

***Iron in the Service of Chromium:
The ortho-Benzannulation of trans,trans-Dienyl
Fischer Carbene Complexes***

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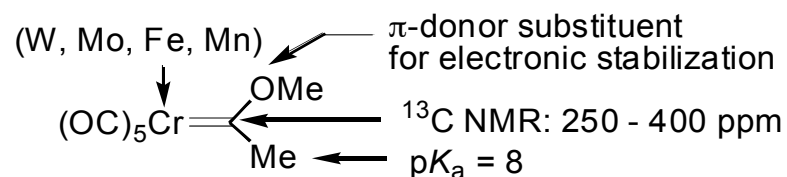
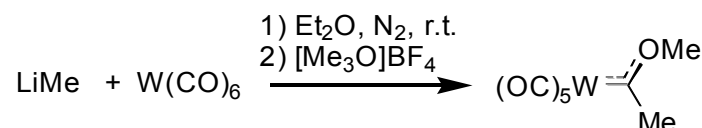
JACS 2005, 127, 17162-17163.

Markus Furegati
Current Literature
January 21st 2006

Transition Metal Carbene Complexes

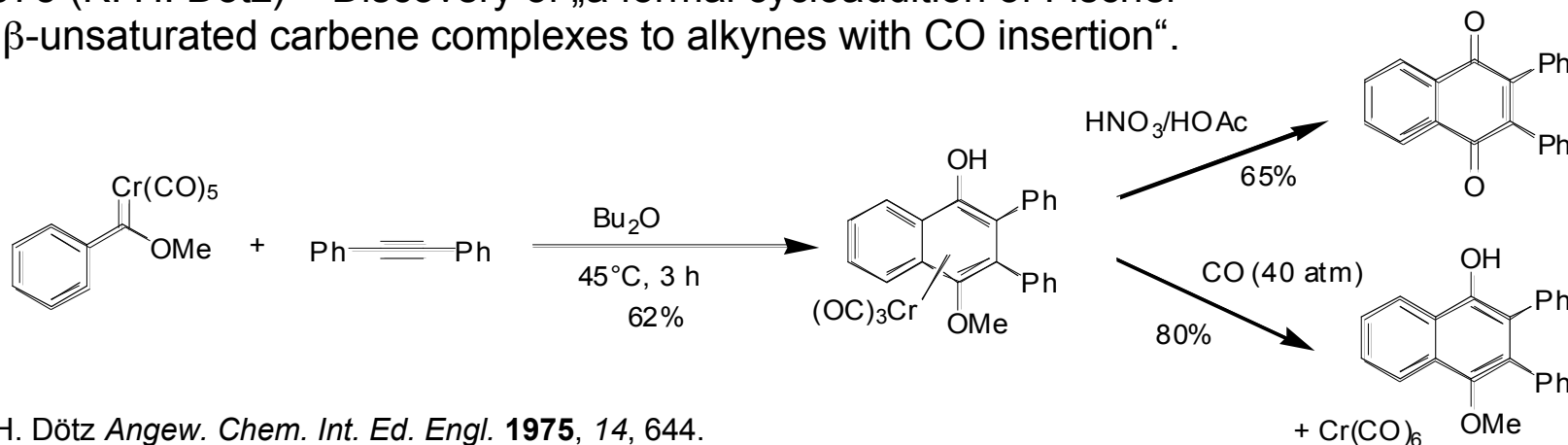
- 1964 (E. O. Fischer) – First report of transition metal carbene complexes with Cr, Mo, W. Initially hesitantly introduced into preparative organic chemistry.

E. O. Fischer *et al.* *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 580.
 „On the Existence of a Tungsten Carbonyl Carbene Complex“



