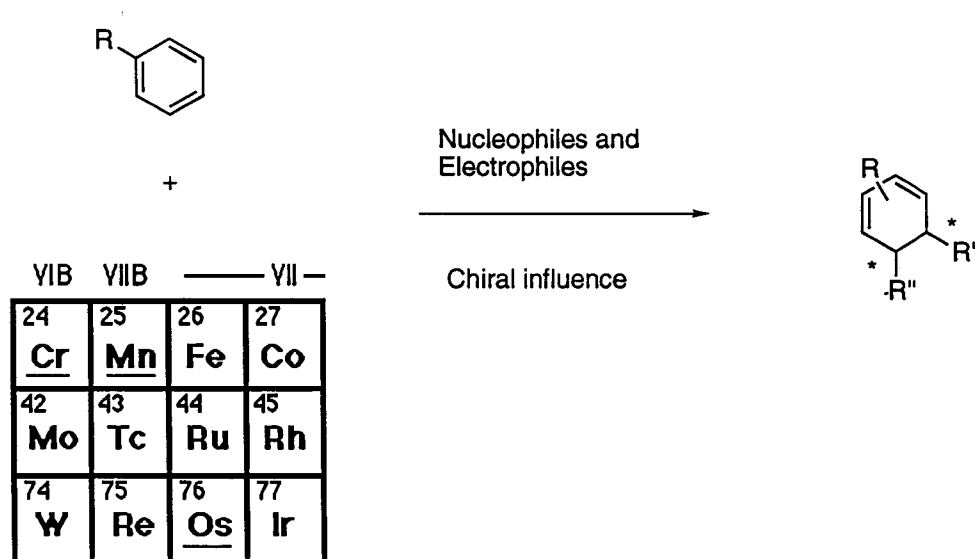
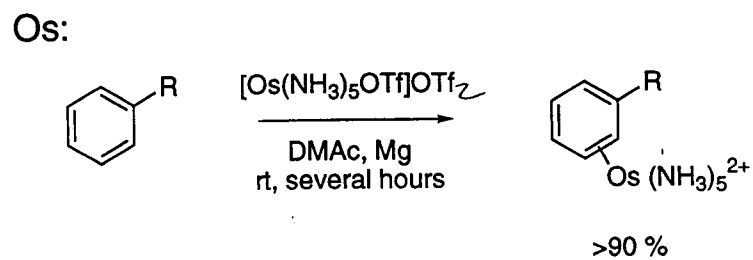
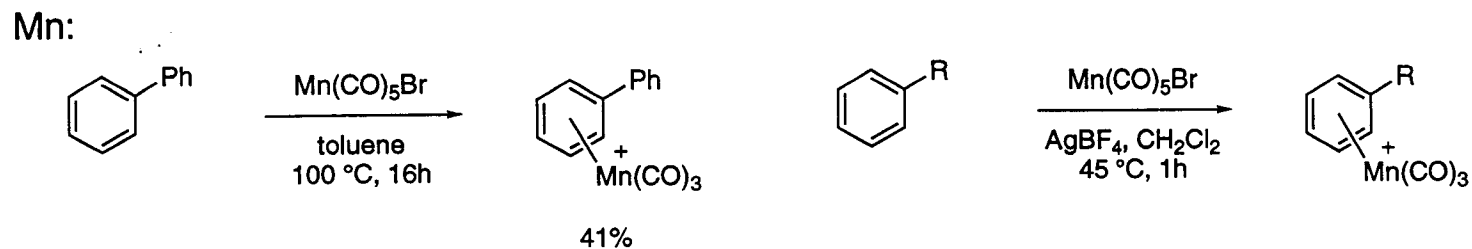
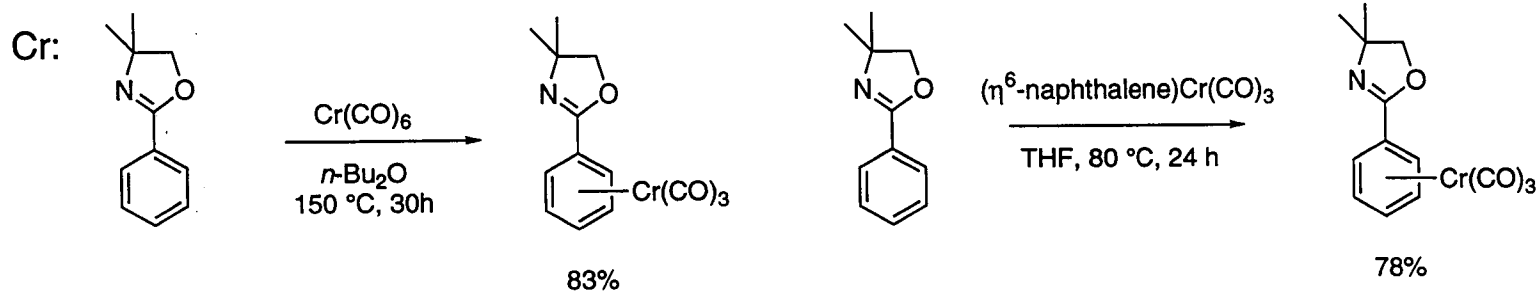


## Transition-Metal Assisted Dearomatization of Arenes



## Preparation of Metal Complexes



- Zn/Hg amalgam  
works instead  
of  $\text{Mg}$   
(Melt  $\rightarrow$  solvent)

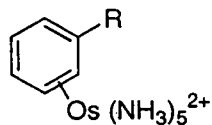
Kundig *Organometallics*, 1993, 12, 3724  
Brookhart *JACS*, 1984, 106, 4161  
Harman *Chem. Rev.* 1997, 97, 1953.

# Osmium Complexation

With mono-substituted benzenes:

-Coordination is preferred at  $5,6\eta^2$  over  $4,5\eta^2$  in the absence of steric factors

-Calculated to 3-5 kcal/mol



ammonium ligands incapable of  $\pi$  interaction

Os  $d_{\pi}$  orbitals available for significant back-bonding

The complexed arene is very electron rich

Other olefins, nitriles, aldehydes and some ketones are not compatible for this method.

