochemical conditions, in clear contrast with the results of Hegedus for analogous reactions of alkoxychromium carbenes and different phosphorus ylides.[11] Moreover, thermal reactions of ylide 8 are considerably slower than those of ylides 2, being accelerated by irradiation, a fact observed by us in the reaction of Fischer carbenes and other ylides.[5] Finally, nitrogen ylide 9 was unreactive with complex 1 under the different conditions used. The methyl cinnamate that arises from the oxidation of the starting carbene is the sole organic reaction product.[12]
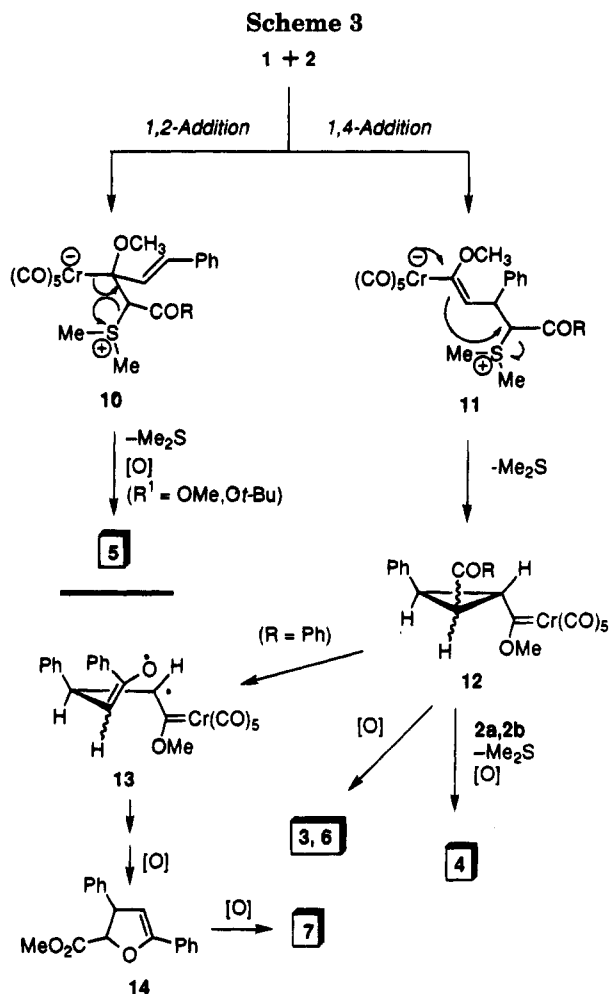
Formation of the products observed in the above reactions may be rationalized as depicted in Scheme 3. Clearly, cyclopropanes 3 and vinyl ethers 5 are formed by competitive 1,2- vs 1,4-addition of the carbon ylide to the complex 1. Vinylcyclopropanes 4 should be formed after cyclopropanation of the starting olefin double bond, through the resulting cyclopropane complexes 12. This is the reaction profile for sulfur ylides 2a and 2b, while ylide 2c appears to be unreactive toward 1,2-addition, at least under the conditions used. In contrast, phosphorus ylide 8 gives exclusively 1,2-addition. Furthermore, CO insertion into the carbene bond to form ketenes which would be trapped by the ylide to form allenes[11] appears to be disfavored under these reaction conditions. Furan 7 may be formed through a homolytic cleavage of the cyclopropane ring in complex 12 to form the biradical intermediate 13. Biradical 13 finally forms 14.[13,14] Finally, it seems clear from the data available that rotation across the former double bond in complex 1 should be restricted, since the *E* stereochemistry of this bond is transferred unaltered to the final cyclopropanes. However, although a steric model may be postulated to account for this behavior, according to the current background for the stereochem-

Scheme 3

1 + 2

1,2-Addition | 1,4-Addition

istry of cyclopropanation of electron-deficient olefins,[15] the presence of the metallic moiety in the cyclopropanation intermediates renders any explanation at this moment speculative.

In conclusion, the competition of 1,2- vs 1,4-addition of sulfur ylides to α,β-unsaturated complex 1 has been studied. This process is strongly enhanced when compared with the reaction of analogous α,β-unsaturated esters. The regio- and stereoselectivity of these processes appears to be remarkably independent of the temperature but is strongly influenced by the nature of the sulfur ylide (especially by the degree of stabilization of the ylide). Moreover, phosphorus ylides give exclusively 1,2-addition, while nitrogen ylides are unreactive under the conditions used. Further work to determine the scope, the factors influencing the stereochemistry of these reactions, and their synthetic applications are underway in our laboratories.

Supplementary Material Available: Text describing the synthesis and all characterization and spectral data (^{1}H NMR, ^{13}C NMR, IR, and analytical data) for compounds 3–7 (9 pages). Ordering information is given on any current masthead page.

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