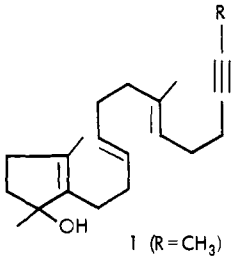
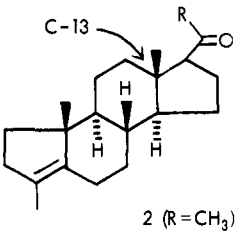
Vinyl Fluoride Function as a Terminator of Biomimetic Polyene Cyclizations Leading to Steroids[1]

Sir:

The methylacetylenic function has proved to be a particularly useful terminator of biomimetic polyene cyclizations because, when it is appropriately incorporated in a substrate, it participates in the ring closure so as to form the trans-fused five-membered



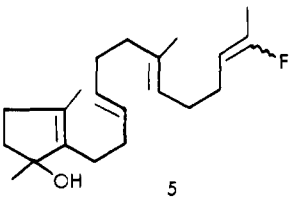
1 (R = CH_3)
3 (R = C_6H_5)



2 (R = CH_3)
4 (R = C_6H_5)

steroidal ring D, e.g., **1** → **2**.[2] This conversion, however, is not totally stereoselective; about 16% of the product consists of isomers presumed (by analogy to an established case, **3** → **4**)[3] to be 13α (17α and 17β) epimers having the C/D cis fusion.[4] Moreover, the product also contains about 10% of what appears to be a *D*-homo isomer.[4] This unfavorable behavior is associated with the acetylenic bond, and the proportion of 13α epimer varies from 0% (in one case) to 20% (in the conversion **3** → **4**)[3] depending on the substituent (R) on the acetylenic bond.

An olefinic group, in contrast, can function as a highly stereoselective terminator of polyene cyclizations as shown in the case of the cyclization of substrate **3** with an ethylenic in place of the acetylenic bond (i.e., the styryl function) which gives tetracyclic material containing <2% of the unnatural 13α isomer.[5] Therefore, we have been in search of other olefinic functions which will behave similarly but will give products with a more useful function at C-17. In addition to the allylsilane residue, which shows some promise of serving this purpose,[6] we felt that there was reason to entertain the hypothesis that the vinyl fluoride function, as in substrate **5**, would serve as a good cyclization terminator[7] despite the fact that in a related system the vinyl



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chloride function failed to participate at all in the cyclization.[8] Accordingly a study of the synthesis and cyclization of **5** was undertaken, and the present communication discloses some preliminary results of this work.

The substrate **5** was first synthesized by a scheme analogous to that used for producing **1**;[2a] however, since the stereoselectivity in the generation of the pro-C-8,9 double bond by the Wittig-Schlosser reaction was only 91% at best, the following alternative scheme (Scheme I) was devised. The epoxide **7**[9] of 1-methylcyclopentene was treated with pyridine–hydrogen fluoride[10] to give the fluorohydrin[11,12d,13] (77% yield) which, on oxidation with Jones reagent, yielded the unstable fluoro ketone **8**[13a] (2,4-DNP[13b] apparently loses HF at ~155 °C and then melts at 207–211 °C). The key reaction for producing the vinyl fluoride function was the photolysis[14] of the crude ketone **8** which afforded the rather sensitive aldehyde **9**.[13a,15] The crude aldehyde, on treatment with isopropenylmagnesium bromide, was then converted into the allylic alcohol **10**.[12d,13]

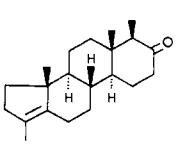
The conversion of **10** into **13** via the Claisen reaction of **10** with the ketal of cyclopropyl methyl ketone[16] to give **11**,[12b,d,13] reduction to the cyclopropyl carbinol,[13] followed by a modified Julia rear-

(1) For a recent paper in the series on biomimetic cyclizations see: Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122.

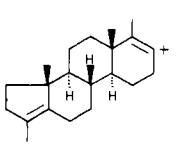
(2) (a) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274. For other examples see: (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.

(3) Johnson, W. S.; Hughes, L. R.; Kloek, J. A.; Niem, T.; Shenvi, A. *J. Am. Chem. Soc.* **1979**, *101*, 1279.