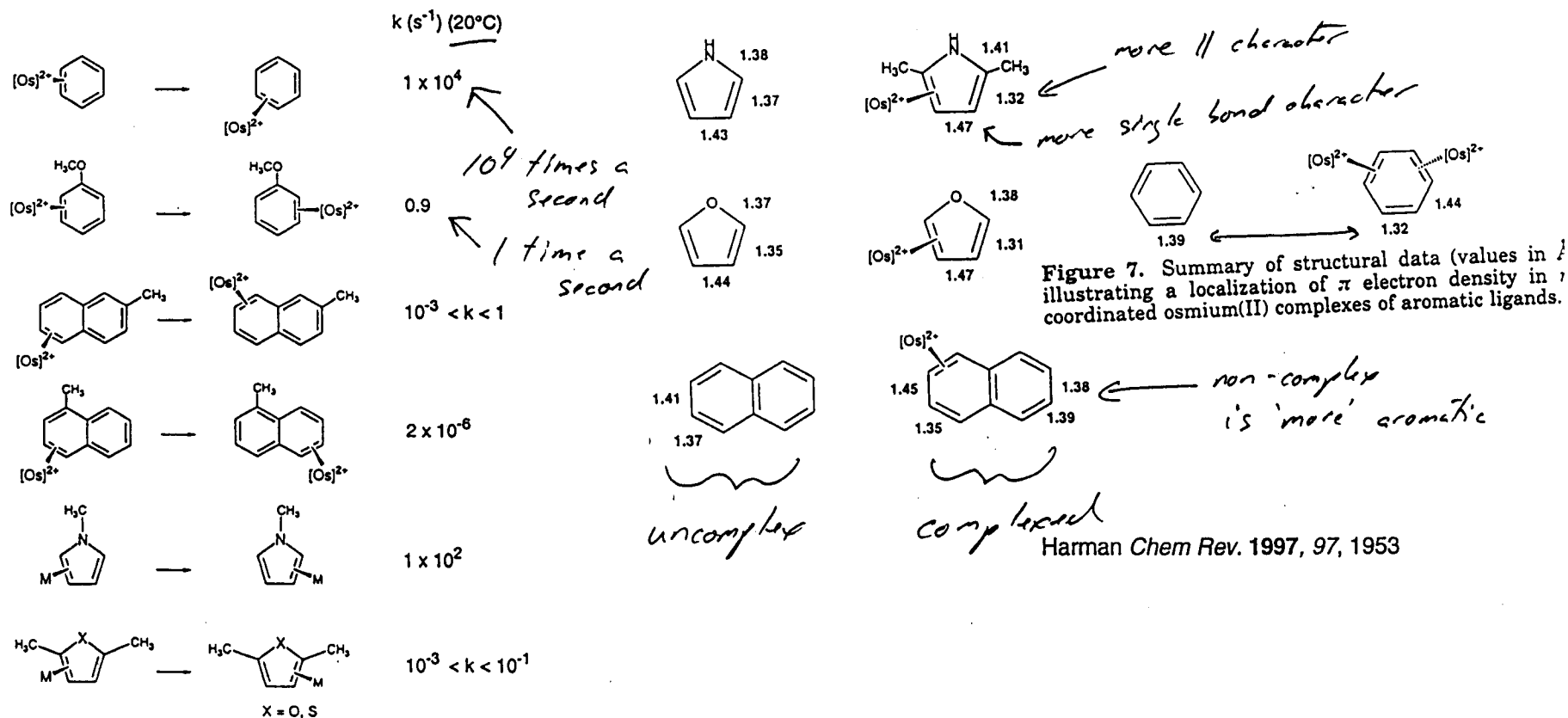
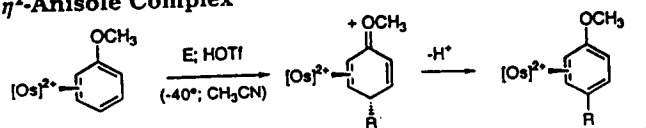


Figure 3. A survey of isoergic linkage isomerizations with corresponding specific rates (20 °C).

Harman Chem Rev. 1997, 97, 1953

Table 4. Electrophilic Addition Reactions with  $\eta^2$ -Anisole Complex



E	R	Yield(%) <sup>a</sup>
		95
		87(81% de)
		> 90 <sup>b</sup>
		95 (> 90% de)
		> 90(>90% de) <sup>b</sup>
		95 (0% de) ← should be 90%
		91(90%de)
		80(>90%de)
		98
		88
CH(OEt) <sub>2</sub>	CHO	86
CH <sub>3</sub> C=NCH <sub>3</sub> <sup>+</sup>		88

### Addition of Electrophiles

Enones

← should be 90%

Acetals

### Protonation Studies

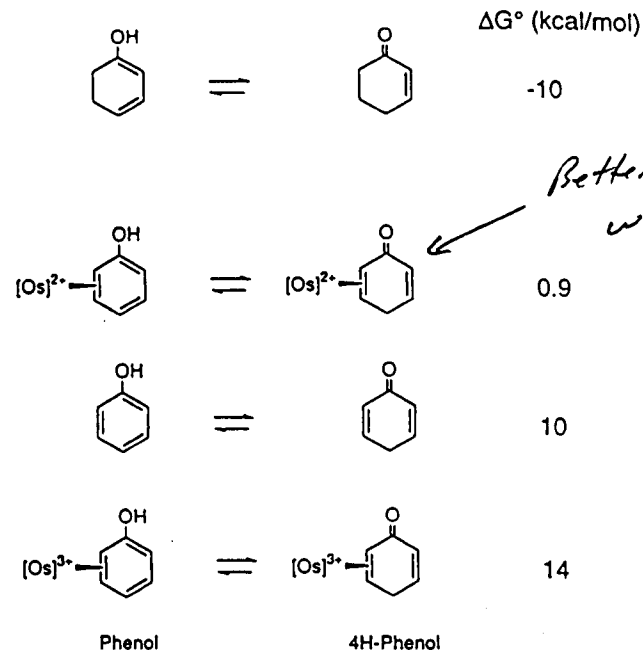


Figure 10. Free energy relationship for the enol-enone equilibrium of the  $\eta^2$ -phenol complexes of osmium(III), uncomplexed phenol, osmium(II), and 1,3-cyclohexadienol.

- studied in CD<sub>3</sub>OD w/ cat DOTA

Harman JOC, 1997, 62, 130

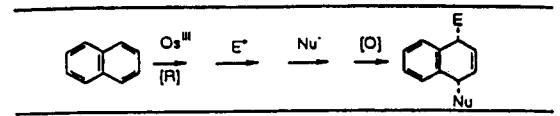
- Electrophilic additions can also be LA catalyzed

<sup>a</sup> Represents isolated yield. <sup>b</sup> Represents yield in solution (NMF).

# Double Addition to Os Complexes

Naphthalene derivatives:

Table 1. Overall Yields for the Tandem Addition to Naphthalene

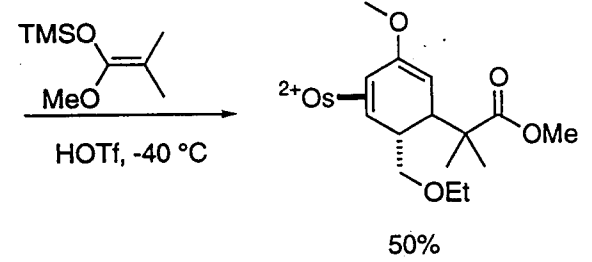
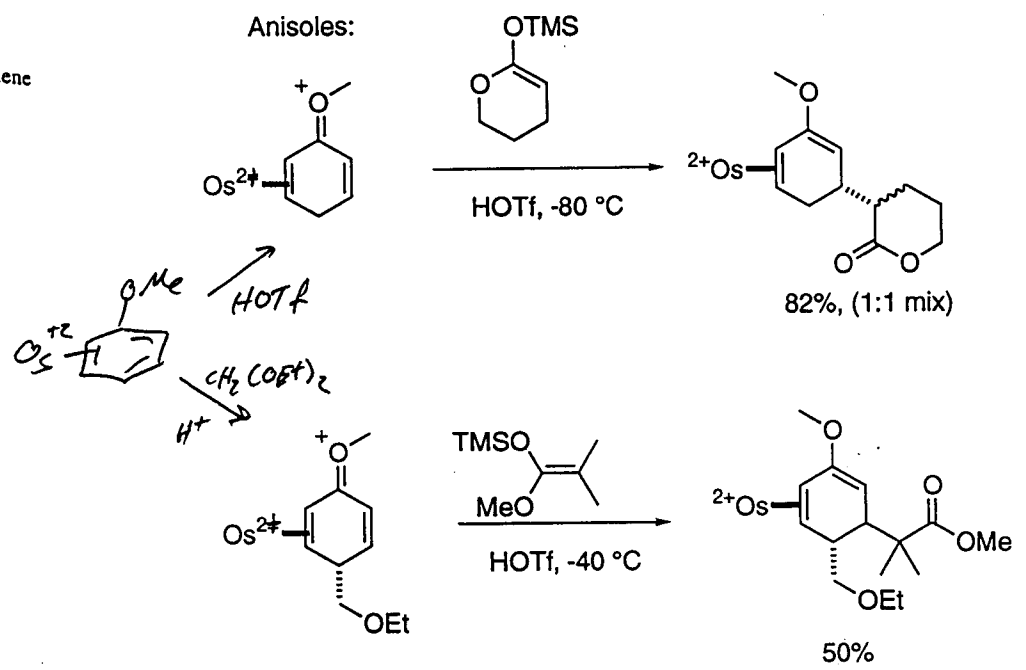


