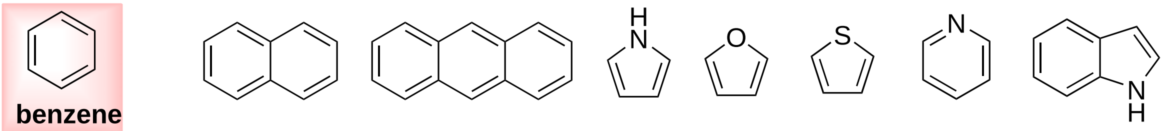
Dearomatization Reaction

2011/11/15
H.Mitsunuma (M2)

0. Introduction



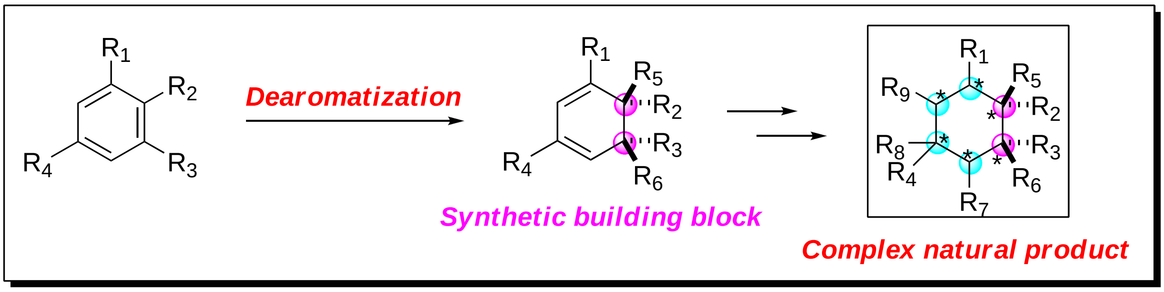
etc.

aromatic rings

1865: Assignment of the benzene structure (F A. Kekule)
Chemically stable, ubiquitous (aromaticity)

One of the most stable molecule in organic chemistry !!

~Aromatic ring as a synthetic scaffold~



The dearomatization of arenes will provide synthetically useful hydrocarbons and alicyclic frameworks !!

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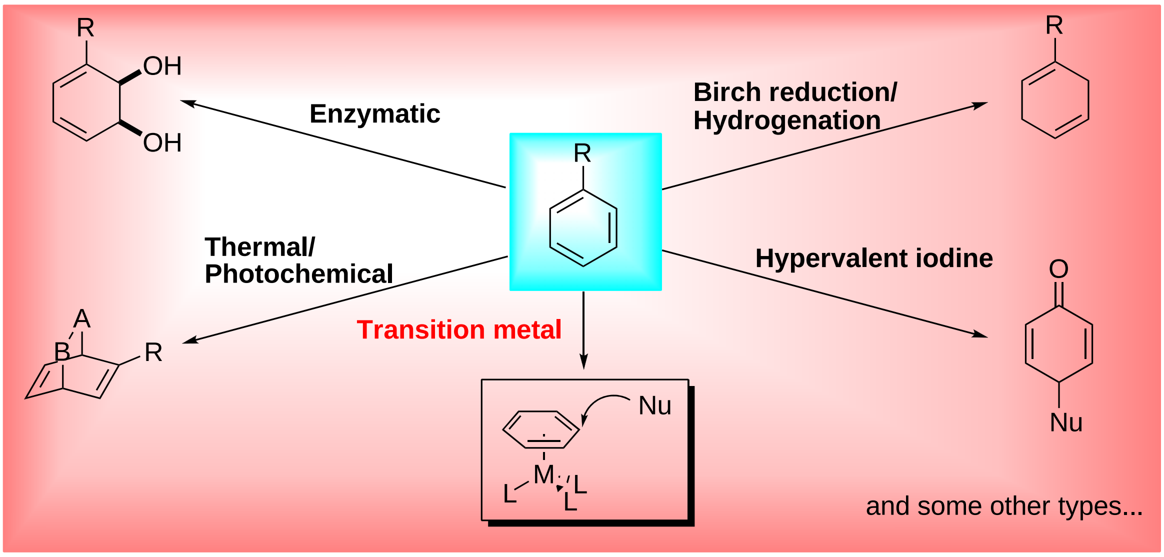
2. Transition Metal Mediated Dearomatization Reactions

- **2.1 Dearomatization through η^6 coordination**
- **2.2 Dearomatization through η^2 coordination**
- **2.3 Multinuclear metal-arene complexes**
- **2.4 Catalytic dearomatization reactions**

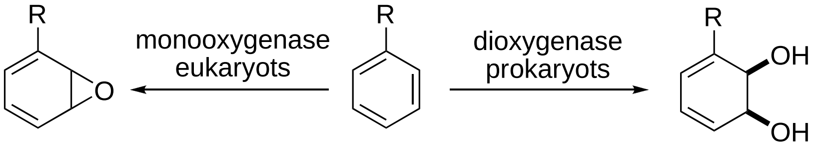
1. Background of Dearomatization Reactions



and some other types...

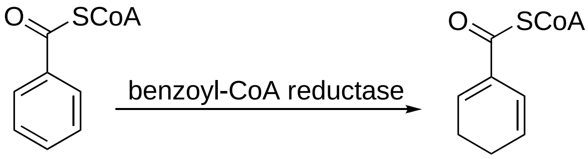
Enzymatic dearomatization

Oxidation



Enantioselective dihydroxylation
Many application to total synthesis (since 1987)
Pseudomonas putida: commercially available from Aldrich

Reduction

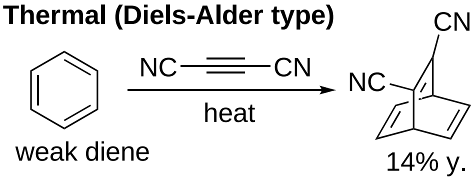


cf) Birch reduction

Advantages:	**Disadvantages**:
enantioselective dihydroxylation functional group tolerance aromatic heterocycles	no C-C bond formation

Thermal/Photochemical dearomatization

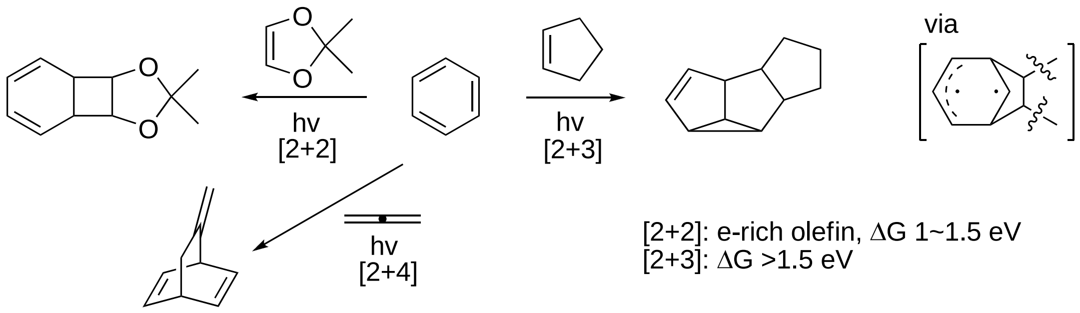
Thermal (Diels-Alder type)



anthracene
phenol
benzyne...

R S. H. Liu *JACS*. **1968**, *90*, 215.

Photochemical ([2+2], [2+3], [2+4]...)

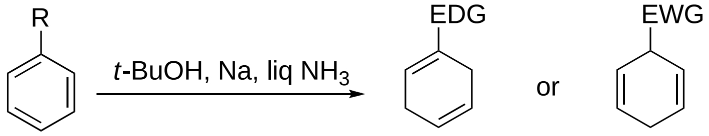


[2+2]: e-rich olefin, ΔG 1~1.5 eV
[2+3]: ΔG >1.5 eV

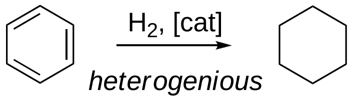
Advantages:	**Disadvantages**:
C-C bond formation atom economical	limited substrate scope position selectivity harsh condition

Birch reduction/ Hydrogenation

Birch reduction

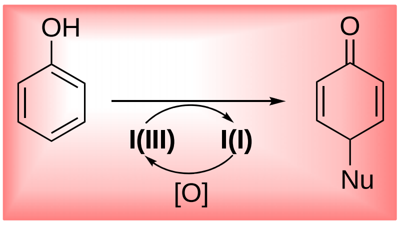


Hydrogenation



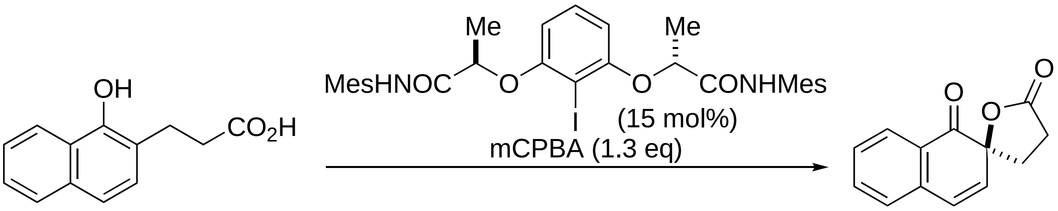
Advantages:	**Disadvantages**:
position selective	harsh condition functional group tolerance C-H bond formation

Hypervalent iodine-catalyzed dearomatization



cf) $Pb(OAc)_4$

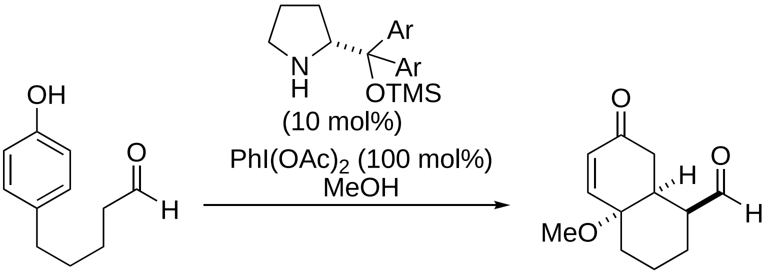
Catalytic asymmetric Kita oxidation



82%y. 85%ee

K Ishihara et al. *ACIE*. **2010**, *49*, 2175.

Organocatalytic desymmetrization of *meso* dienone obtained through oxidative dearomatization



75%y. 99%ee >20/1 dr

M J. Gaunt et al. *JACS*. **2008**, *130*, 404.

