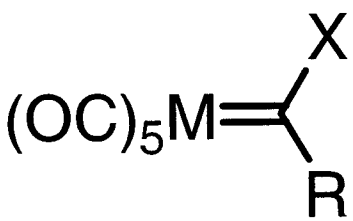
Reaction of Alkynes with Amino Chromium Fischer Carbene Complexes and Synthesis of N-Heterocycles



X = OR, NR_2

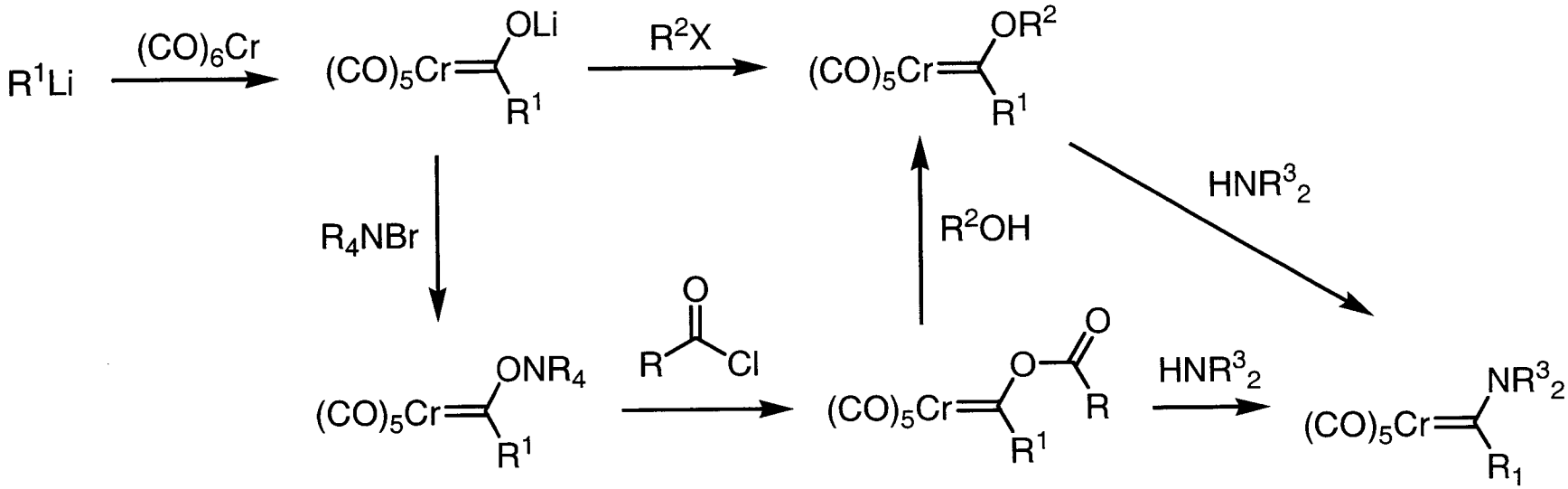
M = Cr, Mo, W

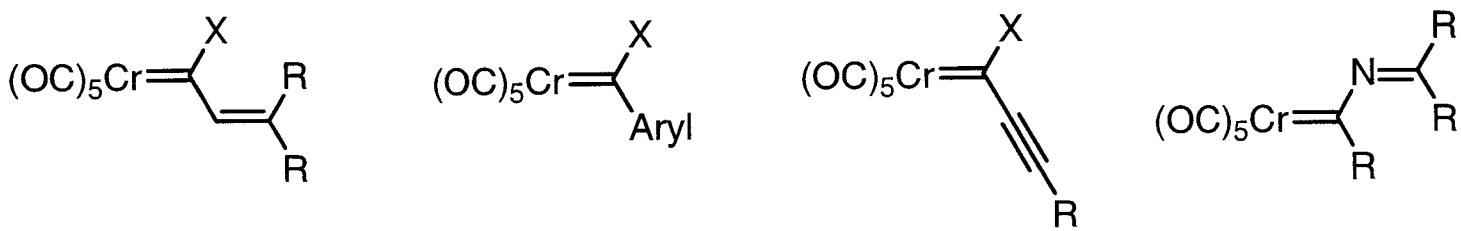
R = Aryl, Alkenyl, Alkynyl

Min Xie

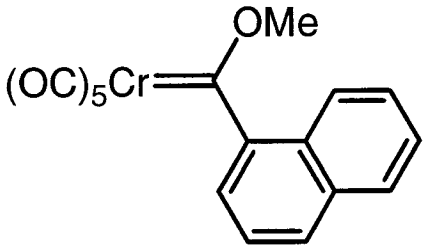
11/29/2005

General Preparation of FCC





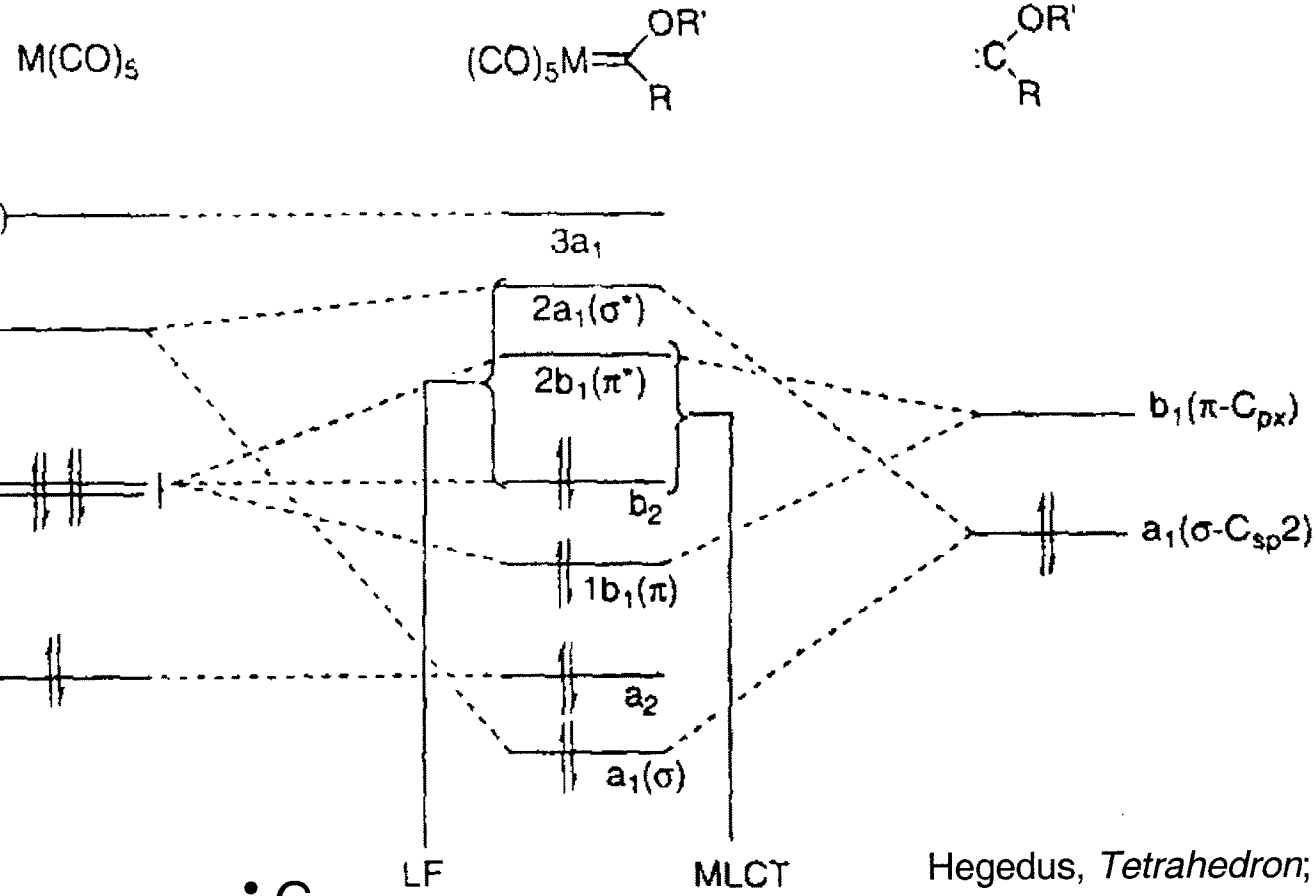
Scalability and Easy Handling



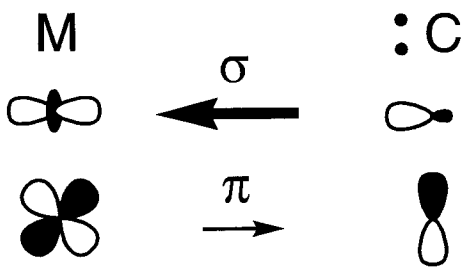
This complex was prepared from 1-bromonaphthalene on a **285 gram scale** in **77 % yield (3 crops)** … The red pile is **250 grams** of the naphthalene complex …