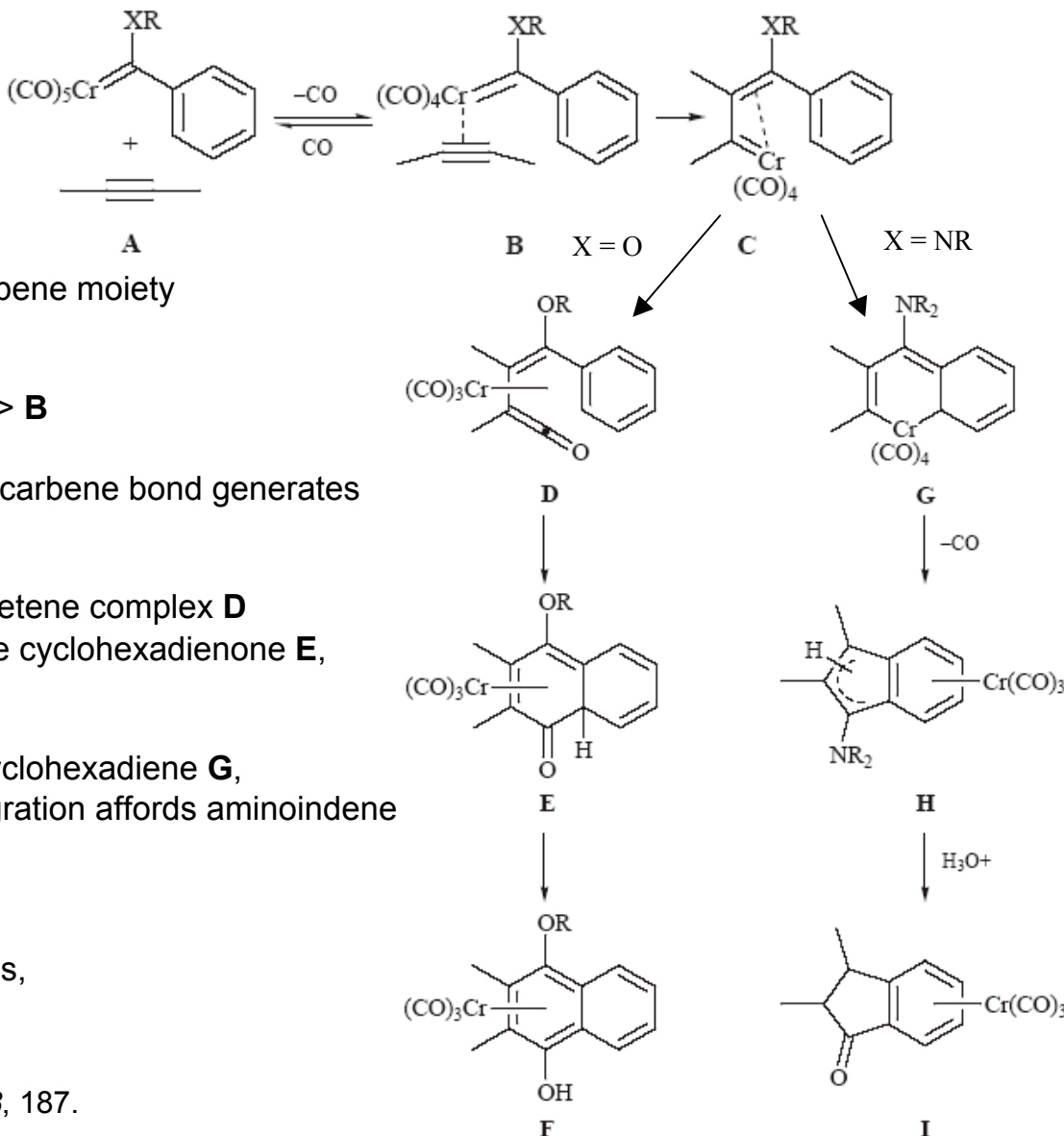
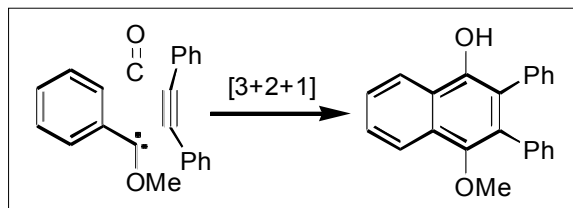
Because of the electron withdrawing character of the pentacarbonyl metal group, they can be regarded as analogues of esters, thioesters or amides.

1975 (K. H. Dötz) – Discovery of „a formal cycloaddition of Fischer α,β -unsaturated carbene complexes to alkynes with CO insertion“.



K. H. Dötz *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 644.
 recent review: K. H. Dötz *et al.* *Chem. Soc. Rev.* **1999**, 28, 187.

