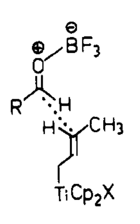
though these findings certainly do not prove a noncyclic mechanism **5**, they are consistent with such a transition state.[6]



5

Interestingly, BF_3 does *not* reverse diastereoselectivity in the case of $CH_3CH{=}CHCH_2Ti(O\text{-}i\text{-}Pr)_3$, which has been shown to be a threo-selective reagent.[7] We have observed that it reacts considerably faster than **1** in the absence of BF_3. η^5-Cyclopentadienyl ligands as in **1** are powerful π donors[8] which reduce the Lewis acidity of titanium drastically.[9]

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

---

[6] A referee has noted that BF_3-induced removal of halide from **1** followed by addition of $CH_3CH{=}CHCH_2{}^+TiCp_2$ via a cyclic transition state could also explain the lack of a halogen effect on diastereoselectivity. We have also considered other possibilities such as BF_3 complexation at RCHO anti to the R group followed by a chair-like pericyclic transition state in which R occupies the quasi-axial position instead of the usual equatorial position. This would make Ti–O coordination possible but also raises the question whether *two* metals can complex at the aldehyde oxygen simultaneously; if C–C bond formation is far advanced in the transition state, electron density at oxygen increases, making double coordination more likely. The initial product would be a Lewis acid complexed titanium alkoxide, for which there is precedence Gmelin Handbuch, Titan-Organische Verbindungen, Springer-Verlag: Berlin, 1977; Part 1, p 63 and 207). These speculations also apply to such reactions as the Mukaiyama aldol addition of silyl enol ethers to RCHO/$TiCl_4$, the mechanism of which is also unclear.

[7] (a) See p 40 of ref 3a. (b) Widler, L.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1085.

[8] Concerning π bonding in bis(cyclopentadienyl)titanium compounds, see: Huffman, J. C.; Moloy, K. G.; Marsella, J. A.; Caulton, K. G. *J. Am. Chem. Soc.* **1980**, *102*, 3009.

[9] We have observed that $CpTiCl_3$ does not induce allylsilane addition to aldehydes, in contrast to $TiCl_4$ (Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 2195).

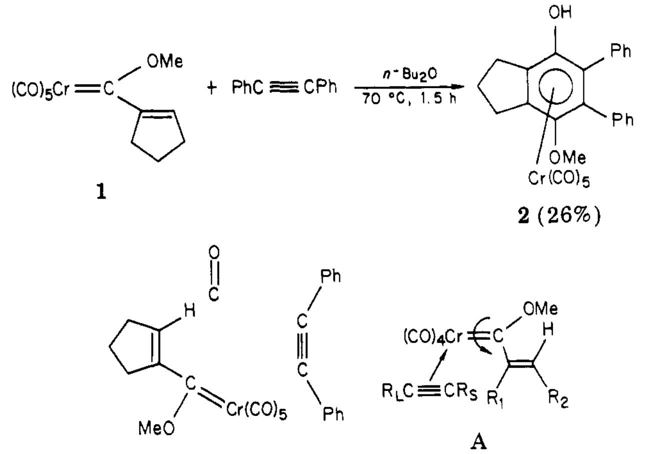
M. T. Reetz,* M. Sauerwald
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse
3550 Marburg, West Germany

Received January 18, 1984

Benzannulation of α,β-Unsaturated Fischer Carbene Complexes with Acetylenes[1]

Summary: The reaction of acetylenes with α,β-unsaturated chromium carbene complexes allows for the controlled construction of an aromatic nucleus under neutral conditions at near ambient temperatures. The synthetic scope of the reaction is examined for eight different carbene complexes with a variety of acetylenes to give three different types of benzannulated products depending on the type of oxidative workup employed.

Scheme I



1

2 (26%)

A

Sir: Fischer carbene complexes of chromium are known to undergo facile reactions with acetylenes leading to products resulting from a benzannulation of one of the carbene carbon substituents. This reaction was first reported by Dötz[2] and has since been developed to the point where applications to natural product syntheses are beginning to appear in the literature.[3,4] However, all of the investigations of this reaction have been limited to those complexes for which the annulated substituent is an aryl group, with the singular exception of the reaction of the cyclopentenyl complex **1** (Scheme I). This complex has been reported to react with diphenylacetylene to give the indanechromium tricarbonyl complex **2** in 26% yield.[5,6] This result suggests that the benzannulation reaction of alkenyl-substituted chromium carbene complexes may also have potential for synthetic applications. We now report the results of an investigation designed to delineate the synthetic scope of this reaction and to explore its applications in natural product synthesis.[7]

