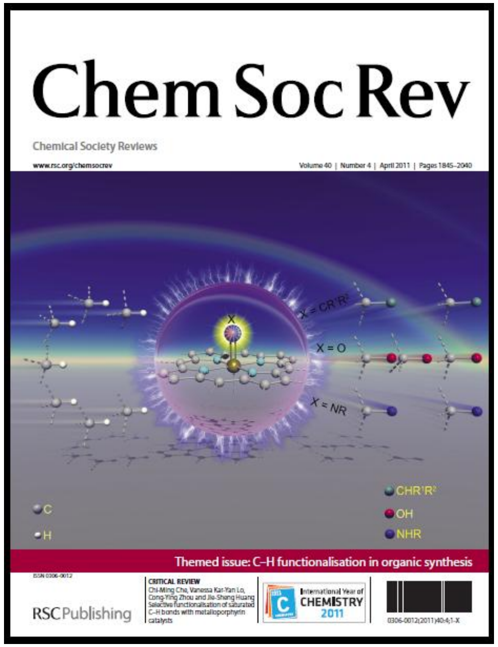
C–H Functionalization in organic synthesis

Zhi Ren

Topics in this series of reviews

- History & logic of C-H functionalization
- Recent C-H in total synthesis
- Stereoselectivity
- Enzymatic C–H functionalization
- Metalloporphyrin complex in C–H
- Oxidation and mechanistic study



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Themed issue: C–H functionalisation in organic synthesis

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CRITICAL REVIEW
Chi-Ming Che, Vanessa Kar-Yan Lo, Cong-Ying Zhou and Jie-Sheng Huang
Selective functionalisation of saturated C–H bonds with metalloporphyrin catalysts

International Year of CHEMISTRY 2011

0306-0012(2011)40:4;1-X

Topics in this series of reviews

The papers I will focus on:

- alpha-C–H functionalization of ethers and alcohols (page 1937–1949)
- Diastereocontrol in C-H of Methylene group (page 2022-2038)

Classification

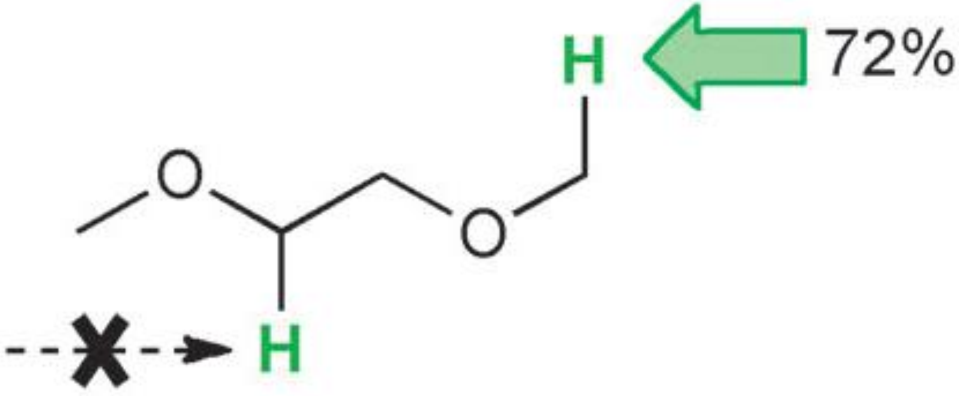
- sp2 C–H functionalization
- Activated sp3 C–H functionalization (allyl, benzyl, propargyl and carbonyl; alpha heteroatomic Hydrogen)
- Deactivated sp3 C–H functionalization (beta heteroatomic Hydrogen). Importantly but rarely.

Alpha H Vs. Beta H

- The heteroatom can stabilized the positive charge (radical) at alpha position.
- The inductive effect of oxygen destablized the positive charge (radical) at beta position.

- Therefore to achieve the C-H activation at beta position, the directing group is usually required.