Mechanism of the Dötz Reaction



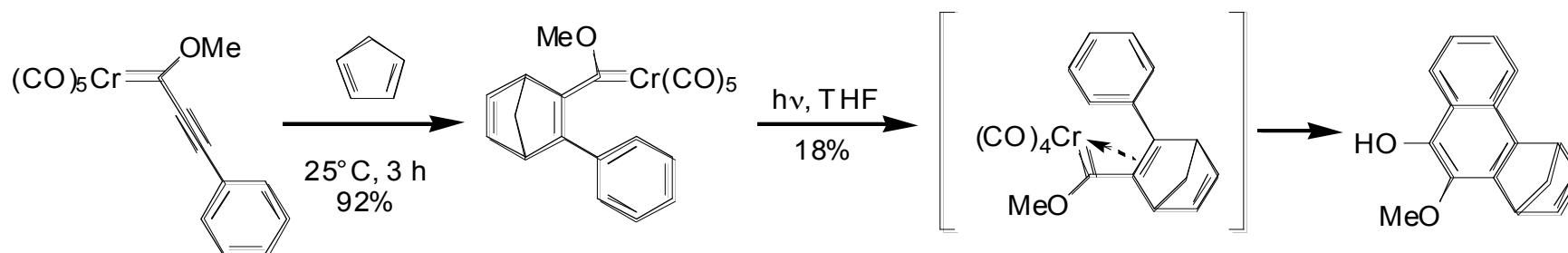
- 1) Dissociation of one CO *cis* to the carbene moiety (rate-determining step)
- 2) Coordination of an alkyne molecule -> **B**
- 3) Insertion of the alkyne into the metal carbene bond generates η^3 -allylidene complex **C**
- 4a) (X=O) CO insertion forms η^3 -vinyl ketene complex **D**
electrocyclic ring closure affords the cyclohexadienone **E**,
tautomerization to **F**
- 4b) (X=NR) Cyclization to the chromacyclohexadiene **G**,
reductive elimination and metal migration affords aminoindene
complex **H**, hydrolysis affords **I**

Tolerant towards many functional groups,
usually high yielding reaction.

K. H. Dötz *et al.* *Chem. Soc. Rev.* **1999**, 28, 187.

The ortho-Benzannulation

Dötz reaction leads to 1,4 relation of the two oxygen atoms.
Possibility for 1,2 arrangement? [1]



Why use of UV?

Fischer has shown that the rates of ligand substitution reactions of pentacarbonyl-(methoxymethylcarbene)chromium complex can be increased under UV irradiation, presumably via a photoinduced dissociation of a CO ligand. [2]

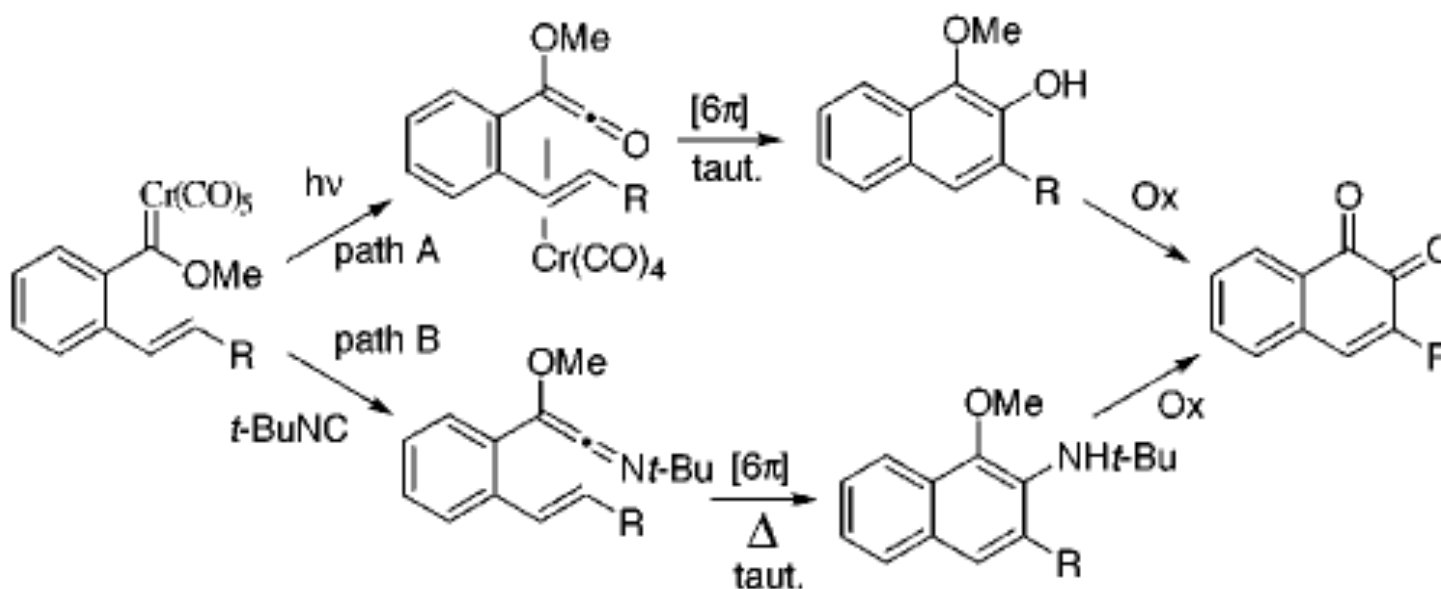
The dissociation proceeds also thermally (standard Dötz conditions).