Electrophile	Nucleophile	Overall Yield
H	H	56%
H		77%
		65%
		54%
		69%
	H	45%
	CH <sub>3</sub>	40%
		40%
		41%
		25%

Acetals

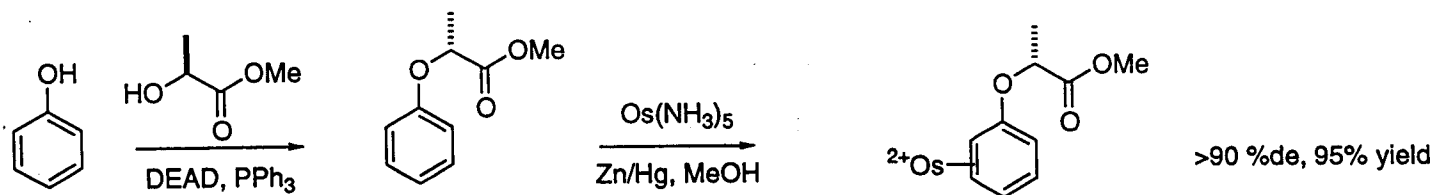
Enones  
~~CH<sub>2</sub>OTf~~

Anisoles:

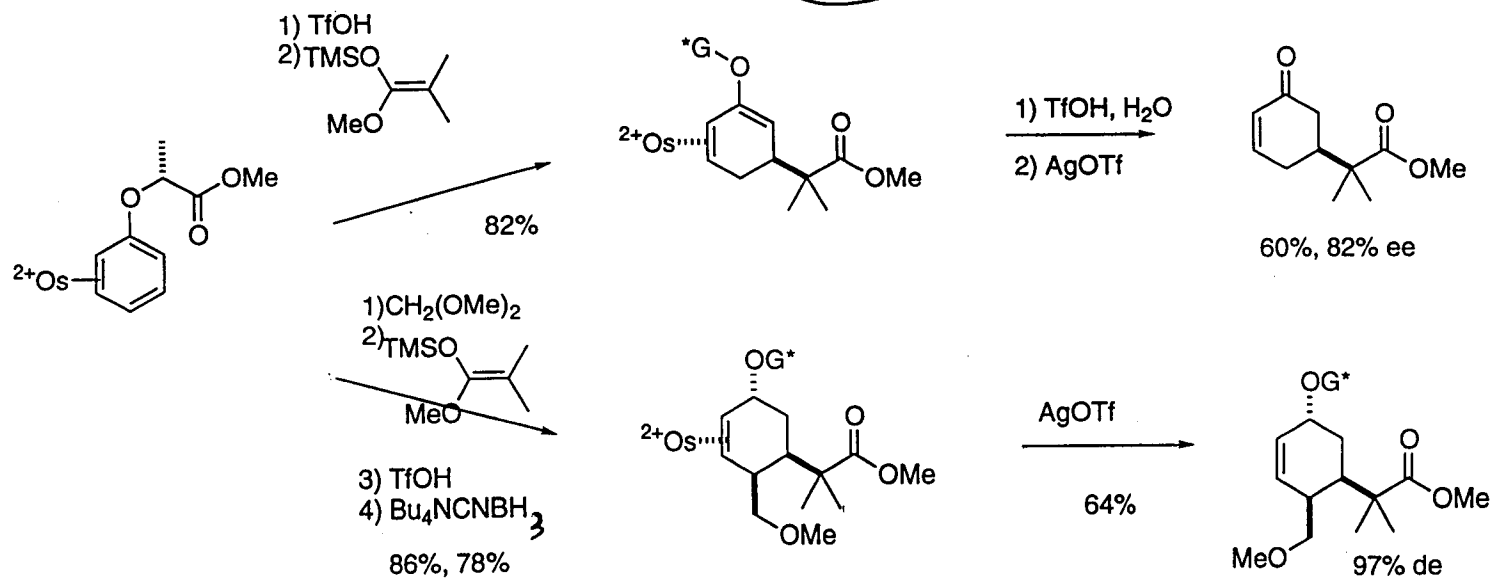
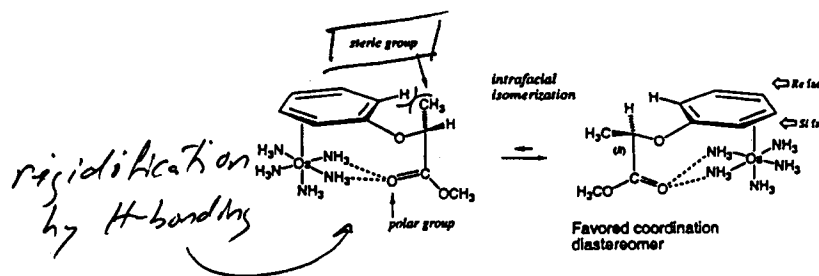


