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Reaction of Cyclopropylcarbene-Chromium Complexes with Alkenes; Synthesis of Cyclopropylcyclopropanes

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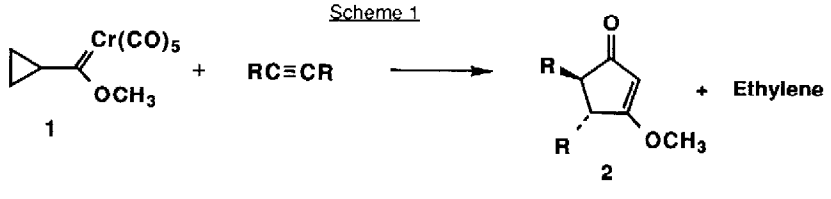
Summary: We have examined the reaction of cyclopropylcarbene-chromium complexes with alkenes. The reaction leads to the formation of cyclopropylcyclopropane derivatives in good yield, accompanied by minor amounts of ring-opened products. Conjugated dienes and α,β-unsaturated esters and amides appear to be suitable substrates for the reaction.

Recently, cyclopropylcarbene-chromium complexes have emerged as valuable reagents for organic synthesis, coupling with alkynes to give cyclopentenones (**2**) in good-excellent yields[1] (Scheme 1). During this transformation, a net ring opening of the original cyclopropane ring occurs and ethylene is expelled. We recently reported thermolysis studies of cyclopropylcarbene-chromium complexes[2]. In these studies, we showed that the cyclopropane ring in these complexes is very reluctant to undergo ring-opening processes unless the ring is activated by the presence of alkenyl substituents. Since the cyclopropane rings in these complexes are somewhat robust, these complexes are potentially useful for cyclopropylcarbene-transfer processes[3]. Free cyclopropylcarbenes are often unstable and undergo ring-opening and/or ring expansion processes[4], and typically do not undergo cyclopropanation reactions with alkenes. Cationic cyclopropylcarbene-iron complexes undergo cyclopropanation reactions with electron-rich alkenes with no complications from opening of the cyclopropane ring[5]. As a complement to this method, we have investigated the reaction of cyclopropylcarbene-chromium complexes with alkenes. If the carbene complex functions as a cyclopropanating reagent, donor-acceptor substituted cyclopropanes[6], which are synthetically very useful compounds, would be provided.

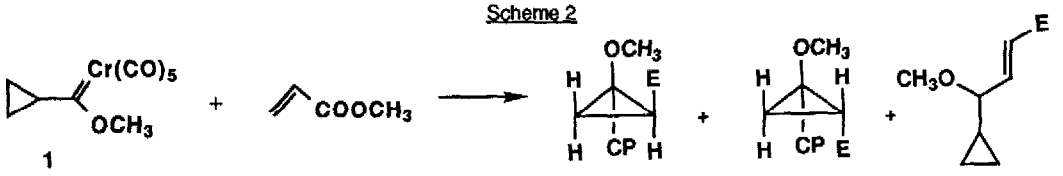
Scheme 1



In our initial studies, we investigated the reaction between cyclopropylcarbene complex **1** and methyl acrylate. When the reaction was conducted at 100°C in dioxane, the cyclopropylcyclopropanes **3A** and **3B** were obtained, along with the open-chain ester **4** (Scheme 2). The yield of the reaction was not improved significantly by the addition of triphenylphosphine.

Interestingly, the reaction was more efficient when conducted at lower temperature in refluxing tetrahydrofuran (THF), but the E-Z selectivity was considerably lower. The proportion of 4 did not change under the different reaction conditions. The yield was not affected significantly by concentration, but was slightly better if the reaction was conducted under high dilution conditions, achieved by syringe pump addition of a solution of the alkene and carbene complex over a period of 4 h to refluxing THF[7].

Scheme 2

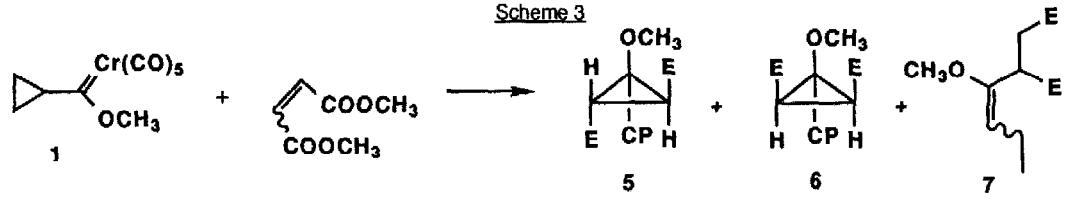


CONDITIONS	YIELD 3A	YIELD 3B	YIELD 4
Dioxane / 100°C	24	3	2
Dioxane / PPh_3 / 100°C	34	12	2
THF / 65°C	35	29	2