[1] W. D. Wulff In *Advances in Metal-Organic Chemistry*; L. S. Liebeskind, Ed.; JAI Press: Greenwich, CT, 1989; Vol 1, p 336.

[2] E. O. Fischer, H. Fischer *Chem. Ber.* **1974**, *107*, 657.

Improvements of the ortho-Benzannulation

The large number of natural products that possess *o*-alkoxy-phenol or *o*-quinone type structures argues for the development of chromium carbene based strategies that will provide access to substitution patterns other than para.



C. A. Merlic *et al.* *JOC* **2001**, 66, 1297.

Path A: a) C. A. Merlic *et al.* *JACS* **1991**, 113, 7418. b) C. A. Merlic *et al.* *THL* **1993**, 34, 7379.

Path B: a) C. A. Merlic *et al.* *JACS* **1992**, 114, 8722. b) C. A. Merlic *et al.* *THL* **1993**, 34, 5401.

ortho-Benzannulation Reaction (Path A)

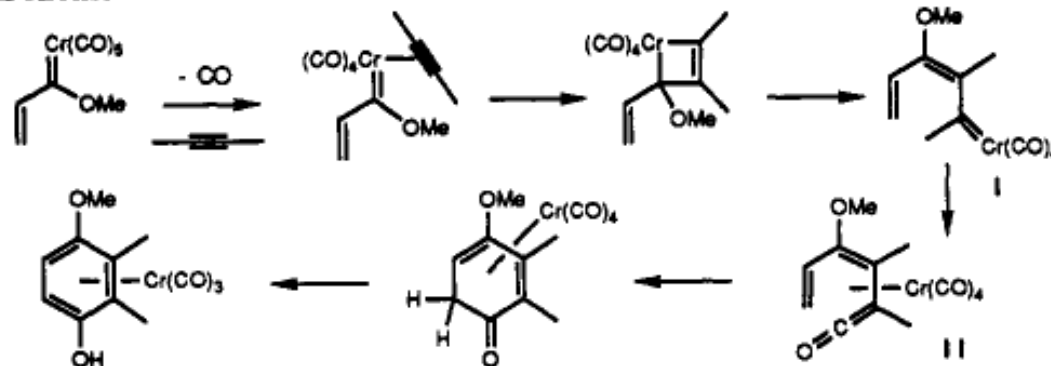
Dötz reaction.

Hegedus [1] demonstrated that direct CO insertion in simple chromium alkoxy- and aminocarbene complexes can be effected by photolysis. Thermal activation gave lower yield.

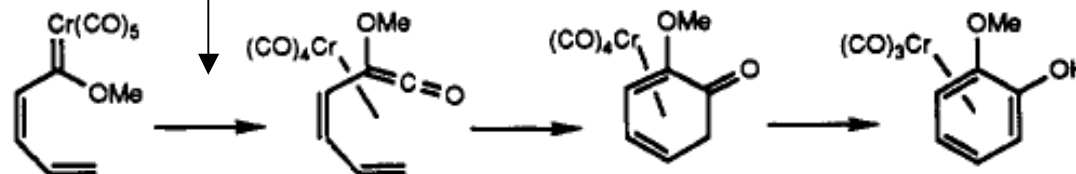
CO sparging increased the yield. Presumably, CO traps tetracarbonyl carbene complexes formed by thermal or photoinduced CO loss.