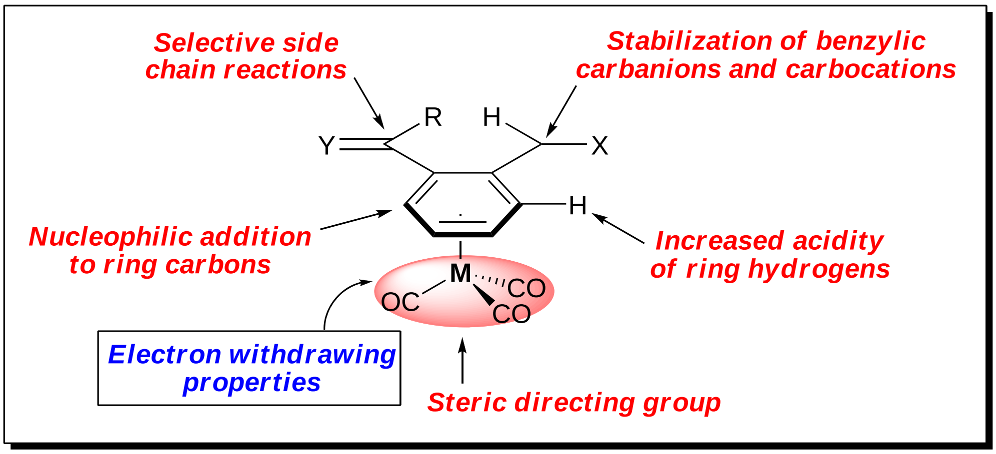
Advantages:
catalytic
asymmetric
mild condition

Disadvantages:
applicable to only phenol derivatives

2. Transition Metal Mediated Dearomatization Reactions

2.1 Dearomatization through η^6 coordination

Changes in arene reactivity after complexation with metal tricarbonyl



Selective side chain reactions

Stabilization of benzylic carbanions and carbocations

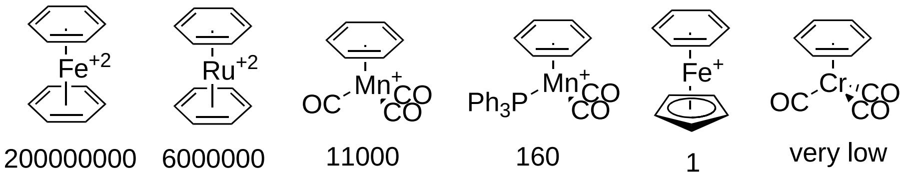
Nucleophilic addition to ring carbons

Increased acidity of ring hydrogens

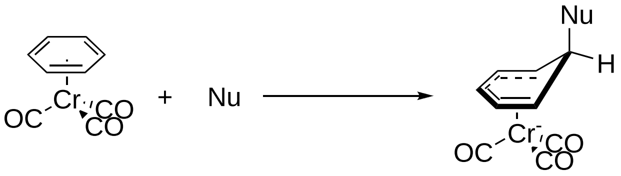
Electron withdrawing properties

Steric directing group

Relative reactivity of arene-metal complexes toward nucleophilic addition



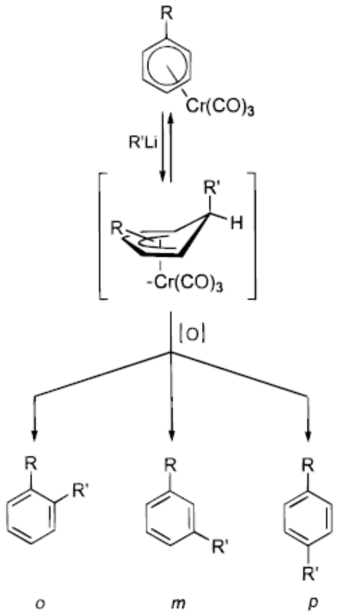
Reactivity of carbanions in the nucleophilic addition process to benzene

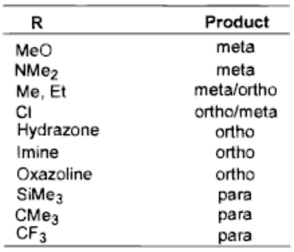


unreactive
$LiCH(CO_2R)_2$, $LiCH_2COR$, CH_3MgBr, $(CH_3)_3CMgBr$, $(CH_3)_2CuLi$, LiC(OR)(CN)Ph
successful
$LiCH_2CO_2R$, $LiCH_2CN$, $KCH_2COC(CH_3)_3$, LiCH(CN)(OR), $LiCH_2SPh$, 2-Li-1,3-dithianyl, $LiCH=CH_2$, LiPh, LiCCR, $LiCH_2CH=CH_2$, *t*BuLi
metalation
*n*BuLi, $LiCH_3$, *s*BuLi

Attack of nucleophiles is reversible.
pKa > 22

Regioselective addition to arene chromium tricarbonyl complexes

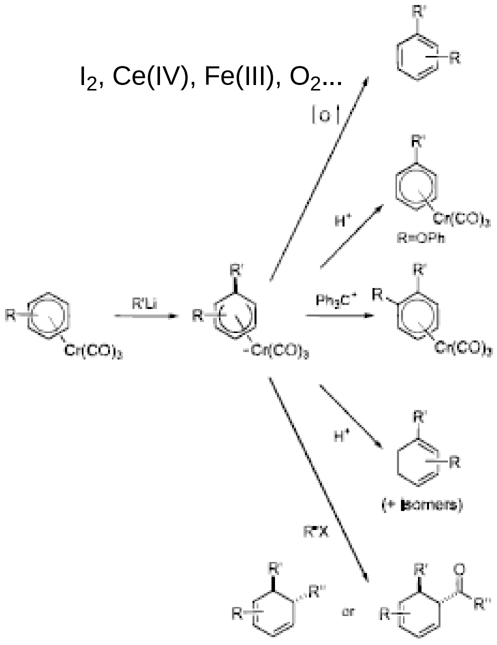




R	Product
MeO	meta
NMe_2	meta
Me, Et	meta/ortho
Cl	ortho/meta
Hydrazone	ortho
Imine	ortho
Oxazoline	ortho
$SiMe_3$	para
CMe_3	para
CF_3	para

(kinetic product)

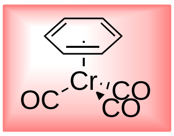
Range of products resulting from the sequential reactions of nucleophiles and electrophiles



oxidation: it makes the metal poorer at backbonding.

In principle, this chemistry could be catalytic if arene exchange occurred after nucleophilic attack.

(η^6arene)$Cr(CO)_3$ complexes



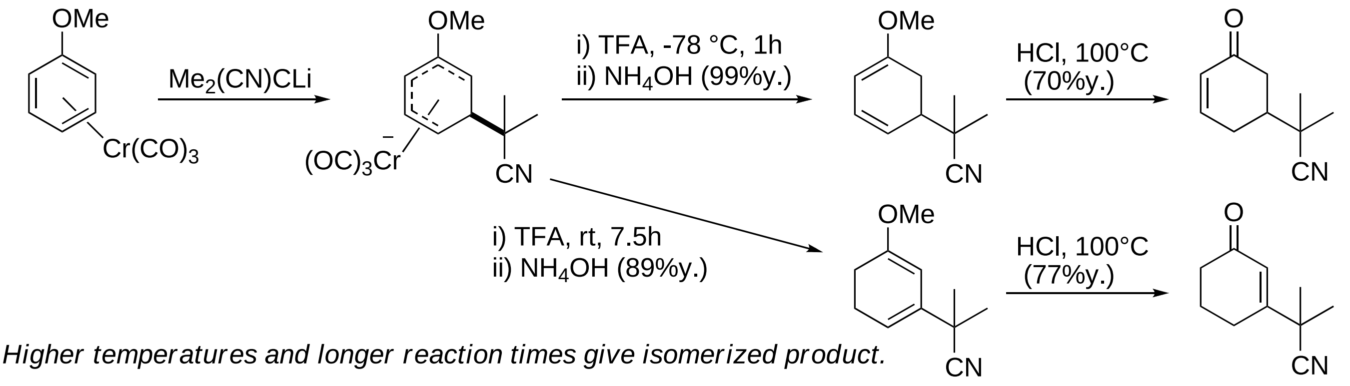
yellow to red
often crystalline compound
stable to air (in solid state), moderately air sensitive (in solution)
they can be stored for long preriods if they are kept away from light.

Preparation

1. $Cr(CO)_6$ + arene (excesss) under Ar (1~4 d)
2. $Cr(CO)_3L_3$ + arene (L = CH_3CN, Py, NH_3)
3. (naphthalene)$Cr(CO)_3$ + arene

Reaction patterns

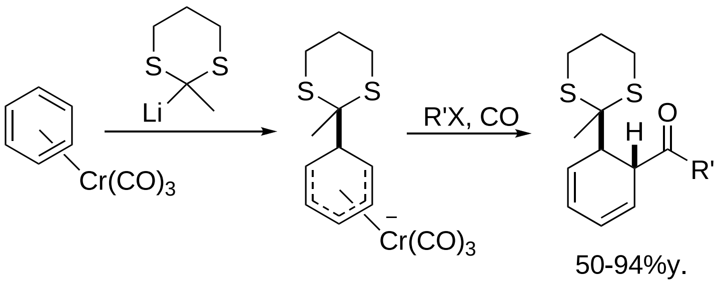
1. Nucleophilic addition/Protonation reactions



Higher temperatures and longer reaction times give isomerized product.

Semmelhack et al. *JOC* **1979**, *44*, 3275.
Semmelhack et al. *Tetrahedron* **1981**, *37*, 3957.

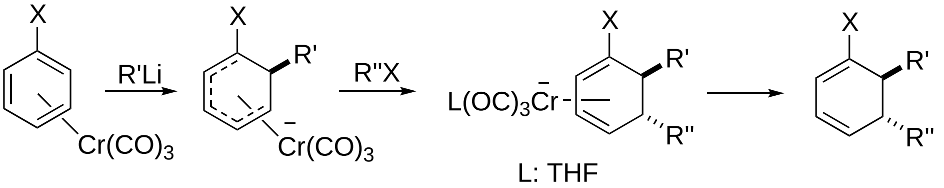
2. Nucleophilic addition/C-electrophile addition reactions

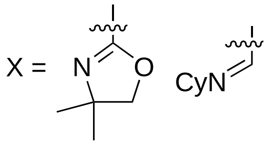


R': all except for propargyl group

Reaction yields higher when carried out under CO or in the presence of an added ligand (PR_3, $P(OPh)_3$, NEt_3).