(4) These products were undetected previously (ref 2a) because they were not resolved on the GC columns then in use. Repetition of the cyclization of **1** with 9:1 pentane–trifluoroacetic acid (0 °C, 4 min) gave (ref 12a) a 77% yield of tetracyclic material which contained, in addition to **2** and its 17α epimer, 6% (by capillary GC on an 8.5-m column) of the 13α,17β epimer (mp 58–61 °C), 10% of the 13α,17α epimer (mp 134–136 °C), and 10% of the *D*-homo ketone i (mp 121–126 °C). These structural assignments, which are tentative, were made on the basis of NMR and IR spectral data, base-catalyzed equilibration studies, combustion analyses, and analogy to results in an established case (ref 3). The presumed *D*-homo ketone i represents a type not



i



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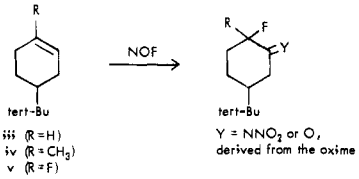
hitherto detected in such cyclizations. Its formation reasonably involves reaction of the vinyl cation ii with trifluoroacetate. For the reaction of such vinyl cations with chloride, see: Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Okorie, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 8604.

(5) Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281.

(6) Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513.

(7) This hypothesis was entertained as the result of a report in a seminar at Stanford given by G. A. Boswell, Jr., of Du Pont, Central Research and Development, disclosing unpublished work by him and his collaborator W. C. Ripka on the addition of nitrosyl fluoride to the vinyl group of the substances iii, iv, and v. The relative rates of reaction with the various substrates were



iii (R = H)
iv (R = CH_3)
v (R = F)

Y = NNO_2 or O, derived from the oxime

v > iv > iii. The surprisingly high reactivity with the vinyl fluoride v may be rationalized by presuming that the reaction involves electrophilic attack by NO^+ and that the transition state for the addition has considerable carbonium ion character which is stabilized by back-bonding with the fluorine atom. (Fluorine is known to be much more effective in this capacity than the other halogen atoms. See: Olah, G. A.; Mo, Y. K. *Adv. Fluorine Chem.* **1973**, *7*, 69. Thus if the transition state for reaction with a carbocation were to be similarly stabilized, the vinyl fluoride function should serve as a good participant in cationic polyene cyclizations.

(8) Johnson, W. S.; Ratcliffe, B. E. Unpublished observation.

(9) Lutz, G. A.; Bearse, A. E.; Leonard, J. E.; Croxton, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 4139.

(10) Cf.: Olah, G. A.; Meidar, D. *Isr. J. Chem.* **1978**, *17*, 148. We are indebted to John Welch for suggesting this reagent.

(11) Cf.: Migliorese, K. G.; Appelman, E. H.; Tsangaris, M. N. *J. Org. Chem.* **1979**, *44*, 1711.

(12) The product was purified by (a) chromatography on Florisil, (b) chromatography on silica gel, (c) distillation at reduced pressure through a short Vigreux column, and (d) (for high-boiling compounds and/or small amounts of material) distillation through a Kugelrohr by using a Büchi Kugelrohrofen or through a short-path apparatus.

(13) (a) The NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

(14) We were prompted to try this reaction because of the reported high-yield photolytic conversion of 2-(carboethoxy)-2-alkylcyclopentanones into ethyl 6-oxo-2-alkyl-2-hexenoates (Kossanyi, J.; Perales, J.; Laachach, A.; Kawenoki, I.; Morizur, J. P. *Synthesis* **1979**, 279), and the published procedure was adapted to the present case.

(15) This aldehyde and all of the products derived therefrom consisted of a 2:1 mixture of the *Z* and *E* isomers as estimated by GC. The configurations were established by ^{19}F NMR of the carboxylic ester obtained by the ortho ester Claisen reaction with a specimen of **10**. For the predominant isomer J_{FH} = 37.3 Hz while for the minor isomer J_{FH} = 21.5 Hz. See: Pasto, D. J.; Johnson, C. R. "Organic Structure Determination", Prentice-Hall: Englewood Cliffs, NJ, **1969**; p 190.