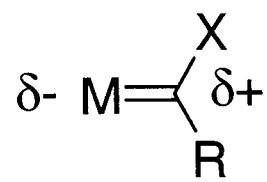
http://poohbah.cem.msu.edu/faculty/wulff/myweb26/research/benzannulation.htm

Electronic Structure of FCC



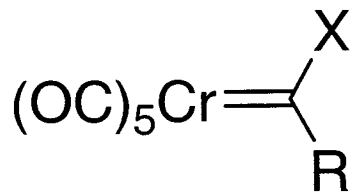
Hegedus, *Tetrahedron*; **1997**





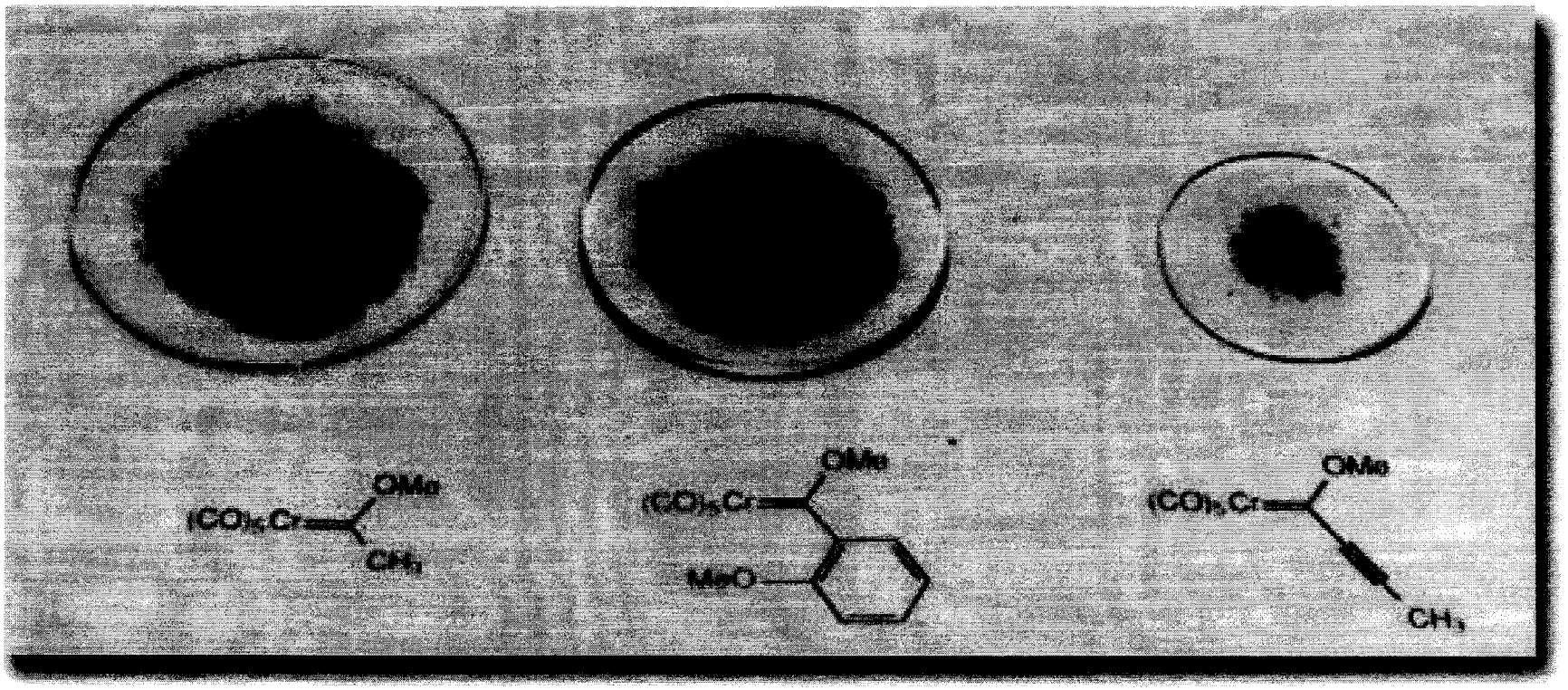
Carbene carbon in FCC is typically electrophilic.

Effect of Heteratom Substituents



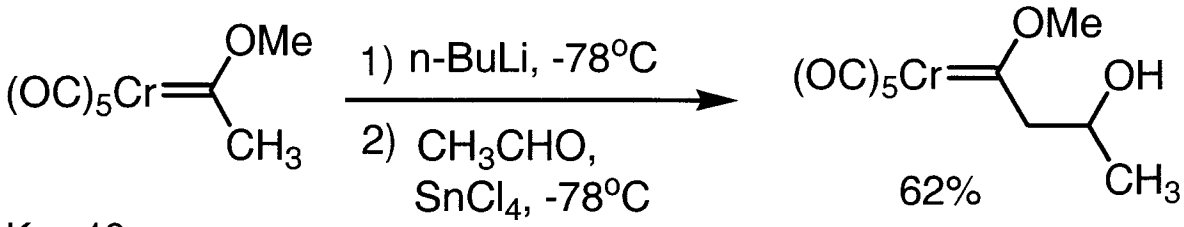
- X a better donor (N vs O)
- Carbene carbon a weaker π-acceptor
- Decreased M→carbene backbonding
- Increased M→CO backbonding
- shortening of the M-CO bond
- lower C=O frequency
- Blue shift of visible spectra
- More stable, less reactive

Effect of Carbon Substituents



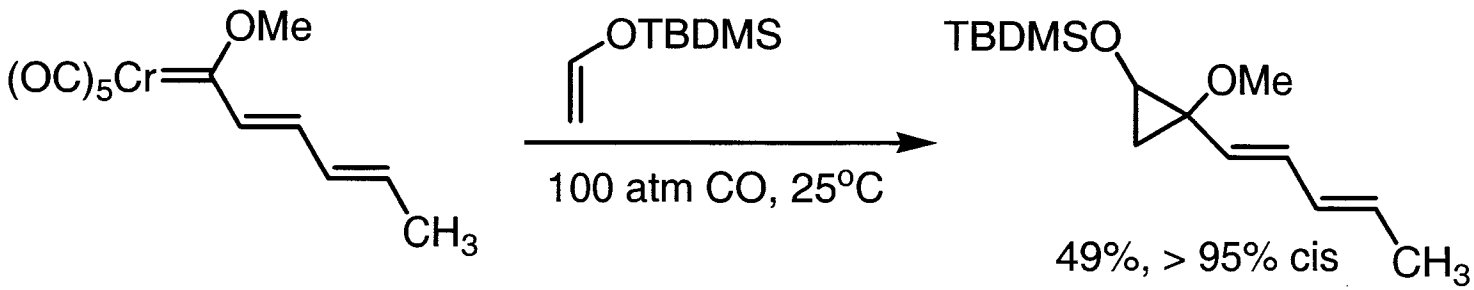
Better π accepter, smaller HOMO-LUMO gap, red shift.