Alpha H Vs. Beta H

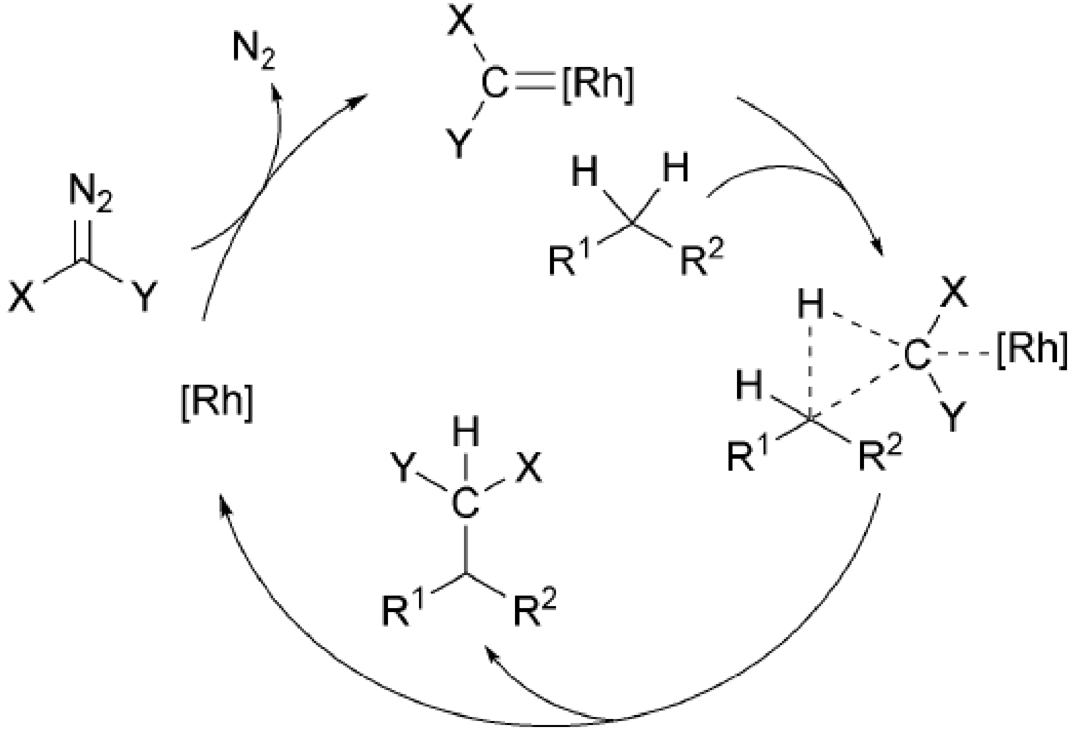


14

C–H activation reactions at methylene groups

- Insertion of transition metal stabilized carbenes and nitrenes into diastereotopic CH2 groups
- Transition metal catalysed diastereoselective C–H activation reactions

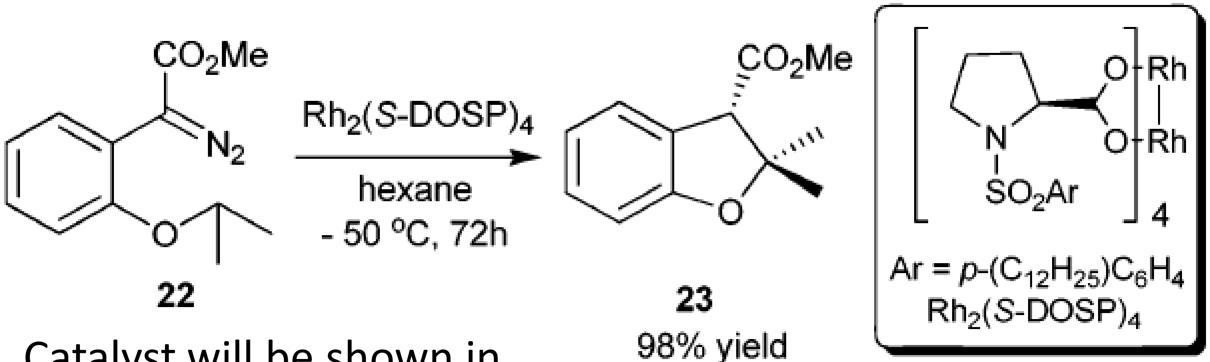
Metal carbenoid insertions



Scheme 1

Asymmetric synthetic method

- Davies and coworkers (page 1857-1869, explain the stereochemistry)