Migratory aptitude of R': ethyl > methyl > benzyl, allyl >> propargyl

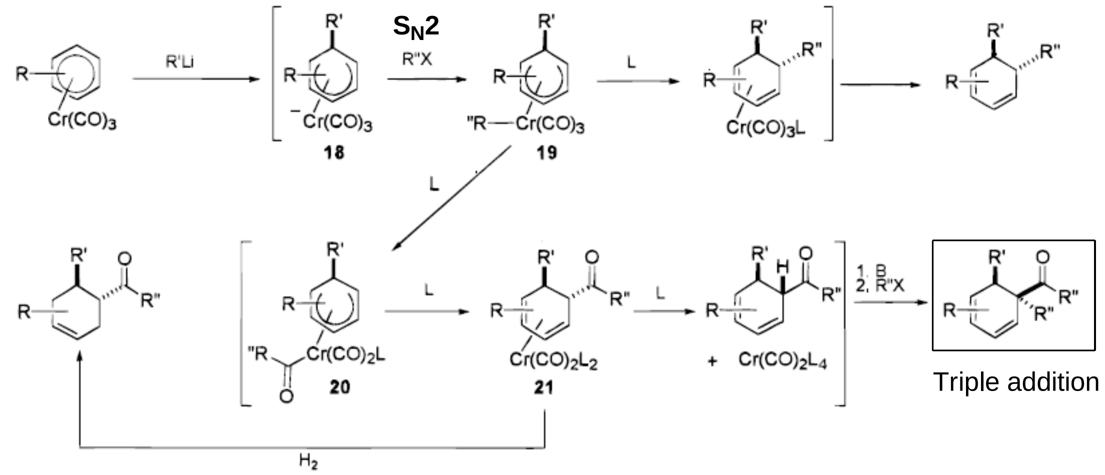




R'' = alkyl: carbonylation
allyl: small carbonylation
propargyl: no carbonylation

Highly regioselective

Mechanism

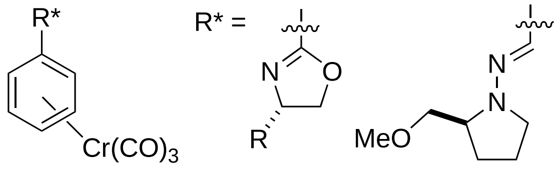


Triple addition

Migratory CO insertion depends very much on the nature of the electrophile and the presence or absence of EWG on the arene ring.

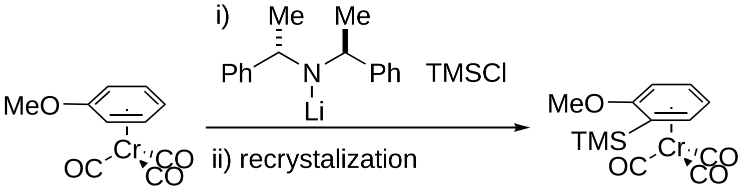
3. Asymmetric version

Chiral auxiliary



good selectivity

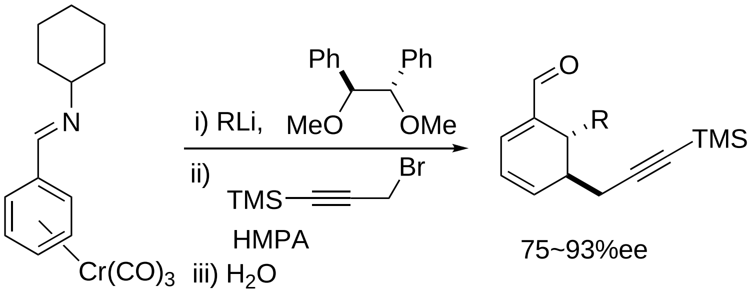
Planer chirality



70% y. 99%ee

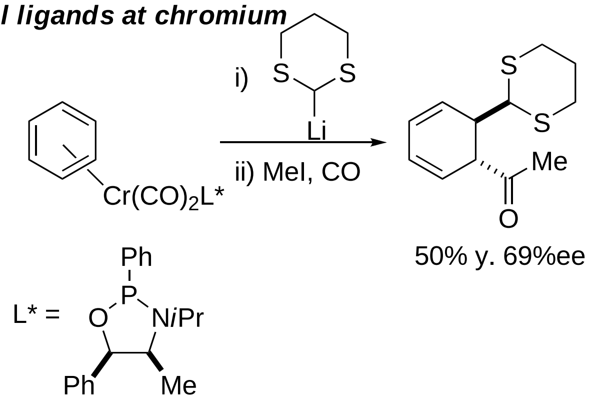
Schmalz et al. *Chem. Eur. J.* **1998**, *4*, 57.

External chiral ligand



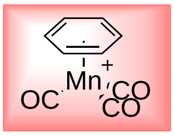
Kundig et al. *JOC.* **1996**, *61*, 2258.

Chiral ligands at chromium



Kundig et al. *Pure. Appl. Chem.* **1996**, *68*, 97.

$[(\eta^6\text{-arene})Mn(CO)_3]^+$ complexes



yellow, stable
crystalline compound
more electrophilic than chromium

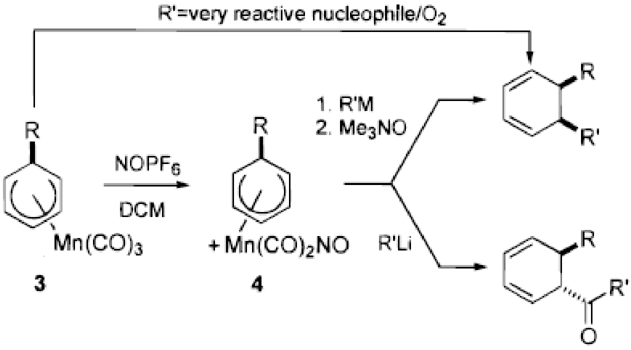
Preparation
$Mn(CO)_5Br + AgBF_4$, then arene

Nucleophiles: Grignard reagent, ketone enolates, malonates, hydride(LAH...)

Reaction patterns

Sequential addition of two nucleophiles

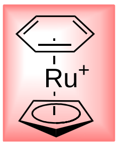
Due to the decreased nucleophilicity of the neutral Mn species, reaction with C-electrophiles are not possible.



Substitution of CO ligand to NO makes the complex more electrophilic.

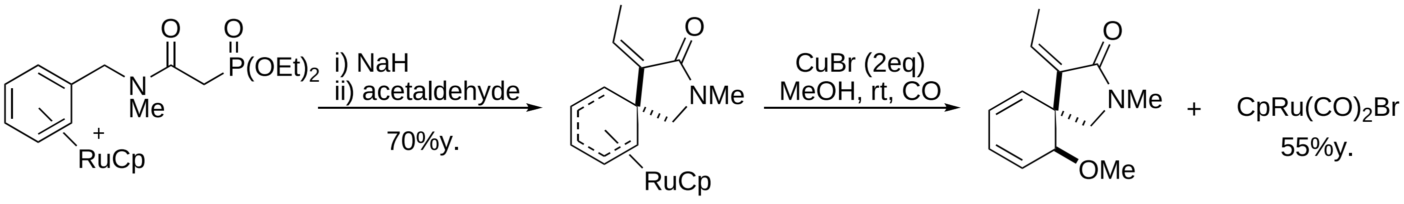
← Reaction occurred at CO ligand.

$[(\eta^6\text{-arene})RuCp]^+$ complexes

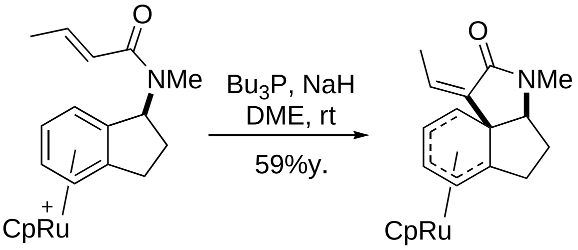


high yielding preparation
functional compatibility of RuCp

Preparation
$[(MeCN)_3RuCp][PF_6]$ + arene



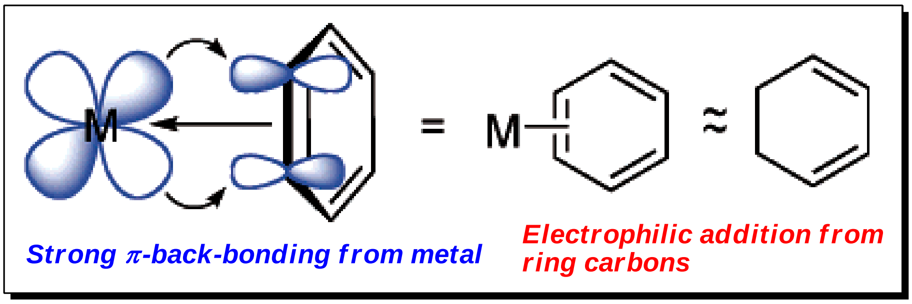
61%y.
Pigge et al. *JACS.* **2006**, *128*, 3498.



Pigge et al. *Organometallics.* **2009**, *28*, 3869.

2.1 Dearomatization through η^2 coordination

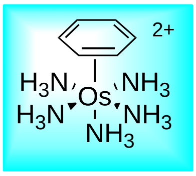
Changes in arene reactivity after complexation with metal tricarbonyl



M = Os, Re, Mo, W

This chemistry can be applicable to hetero aromatic rings.

$[(\eta^2\text{arene})Os(NH_3)_5]^{2+}$ complexes



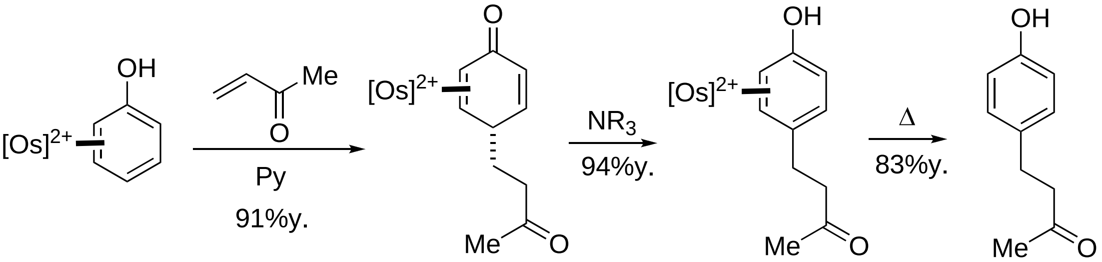
yellow to red crystalline
thermally stable
sensitive to air
coordination to nitrile, aldehyde, some ketones, alkenes and alkyne
(not to ester, amide, ether, alcohol, water protonated amine)
ammine ligand: powerful σ-donor, poor π-interaction with metal

Preparation

$[Os(NH_3)_5(OTf)][(OTf)_2]$ + arene with Zn^0/Hg^0

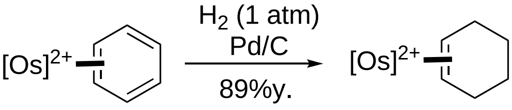
Reaction patterns

1. Electrophilic addition



Harman et al. *JACS.* **1994**, *116*, 6581.