Typical Reactions of FCC

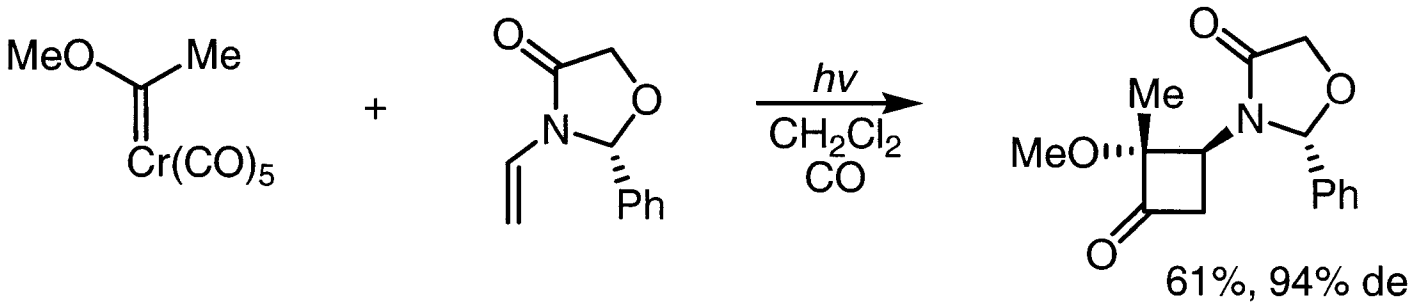


pKa ~12
metyl acetate pKa ~ 25
diethyl malonate pKa ~13

Wulff, *Tetrahedron Lett.*, **1998**

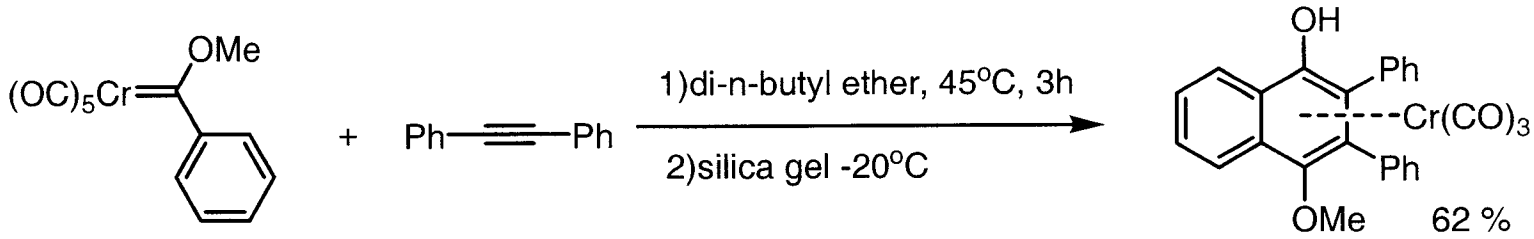


Wulff, *JACS.*, **1988**

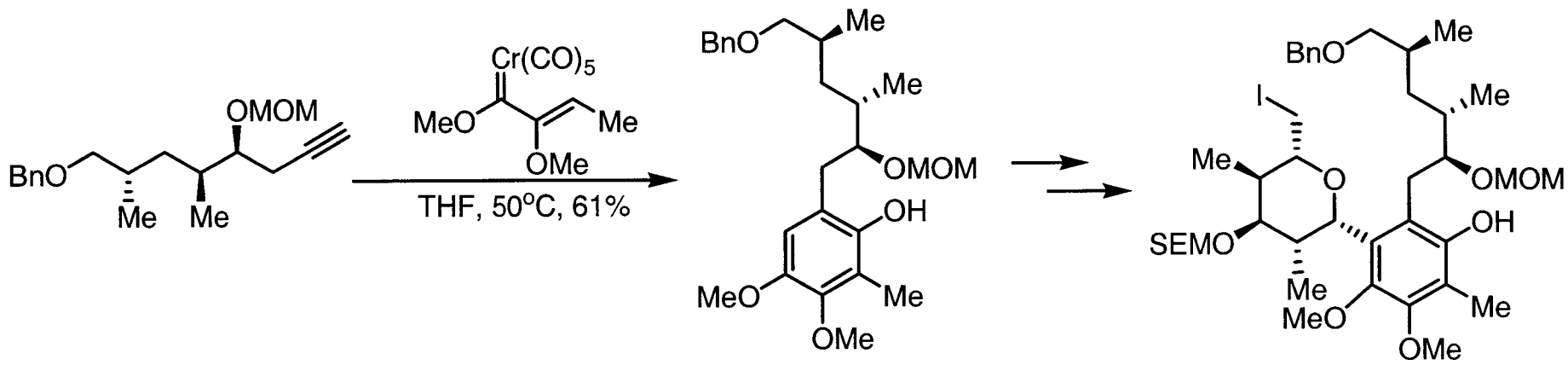


Hegedus, *JACS*, **1991**

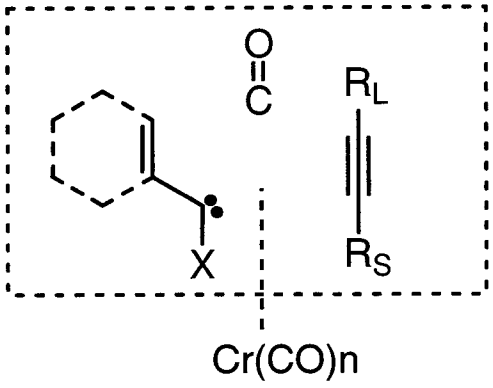
Dotz Reaction of Alkoxy Substituted FCC

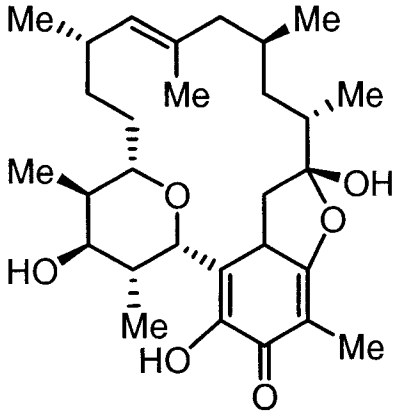


Dotz, *ACIEE*, **1975**



Chromium-Templated [3+2+1]