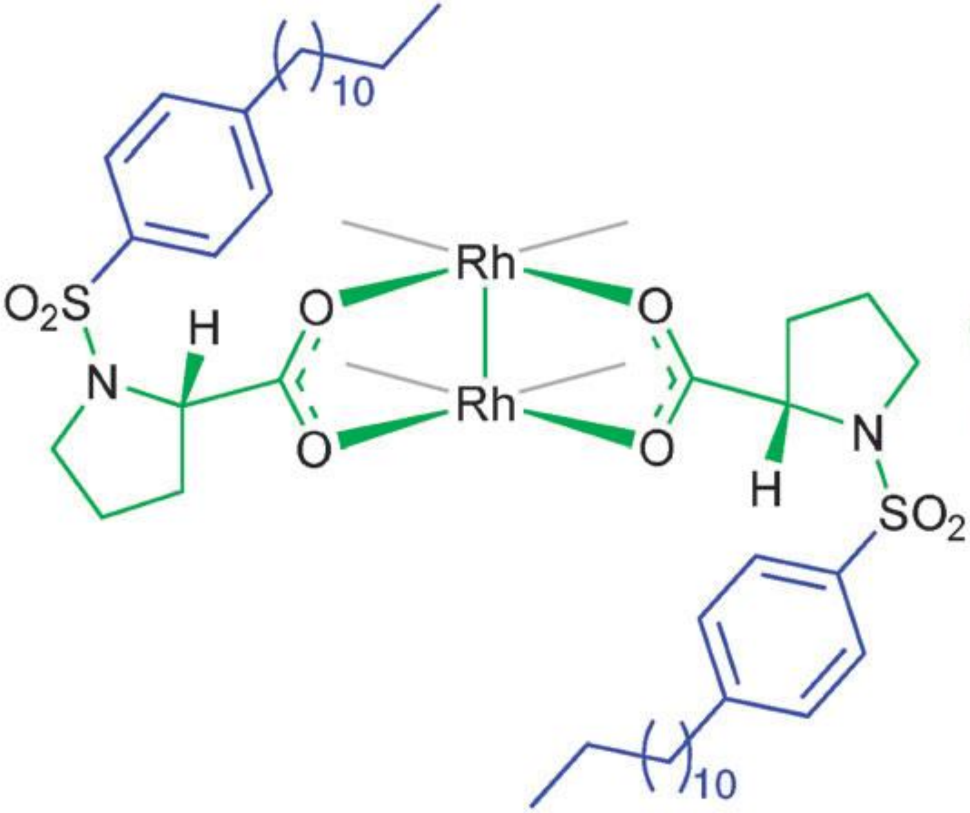
22

23

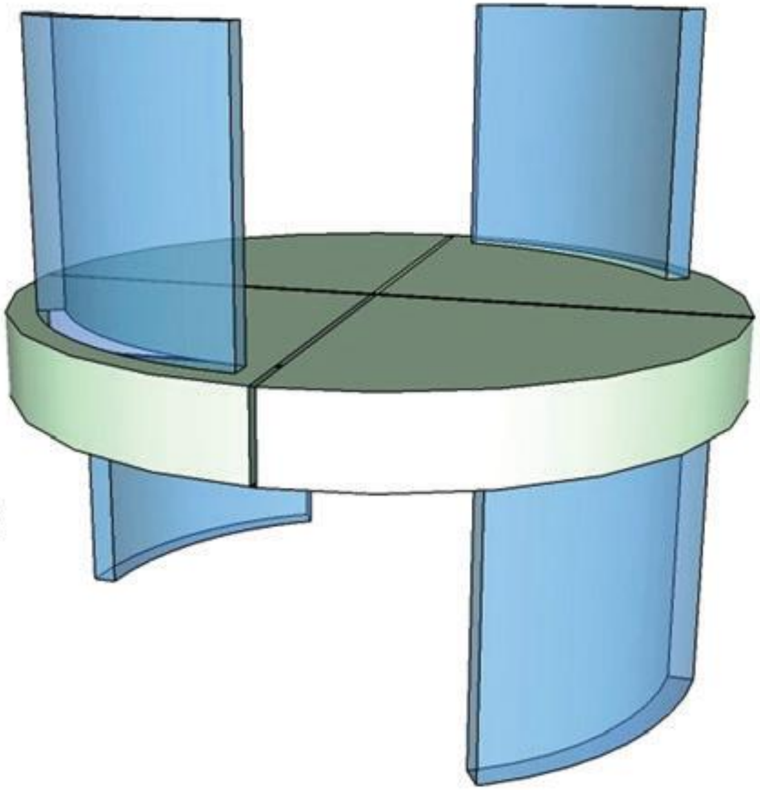
98% yield
94% ee

Catalyst will be shown in the next slide

Rh2(DOSP)4 Catalyst