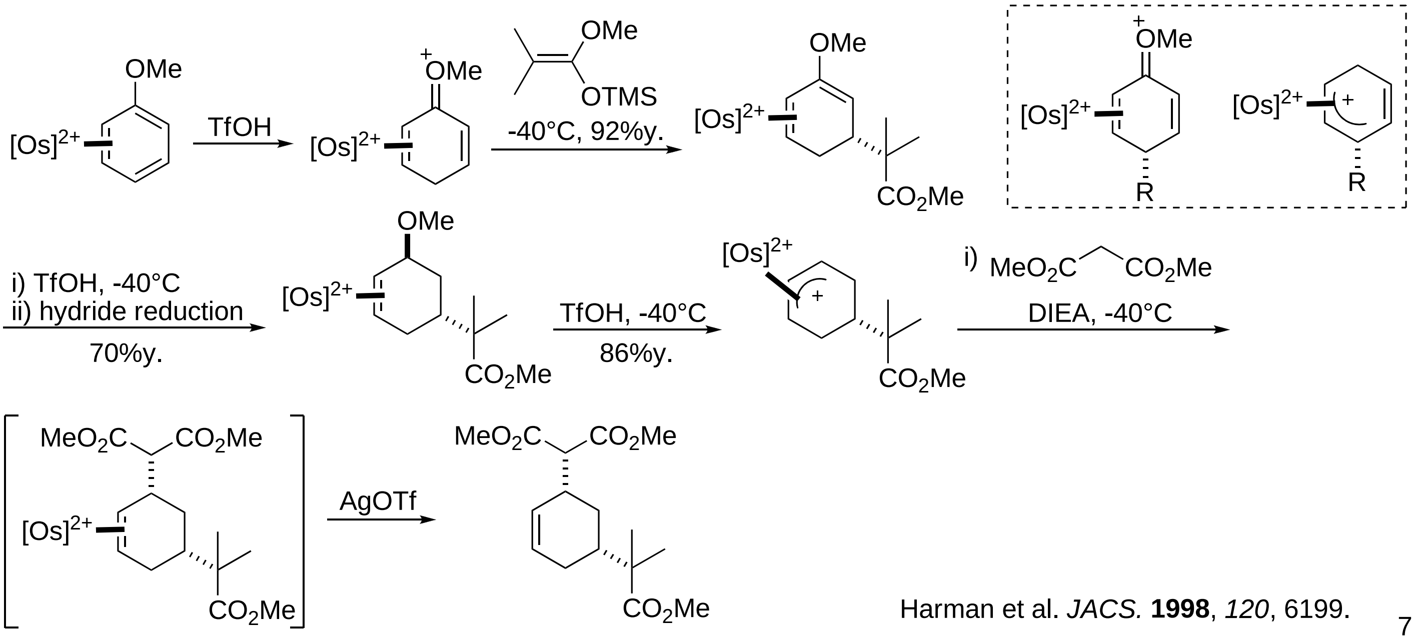
2. Hydrogenation



Harman et al. *JACS.* **1988**, *110*, 7906.

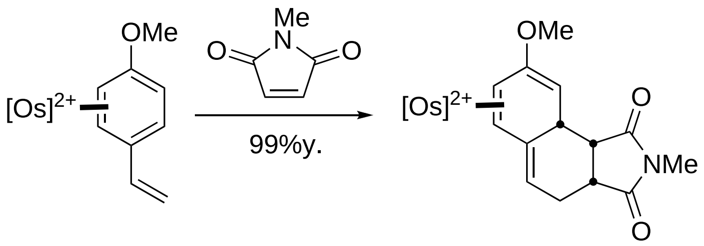
3. Sequential electrophilic/nucleophilic addition

The greatest synthetic potential of this method lies in the *ability to stabilize the cationic intermediate.*



Harman et al. *JACS.* **1998**, *120*, 6199.

4. Diels-Alder reaction

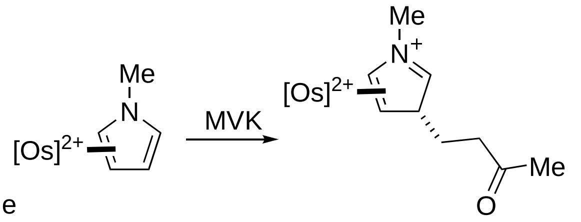


normal styrene as a diene: harsh condition, reactive dienophile

Harman et al. *JACS.* **1998**, *120*, 2218.

5. Electrophilic addition from heterocycles

Pyrroles, furanes, thiofenes: same reactivity as above



Re, Mo, W complexes (Harman's chemistry)

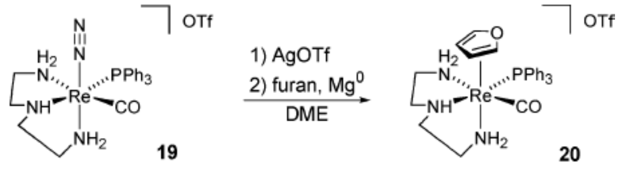
Harman et al. *Organometallics.* **2005**, *24*, 1786.

Problems of osmium system: racemic reaction (use of chiral auxiliary)
ligand tuning is difficult
cost of osmium

Alternative system

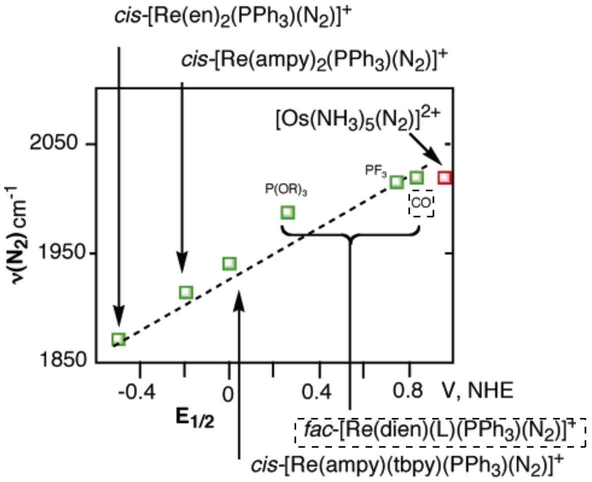
coordinatively saturated
e-rich metal center to overcome the aromatic stability
(but not so e-rich as tofavor C-H insertion)
σ-donating ligand

Re(dien)(PPh$_3$)(CO)



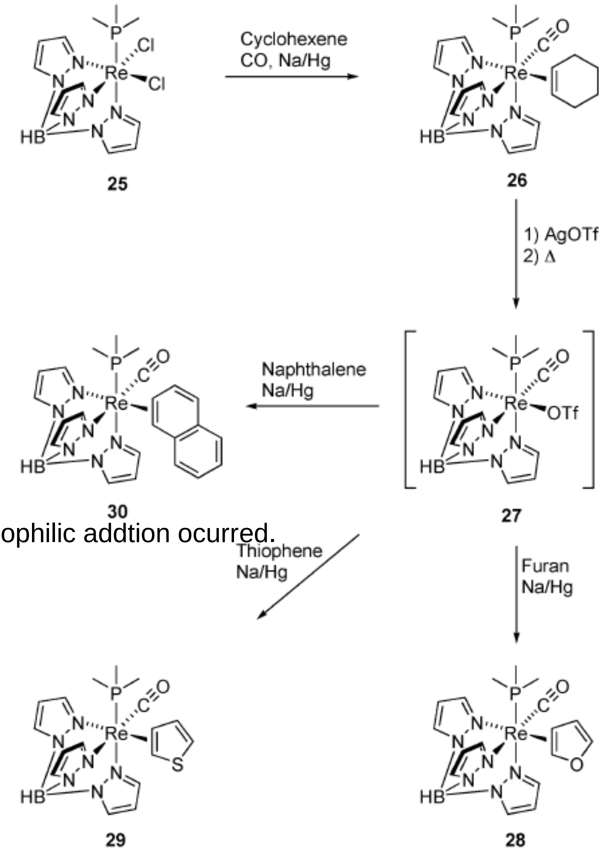
only furan
(inactive to novel reaction)

Dinitrogen IR stretching frequencies and electrochemical date



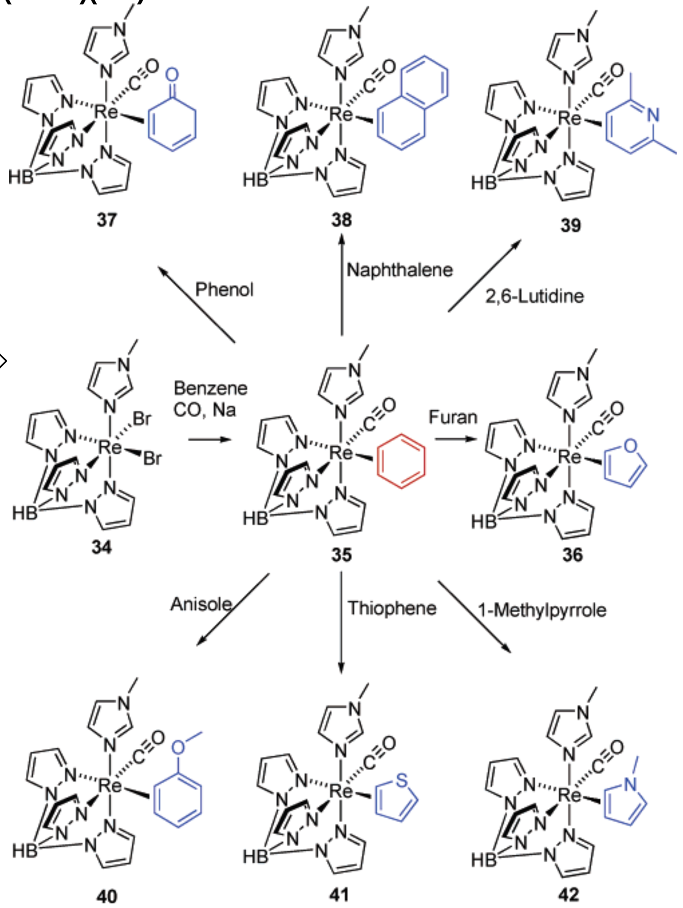
ampy = 2-(aminomethl)lpyridine
tbpy = 4,4'-di-tert-butylbipyridyl

TpRe(PMe$_3$)(CO)

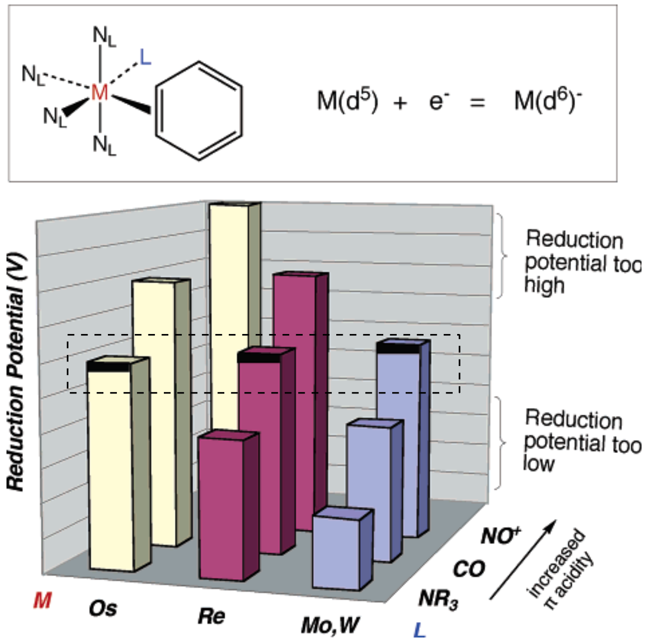


Electrophilic addtion ocurred.