(16) Cf.: Werthemann, L.; Johnson, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1465, 1810.

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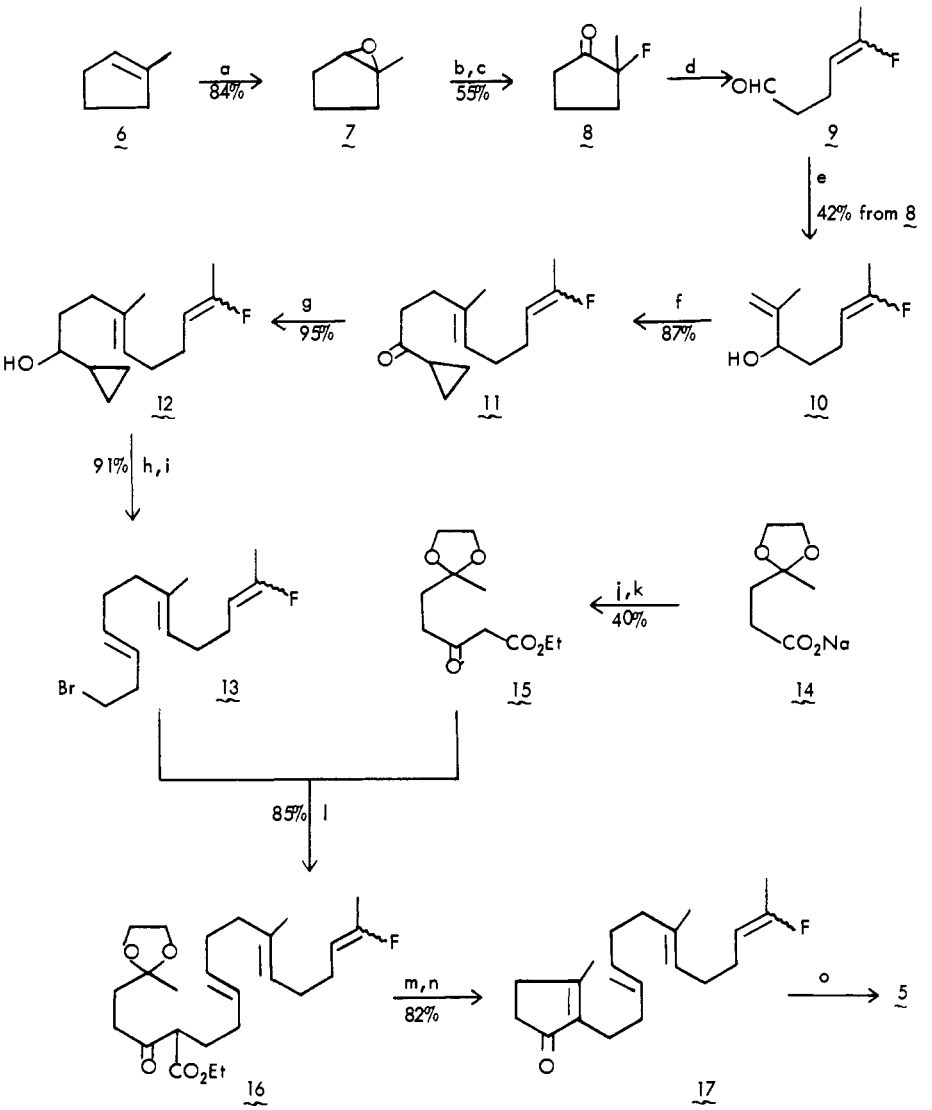
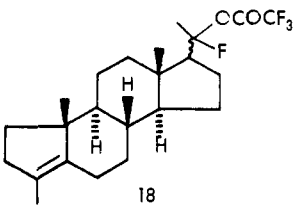
Scheme I[a]