cis-configuration required

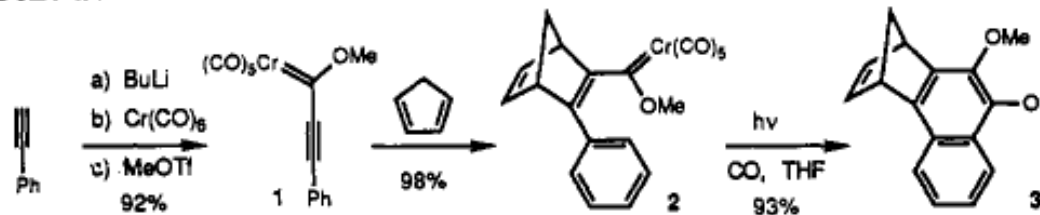
Scheme I



Scheme II



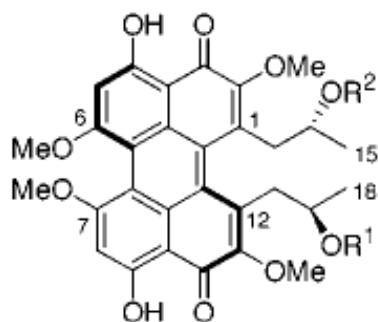
Scheme III



Path A: a) C. A. Merlic *et al.* *JACS* **1991**, *113*, 7418. b) C. A. Merlic *et al.* *THL* **1993**, *34*, 7379.
[1] S. Hegedus *et al.* *JACS* **1990**, *112*, 4364.

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Application in the Total Synthesis of Calphostins A-D



Calphostin A (**1**) $R_1 = \text{Bz}$, $R_2 = \text{Bz}$

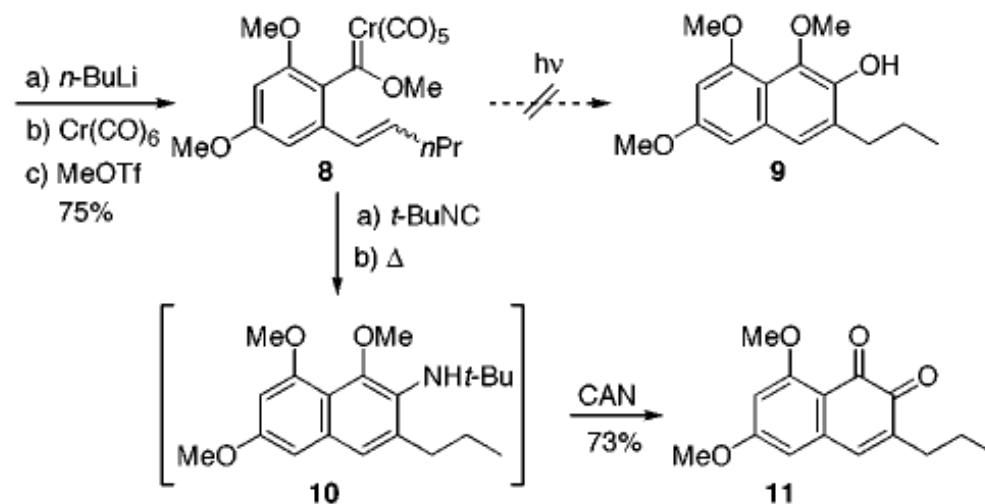
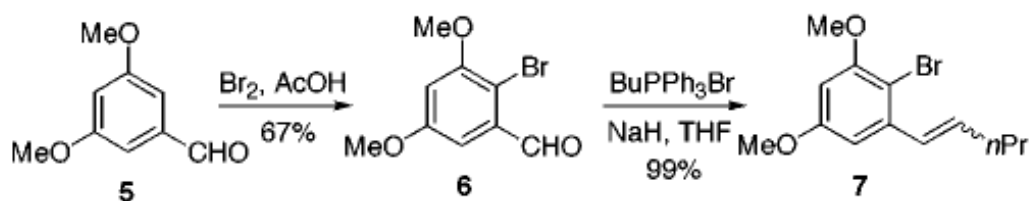
Calphostin B (**2**) $R_1 = \text{Bz}$, $R_2 = \text{H}$

Calphostin C (**3**) $R_1 = \text{Bz}$, $R_2 = \text{CO}_2\text{-C}_6\text{H}_4\text{-OH}$

Calphostin D (**4**) $R_1 = \text{H}$, $R_2 = \text{H}$

Isolated by Tamaoki et al. in 1989 from *Cladosporium cladosporioides*. Calphostin C in particular is a potent inhibitor of PKC.

Key step applied on a model system:
Path A (last slide) did not work due to high electron density in aryl ring. [2]



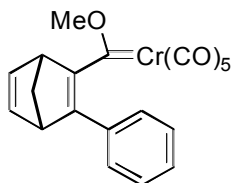
[1] T. Tamaoki et al. *J. Antibiot.* **1989**, 42, 153 and 1470.