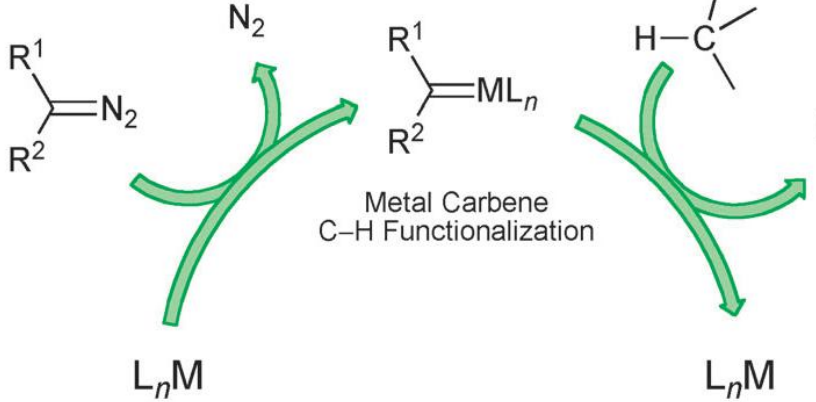


Rh_2(*S*-DOSP)$_4$

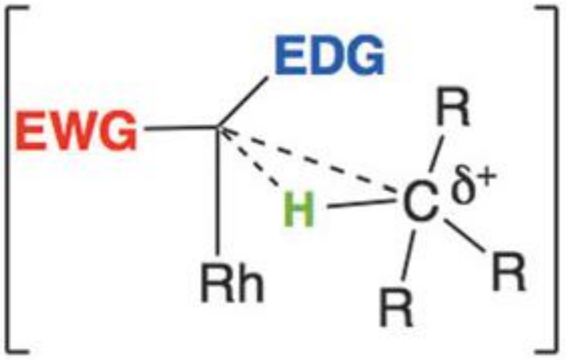


***D_2*-symmetric**

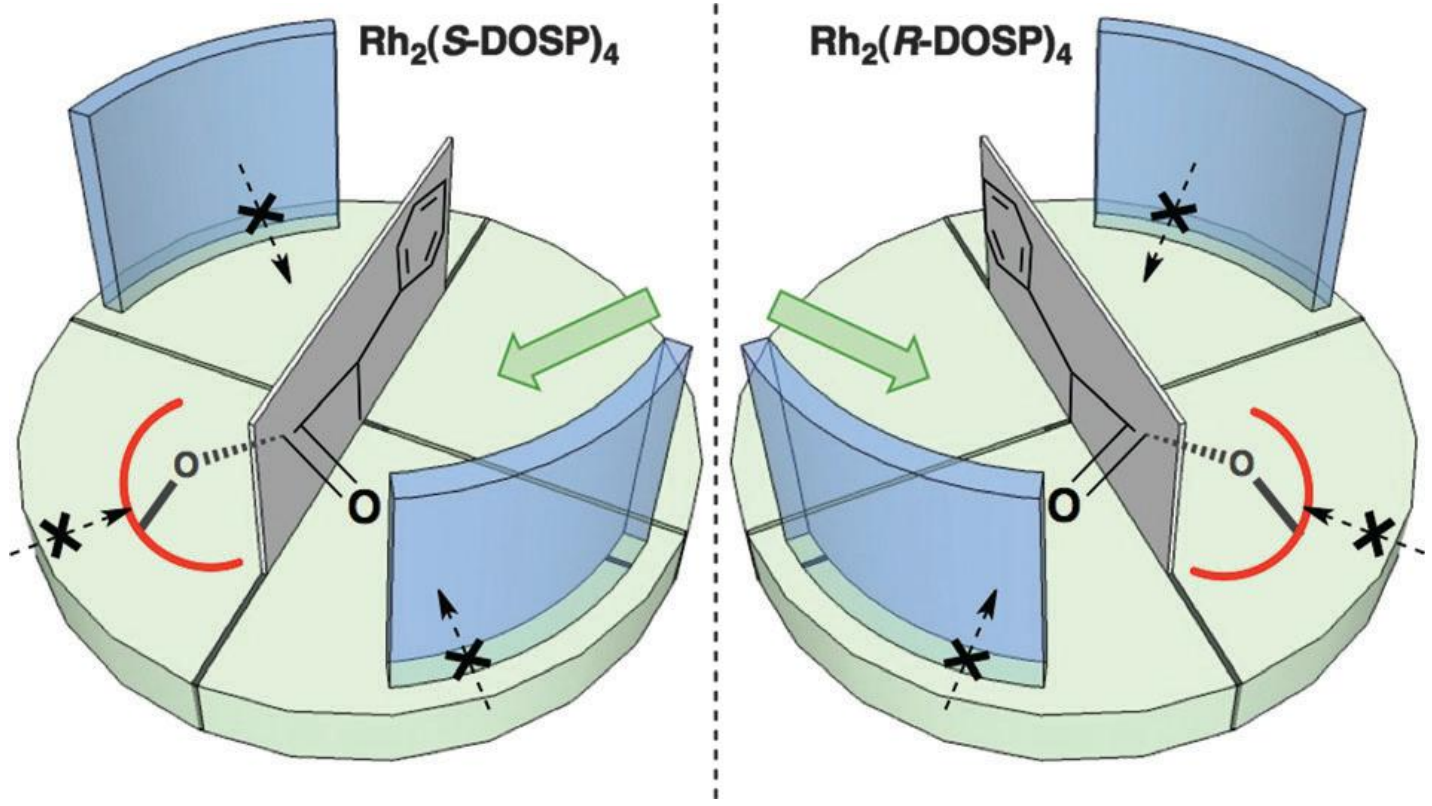
“Typically catalyst loadings of 1 mol% are employed. A recent study has shown, however, that the catalyst is efficient at loadings as low as 0.0001 mol%.”