[a] (a) 1.0 mol equiv of *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0.5 M $NaHCO_3$, 4 h, 24 °C; (b) to give the fluorohydrin: 42% HF–pyridine, CH_2Cl_2, 11 h, 22 °C; (c) excess Jones reagent, 4 h, 15 °C; (d) $h\nu$, pyrex, 7 h, 0 °C; (e) excess $CH_2{=}C(CH_3)MgBr$, THF, 1.5 h, 0–23 °C; (f) 2,4-dinitrophenol, toluene, 1-cyclopropyl-1,1-dimethoxyethane (1:39:2.8 by weight), 16 h, reflux; (g) 1 mol equiv of $LiAlH_4$, Et_2O, 1.5 h, 0 °C; (h) to give the cyclopropylcarbinyl bromide: 1.1 mol equiv of PBr_3, collidine, Et_2O, 2 h, −78–24 °C; (i) 3.3 mol equiv of $ZnBr_2$, Et_2O, 2 h, −78–24 °C; (j) to give the acid chloride: 3.0 mol equiv of $(COCl)_2$, C_6H_6, 1.5 h, 22 °C; (k) $LiCH_2CO_2Et$ (from 2.0 mol equiv of $LiN(CH(CH_3)_2)_2$, 1 mol equiv of CH_3COOEt, THF) 1 h, −78 °C; (l) 2.0 mol equiv of Na enolate of **15**, CH_3CN, 0.07 mol equiv of NaI, 96 h, 42–64 °C; (m) to give the dione: 4:4:1 THF–CH_3OH–5% NaOH, 3 h, reflux, then 3:1 CH_3OH–5% HCl, 1.5 h, 24 °C; (n) 4:4:1 THF–CH_3OH–5% NaOH, 4 h, reflux; (o) excess CH_3Li, Et_2O, 0 °C (four treatments).

rangement[17] to give **13**,[13] is an adaptation of methodology developed by R. G. Finn.[18] The *E* to *Z* ratios of the new olefinic bonds formed in the conversions **10** → **11** and **12** → **13** were 39:1 and 99:1, respectively, as determined by GC. Alkylation of the sodium enolate of the keto ester **15**[19] with the bromide **13** afforded **16**.[12a,13] This on hydrolysis and decarboxylation gave the dione[13] which on cyclodehydration yielded the cyclopentenone **17**.[12a,d,13] Finally, reaction of **17** with methyllithium afforded the substrate **5** which, because of its susceptibility to dehydration, was used without purification for the cyclization experiment.

A solution of 183 mg of **5** in 3 mL of methylene chloride was added over a 4-min period to a stirred solution of 0.88 mL of trifluoroacetic acid in 45 mL of methylene chloride under argon at −7 °C. An additional 2 mL of methylene chloride was used to rinse the syringe, and then the mixture was allowed to stand for 1 min before being neutralized. If the neutralization of such a mixture was carried out with excess sodium bicarbonate solution, the IR spectra of the crude product showed strong absorption at 1800 cm^{-1} characteristic of the carbonyl stretching frequency of the trifluoroacetate group; hence it is regarded tentatively as having the structure **18**. For preparative purposes the reaction mixture



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was treated with 17 mL of 2.5 M methanolic potassium hydroxide at 0–11 °C for 9 min, which effected hydrolysis of **18** to the

(17) Brady, S. F.; Ilton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882.
(18) Finn, R. G. Ph.D. dissertation, Stanford University, 1978.
(19) An improved method of preparing the known keto ester **15** (Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994) involved conversion of the sodium salt **14** of the ketal of levulinic acid into the acid chloride, followed by reaction with $LiCH_2CO_2Et$, according to: Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953.

known[2] tetracyclic ketone **2**. Chromatography[12a] afforded 133 mg (78% yield) which, as shown by GC coinjection experiments, consisted of a 58:42 mixture of **2** and its 17α epimer. The GC response for these epimers (with "natural" configuration) represented 95% of the total peak area while that for the 13α,17β isomer was only 2% and for the 13α,17α, 1.5%; moreover, there was no response for the *D*-homo isomer.

Thus a dramatic improvement in regio- as well as stereoselectivity, with commensurate increase in yield, was realized when the vinyl fluoride was used in place of the methylacetylenic function for terminating a biomimetic polyene cyclization.