The data in Table I establish that this annulation reaction will be synthetically useful for a variety of α,β-unsaturated chromium carbene complexes and acetylenes. The benzannulated products can be obtained in good to moderate yields and in the oxidation state of choice as illustrated in Scheme II for the cyclohexenyl complex **3**.[8] Rather than isolating the air-sensitive chromium tricarbonyl complex **5**, an oxidative workup with $FeCl_3 \cdot DMF$ complex[9] gives the 4-methoxytetrahydronaphthol **6f** in 64% yield, or an oxidative workup with $(NH_4)_2Ce(NO_3)_6$[9] can give either the quinone **7e** (65%) or the quinone

---

[1] This work was presented at the 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983.

[2] Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.

[3] (a) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *204*, C4. (b) Dötz, K. H.; Pruskil, I.; Muhlemeier, J. *Chem. Ber.* **1982**, *115*, 1278.

[4] Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850.

[5] Dötz, K. H.; Dietz, R. *Chem. Ber.* **1978**, *111*, 2517.

[6] (a) A preliminary report on the reactions of one other alkenyl complex has appeared: Semmelhack, M. F. *Pure Appl. Chem.* **1981**, *53*, 2379. (b) Subsequent to the disclosure of this work and the preparation of this manuscript, two communications appeared describing five additional examples: Dötz, K. H.; Kuhn, W. *J. Organomet. Chem.* **1983**, *252*, C78. Dötz, K. H.; Kuhn, W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 732.

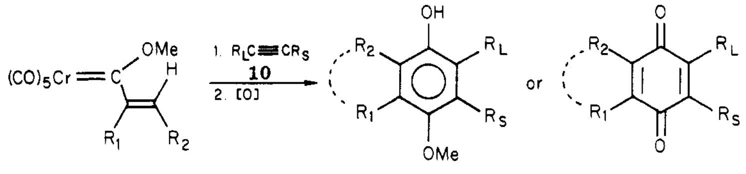
[7] Wulff, W. D.; Tang, P. C. *J. Am. Chem. Soc.* **1984**, *106*, 434.

[8] The carbene complexes in Table I are prepared by the standard Fischer method involving addition of an alkenyllithium (cyclopentenyllithium in the case of **3**) to chromium hexacarbonyl followed by methylation. For example, the cyclopentenyl complex **3** can be prepared in 71% yield from cyclopentenyl bromide.

[9] The procedures for the use of these oxidants in the workup of other benzannulations has been previously described.[10] The workup with tri-*n*-butylphosphine involves stirring the reaction mixture with 3 equiv at 25 °C for 36 h followed by destruction of the excess phosphine by sequential treatment with excess methanol and carbon tetrachloride.

0022-3263/84/1949-2293$01.50/0

Table I. Benzannulation of Alkenyl Complexes[a]



6 7

				10			
entry	complex[b]	R_1	R_2	R_L	R_S	yield of 6,[c] %	yield of 7,[c] %
a	1	$-(CH_2)_3-$		Ph	Ph	36[d]	
b				Ph	H	76	
c				Et	Et		37
d				*n*-Pr	H	54	
e	3	$-(CH_2)_4-$		Et	Et		65
f				Et	Et	64	
g				*n*-Pr	H		61
h				Me_3Si	H	71[e]	
i				(*Z*)-MeOCHCH	H	68[e]	
j				$AcOCH_2$	H	33	
k				MeO_2C	H	22[f]	
l				PhCO	H	17[f]	
m				MeO_2C	MeO_2C	8[f]	
n	11	$-(CH_2)_5-$		*n*-Pr	H	66	
o				$CH_2CH(Me)C$	H	57	
p	4	$-O(CH_2)_3-$		Et	Et	80[e]	
q				Et	Et		73
r				$(EtO_2C)_2(NHAc)CCH_2$	H		71
s				*n*-Pr	H		67
t	12	$-O(CH_2)_2-O-$		Et	Et		58
u				*n*-Pr	H		38
v	13	EtO	CH_3[g]	Ph	Ph	67	
w				*n*-Pr	H		40
x	14	EtO	H	Me_2CCHCH_2	H	23[e]	
y	15	CH_3	H	*n*-Pr	H		51[h]
z	16	H	CH_3[i]	*n*-Pr	H		75[j]
zz				*n*-Pr	H	60[k]	