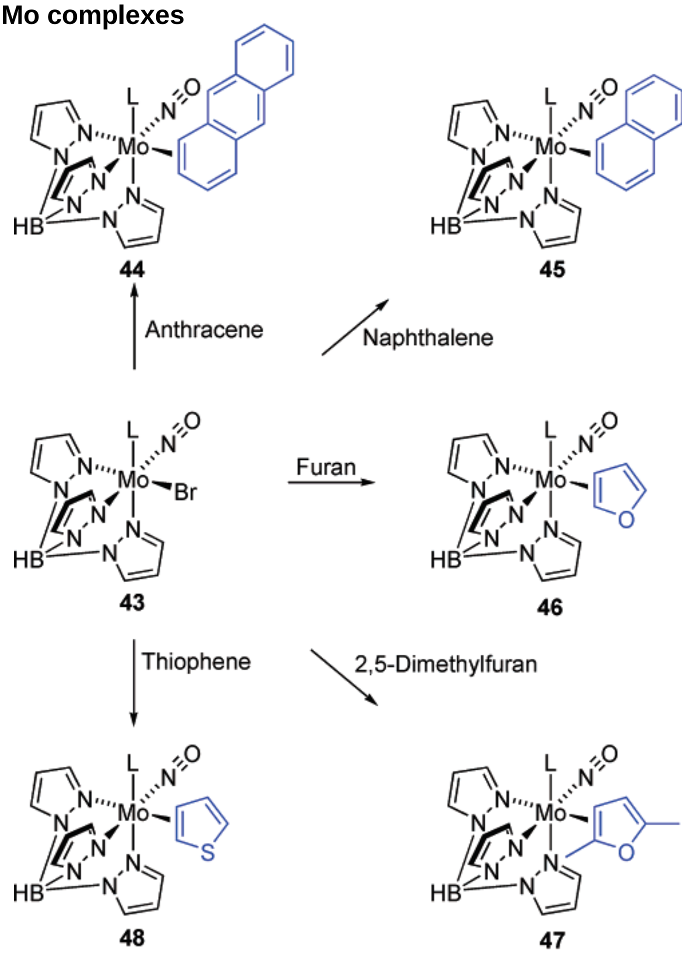
TpRe(MeIm)(CO)



Reduction potentials of d^6 metal complexes as a function of ligand identity

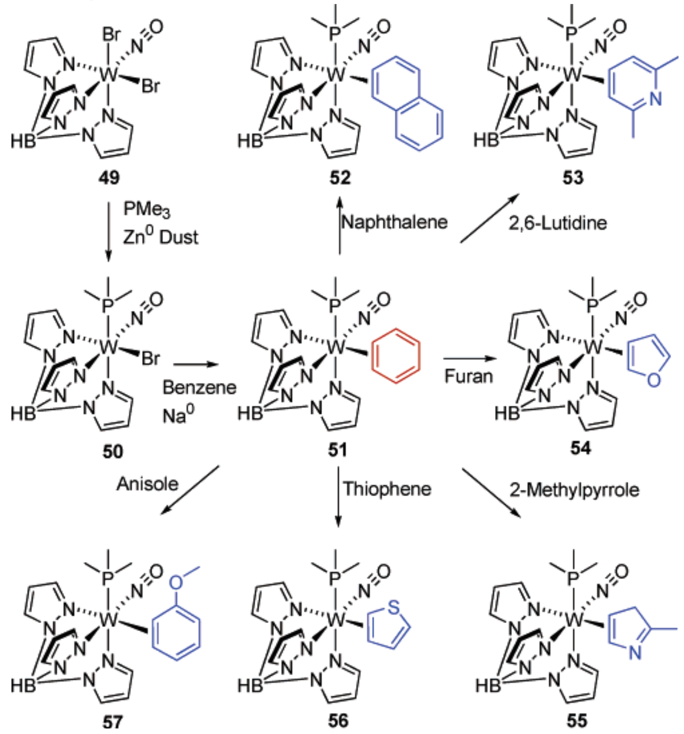


Mo complexes



L = MeIm or NH_3

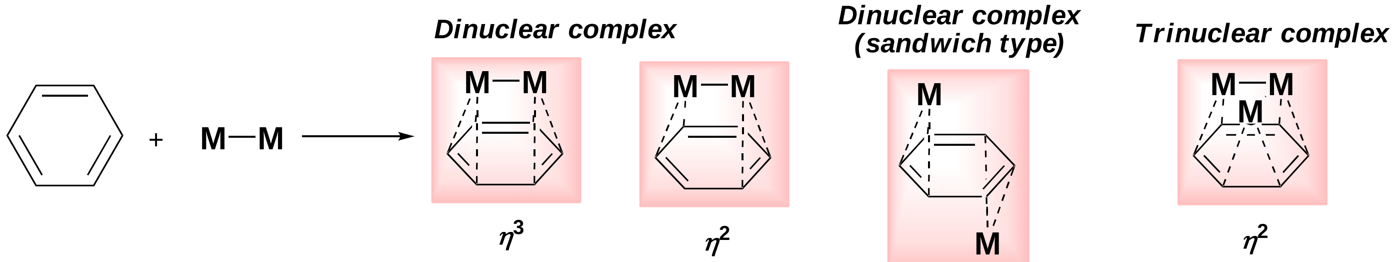
W complexes



Resolution of enantiocontrol (using chiral pinene)

These complexes have revealed a vast array of useful reaction pathway.

2.3 Multinuclear metal-arene complexes



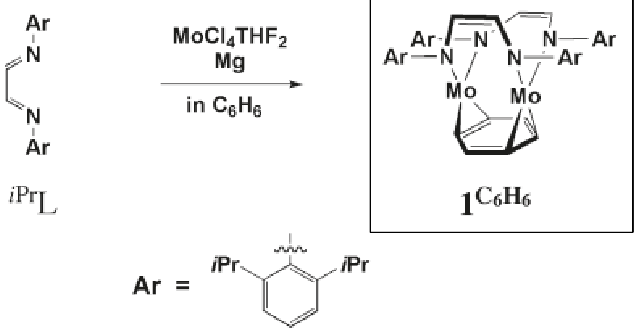
There are some μ-η^3:η^3-arene dinuclear complexes.
This type of chelation changes the nature of arene.

η^3

Dinuclear Mo-Mo complex

H Masuda et al. *Inorg. Chem.* **2009**, *48*, 9069.

Synthesis of dimolybdeum complex



Mo-Mo: 2.1968Å
quadruple bond: 2.0~2.2Å
triple bond: 2.5~2.6Å

Xray

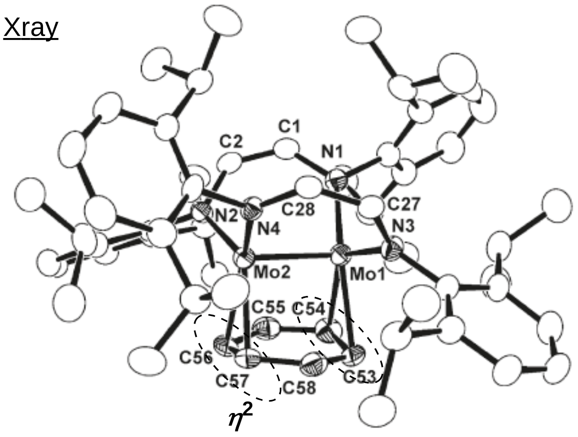
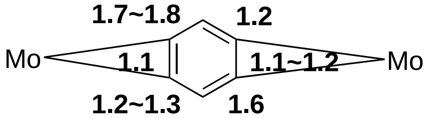


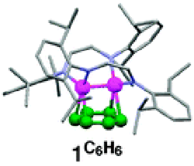
Figure 1. X-ray structure of $1^{C_6H_6}$ with the atom numbering scheme (50% probability thermal ellipsoids). Selected bond lengths (Å) for $1^{C_6H_6}$: Mo1−Mo2 2.1968(4), Mo1−N1 2.018(3), Mo1−N3 2.052(3), Mo1−C53 2.261(3), Mo1−C54 2.194(3), Mo2−N2 2.061(3), Mo2−N4 2.010(3), Mo2−C56 2.253(3), Mo2−C57 2.189(3), C1−C2 1.349(5), C1−N1 1.398(4), C2−N2 1.389(5), C27−C28 1.347(5), C27−N3 1.405(4), C28−N4 1.396(5), C53−C54 1.456(5), C54−C55 1.442(5), C55−C56 1.365(5), C56−C57 1.463(5), C57−C58 1.433(5), C58−C53 1.384(5).

Distortion of benzene ligand !!

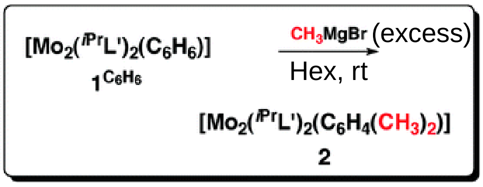
Bond order



Reactivity of benzene ligand



$1^{C_6H_6}$



Dimethylation ocurred !!

Dimethylated product **2** was detected by ESI-MS analysis.
Methylation took place at benzene not diimine ligand.
(C_6D_6 complex : mass value **2**+4)

GC analysis of decomposed products of **2** demonstrates the generation of xylene. (*o*/*m*/*p* = 33/18/49)

Reaction mechanism is unclear (C-H activation path ?).