Harman JACS, 1998, 120, 7835

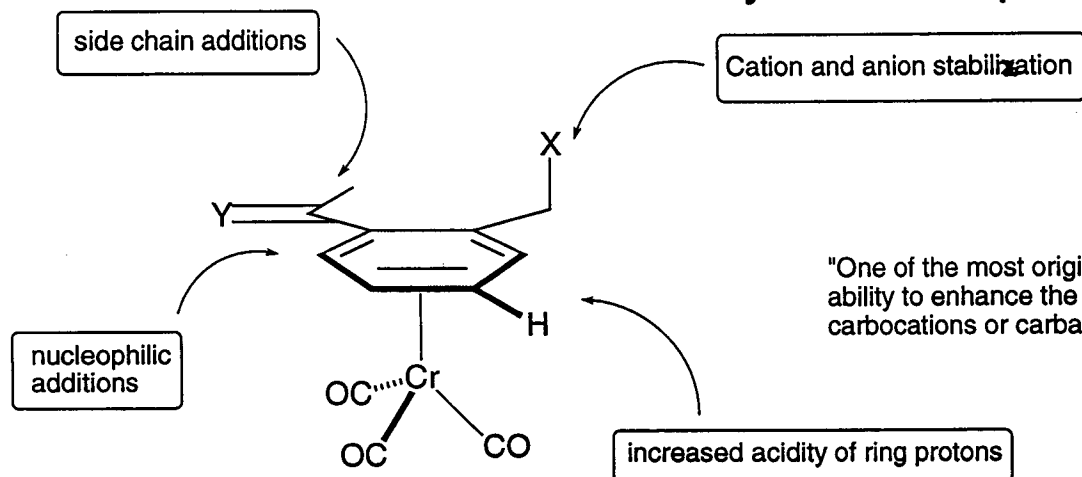
## Incorporation of Chiral Auxiliaries



*(S)-Methyl lactate*

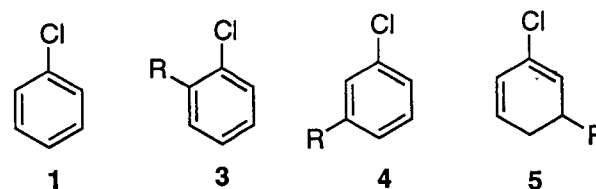
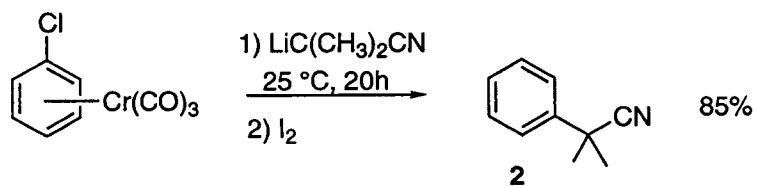


# Reactivity of Cr Complexes



"One of the most original characteristics of this series is the hermaphroditic ability to enhance the kinetic generation and the stabilization of either carbocations or carbanions in the benzylic position"

Jaouen *J. Organomet. Chem.* **1980**, *195*, C5



Quenching experiments:

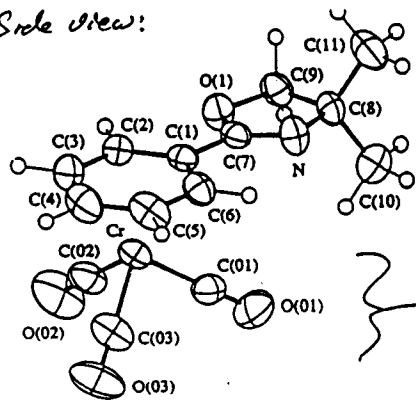
			1	2	3	4	5
1	3h, 0 °C	a. $\text{H}_2\text{O}$ , b. $\text{I}_2$	18	40	10	2	12
2	3h, 0 °C	a. $\text{CF}_3\text{CO}_2\text{H}$ , $\text{I}_2$	0	39	19	4	22
3	3h, 0 °C	$\text{I}_2$	0	19	56	12	0

Suggests: 1 - reversible addition

2 - intermediate may be trapped by  $\text{E}^+$

Semmelhack *JACs*, **1974**, *94*, 7092

Side view:

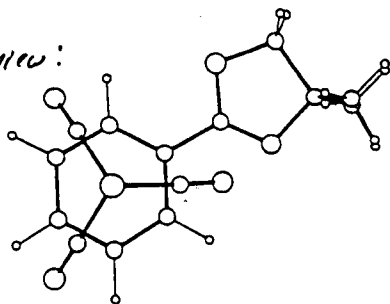


### Cr Complexes

Suggest only top face interactions

$(CO)_3$  blocks bottom face of arene

Top view:



benzene →

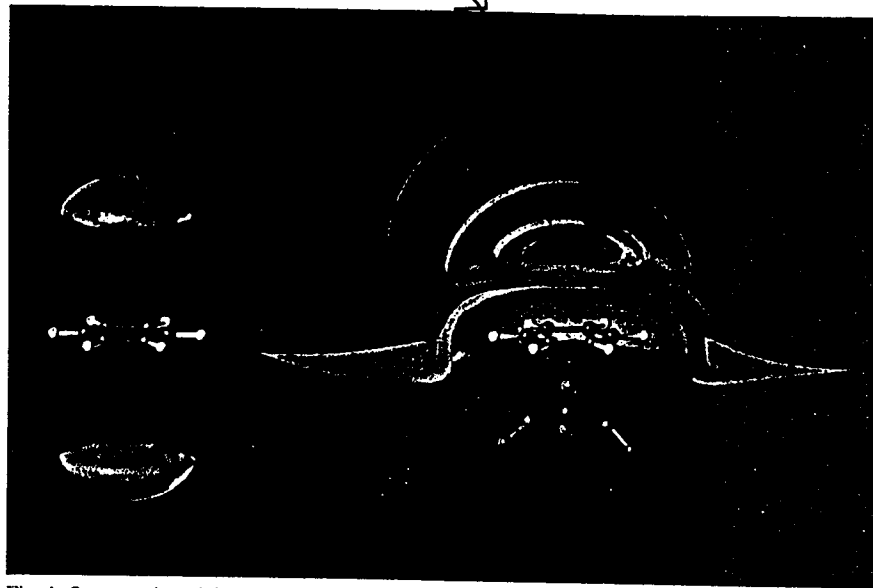


Fig. 1. Structural models of benzene (left) and  $[Cr(\eta^6\text{-benzene})(CO)_3]$  (right) represented together with solid models of  $E_{im}$  isovalue surfaces calculated for nucleophilic attack. Color-coding of the surfaces: blue = -0.15, purple = -5.0, green = -10.0, yellow = -15.0, brown = -17.0 and red = -18.0 kcal/mol.

Exclusive exo face addition

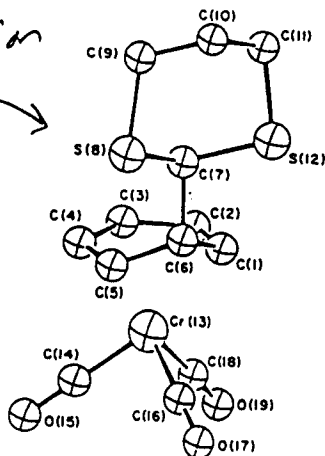
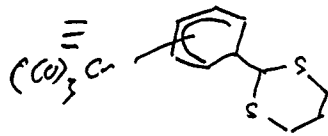


Figure 1. ORTEP drawing of adduct 8c.



'Interaction Energy' of an incoming  $Nu^-$  or  $E^+$   
 - combination of - electrostatic pot.  
 - charge-transfer  $E$   
 - exchange  $E$

Kundig *Organometallic* 1993, 12, 3724  
 Kundig *Chimia*, 1992, 46, 126  
 Semmelhack *JACS*, 1979, 101, 3535



# Scope and regiochemistry

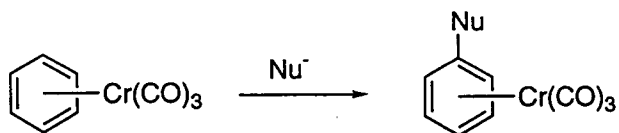


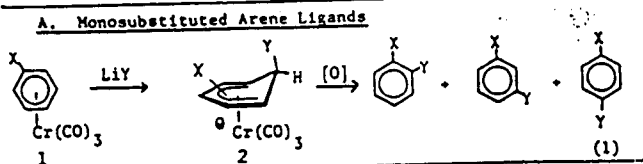
Table 1. Reactivity of carbanions in the addition process