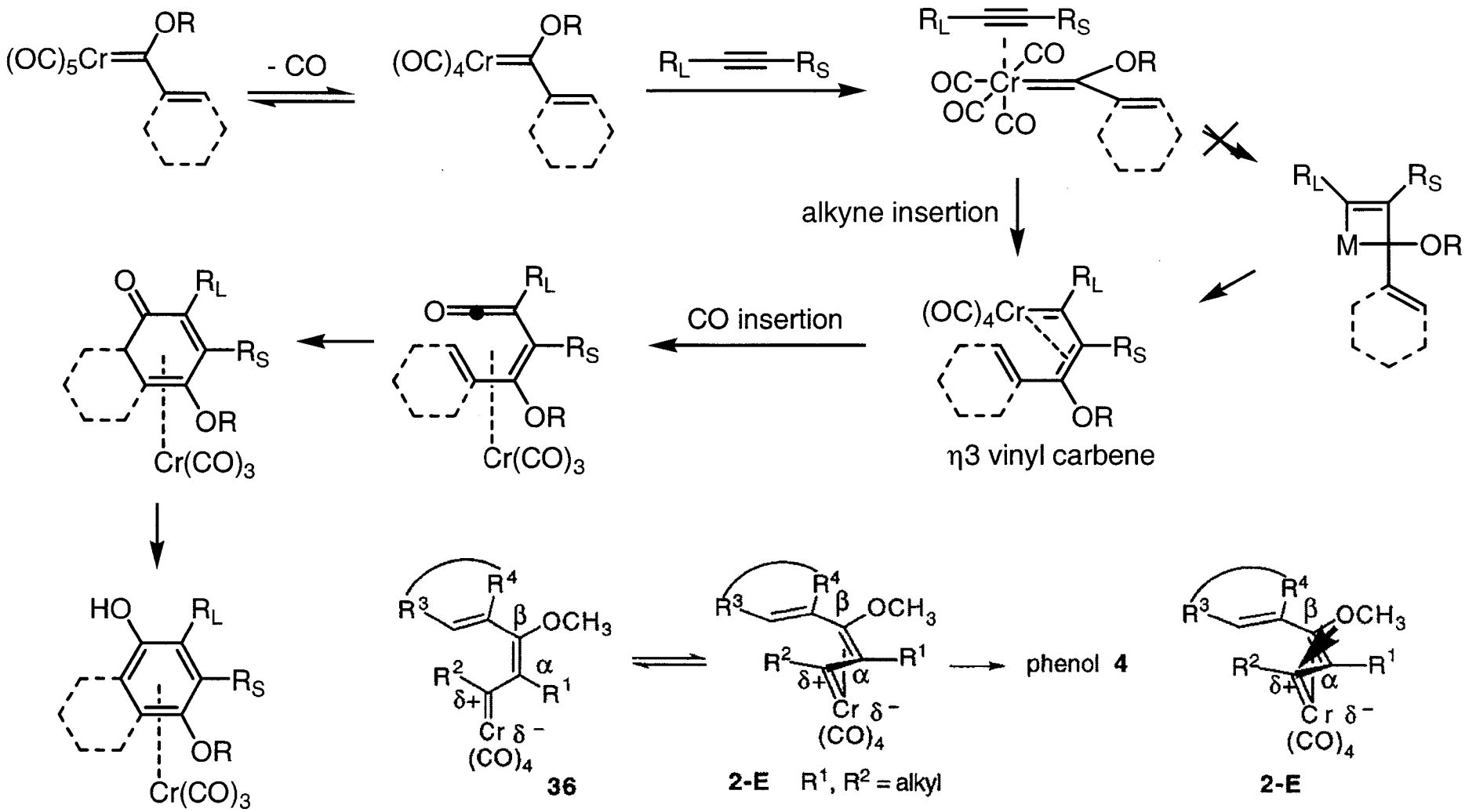




(-)-Kendomycin

White, *OL*, **2004**

General Mechanism of Dotz Reaction



Meijere, *ACIE*, **2000**

Wulff, *Organometallics*, **1998**

Dissociation of CO

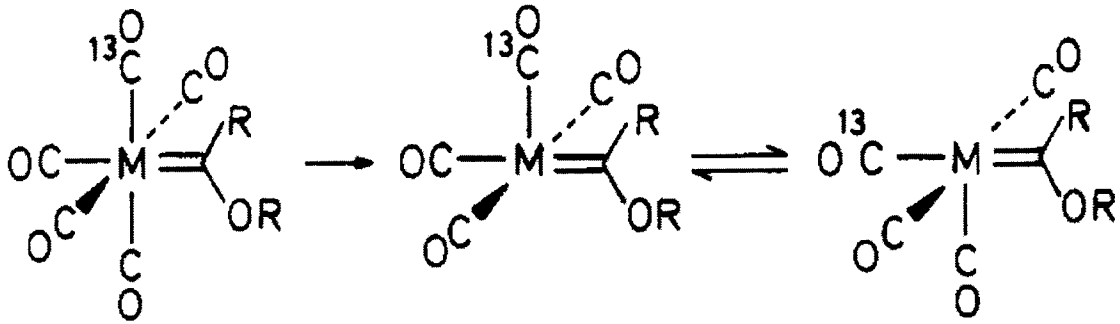
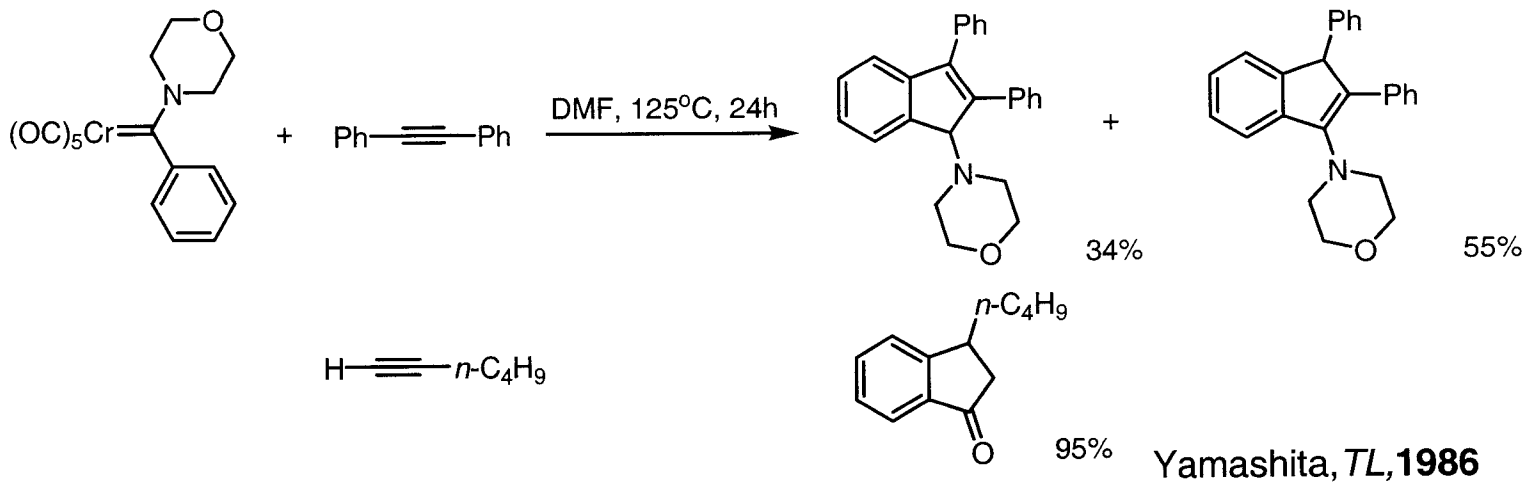


Table III. Rates of CO Dissociation from $(CO)_5M{=}CRR'$

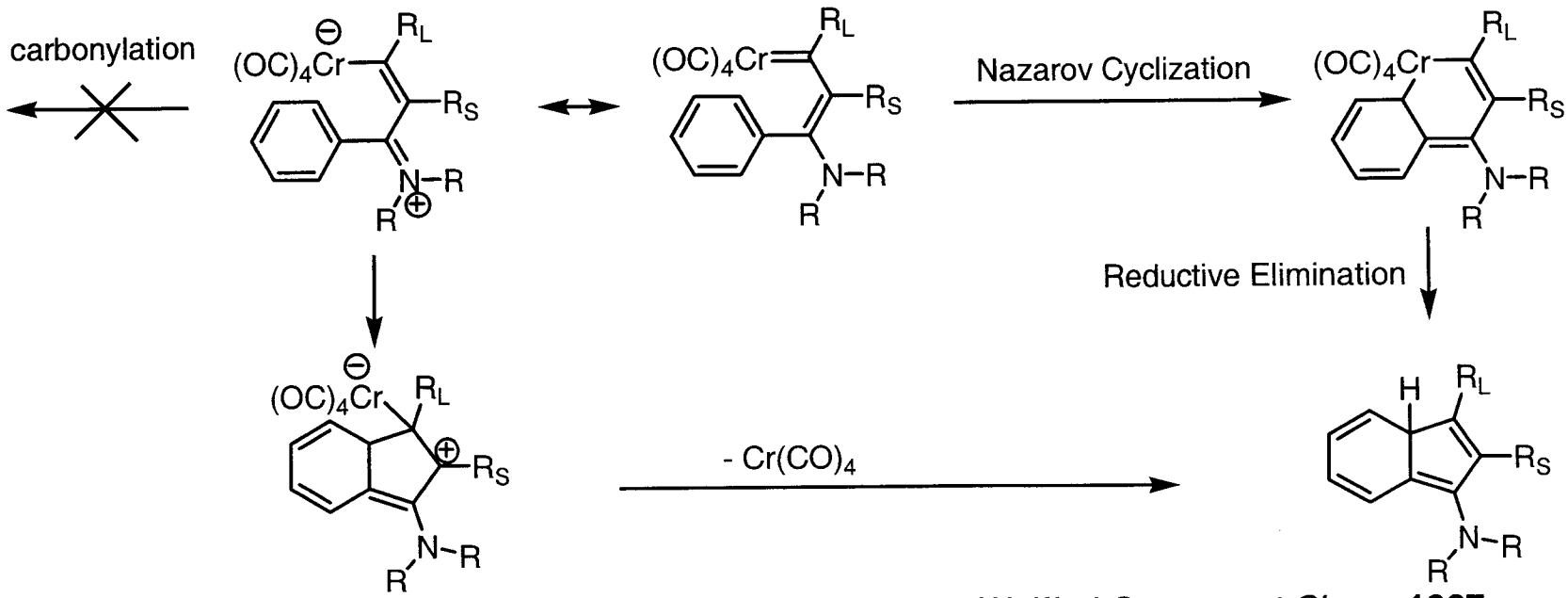
compd	temp, °C	rate,[a] $s^{-1} \times 10^5$	$\Delta G^{\ddagger}$, kcal mol^{-1}
3Cr	44[b]	18.0	24.0
3Mo	27[b]	4.9	23.4
3W	77[c]	2.3	28.0