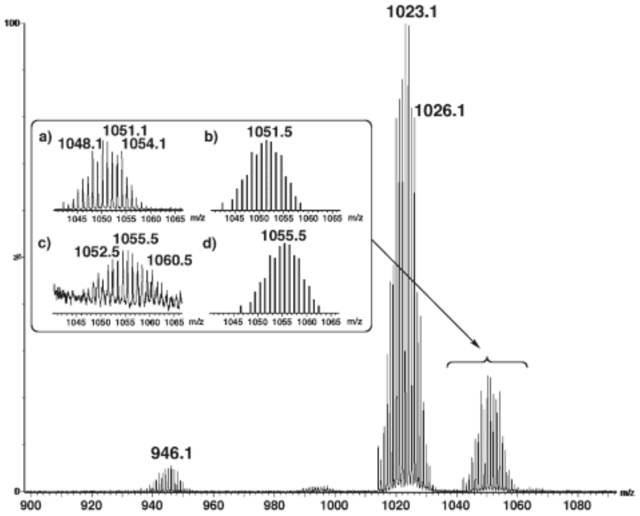
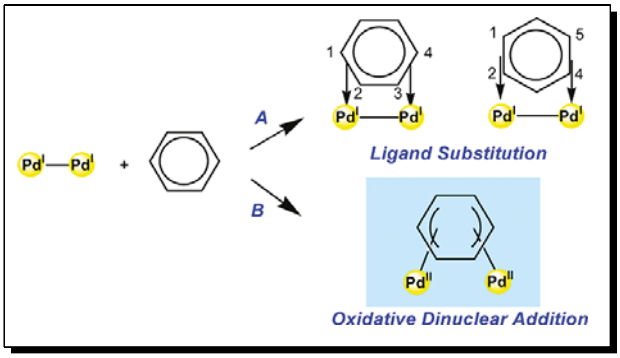


Figure 4. ESI-MS spectrum of the reaction products of $1^{C_6H_6}$ with MeMgBr. Inset: Expanded views of the range of m/z = 1040−1065 for **2**-*d* (a), for the simulation of **2**-*d* (b), **2** (c), and for the simulation of **2** (d).

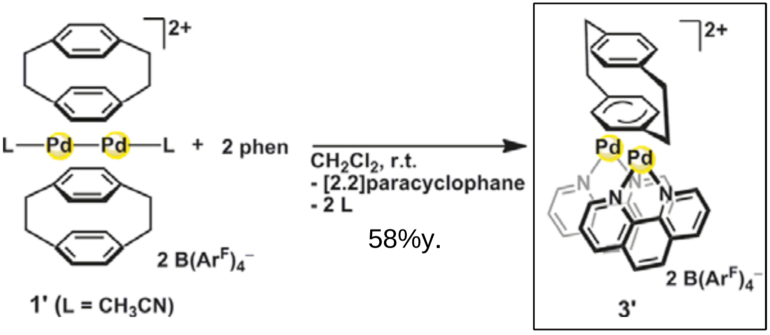
Dinuclear Pd(I)-Pd(I) complex

T Murahashi et al. *JACS.* **2011**, *133*, 14908.

Concept

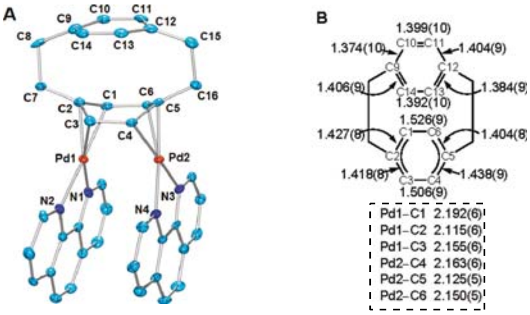


Oxidative addition to arene



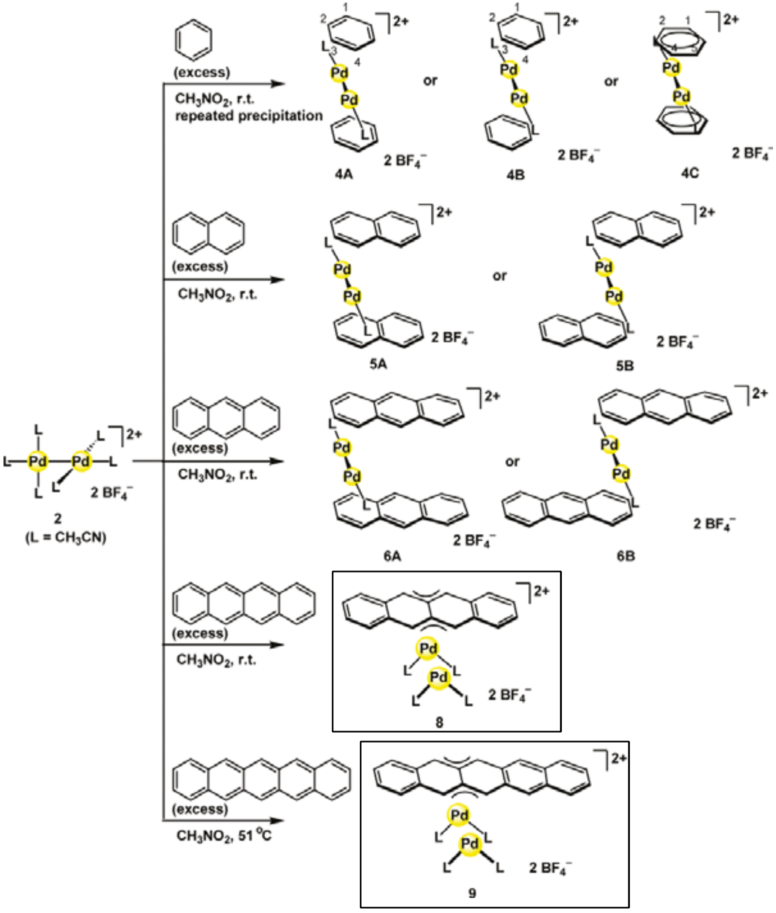
(1)

Xray



Bi-η^3-allyl structure

Reaction with various arenes



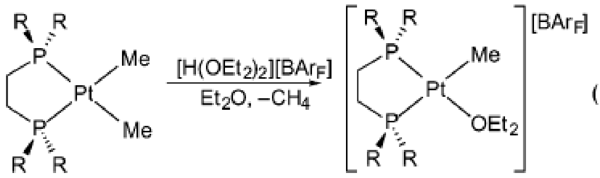
The number of fused rings in polyacenes gave oxdative dinuclear addition products.

→ formal [4π+2σ] Diels-Alder reaction

Dinuclear Pt sandwich complex

Kubas et al. *JACS.* **2002**, *124*, 12550.

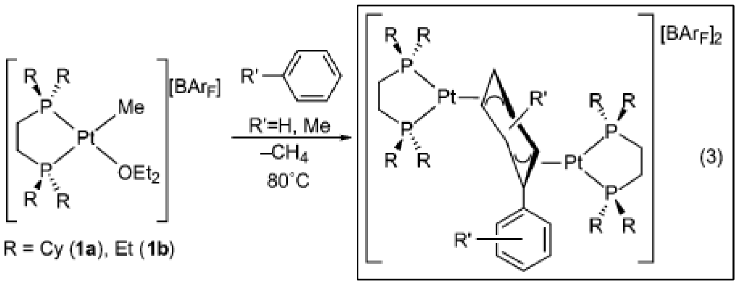
Synthesis of cationic methyl platinum complexes



(1)

R = Cy (**1a**), Et (**1b**)

Synthesis of dinuclear Pt complexes



(**3a**): R = Cy, R' = H; (**3b**):R = Et, R' = H
(**4a**): R = Cy, R' = Me

C-H activation and C-C coupling of arene are occured!!

Xray analysis

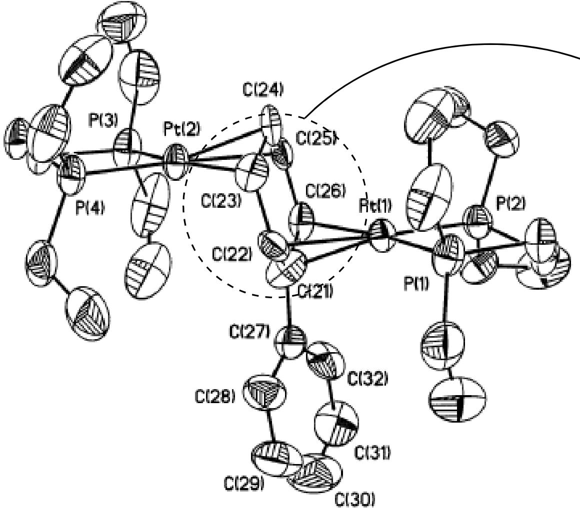


Figure 2. Molecular structure of **3b** (50% probability ellipsoids).

^{1}H NMR: phenyl peaks were shifted upfield. (4.74~5.67)

→ π-type coordination

bridging dianionic biphenyl ligand

C-C distance in benzene units matched with the allylic carbons.

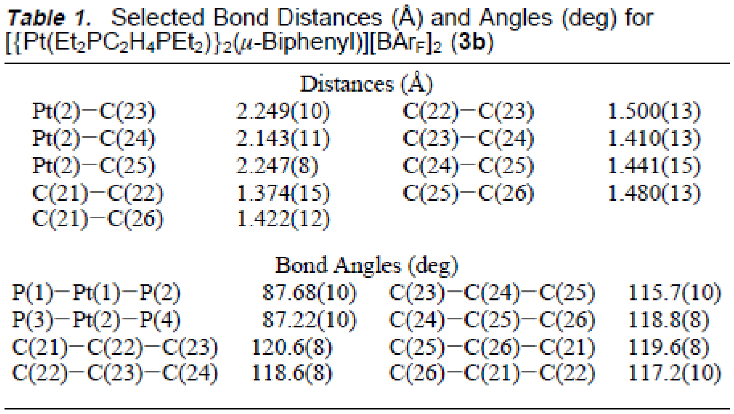


Table 1. Selected Bond Distances (Å) and Angles (deg) for $[\{Pt(Et_2PC_2H_4PEt_2)\}_2(\mu\text{-Biphenyl})][BAr_F]_2$ (**3b**)