A. Unreactive	B. Successful	C. Metalation
1. $\text{LiCH}(\text{CO}_2\text{R})_2$	1. $\text{LiCH}_2\text{CO}_2\text{R}$	1. $n\text{BuLi}$
2. $\text{LiCH}_2\text{COR}$	2. $\text{LiCH}_2\text{CN}$	2. $\text{LiCH}_3$
3. $\text{CH}_3\text{MgBr}$	3. $\text{KCH}_2\text{COC}(\text{CH}_3)_3$	3. $s\text{BuLi}$
4. $(\text{CH}_3)_3\text{CMgBr}$	4. $\text{LiCH}(\text{CN})(\text{OR})$	
5. $(\text{CH}_3)_2\text{CuLi}$	5. $\text{LiCH}_2\text{SPh}$	
6. $\text{LiC}(\text{OR})(\text{CN})\text{Ph}$	6. 2-Li-1,3-dithianyl	
	7. $\text{LiCH-CH}_2$	
	8. $\text{LiPh}$	
	9. $\text{LiC}=\text{CR}$	
	10. $\text{LiCH}_2\text{CH=CH}_2$	
	11. $\text{LiC}(\text{CH}_3)_3$	

No Grignard reagents

ester here enolates and stabilized anions

Table I. Addition/Oxidation of Carbanions with Substituted  $\pi$ -Arenechromium Tricarbonyl Complexes



Entry	Substituent (X)	Carbanion (LiY)	Product Ratios o:m:p (combined yield)
1	$\text{CH}_3^a$	$\text{LiCH}_2\text{CO}_2\text{R}$	28:72:0 (89%)
2	$\text{OCH}_3^a$	$\text{LiCH}_2\text{CO}_2\text{R}$	4:96:0 (93%)
3	Cl	$\text{LiCH}_2\text{CO}_2\text{R}$	54:45:1 (98%)
4	Cl	$\text{LiCH}(\text{CH}_3)\text{CO}_2\text{R}$	53:46:1 (88%)
5	Cl	$\text{LiC}(\text{CH}_3)_2\text{CO}_2\text{R}$	5:95:1 (84%)
6	Cl	$\text{LiCH}_2\text{COC}(\text{CH}_3)_3$	70:24:0 (87%)
7	Cl	$\text{LiC}(\text{CH}_3)_2\text{CN}$	10:89:1 (84%)
8	Cl	Li-(1,3-dithianyl)	46:53:1 (56%)
9	$\text{Si}(\text{CH}_3)_3$	$\text{LiC}(\text{CH}_3)_2\text{CN}$	0:2:98 (65%)
10	$\text{CF}_3$	$\text{LiC}(\text{CN})(\text{OR}_1)\text{CH}_3^b$	0:30:70 (33%)
11	$\text{N}(\text{CH}_3)_2$	$\text{LiC}(\text{CH}_3)_2\text{CN}$	1:99:0 (92%)
12	$\text{C}(\text{CH}_3)_3$	$\text{LiC}(\text{CN})(\text{OR}_1)\text{CH}_3^b$	0:35:65 (85%)
13	$\text{CH}_2\text{CH}_3$	$\text{LiC}(\text{CN})(\text{OR}_1)\text{CH}_3^b$	0:94:6 (89%)

High meta preference

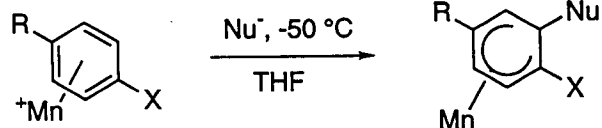
Me, Cl  $\rightarrow$  poor directing groups

Semmelhack JACS, 1979, 101, 217  
Semmelhack Tet. 1981, 37, 3957

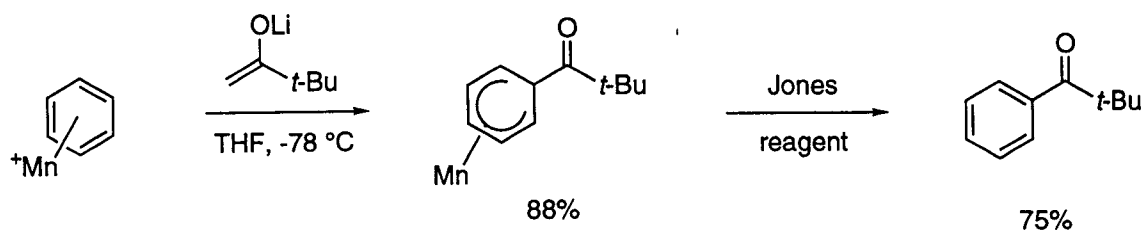
High meta preference

$\hookrightarrow$  bulk of R group affects addition

## Application to Mn complexes



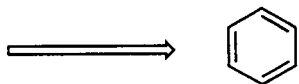
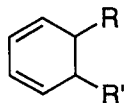
R	X	Nu	ortho	meta	para	yield
Me	Cl	LAH	69	31		
Me	Cl	MeLi	74	26		
Me	Cl	PhLi	61	39		
H	OMe	LAH	37	63		
H	NMe <sub>2</sub>	LAH	3	97		
Me	Cl	MeMgBr	77	23		90
Me	Cl	PhMgBr	80	20		90
H	OMe	MeMgBr		100		85
H	Me	MeMgBr	66	33		
H	Cl	PhMgBr	50	35	15	



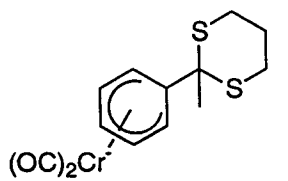
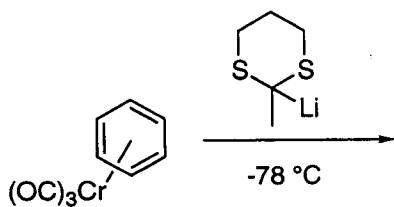
- Mn complex is reactive enough for ketone enolates, Grignard reagents

Pauson *JCS Dalton*, 1975, 1683  
Sweigart *Organometallics*, 1982, 1, 1053

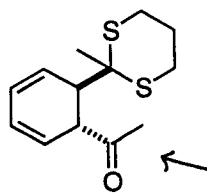
# Double addition to Cr



R, R' = nucleophile or electrophile ???

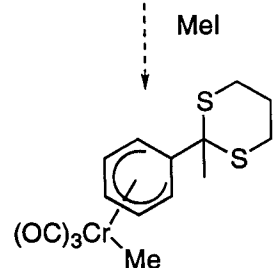


1) MeI, -78 °C  
THF, HMPA  
2) I<sub>2</sub>

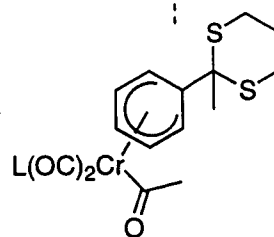


88% , single isomer

*Insertion of CO ligand from Cr metal*



L



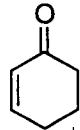
*- can run under CO to recover Cr(CO)<sub>6</sub>*

Electrophile	Yield
MeI	88%
EtBr	28%
	62%
	89%
	70%

-only alkyl groups are sufficient electrophile

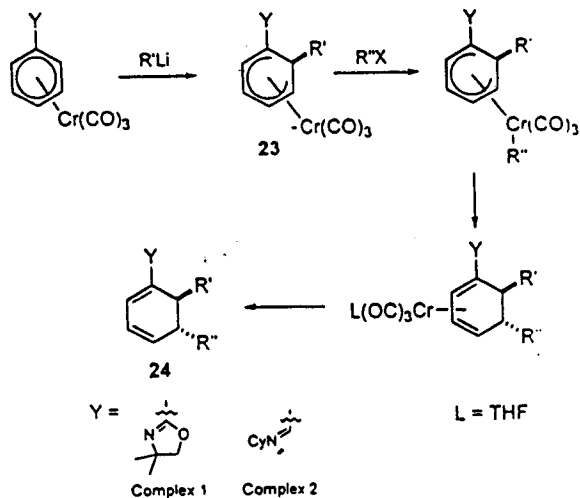
no pds observed with:

AcCl, BzCl, PhI,



## Addition without carbonylation

**Scheme 16. Sequential Addition of Organolithium Reagents and Allyl/Benzyl/Propargyl Bromides to Arene Chromium Tricarbonyls Substituted with an Oxazoline or Cyclohexylamine Appendage**

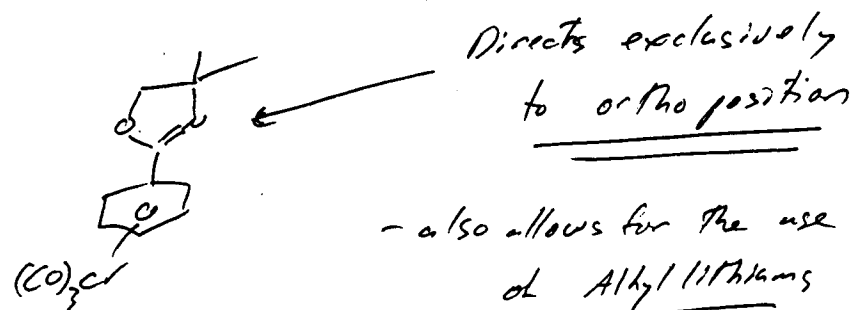


Complex	R'Li	R''X	Yield, %
1/2	MeLi	CH <sub>2</sub> CHCH <sub>2</sub> Br	68/57 <sup>a</sup>
1		CH <sub>2</sub> CH(Me)CH <sub>2</sub> Br	61
1		PhCH <sub>2</sub> Br	52
1		HC≡CCH <sub>2</sub> Br	71 <sup>b</sup> /76 <sup>a</sup>
1/2		Me <sub>3</sub> SiC≡CCH <sub>2</sub> Br	72 <sup>b</sup>
1	n-BuLi	CH <sub>2</sub> CHCH <sub>2</sub> Br	63
1		HC≡CCH <sub>2</sub> Br	87 <sup>b</sup>
1	PhLi	CH <sub>2</sub> CHCH <sub>2</sub> Br	67
1		HC≡CCH <sub>2</sub> Br	77 <sup>b</sup>
1	CH <sub>2</sub> CHLi	CH <sub>2</sub> CHCH <sub>2</sub> Br	54
1		HC≡CCH <sub>2</sub> Br	82 <sup>b</sup>
1		Me <sub>3</sub> SiC≡CCH <sub>2</sub> Br	88 <sup>b</sup>
1	NCCH <sub>2</sub> Li	CH <sub>2</sub> CHCH <sub>2</sub> Br	48 <sup>b</sup>

<sup>a</sup> reaction proceeds with hydrolysis of the imine to give the aldehyde  
<sup>b</sup> use of HMPA as co-solvent

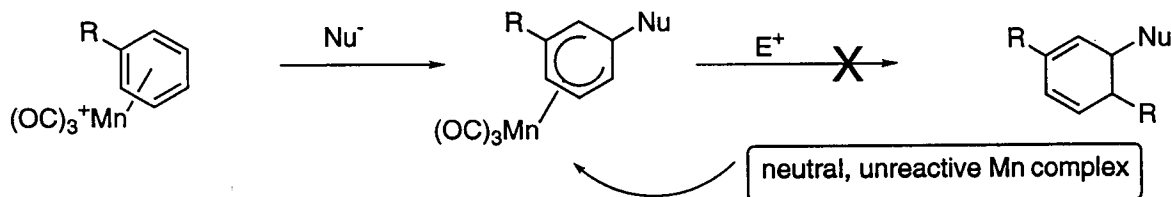
*Are known to undergo  $\sigma$  migration slower than allyl groups*

Addition of allyl, benzyl and propargyl electrophiles do not undergo carbonylation

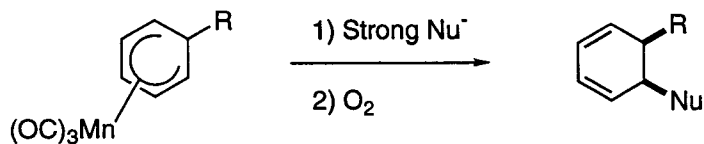


Kundig JOC, 1994, 59, 4773

## Double Addition to Mn complexes

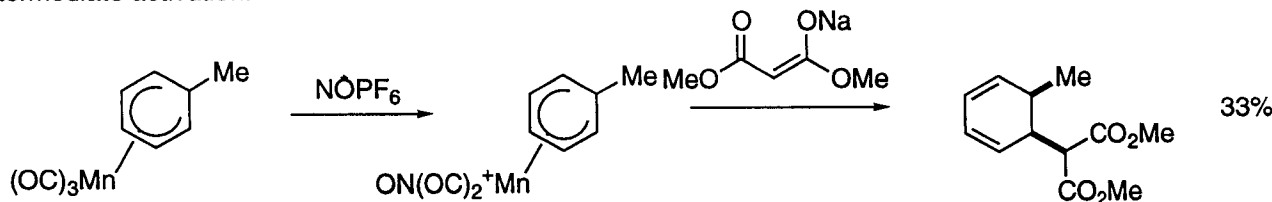


*does not add to electrophiles*



R	Nu	Yield
H	$\text{Ph}-\text{C}(\text{Ph})-\text{Li}$	77%
Me	$\text{Li}-\text{C}(\text{Me})_2$	73%
H	$\text{Li}-\text{C}(\text{Me})_2-\text{CN}$	88%
Me	$\text{Li}-\text{C}(\text{Me})_2$	58%

Intermediate activation:



-moderate yields with hydride donors

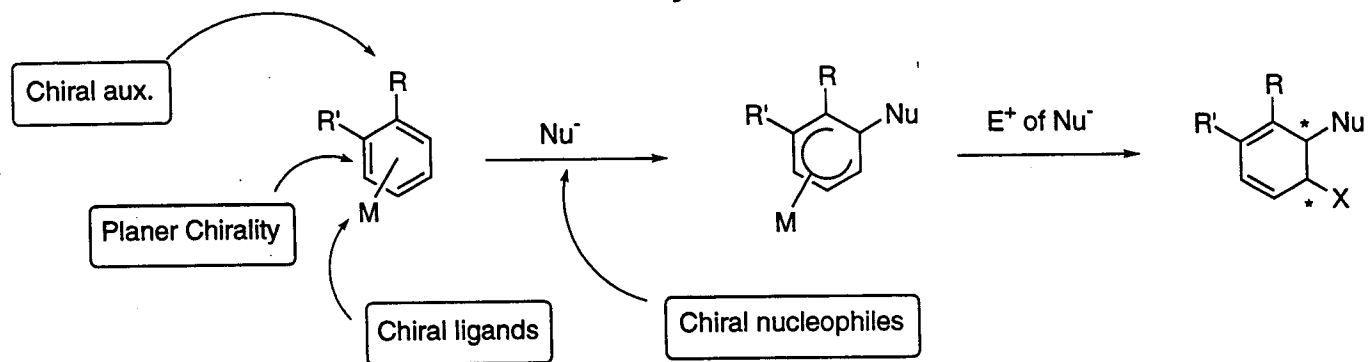
*Have been shown to react w/ PhLi: analogously to Cr*