Casey, *Organometallics*; 1982

Cyclopentannulation of Amino FCC



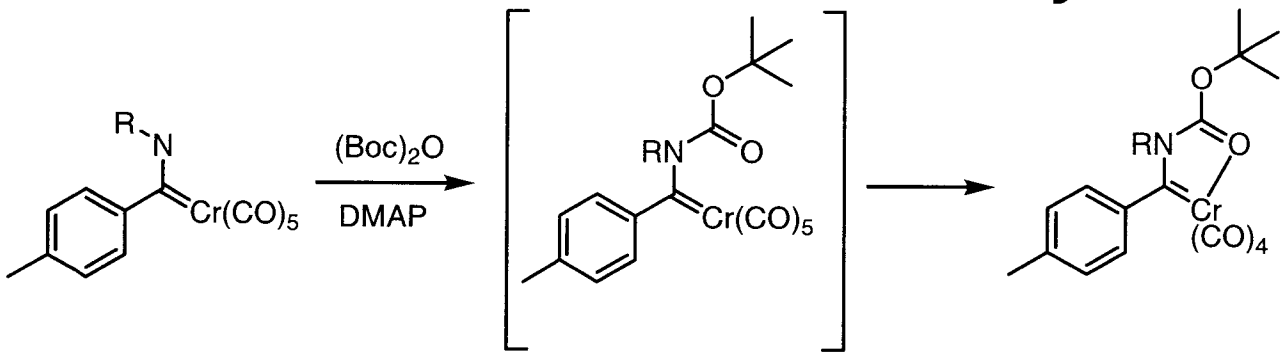
Yamashita, *TL*, **1986**

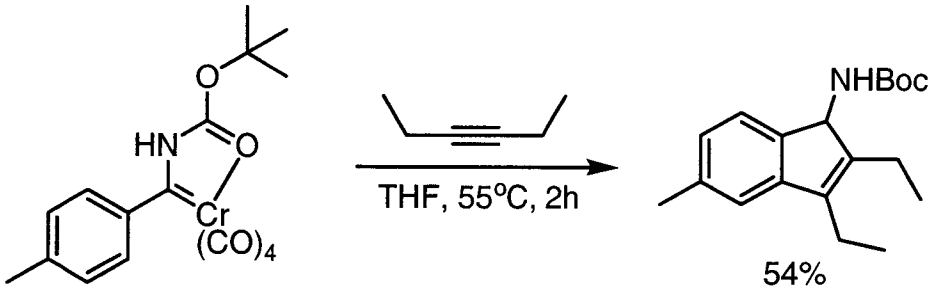


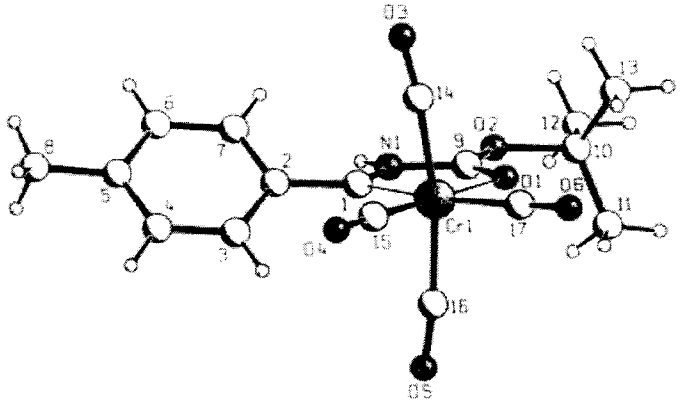
Wulff, *J Organomet Chem*, **1987**

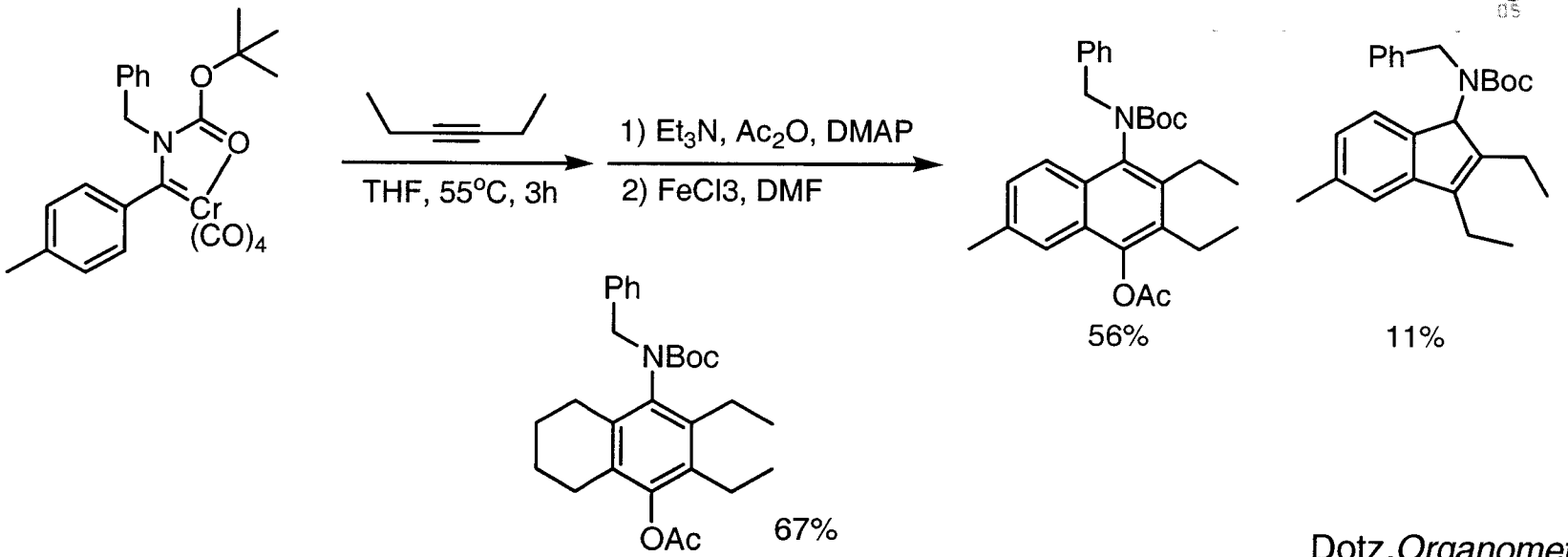
Amino Aryl FCC generally favors the formation of indenes.

Benzannulation of Acylamino FCC



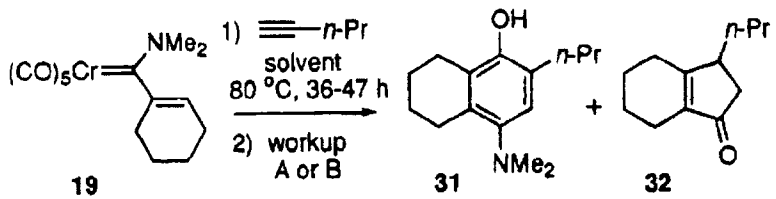






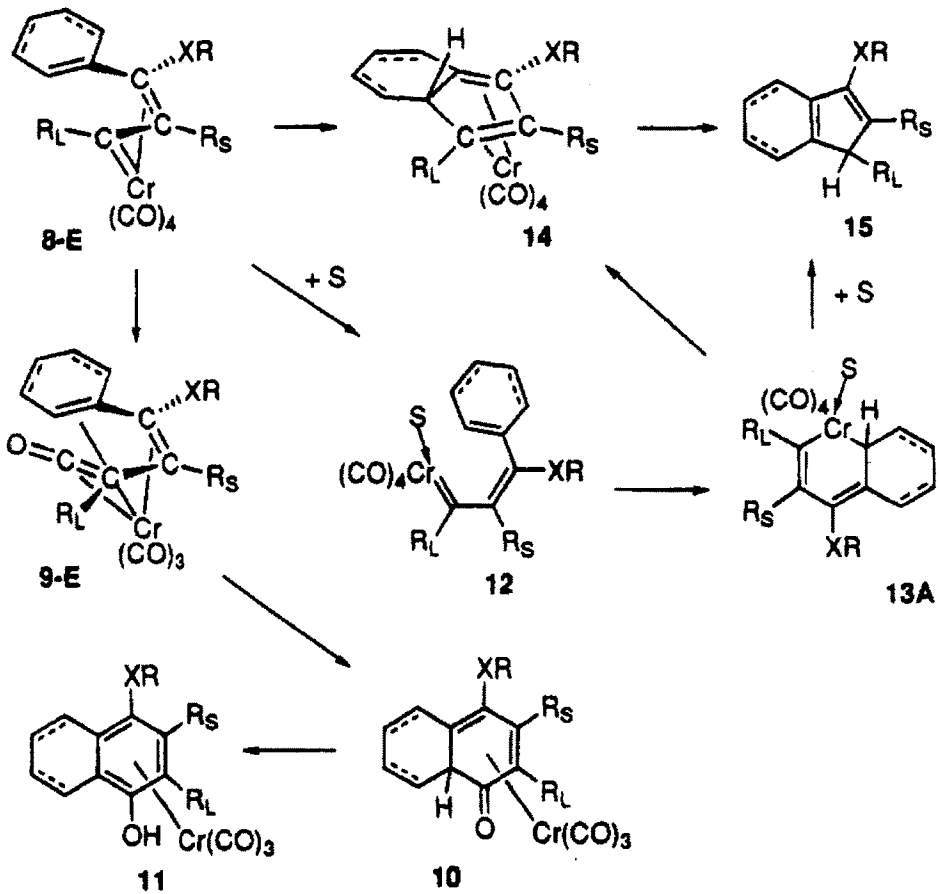
Dotz, *Organometallics*, **1992**

Solvent Effect upon Benzannulation



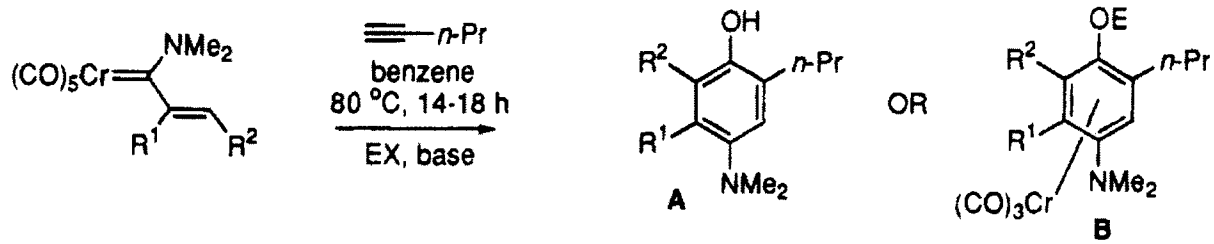
[19], M	solvent	workup[b] method	% yield 31[c]	% yield 32[c]
0.5	benzene	A	64	<1[d]
0.5	THF	A	57	12
0.5	CH_3CN[f]	A	<5[d]	13
0.5	DMF	A	25	13

Method A: 1 N HCl, THF/H_2O, 25 °C, 1 h.