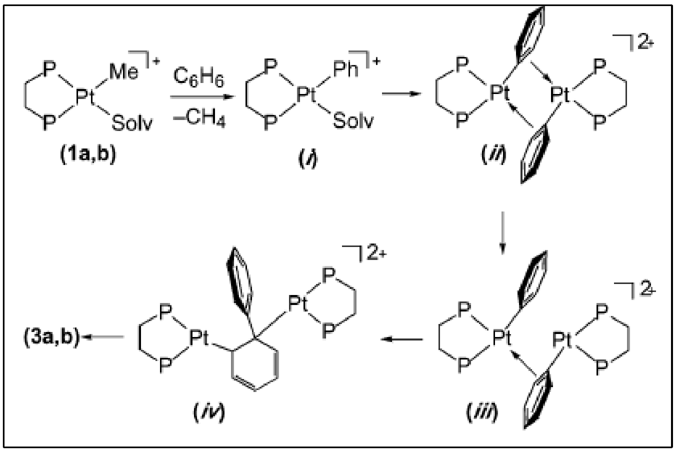
Distances (Å)

Pt(2)−C(23)	2.249(10)	C(22)−C(23)	1.500(13)
Pt(2)−C(24)	2.143(11)	C(23)−C(24)	1.410(13)
Pt(2)−C(25)	2.247(8)	C(24)−C(25)	1.441(15)
C(21)−C(22)	1.374(15)	C(25)−C(26)	1.480(13)
C(21)−C(26)	1.422(12)		

Bond Angles (deg)

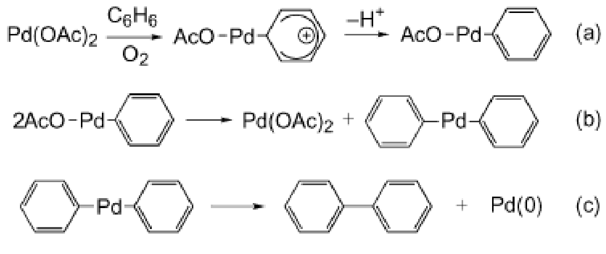
P(1)−Pt(1)−P(2)	87.68(10)	C(23)−C(24)−C(25)	115.7(10)
P(3)−Pt(2)−P(4)	87.22(10)	C(24)−C(25)−C(26)	118.8(8)
C(21)−C(22)−C(23)	120.6(8)	C(25)−C(26)−C(21)	119.6(8)
C(22)−C(23)−C(24)	118.6(8)	C(26)−C(21)−C(22)	117.2(10)

Proposed reaction mechanism



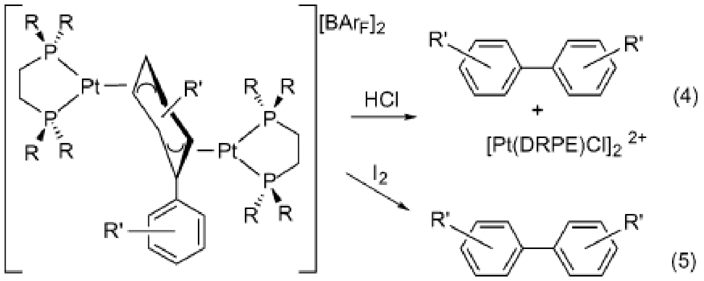
The feature of this mechanism is the coupling occurs without a change in the formal oxidation state of the metal.

cf)



C-C coupling reaction is proposed to occur via ii .

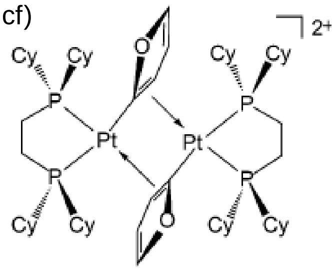
Reactions of bridging biaryl complexes



R = Cy, R' = H (**3a**)
R = Et, R' = H (**3b**)
R = Cy, R' = Me (**4a**)

C-C coupling in C_6D_6:
no deuterium incorporation in **3**

cf)



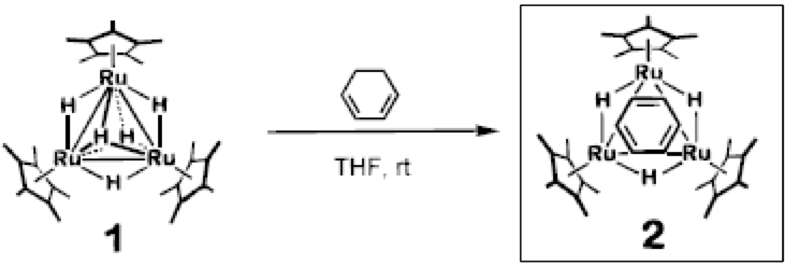
Hydrolysis similar to Birch reduction:
H^+ is reduced to H_2, while biphenyl^{2-} ligand is oxidized to free biphenyl.

4a + I_2: no *o*-bitolyl, mixture of *m,m'*-bitolyl, *m,p'*-bitolyl and *p,p'*-bitolyl
(due to steric effect?)
This result is against an electrophilic aromatic substitution of C-H bond activation step.

Trinuclear Ru complex

H Suzuki et al. *JACS.* **1997**, *119*, 625.
Angew. Chem. Int. Ed. **2006**, *45*, 7615.

Synthesis of trinuclear Ru arene complex



2 was synthsized through allylic C-H bond activation.

Xray analysis of **2**

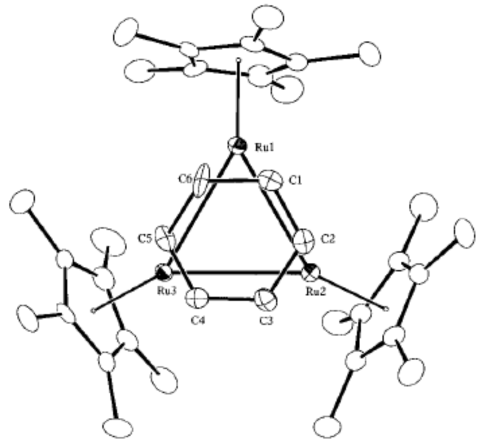
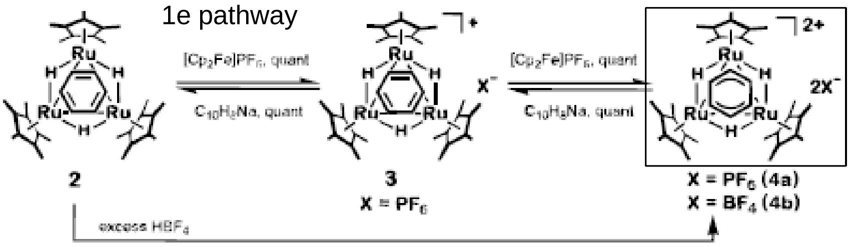


Figure 1. Molecular structure of $\{(C_5Me_5)Ru\}_3(\mu\text{-}H)_3(\mu_3\text{-}\eta^2{:}\eta^2{:}\eta^2\text{-}C_6H_6)$ (**2**) with thermal ellipsoids at the 30% probability level. Selected bond length (Å) and angles (deg) are as follows: Ru(1)−Ru(2) 3.0493(8), Ru(1)−Ru(3) 3.0468(9), Ru(2)−Ru(3) 3.0537(8), Ru(1)−C(6) 2.221(8), Ru(1)−C(1) 2.192(7), Ru(2)−C(2) 2.173(7), Ru(2)−C(3) 2.240(7), Ru(3)−C(4) 2.176(7), Ru(3)−C(5) 2.180(7), C(1)−C(2) 1.436(10), C(2)−C(3) 1.45(1), C(3)−C(4) 1.43(1), C(4)−C(5) 1.40(1), C(5)−C(6) 1.42(1), C(6)−C(1) 1.43(1); Ru(2)−Ru(1)−Ru(3) 60.10(3), Ru(1)−Ru(2)−Ru(3) 59.91(2), Ru(1)−Ru(3)−Ru(2), 59.98(3), C(6)−C(1)−C(2) 118.7(6), C(1)−C(2)−C(3) 118.4(6), C(2)−C(3)−C(4) 121.4(6), C(3)−C(4)−C(5) 119.7(6), C(4)−C(5)−C(6) 119.7(7), C(5)−C(6)−C(1) 121.9(7).

Average coordinated and uncoordinated C-C distances of benzene are almost equal.

Oxidation of complex **2**



1e pathway

2e pathway

Protonation of **2** and successive reductive elimination of H_2

Xray analysis of **4**

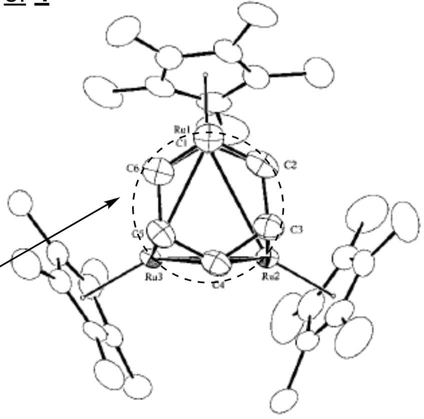
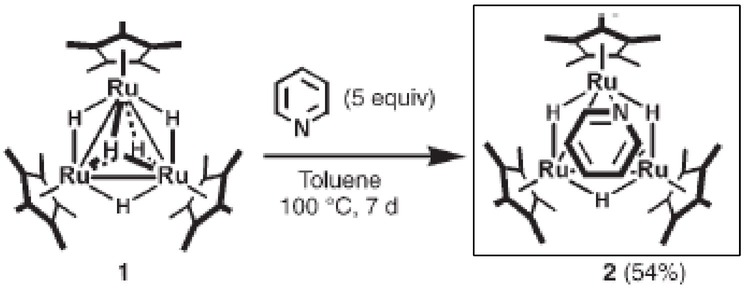
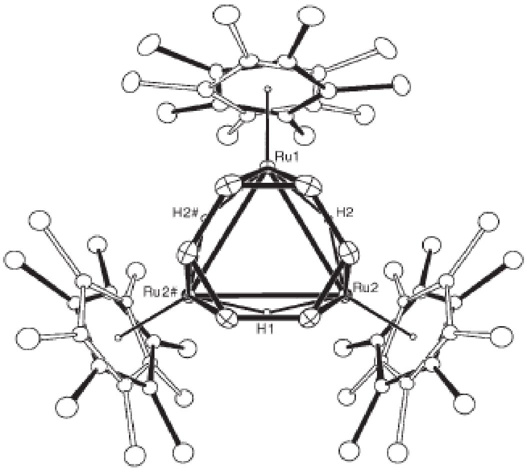


Figure 2. Molecular structure of $[\{(C_5Me_5)Ru\}_3(\mu\text{-}H)_3(\mu_3\text{-}\eta^3{:}\eta^3\text{-}C_6H_6)](BPh_4)_2$ (**4c**) with thermal ellipsoids at the 30% probability level. Selected bond length (Å) and angles (deg) are as follows: Ru(1)−Ru(2) 2.972(1), Ru(1)−Ru(3) 2.972(1), Ru(2)−Ru(3) 2.731(1), Ru(1)−C(6) 2.376(8), Ru(1)−C(1) 2.165(8), Ru(1)−C(2) 2.34(1), Ru(2)−C(3) 2.151(8), Ru(2)−C(4) 2.329(7) Ru(3)−C(4) 2.43(1), Ru(3)−C(5) 2.126(8), C(1)−C(2) 1.42(1), C(2)−C(3) 1.47(1), C(3)−C(4) 1.50(1), C(4)−C(5) 1.48(1), C(5)−C(6) 1.46(1), C(6)−C(1) 1.44(1); Ru(2)−Ru(1)−Ru(3) 54.35(2), Ru(1)−Ru(2)−Ru(3) 62.18(2), Ru(1)−Ru(3)−Ru(2), 63.48(2), C(6)−C(1)−C(2) 117.7(7), C(1)−C(2)−C(3) 122.2(7), C(2)−C(3)−C(4) 117.7(7), C(3)−C(4)−C(5) 117.5(7), C(4)−C(5)−C(6) 120.0(6), C(5)−C(6)−C(1) 120.0(8). The BPh_4 anions are omitted for clarity.