*- limited number of nucleophiles*

McDaniel *Organometallics* 1993, 13, 224  
 Schweigart *JACS*, 1985, 107, 2388

*- gives acyl compound (charge transfer process)*

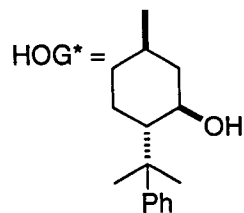
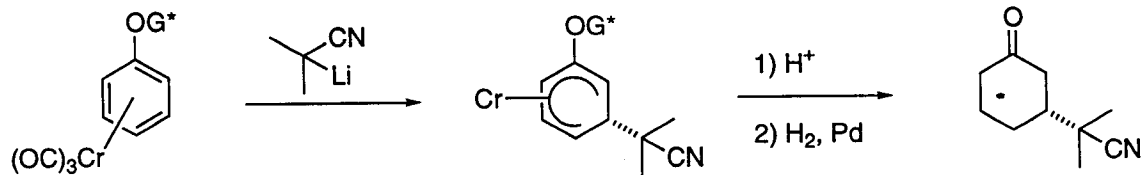
# Asymmetric induction



-Works best when regioselectivity is high --- Heteroatom substituted, *ortho* directing

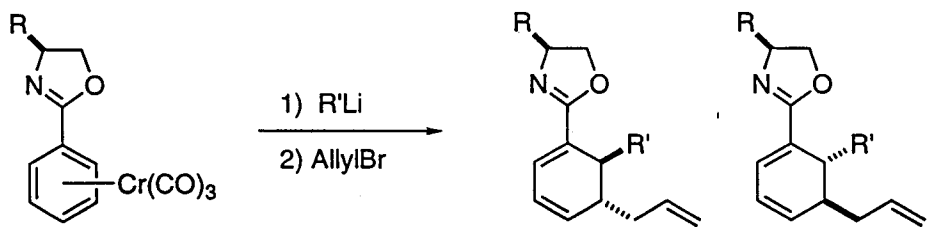
*only groups investigated so far*

Chiral auxiliary:

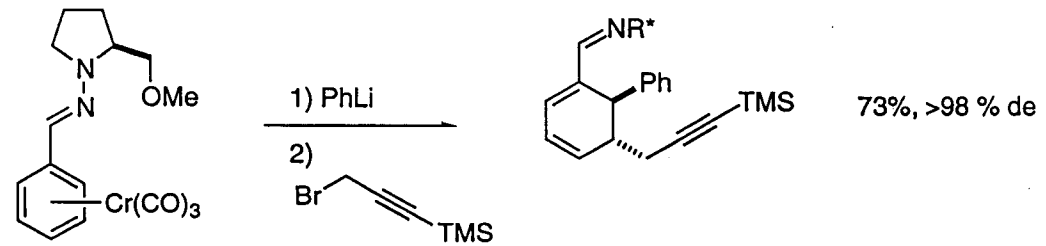


Best ligand  $\rightarrow$  48% ee (other menthyl deriv. tried)

### Better Chiral Auxiliaries



- selectivity increases with larger R groups



- delivery is by N  
was proven in ferrocenes  
ferrocenes

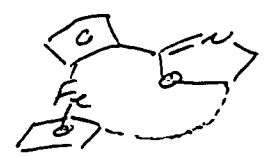


Table 1. Sequential diastereoselective addition of organolithium reagents and allyl bromide to complexes 5 and 6.

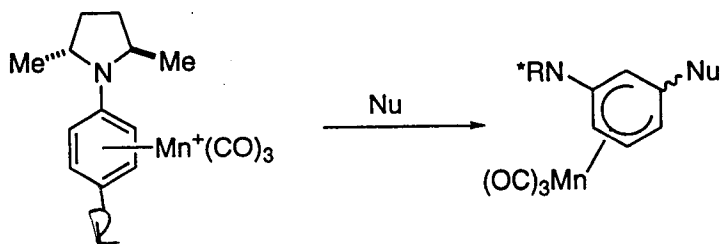
R	R <sup>1</sup> Li	Product 7, 8	Yield [%] [a]	7:8 [b]
iPr	MeLi	a	61	96:4
iPr	nBuLi [c]	b	54	95.5:4.5
iPr	VinylLi [d, e]	c	48	95.5:4.5
iPr	PhLi [f]	d	60	81:19
tBu	MeLi	e	69	≥99:1
tBu	nBuLi	f	62	≥99:1
tBu	PhLi [f]	g	51	95.5:4.5

[a] Ketone products were also formed in 10-25% yield; see Ref. [7].  
 [b] Determined by 400-MHz <sup>1</sup>H NMR and HPLC. [c] Reaction run in THF/toluene (1:10) at -90 °C. [d] Generated in situ from MeLi and tetravinyltin. [e] Reaction run at -90 °C. [f] Reaction run in THF/toluene (1:5) at -80 °C.

very good selectivities

too far away from Cr(CO)<sub>3</sub> by x-ray

## Chiral Auxiliaries with Mn Complexes



3: R=H  
4: R=Me

Attempts to cleave Aux. have been unsuccessful

*unexplained switch in selectivity*

Table 1. Reactions of Complexes 3 and 4 with Nucleophiles. All reactions were run in THF at -78 °C unless otherwise noted.

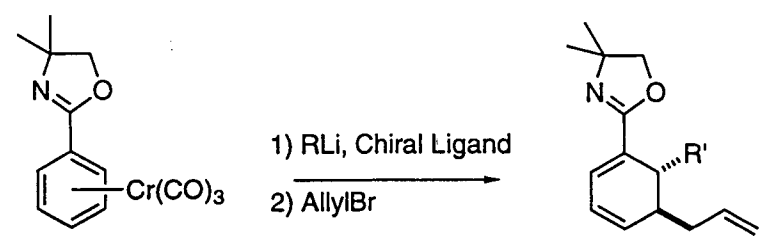
Entry	Complex	Nucleophile	Ratio 5:6	Combined Yield (%)
1	3	PhLi	2.0:1	52
2	4	PhLi	6.6:1	78
3	3	PhMgBr	19:1	60
4	4	PhMgCl	48:1	93
5	3	VinylMgBr	1.6:1	50
6	4	VinylMgBr	3.6:1	36 <sup>a</sup>
7	4	AllylMgBr	4.1:1	65
8	3	LS-Selectride <sup>®</sup>	11.5:1	84
9	4	LS-Selectride <sup>®</sup>	n.d.	no reaction <sup>b</sup>
10	3	L-Selectride <sup>®</sup>	5.3:1	77
11	4	L-Selectride <sup>®</sup>	5.7:1	30 <sup>b</sup>
12	3	Superhydride <sup>®</sup>	2.8:1	75
13	4	Superhydride <sup>®</sup>	1.7:1	37 <sup>b</sup>
14	3	LiAlH <sub>4</sub>	2.1:1	81
15	4	LiAlH <sub>4</sub>	1.0:1.4	83
16	3	LiAl( <i>t</i> -OBu) <sub>3</sub> H	1.4:1	70
17	4	LiAl( <i>t</i> -OBu) <sub>3</sub> H	ca 1:1	Trace <sup>a</sup>
18	3	NaBH <sub>4</sub>	1:4.3	80
19	4	NaBH <sub>4</sub>	1:3	93
20	3	LiBH <sub>4</sub>	1:3.8	85
21	4	LiBH <sub>4</sub>	1:8.2	73
22	3	MeLi <sup>c</sup>	1:3	60
23	4	MeLi	1:3.5	67
24	4	Vinyl-Li	1:2.5	62
25	4	LiCH <sub>2</sub> CO <sub>2</sub> Bu <sup>t</sup>	1:2.8	65

<sup>a</sup>Unreacted starting material recovered. <sup>b</sup>Substantial decomplexation of arene complex observed. <sup>c</sup>Reaction conducted in CH<sub>2</sub>Cl<sub>2</sub> at -95 to -85 °C, owing to very low yield in THF.