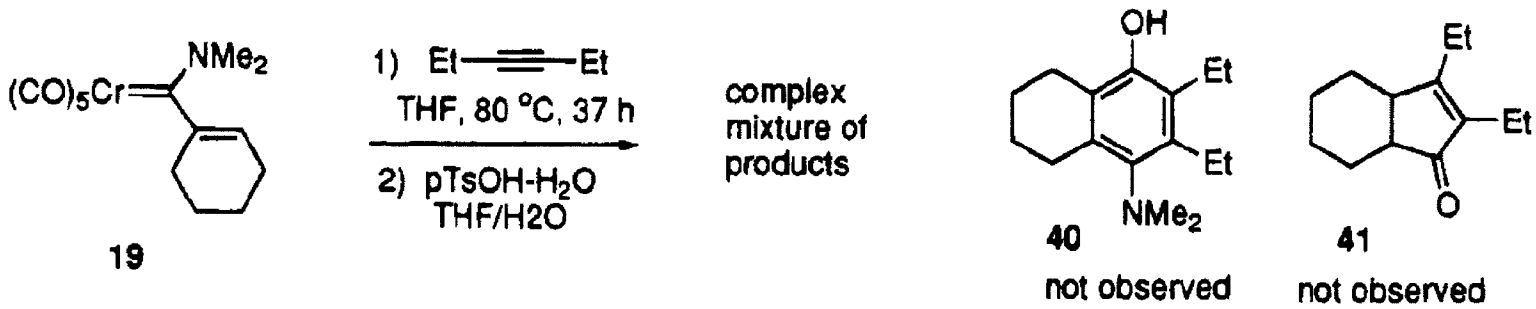


Wulff, *TL*, **1995**

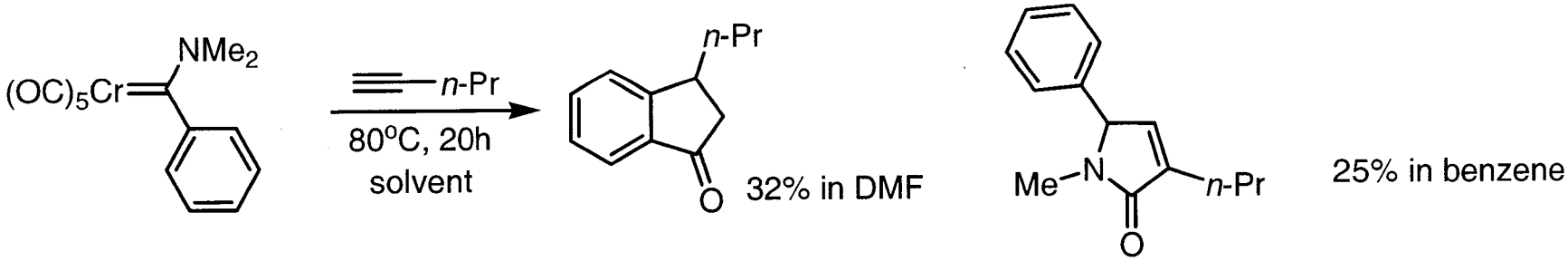
Benzannulation of Amino Alkenyl FCC

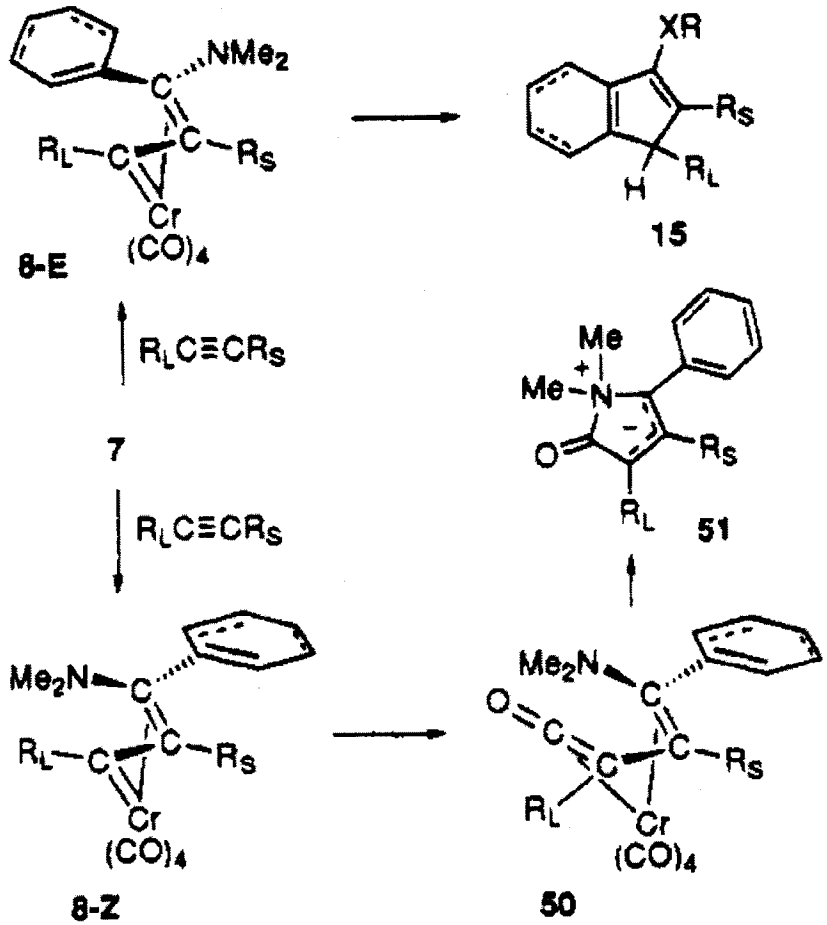


entry	complex	R^1	R^2	Ex (equiv)	base (equiv)	phenol **A** (% yield)[b]	complex **B** (% yield)[b]
1	**30**	Me	H	none	none	**33** (57)	
2	**30**	Me	H	TBSCl (2.0)	*i*-Pr_2EtN (3.0)		**36** (65)
3	**26**	H	Me	none	none	**34** (57)	
4	**26**	H	Me	TBSCl (2.0)	*i*-Pr_2EtN (3.0)		**37** (42)
5	**27**	H	Ph	none	none	**35** (39)	
6	**19**	$-(CH_2)_4-$		none	none	**31** (64)[c,d]	
7	**19**	$-(CH_2)_4-$		TBSOTf (1.5)	2,6-lutidine (2.5)		**38** (50)[c,e,f,g]