[2] C. A. Merlic et al. *JOC* **2001**, 66, 1297.

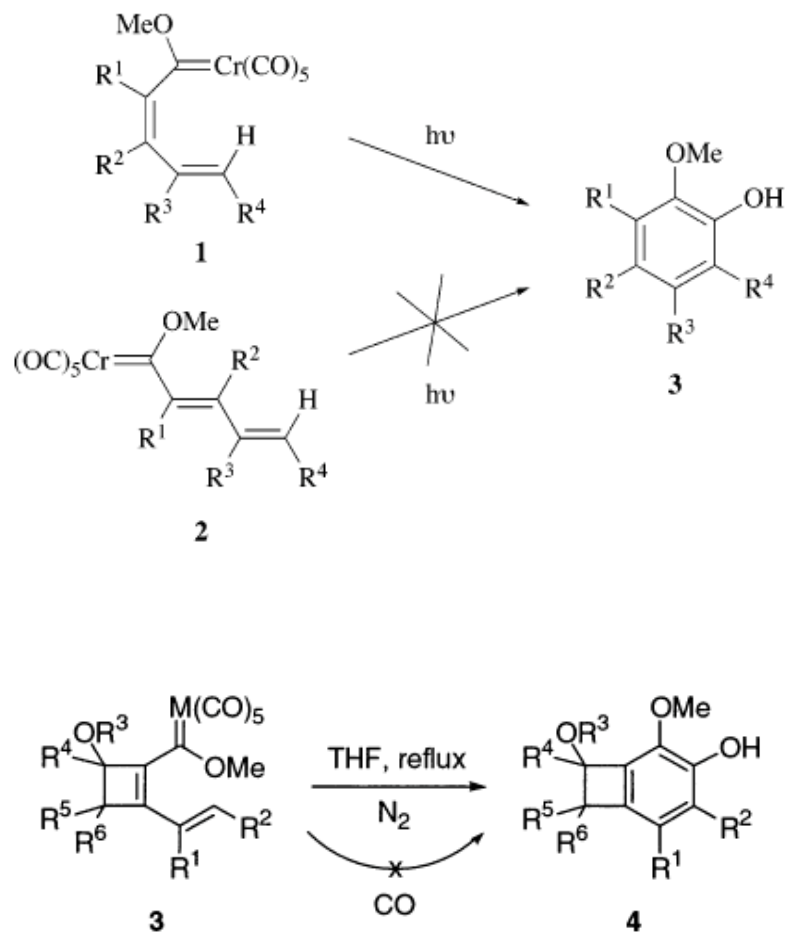
The *ortho*-Benzannulation of *trans,trans*-Dienyl Fischer Carbene Complexes I

The *ortho*-benzannulation requires that the α,β -double bond in **1** has a *cis*-disposition of the carbene complex and the second double bond.

- Incorporation in a ring
- Prepared by [4+2] or [2+2] cycloaddition onto the alkyne function of an enynyl carbene complex.



The reaction usually requires light, but if R^1 and R^2 were embedded into a strained four-membered ring (**3**), the formation of *o*-alkoxyphenols could be induced thermally. [1]



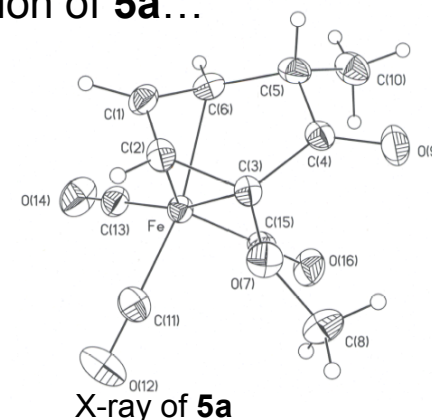
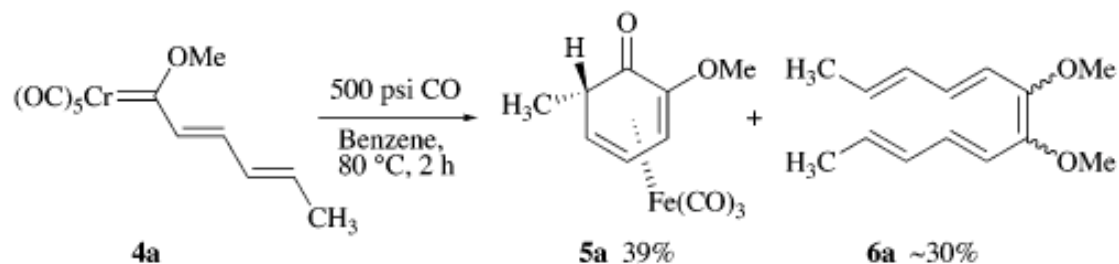
M = W, Cr; reaction time: 2-12 h
c = 20 mM; yield: 60 – 95%