η^3-η^3 coordination
An allyl moiety is coordinated to one of three Ru,
another allyl moiety bridges two Ru.

Trinuclear Ru pyridine complex

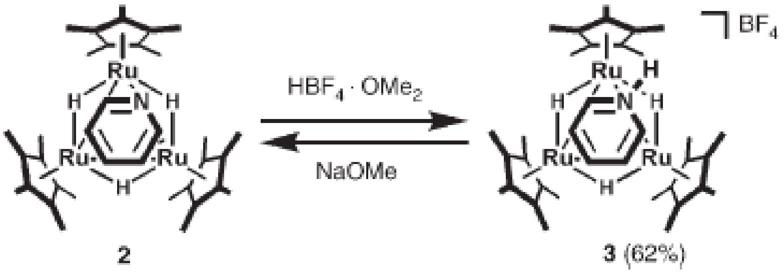




^1H NMR suggests that pyridine ligand does not rotate on the NMR time scale.

Nitrogen of pyridine ligand does not coordinate.

Protonation



DBF_4: only N-D
direct attack of nitrogen atom (not protonation of metal center)

2.4 Catalytic dearomatization reactions

Catalytic oxidation of arenes

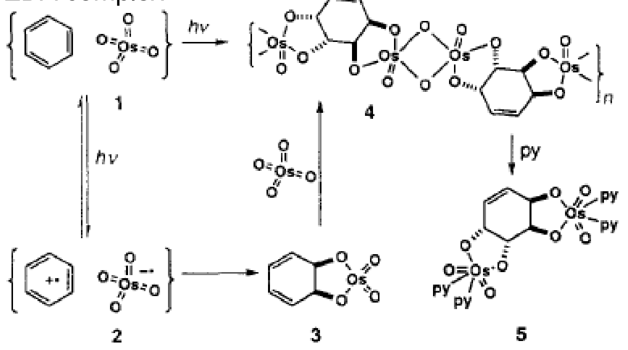
Catalytic photoinduced charge-transfer osmylation

Mortherwell et al. *Angew. Chem. Int. Ed.* **1995**, *34*, 2031.
Chem. Commun. **1997**, 1283.

ozone, RuO_4: concomitant cleavage of the carbocyclic ring

Aromatic electron donor-acceptor (EDA) complex

EDA complex

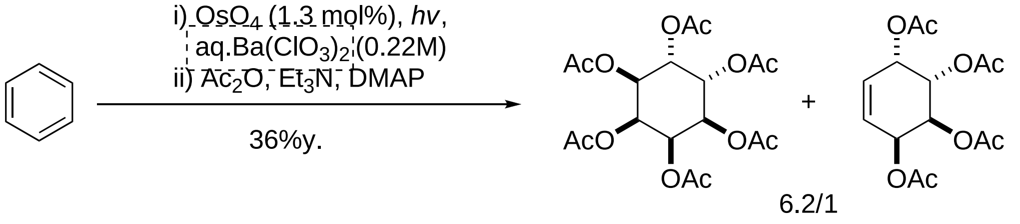


J K. Kochi et al. *JACS.* **1998**, *110*, 8207.

Toward catalytic reaction

Selection of suitable solvent system and oxygen transfer reagent is important.

NMP, pyridine, acetone, t-butanol: inhibitors of EDA complex



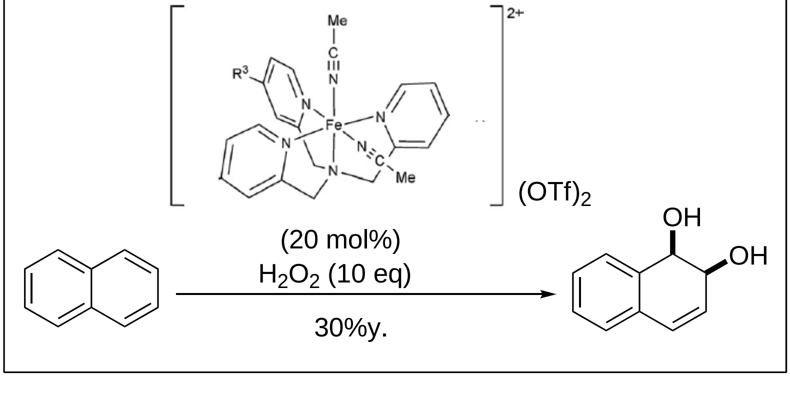
i) OsO_4 (1.3 mol%), *hν*, aq.$Ba(ClO_3)_2$ (0.22M)
ii) Ac_2O, Et_3N, DMAP

36%y.

6.2/1

Bio-inspired arene dihydroxylation by a non-haem iron catalyst

L Que, Jr et al. *Chem. Commun.* **2009**, 50.

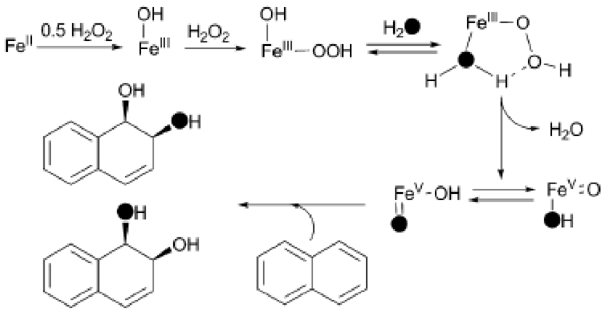


$(OTf)_2$

(20 mol%)
H_2O_2 (10 eq)

30%y.

Proposed reaction mechanism

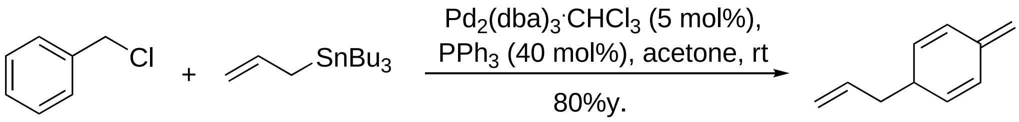


Scheme 2 Proposed mechanism for the *cis*-dihydroxylation of naphthalene catalysed by **1**.

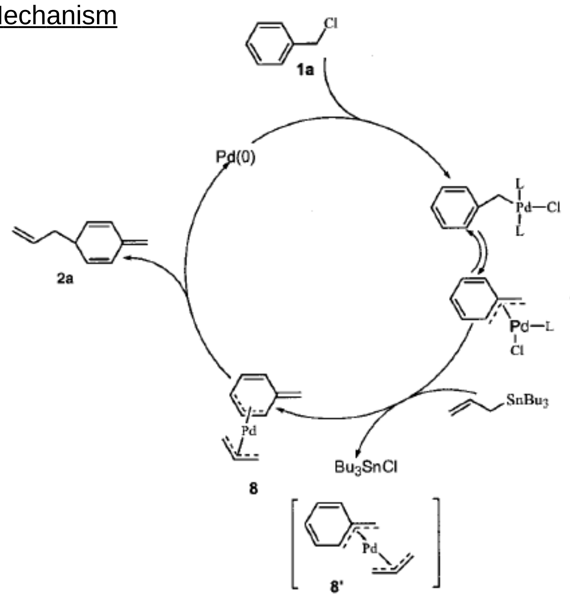
Fe catalyst is the mimic of Riesk dioxygenage (naphthalene 1,2-dioxygenase).

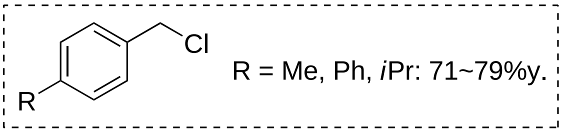
Catalytic dearomatization via η^3-benzylpalladium intermediate

M Bao, Y Yamamoto et al. *JACS.* **2001**, *123*, 759.



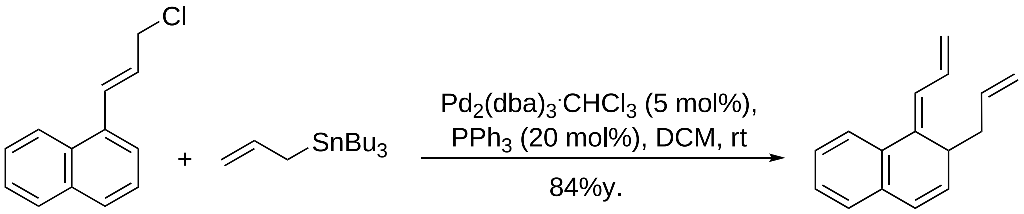
Mechanism



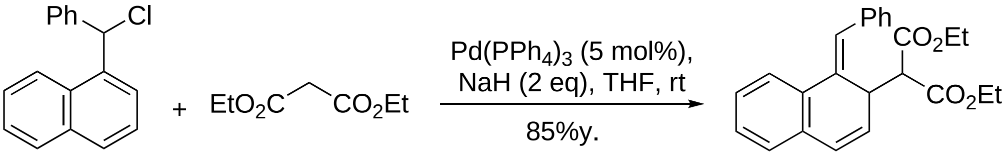


The reason of regioselectivity was unclear...
(**8** is more stable or reactive than **8'** ?)

Related works



M Bao, Y Yamamoto et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 4366.



M Bao et al. *OL.* **2011**, *13*, 5402.

Summary of chaptor 2

	η^6-arene complex	**η^2-arene complex**	**Multinuclear metal complex**	**Catalytic dearomatization reactions**
Advantages	Selective coordination to arene Sequential addition Asymmetric version	Sequential addition Asymmetric version Heteroaromatic ring	Under development	Catalytic
Disadvantages	Stoichiometric	Stoichiometric Coordination to several FG		Narrow substrate scope