[a] Conditions: ~0.3 M in THF, 45 °C, 24 h, 1.5 equiv of acetylene; oxidation with $FeCl_3$·DMF complex[9] for **6**, $(NH_4)_2Ce(NO_3)_6$ oxidation[9] for **7**. [b] Reference 8. [c] Isolated yields. [d] *n*-Bu_2O solvent at 70 °C. [e] Air oxidation. [f] I_2 oxidation. [g] 1.6:1.0 mixture of *E*:*Z*. [h] Contains 7.0% of quinone **7z**. [i] *E* isomer. [j] Contains ≤1.0% of quinone **7y**. [k] Tri-*n*-butylphosphine workup.[9]

monoacetal **8** (59%). In some cases the phenols can be obtained cleanly from the crude reaction mixture by chromatography on silica gel in air as is the benzopyran **6p**[11] (Scheme II).

Those reactions that involve terminal acetylenes were found to be regioselective, giving only those products where the acetylene substituent becomes ortho to the carbon monoxide derived hydroxyl group in **6**. This is confirmed by the fact that the tetrahydronaphthol **6i** can be cyclized to the benzofuran **9** (Scheme II) and by intramolecular hydrogen bonding in the products **6k** and **6l** and by the fact that the isopentenyl phenol **6x**, a suicide substrate for juvenile hormone biosynthesis, can be cyclized with phenylselenium chloride and with subsequent oxidation–elimination converted to 7-ethoxyprecocene.[12,13] The regiochemistry has also been confirmed by employing this reaction in the synthesis of an anthracyclinone intermediate.[7] The direction of the acetylene incorporation is thus the same as that we have previously established for the annulation of arylchromium carbene complexes.[10] It has been suggested that the regioselectivity of this reaction arises from a conformational preference of an acetylene complex of the type A.[15]

The extent of the regioselectivity is indicated by entries y and z. The complexes **15** and **6** were chosen since the pair of quinone products **7y** and **7z** are mutually shared as the two possible regioisomers from each reaction with 1-pentyne and also because according to the model suggested by complex A, **15** and **16** may be expected to be the least regioselective of all the complexes in Table I. The reaction of the complex **15** with 1-pentyne gives quinone **7y** which is contaminated with the isomeric quinone **7z** to the extent of 7.0%. In the corresponding reaction of complex **16** which was carried out and worked up in an identical manner, the quinone **7z** is free of the quinone **7y** to the extent of ≤1.0% which is on the order of the extent of the regioselectivity found for the aryl complexes with terminal alkynes.[10] It is not clear why the complex **15** is less regioselective than **16**; and we plan to examine this in further detail.[16]

---

(10) Wulff, W. D.; Tang, P. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677.

(11) Satisfactory spectral data were obtained for all new compounds, and with the exception of the relatively unstable complexes 14 and 15[13] satisfactory elemental analyses or high-resolution mass spectra were obtained as well.

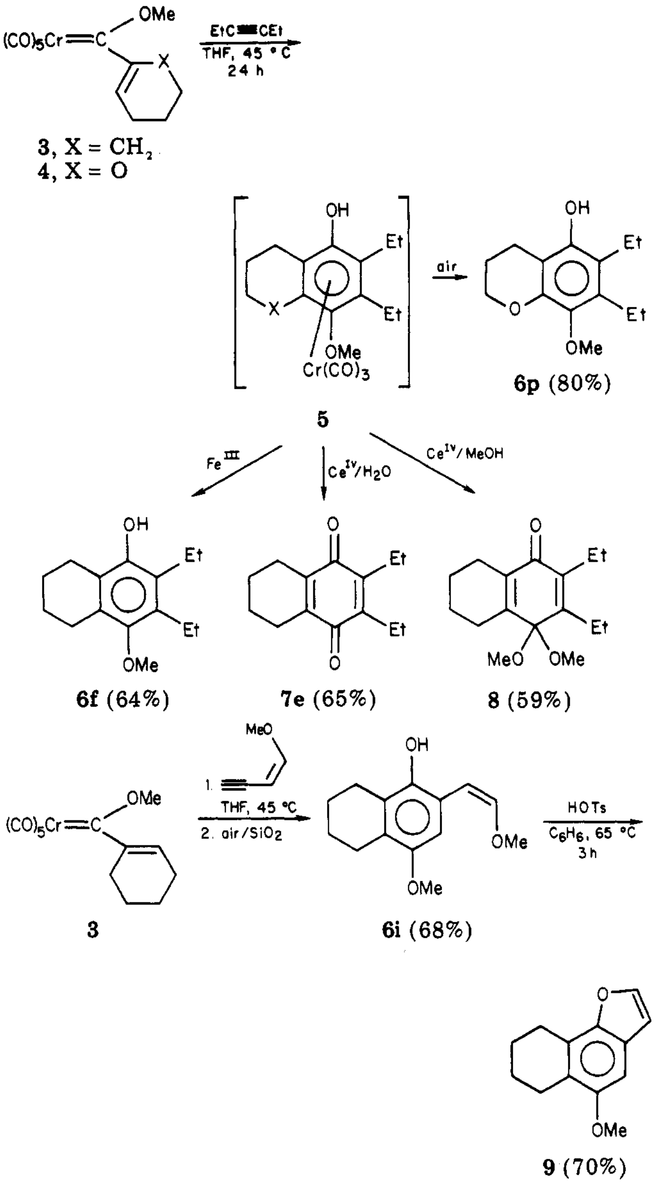
(12) Bowers, W. S.; Evans, P. H.; Marsella, P. A.; Soderlund, D. M.; Bettarini, F. *Science (Washington, D.C.)* **1982**, *217*, 647.