E = $COOCH_3$; CP = Cyclopropyl

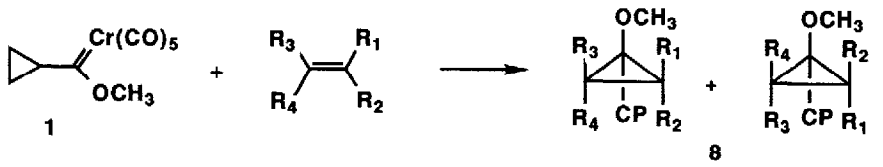
The reactivity of complex 1 with a variety of alkenes was examined. As can be seen in the Table, the reaction is quite general for ester-substituted alkenes. The reaction appears to be stereoselective[8], both fumarate and crotonate esters lead to products where the original alkene substituents are in the trans relative configuration (Entry B, E). The analogous reaction employing maleate esters leads to a mixture of cyclopropane 5 and the expected cyclopropane 6, in which the esters groups are in the cis relative configuration[8b]. Under the conditions of the reaction, maleate to fumarate isomerization occurs; ^1H NMR analysis of the reaction mixture in Entry C before the reaction has gone to completion shows that both dimethyl maleate and dimethyl fumarate are present, which presumably accounts for the lack of stereoselectivity in the reaction of 1 with dimethyl maleate. In reactions employing maleate and fumarate esters, the reduction products dimethyl succinate and compound 7, in which both of the cyclopropane rings have been opened, were also observed. These products were observed only in reactions employing maleate and fumarate esters. The cyclopropanation reaction also proceeds using α,β–unsaturated amides, but α,β–unsaturated ketones gave complex reaction mixtures. The reaction appears to be restricted to activated alkenes since norbornene, a highly strained alkene which complexes readily to metals, and styrene both fail to give cyclopropylcyclopropanes in their reaction with complex 1. Interestingly, simple 1,3-dienes appear to be suitable substrates for the reaction. 1-Vinylcyclopentene couples readily with carbene complex 1, giving the cyclopropylcyclopropane 8G in 60% yield. Previously only electron-deficient dienes were reported to couple with chromium-carbene complexes[3b]. The E-Z stereoselectivity appears to be better in these systems than that reported for reaction of these alkenes with pentacarbonyl[methoxy(phenyl)methylene]chromium(0)[3]. The reactions in reference 3 were performed under different conditions, which may account for the observed differences in stereoselectivity.

Scheme 3



+ Dimethyl Succinate

TABLE: Reaction of Complex 1 with Alkenes



ENTRY[a]	R_1	R_2	R_3	R_4	YIELD 8[b]	E/Z 8[c]
A	$COOCH_3$	H	H	H	64[d]	45:55
B	$COOCH_3$	H	H	$COOCH_3$	55[e]	
C	$COOCH_3$	H	$COOCH_3$	H	41[f]	
D	$COOCH_3$	CH_3	H	H	69	23:77
E	$COOCH_3$	H	H	CH_3	57	>95% Z[g]
F	$CON(CH_3)_2$	H	H	H	79	21:79
G	1-cyclopenten-1-yl	H	H	H	60	40:60[h]

a. Table entry letters define substituents for compound **8**. b. The yield refers to compounds which are pure by combustion analysis and/or chromatographic data. c. See reference 9. d. A 2% yield of compound **4** was also obtained. e. A 16% yield of compound **7** was also obtained. f. A 10% yield of compound **7** was also obtained; the total yield refers to a 40:60 mixture of E,Z: Z,Z-isomers. g. The relative stereochemistry of the methyl and carbomethoxy groups was trans. h. The stereochemistry could not be assigned reliably; the major product has been suggested as the Z isomer by analogy with the other systems.

In summary, we have shown that cyclopropylcarbene-chromium complexes such as **1** react with alkenes to produce predominantly dicyclopropanes. The reaction proceeds with minimal ring opening of the original three-membered ring. Donor-acceptor substituted cyclopropanes are produced in which the donor substituents are alkoxy groups and cyclopropane rings. We are further examining the scope, limitations, and mechanistic details of this reaction, and exploring the chemistry of the dicyclopropanes formed as a result of the cycloaddition reaction.

Acknowledgements

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7. The following is a typical procedure. Complex **1** (0.276 g, 1.00 mmol) and methyl acrylate (0.18 mL, 2.0 mmol) were dissolved in THF (20 mL). This solution was added dropwise via syringe pump over a period of 5 h to 100 mL of refluxing THF, under nitrogen. After the addition was complete, the solution was refluxed for an additional 12 h, after which time the solvent was removed on a rotary evaporator. The residue was then dissolved in ethyl acetate and the resulting suspension was filtered through Celite. The solvent was removed on a rotary evaporator, and the residue was purified by bulb to bulb distillation; b.p. 30 - 60°C, 0.025 mmHg. The distillate was subjected to flash chromatography on silica gel using 9:1 hexane: ethyl acetate as the eluent. The product in the first fraction (0.049 g, 29%) was identified as **3B**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.67 (s, 3H); 3.36 (s, 3H); 1.97 (dd, 1H, J = 8.9, 7.3); 1.09 - 1.24 (m, 3H); 0.43 - 0.64 (m, 4H). IR: ($CDCl_3$) 1728 cm^{-1}. Mass Spec (CI): 171 (M+1). The product in the second fraction (0.003 g, 2%) was identified as **4**. ^{1}H NMR ($CDCl_3$): δ 6.87 (dd, 1H, J = 15.8, 6.2); 5.97 (dd, 1H, J = 15.8, 1.2); 3.73 (s, 3H); 3.33 (s, 3H); 3.12 (ddd, 1H, J = 7.7, 6.2, 1.2); 0.93 (m, 1H); 0.36 - 0.63 (m, 3H); 0.20 (m, 1H). IR($CDCl_3$): 1722 cm^{-1}. Mass Spec (EI): 170 (M). The product in the third fraction (0.058 g, 35%) was identified as **3A** . ^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3H); 3.33 (s, 3H); 1.63 (dd, 1H, J = 8.6, 6.6); 1.40 - 1.52 (m, 2H); 0.81 (dd, 1H, J = 8.6, 5.8); 0.47 - 0.58 (m, 2H); 0.26 (m, 1H); 0.07 (m, 1H). IR($CDCl_3$): 1733 cm^{-1}. Mass Spec(EI): 170 (M). Anal: Calcd. for $C_9H_{14}O_3$, C 63.51, H 8.29; Found, C 63.28, H 7.99.

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