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Reactions of η^5-$C_5H_5(CO)_2FeCHC_6H_5^+$ with Alkenes and Alkynes. Observation of Efficient Benzylidene-Transfer Reactions

Sir:

The transfer of carbene ligands from transition-metal–carbene complexes to alkenes with formation of cyclopropanes represents a general class of reactions with considerable potential synthetic utility. Unfortunately, however, few of the stable, isolable carbene complexes prepared to date exhibit this mode of reactivity.[1] The most notable exception is the report by Casey that $(CO)_5WCHC_6H_5$ generated in situ (trifluoroacetic acid–methylene chloride solutions) reacts with numerous substituted alkenes to form phenylcyclopropanes.[2,3] Several systems of the type $CpLL'FeCH_2X$ have been used as methylene-transfer reagents[4] in which the cationic methylene complex is an unsubstantiated but plausible intermediate and, indeed, $Cp(Ph_2PCH_2CH_2PPh_2)FeCH_2^+$ generated in situ is capable of methylene transfer.[10]

Table I. Products of the Reaction of Alkenes with $Cp(CO)_2Fe{=}CHC_6H_5^+$

alkene	cyclopropane product[a]	cis:trans isomer ratios	% yield[b] GC	% yield[b] isolated
				
$R_1 = R_2 = R_3 = R_4 = H$			75	47
$R_1 = CH_3$; $R_2 = R_3 = R_4 = H$		7.8 (0 °C)[c]	90	54
$R_1 = CH_2CH_3$; $R_2 = R_3 = R_4 = H$		6.5 (0 °C)[c]		75
$R_1 = CH(CH_3)_2$; $R_2 = R_3 = R_4 = H$		4.6 (0 °C)[c]		76
$R_1 = C_6H_5$; $R_2 = R_3 = R_4 = H$		≥100[d]		88
$R_1 = R_4 = CH_3$; $R_2 = R_3 = H$		*f*	89	52
$R_1 = R_3 = CH_3$; $R_2 = R_4 = H$		>100[e]	93	57
R_1 $R_3 = CH_2CH_2CH_2$ (cyclopentene); $R_2 = R_4 = H$		≥200[d] (endo:exo)		78
$R_1 = R_2 = CH_3$; $R_3 = R_4 = H$			82	45
$R_1 = R_2 = C_6H_5$; $R_3 = R_4 = H$				75
$R_1 = R_4 = C_6H_5$; $R_2 = R_3 = H$		*f*		96
$R_1 = R_2 = R_3 = CH_3$; $R_4 = H$		>50		91
$R_1 = R_2 = R_3 = R_4 = CH_3$				59

[a] Reaction conditions are described in the text. [b] Yields are based on carbene salt. Isolated yields are reported after bulb-to-bulb distillation of oils or recrystallization of solids. Isolated yields of volatile products are low relative to GC yields due to loss in distillation of small quantities. [c] Carried out at a constant temperature (0 °C) for accurate comparison of isomer ratios. Selectivity increases at lower temperatures. [d] Minor isomer detected by GC but not otherwise characterized. [e] Refers to the *r*-1-phenyl-*cis*-2,*cis*-3-dimethylcyclopropane:*r*-1-phenyl-*trans*-2,*trans*-3-dimethylcyclopropane ratio. [f] No isomers (<1%) detected corresponding to isomerization about the double bond.

We report here that the highly electrophilic benzylidene iron carbene complex $Cp(CO)_2FeCHC_6H_5^+$, **1**, which can be readily isolated as a stable crystalline PF_6^- salt,[11] reacts rapidly with unactivated alkenes and alkynes to effect efficient transfer of the benzylidene ligand. Table I summarizes the results of the reaction of **1** with alkenes to form phenylcyclopropanes. In a typical procedure, a twofold excess of olefin is added to the carbene salt **1** in methylene chloride at −78 °C. After 1–2 h of stirring at −78 °C the solution is slowly warmed to 25 °C. Pentane is added to precipitate iron-containing salts[12] and after filtration and solvent removal the phenylcyclopropanes can be isolated in good yields.