(13) Part of the problem with the low yields for entries X and Y may be that the complexes 14 and 15 are relatively unstable as are most α,β-unsubstituted alkenylchromium complexes.[14] We are currently seeking to circumvent this shortcoming.

(14) Wilson, J. W.; Fischer, E. O. *J. Organomet. Chem.* **1973**, *57*, C63.

(15) For mechanistic discussions of this reaction, see: (a) Fischer, H.; Mulhemeier, J.; Markl, R.; Dötz, K. H. *Chem. Ber.* **1982**, *115*, 1355. (b) Casey, C. P. In "Reactive Intermediates", Jones, M., Jr., Moss, R. A., Eds.; Wiley: New, York, 1981; Vol. 2.

Scheme II



It was also interesting to find that whereas both of the *E* and *Z* isomers of **16** (1:1 mixture) can be converted to the quinone **7**, it cannot be assumed that the *Z* isomer is annulated directly since the same mixture will isomerize completely to the *E* isomer (E:$Z \gtrsim 100$) under the reaction conditions (THF, 45 °C) in approximately the same time period (24 h). This facile isomerization is very intriguing as there are a number of possible explanations, and investigations are continuing on this matter.

An examination of the data in Table I reveals that the yields of the benzannulated products are dependent on the nature of the acetylene and the structure of the chromium carbene complex. Most notably, those acetylenes bearing electron-withdrawing substituents α to or conjugated with the acetylene give poor yields (entries j–m).[17] Nonetheless, these results are of interest in that these acetylenes (entries k–m) fail to give annulated products with arylchromium carbene complexes.[18] However, as indicated by entry r electron-withdrawing groups further removed from the acetylene do not affect the reaction, nor do alkenyl or aryl groups conjugated with the acetylene (entries a, b, i, o, v).[20]

The reaction of acetylenes with α,β-unsaturated chromium carbene complexes allows for the controlled construction of an aromatic nucleus under neutral conditions at near ambient temperatures. It thus offers an allternative to the normal synthetic strategy of employing the aromatic nucleus in the starting material. We have utilized this reaction in the formal syntheses of anthracyclinones[7] and are currently employing it in synthetic approaches to other natural products. We will report at a later date on mechanistic studies[15] and on the effects of solvent[21] and the metal[22] on product distribution.

Acknowledgment. This work was supported by a grant from Dow Chemical Co. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by NCI via the University of Chicago Cancer Research Center (CA-14599). We thank Dr. Phillipson and J. Carter Cook at the University of Illinois for their help with some mass spectral analysis. We also thank Tina Lee for help with some preliminary experiments.