W. D. Wulff et al. *JACS* **2005**, *127*, 17162-17163.

[1] J. Barluenga et al. *JOC* **2003**, *68*, 537.

The ortho-Benzannulation of trans,trans-Dienyl Fischer Carbene Complexes II

In the course of a control experiment Wulff et al. observed the formation of **5a**...



... with the mass of the stirrer rapidly diminishing.

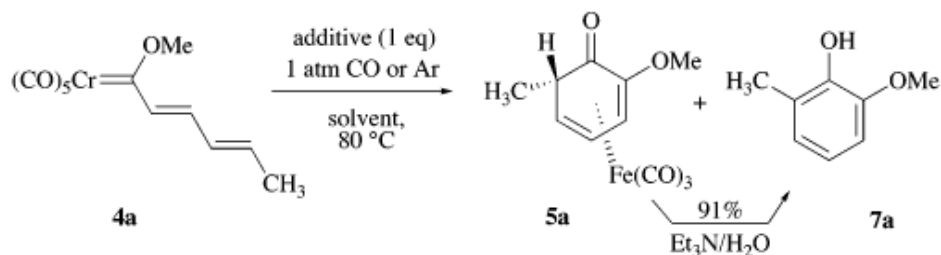


Table 1. Optimization with Added Iron Tricarbonyl Sources

additive	solvent	CO/Ar	time, h	5a , % yield	7a , % yield
	benzene	CO	144		< 0.5 ^a
		Ar	144		8
$\text{Fe}_2(\text{CO})_9$	benzene	CO	18	70	8
		Ar	28	58	6
$\text{Fe}_2(\text{CO})_9$	heptane	CO	36	68	7
		Ar	20	54	5
$\text{Fe}_2(\text{CO})_9$	THF	CO	36	61	20
		Ar	20	50	10
$\text{Fe}_2(\text{CO})_9$	CH_3CN	CO	17	68	12
		Ar	20	34	8
$\text{Fe}(\text{CO})_3(\text{ba})^b$	benzene	CO	48	60	7

^a With 70% recovery of **4a**. ^b Benzylideneacetone iron tricarbonyl.