Reaction of Amino Aryl FCC





Benzannulation of Electron Poor Amino Alkenyl FCC

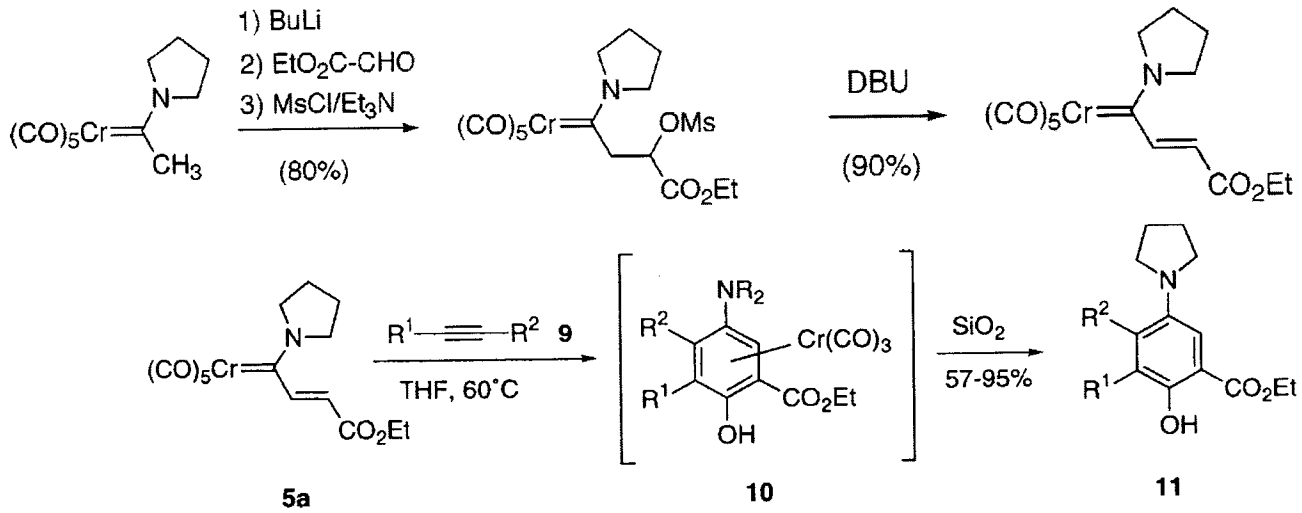
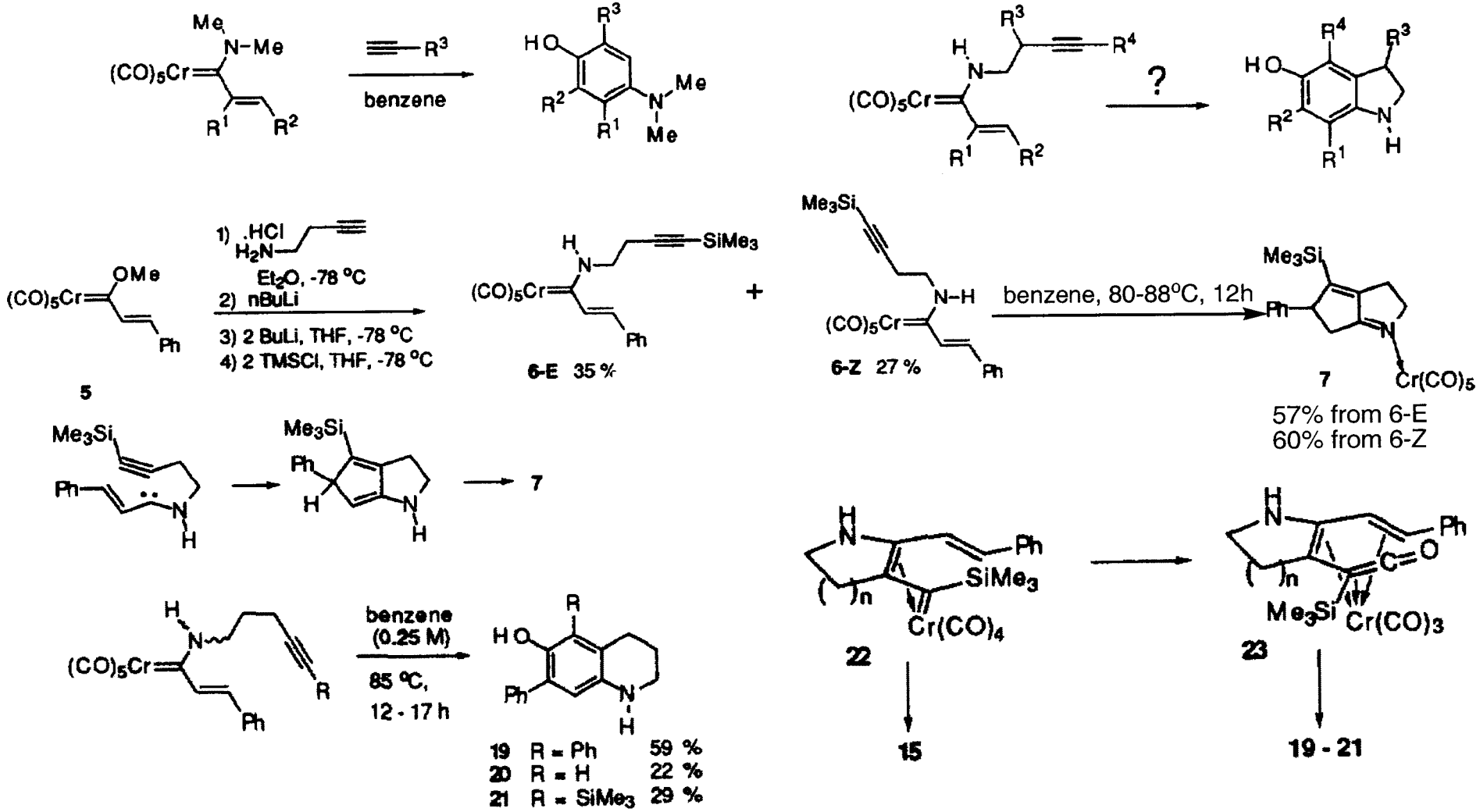


Table 1. Benzannulation of carbene complex **5a** (all the reactions were carried out in THF at 60°C at 0.03 M in carbene complex)

Entry	Compd	R^1	R^2	Yield[a] (%)
1	**11a**	*n*-Pr	H	72
2	**11b**	*n*-Bu	H	88
3	**11c**	*n*-Hex	H	66
4	**11d**	Ph	H	95
5	**11e**	*p*-Tolyl	H	58
6	**11f**	Ferrocenyl	H	85
7	**11g**	1-Cyclopentenyl	H	82
8	**11h**	CH_2OTMS	H	73
9	**11i**[b]	$(CH_2)_2OTs$	H	68
10	**11j**	COOEt	H	94
11	**11k**	COOMe	H	89

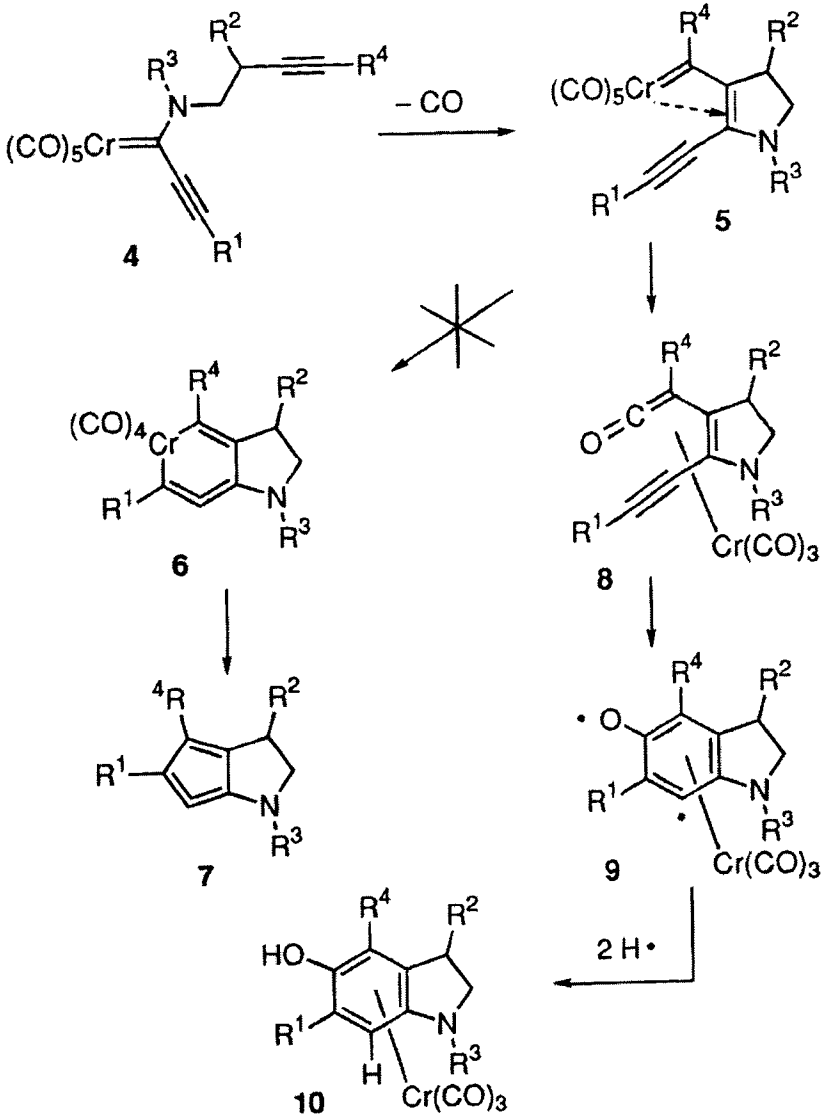
Barluenga, *JOC*, **1998**
Barluenga, *Tetrahedron*, **2000**

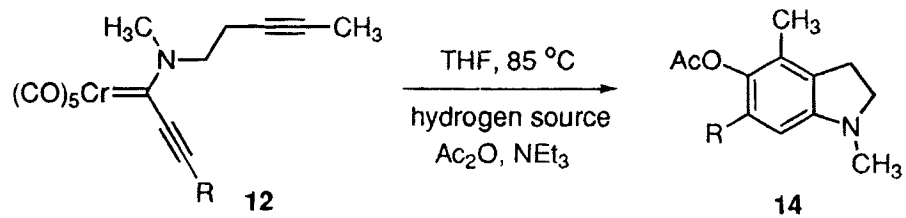
Intramolecular Reaction of Alkyne with Amino Alkenyl FCC