Registry No. **1**, 67746-50-3; **3**, 88426-08-8; **4**, 90150-06-4; **4** (acylate·nBu$_4$N$^+$), 90150-13-3; **6a**, 90150-22-4; **6b**, 90150-23-5; **6d**, 90150-25-7; **6f**, 90150-27-9; **6h**, 90150-30-4; **6i**, 90150-31-5; **6j**, 90150-32-6; **6k**, 88426-25-9; **6l**, 88426-24-8; **6m**, 90150-33-7; **6n**, 90150-34-8; **6o**, 90150-35-9; **6p**, 90150-36-0; **6v**, 90150-41-7; **6x**, 83053-40-1; **6zz**, 90150-44-0; **7c**, 90150-24-6; **7e**, 90150-26-8; **7g**, 90150-29-1; **7q**, 90150-21-3; **7r**, 90150-37-1; **7s**, 90150-38-2; **7t**, 90150-39-3; **7u**, 90150-40-6; **7w**, 90150-42-8; **7y**, 65644-50-0; **7z**, 90150-43-9; **8**, 90150-28-0; **9**, 90150-45-1; **10** (R_L = R_S = Ph), 501-65-5; **10** (R_L = Ph, R_s = H), 536-74-3; **10** (R_L = R_s = Et), 928-49-4; **10** (R_L = n-Pr, R_s = H), 627-19-0; **10** (R_L = Me$_3$Si, R_s = H), 1066-54-2; **10** (R_L = (*Z*)-MeOCH=CH, R_s = H), 3685-19-6; **10** (R_L = AcOCH$_2$, R_s = H), 627-09-8; **10** (R_L = MeO$_2$C, R_s = H), 922-67-8; **10** (R_L = PhCO, R_3 = H), 3623-15-2; **10** (R_L = R_s = MeO$_2$C), 762-42-5; **10** (R_L = CH$_2$=CHCH$_2$, R_3 = H), 871-28-3; **10** (R_L = (EtO$_2$C)$_2$(NHAc)CCH$_2$, R_s = H), 61172-60-9; **10** (R_L = Me$_2$C=CHCH$_2$, R_s = H), 26216-06-8; **11**, 90150-07-5; **12**, 90150-08-6; **12** (acylate·n-Bu$_4$N$^+$), 90150-16-6; (*E*)-**13**, 90150-09-7; (*Z*)-**13**, 90242-18-5; (*E*)-**13** (acylate·n-Bu$_4$N$^+$), 90150-18-8; (*Z*)-**13** (acylate·n-Bu$_4$N$^+$), 90242-20-9; **14**, 90150-10-0; **14** (acylate·n-Bu$_4$N$^+$), 90150-20-2; **15**, 87965-61-5; (*E*)-**16**, 90150-11-1; (*Z*)-**16**, 90242-17-4; Cr(CO)$_6$, 13007-92-6; 1-bromocyclopentene, 1192-04-7; cyclohexanone 2,4,6-triisopropylbenzenesulfonylhydrazone, 61835-95-8; 1-bromocyclohexene, 2044-08-8; dihydropyran, 110-87-2; [1-(4-methoxybutoxy)-1-dihydropyranylmethylene]pentacarbonylchromium, 90150-14-4; cycloheptanone 2,4,6-triisopropylbenzenesulfonylhydrazone, 75415-79-1; p-dioxene, 543-75-9; *trans*-1-chloropropene, 16136-85-9; *trans*-1-bromopropene, 590-15-8; 2-bromopropene, 557-93-7; 7-ethoxyprecocene, 65383-73-5.

Supplementary Material Available: Spectral data for all compounds and experimental procedures (19 pages). Ordering information is given on any current masthead page.

William D. Wulff,* Kin-Shing Chan, Peng-Cho Tang

Searle Chemistry Laboratory
Department of Chemistry
The University of Chicago, Chicago, Illinois 60637

Received December 15, 1983

---

[16] The reactions of entries y and z were subjected to GC–mass spectral analysis (University of Illinois). All of the other products in Table I were judged to be isomerically pure by 500-MHz ^{1}H NMR, by TLC, and in some cases by ^{13}NMR and by HPLC.

[17] It is interesting that the electron-rich 4-methoxybutenyne (entry i) reacts, since ethoxyacetylene gives no annulated products with either **4** or various aryl chromium carbene complexes.[18] The latter may be related to the reactions of ynamines with aryl complexes.[19]

(18) Unpublished results from this laboratory.

(19) Fischer, H.; Dötz, K. H. *Chem. Ber.* **1980**, *113*, 193.

(20) This is in contrast to the reactions of conjugated enynes with aryl complexes which yield complex mixtures.[18]

(21) Dötz, K. H. *J. Organomet. Chem.* **1977**, *140*, 177.

(22) Foley, H. C.; Strubinger, L. M.; Targos, T. S.; Geoffroy, G. L. *J. Am. Chem. Soc.* **1983**, *105*, 3064.