There are two remarkable features of these reactions. First, carbene complex **1** is sufficiently electrophilic to react with unactivated ethylene,[13] yet steric factors do not prevent transfer to tetrasubstituted olefins. Thus, good yields of phenylcyclopropanes may be obtained for olefins ranging from unsubstituted ethylene to tetrasubstituted systems. Secondly, the reaction is highly stereoselective, giving exceptionally high fractions of the thermodynamically less stable cis or syn isomers. For example, from styrene the cis:trans ratio of 1,2-diphenylcyclopropane formed was ≥100 while for cyclopentene was ≥200. The stereoselectivity of the iron carbene **1** seems for all olefins to be considerably greater than that for the $(CO)_5WCHC_6H_5$ system,[2] but the relative stereoselectivities of the two complexes generally parallel one another.[14]

By what mechanism(s) are the cyclopropanes formed and how can the high stereoselectivities be explained? The addition of **1** to olefins to form carbonium ion intermediates seems unlikely since

(1) For recent reviews of transition-metal–carbene complexes, see: (a) Casey, C. P. *Transition Met. Organomet. Org. Synth.* **1976**, *1*, 190–233. (b) Cardin, D. J.; Cetinkaya, B.; Doyle, M. J.; Lappert, M. F. *Chem. Soc. Rev.* **1973**, *2*, 99–144. (c) Fischer, E. O. *Adv. Organomet. Chem.* **1976**, *14*, 1–32. (d) Cotton, F. A.; Lukehart, C. M. *Prog. Inorg. Chem.* **1972**, *16*, 487–613.

(2) (a) Casey, C. P.; Polichnowski, S. W. *J. Am. Chem. Soc.* **1977**, *99*, 6097–9. (b) Casey, C. P.; Polichnowski, S. W.; Shusterman, A. J.; Jones, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 7282–92.

(3) (a) The heteroatom carbene complexes $(CO)_5MC(OCH_3)(C_6H_5)$ (M = W, Mo, Cr) react at high temperatures with certain electron-deficient olefins and under mild conditions with electron-rich olefins to yield cyclopropanes.[3b] The reactions likely proceed by different mechanisms[1a] and do not appear to be general for unactivated olefins. (b) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 1356–67, 3966–73.

(4) The α-ethers $Cp(CO)_2FeCH_2OCH_3$[5] and $Cp(Ph_2PCH_2CH_2PPh_2)FeCH_2OCH_3$[6] and chiral $Cp(CO)(PPh_3)FeCH_2O$-menthyl[7] transfer methylene under acidic conditions while chiral $Cp(CO)(PPh_3)FeCH_2Br$[8] and $Cp(CO)_2FeCH_2S^+(CH_3)_2$[9] transfer methylene thermally. The latter reagent appears particularly useful synthetically due to its ease of preparation, stability, and efficient methylene transfer.

(5) Jolly, P. W.; Pettit, R. *J. Am. Chem. Soc.* **1966**, *88*, 5044–5.

(6) Riley, P. E.; Capshaw, C. E.; Pettit, R.; Davis, R. E. *Inorg. Chem.* **1978**, *17*, 408–14.

(7) Davison, A.; Krusell, W. C.; Michaelson, R. C. *J. Organomet. Chem.* **1974**, *72*, C7–C10.

(8) Flood, T. C.; DiSanti, F. J.; Miles, D. L. *Inorg. Chem.* **1976**, *15*, 1910–8.

(9) Brandt, S.; Helquist, P. *J. Am. Chem. Soc.* **1979**, *101*, 6473–5.

(10) Brookhart, M.; Tucker, J. R.; Flood, T. C.; Jensen, J. *J. Am. Chem. Soc.* 1980, *102*, 1203–5.

(11) Brookhart, M.; Nelson, G. O. *J. Am. Chem. Soc.* **1977**, *99*, 6099–101.

(12) These salts have been fully characterized as $Fp(olefin)^+$ salts for the alkenes ethylene and propene but are not normally characterized.

(13) The $(CO)_5WCHC_6H_5$ system does not react with ethylene.[2b]

(14) The increased selectivity of the reaction of **1** with cyclopentene appears to be an exception. Casey reports an endo:exo ratio of 2.6 for $(CO)_5WCHC_6H_5$.[2b]

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