W. D. Wulff et al. *JACS* **2005**, *127*, 17162-17163.

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Scope of the reaction

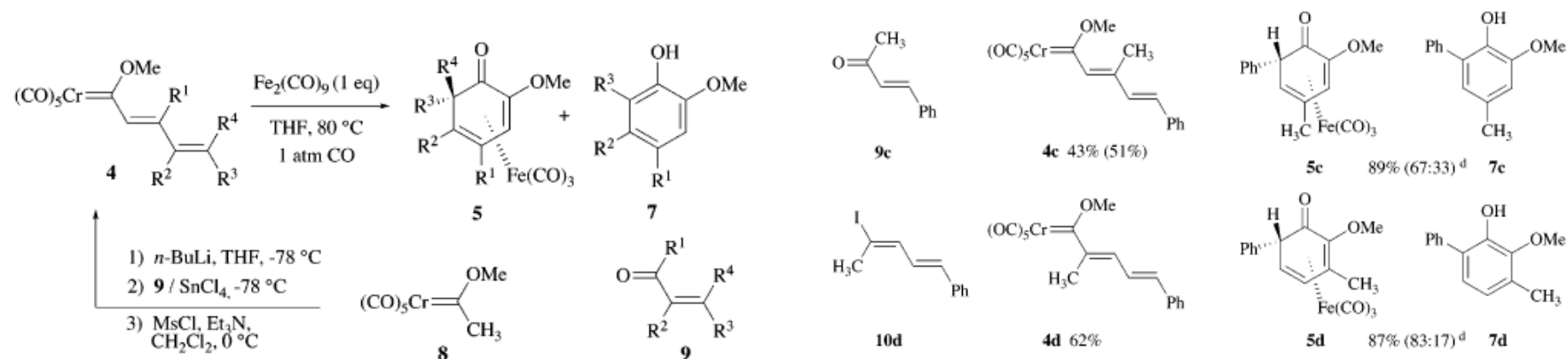


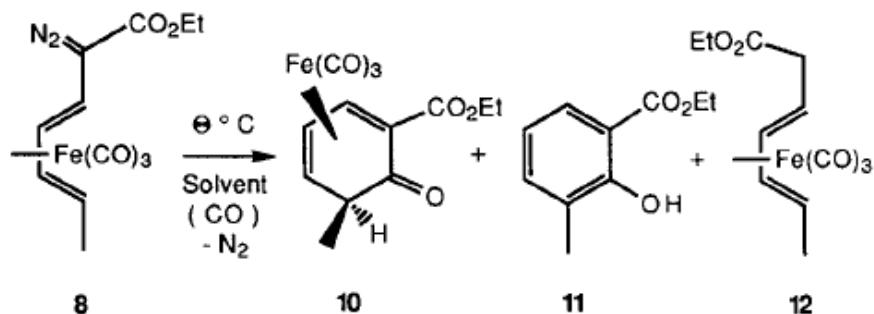
Table 2. Iron-Mediated Reactions of Dienyl Fischer Carbene Complexes^a

aldehyde	carbene complex ^b	dienone	phenol
9a	4a 52% (63%)	5a 81% (75:25)	7a
9b	4b-Cr 68%	5b 82% (40:60) 78% (0:100) ^c	7b
9c	4c 43% (51%)	5c 89% (67:33) ^d	7c
9d	4d 62%	5d 87% (83:17) ^d	7d
9e	4e 31% (61%)	5e 91% (93:7)	7e
9f	4f 72%		7f 70%
9g	4g 51% (72%)	5g 85%	

^a Unless otherwise specified, all reactions were carried out in THF at $80\text{ }^\circ\text{C}$ with 1 equiv of $\text{Fe}_2(\text{CO})_9$ under 1 atm of CO at 0.02 M in **4**. ^b Yields in parentheses are based on unrecovered starting material. ^c The crude reaction mixture was stirred with silica gel for 2–3 days. ^d In benzene.

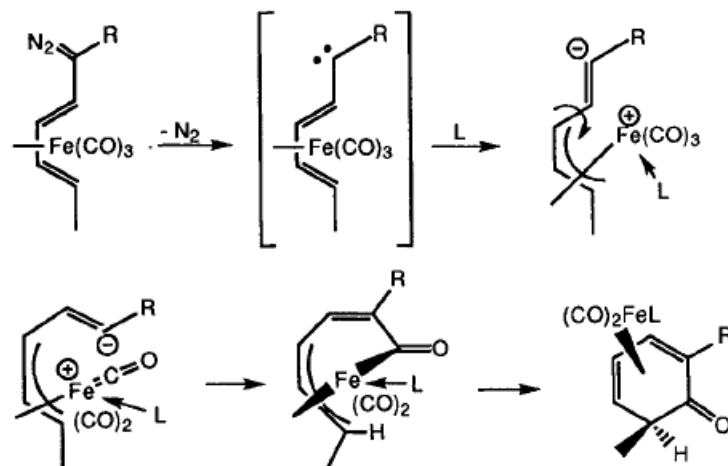
Possible Mechanism

Related chemistry, thermolysis of diazoester **8**: [1]



Solvent	$\theta^\circ \text{C}$	Time	10	11	12
cumene	$20^\circ \rightarrow 100^\circ$	2 h	45 %	15 %	–
cumene (CO)	140°	10 min	30-35 %	40-45 %	20-10 %
mesitylene (CO)	160°	10 min	–	95 %	trace < 2%

- Loss of Nitrogen and
- formation of a zwitterionic π -allyl complex
- Rotation around the formerly terminal diene C=C bond
- Intramolecular insertion of a CO ligand
- the pseudo cyclic structure cyclizes to an iron π -coordinated cyclohexadienone.



[1] M. Franck-Neumann *et al.* *Synlett* **1995**, 341.

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Summary & Outlook

During three decades metal carbenes have evolved from organometallic curiosities to valuable tools in stereoselective organic synthesis.

Title paper:

The carbonylative cyclization of *trans,trans*-dienyl complexes is not known and has been reported to fail under photochemical conditions.

Easy access to *trans,trans*-dienyl Fischer carbenes by aldol reaction.

Mechanistic and further synthetic studies will be reported in due course.