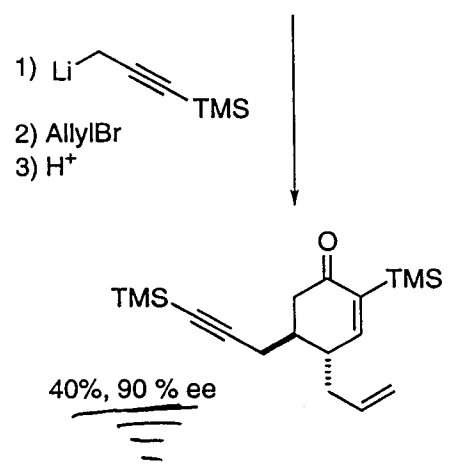
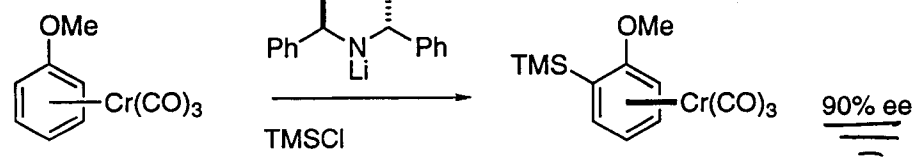


## Other Asymmetric Application

Chiral nucleophiles:



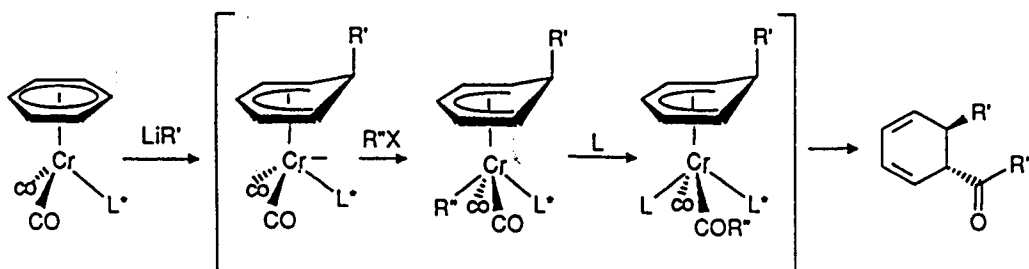
Chiral complexes:



Entry	RLi <sup>a</sup>	Ligand <sup>b</sup>	Product (Yield, %) <sup>c</sup>	Config. <sup>d</sup>	ee <sup>e</sup> (%)
1	PhLi <sup>f</sup>		(+)-2a (72)	5 <i>S</i> ,6 <i>S</i>	54
2	VinylLi <sup>g</sup>		(+)-2b (87)	5 <i>S</i> ,6 <i>R</i>	34
3	MeLi <sup>h</sup>		(+)-2c (70)	5 <i>S</i> ,6 <i>R</i>	47
4	n-BuLi <sup>i</sup>		(+)-2d (65) <sup>j</sup>	5 <i>S</i> ,6 <i>R</i>	36
5	PhLi <sup>f</sup>		(-)-2a (72)	5 <i>R</i> ,6 <i>R</i>	81
6	VinylLi <sup>g</sup>		(-)-2b (85)	5 <i>R</i> ,6 <i>S</i>	50
7	MeLi <sup>h</sup>		(-)-2c (60)	5 <i>R</i> ,6 <i>S</i>	47
8	n-BuLi <sup>i</sup>		(-)-2d (68)	5 <i>R</i> ,6 <i>S</i>	45
9	PhLi <sup>f</sup>		(+)-2a (66)	5 <i>S</i> ,6 <i>S</i>	81
10	VinylLi <sup>g</sup>		(+)-2b (60)	5 <i>S</i> ,6 <i>R</i>	61
11	MeLi <sup>h</sup>		(+)-2c (50)	5 <i>S</i> ,6 <i>R</i>	84
12	n-BuLi <sup>i</sup>		(+)-2d (75)	5 <i>S</i> ,6 <i>R</i>	61
13	PhLi <sup>f</sup>		(+)-2a (66)	5 <i>S</i> ,6 <i>S</i>	93 <sup>k</sup>
14	VinylLi <sup>g</sup>		(+)-2b (53)	5 <i>S</i> ,6 <i>R</i>	87
15	MeLi <sup>h</sup>		(+)-2c (51)	5 <i>S</i> ,6 <i>R</i>	87
16	n-BuLi <sup>i</sup>		(+)-2d (67)	5 <i>S</i> ,6 <i>R</i>	65

Kundig *JOC*, 1996, 61, 2259  
 Kundig, *JACS* 1997, 119, 4773  
 Simpkins *JOC*, 1994, 59, 1961

## Chiral Ligands



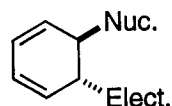
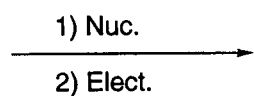
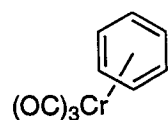
- chiral discrimination  
is in the red. elim.  
step, not in nucleophilic  
addition.

$\text{L}^*$		Yield [%]	ee [%]	abs. config.
	$\text{R}'' = \text{Et}, \text{L} = \text{CO}$	82	26	RR
	$\text{R}'' = \text{Me}$ $\text{L} = \text{P(OPh)}_3$	70	31	SS
	$\text{R}'' = \text{Me}$	71	41	SS
	$\text{L} = \text{CO}$	60	56	SS
	$\text{R}' = \text{Me}$ $\text{Cy}$ $i\text{Pr}$	50	69	SS

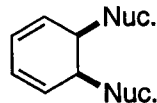
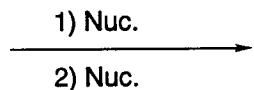
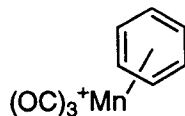
- bidentate ligands have  
not been explored

Scheme 6. Ligand mediated asymmetric transformation of benzene into a disubstituted cyclohexadiene

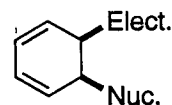
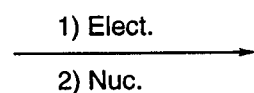
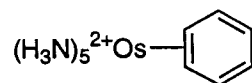
## Conclusion



- most general, and most well studied
- limited to strong nucleophiles, alkyl electrophiles
- several methods of high asymmetric induction



- least studied
- good generality in initial nucleophiles
- needs strong second nucleophile or intermediate activation
- poor asymmetric induction



- most novel approach, orthogonal to others
- good generality in electrophiles
- more difficult to work with (Os)
- only one example of asym. induction

Overall, these methods are very promising, but have yet to see many applications