Wulff, *TL*, **1995**

Reaction of Amino Alkynyl FCC: Enynyl Ketene Cycloaromatization

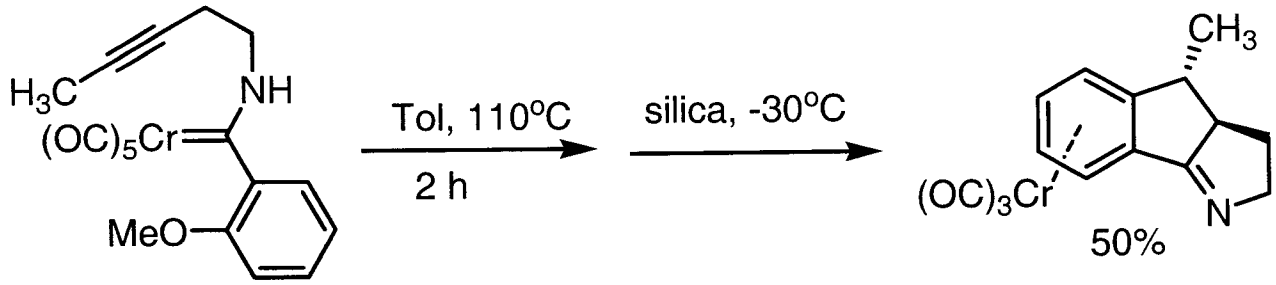


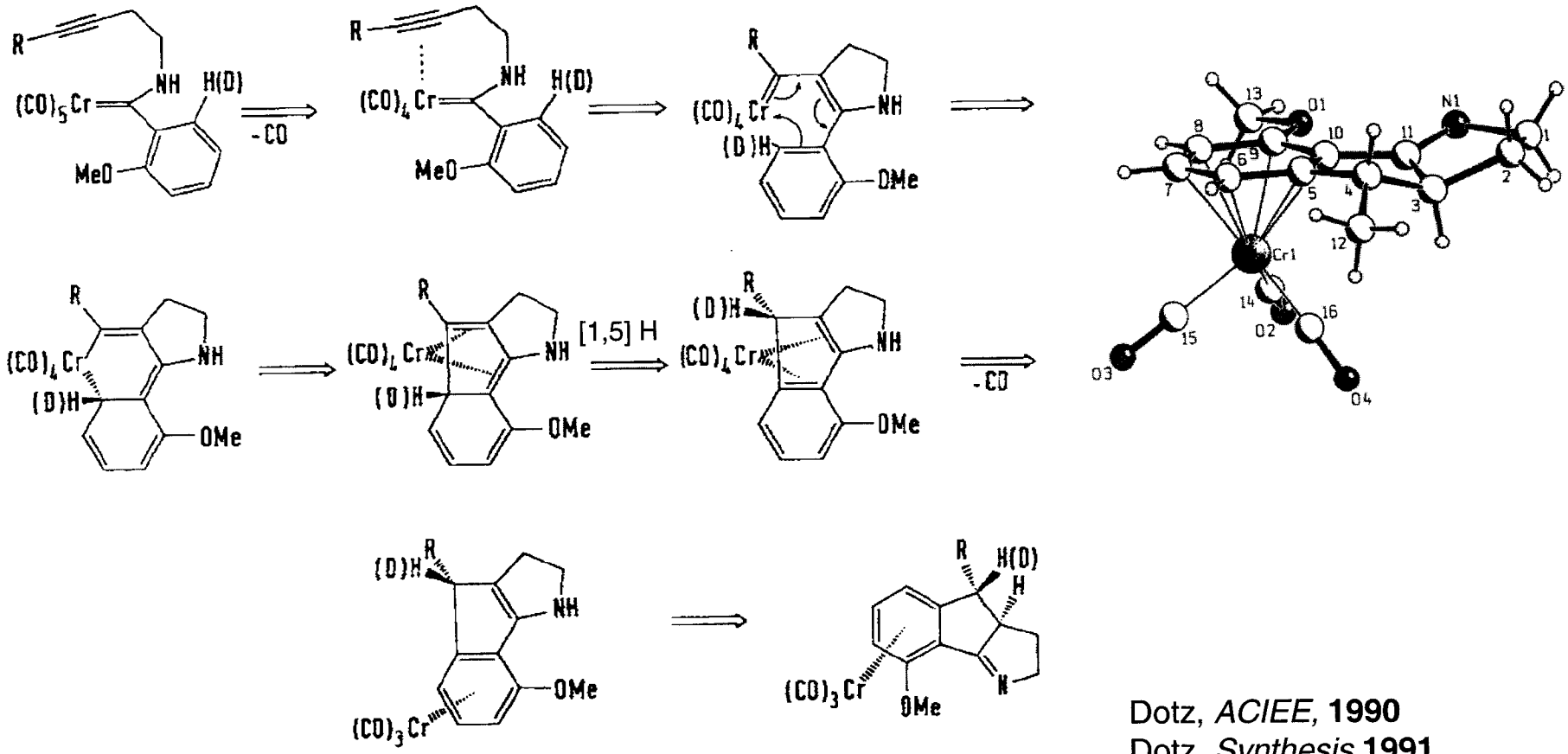


R	carbene complex[a]	hydrogen source (HS)	[12]	[HS]	% yield of **14**
Ph	**12a**	1,4-cyclohexadiene	0.02	2.0	49
Ph	**12a**	γ-terpinene	0.02	2.0	53
t-Bu	**12b**	γ-terpinene	0.02	2.0	31
$SiMe_3$	**12c**	γ-terpinene	0.02	2.0	ND[b]
1-C_6H_9	**12d**	γ-terpinene	0.02	2.0	41

Dotz, *Synthesis* **1992**

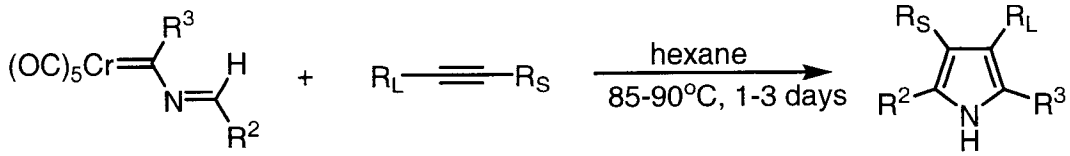
Diastereoselective Synthesis of Indenpyroles

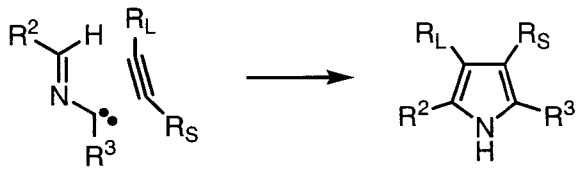




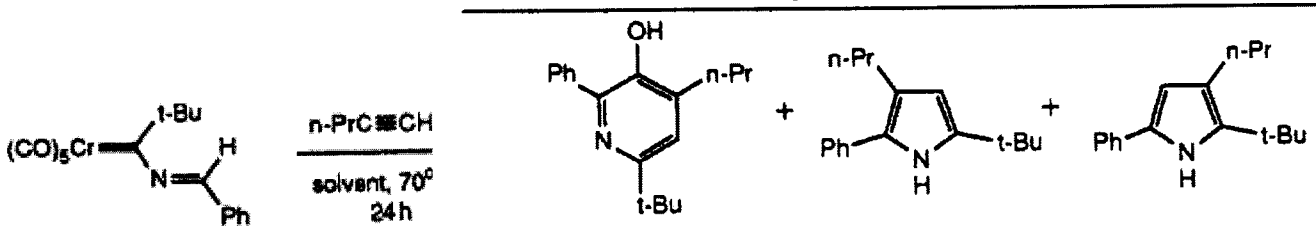
Dotz, *ACIEE,* **1990**
Dotz, *Synthesis* **1991**

Reaction of Imino FCC



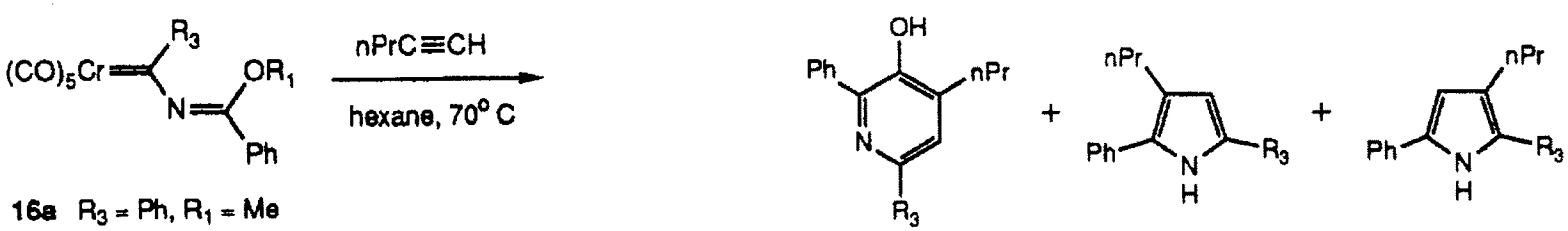


entry	complex	R_2	R_3	R_L	R_S	% yield of **13**
1	**4a**	Ph	Ph	Et	Et	97
2	**4a**	Ph	Ph	*n*-Pr	OEt	94
3	**4a**	Ph	Ph	Et	(C=O)CH_3	98
4	**4b**	Ph	CH_3	Et	Et	81
5	**4c**	Ph	*t*-Bu	*n*-Pr	H	94
6	**4c**	Ph	*t*-Bu	Et	Et	85
7	**4d**	CH_3	Ph	Et	Et	84



4c **5e** **6e** **13e**

	5e	**6e**	**13e**
hexane	5 %	< 1 %	94 %
acetonitrile	14 %	61 %	20 %



16a R_3 = Ph, R_1 = Me
16b R_3 = Ph, R_1 = C(O)CH_3

complex		
16a	**5g** 51 %	**6g** 4 %
16b	**5g** 31 %	**6g** 9 %

Wullf, *JACS*, **1990**

Summary on Amino FCC

- Relatively low reactivity.
- Highly substrate and condition dependent. Tunable Selectivity.
- Mechanistically Complicated.
- Especially effective in construction of highly functionalized 5-membered heterocycles
- Stoichometric amount of metal