R1
R2
N2
N2
R1
R2
MLn
H–C
H
R1
R2
C
Metal Carbene
C–H Functionalization
LnM
LnM



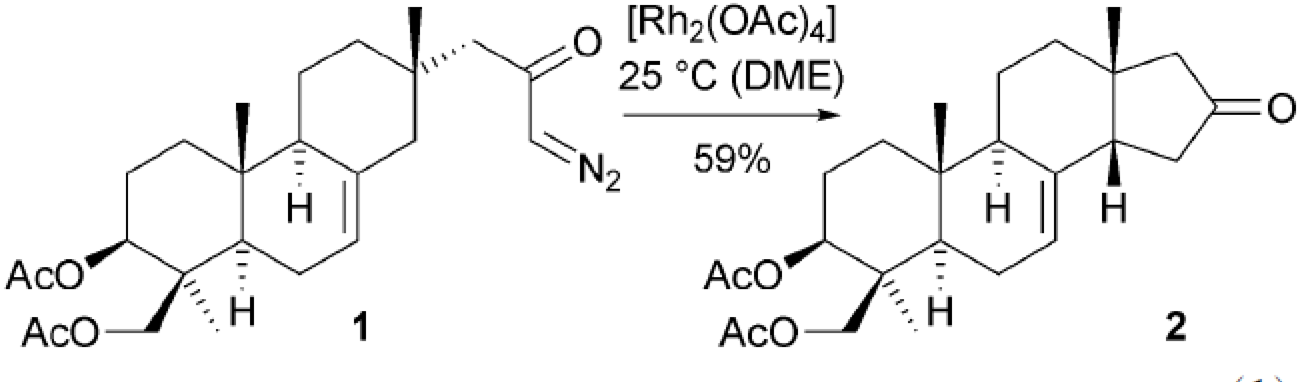
EDG
EWG
R
H
C δ+
R
Rh
R



Rh2(S-DOSP)4
Rh2(R-DOSP)4
O
O
O
O

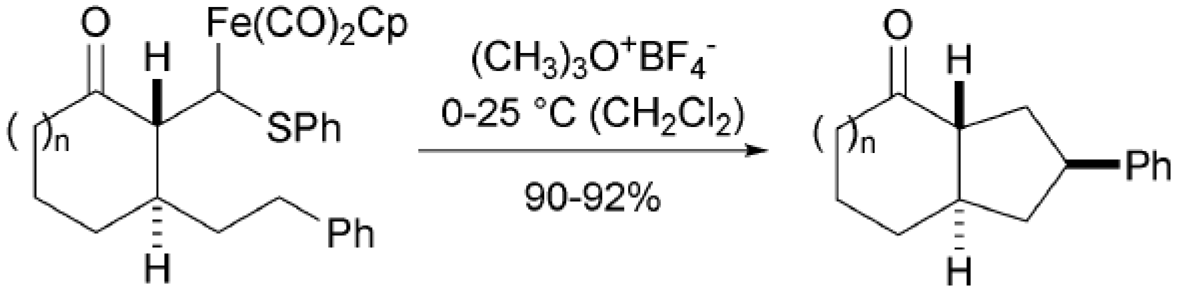
Reactions

- The first example of a diastereoselective intramolecular carbene insertion into a methylene group was observed as early as 1982 by Wenkert and co-workers.



(1)

Iron Carbenoid

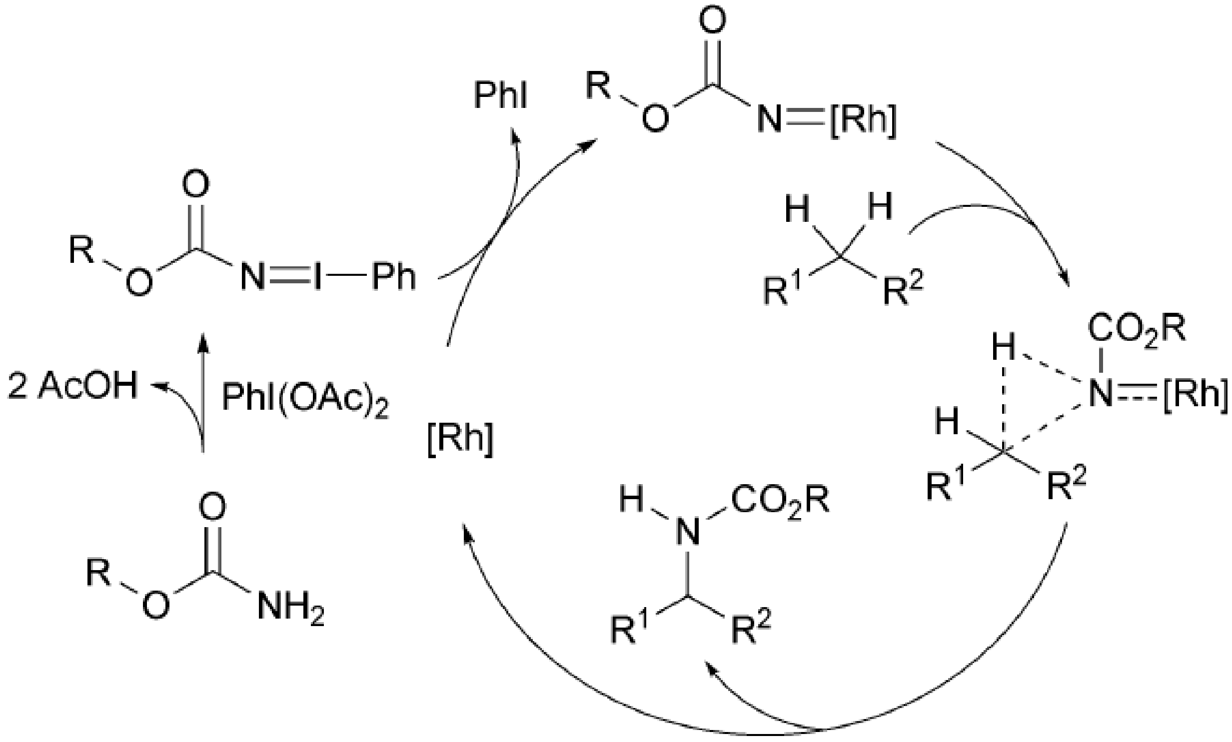


n = 1-3 *rac*-**38**

rac-**39**

(11)

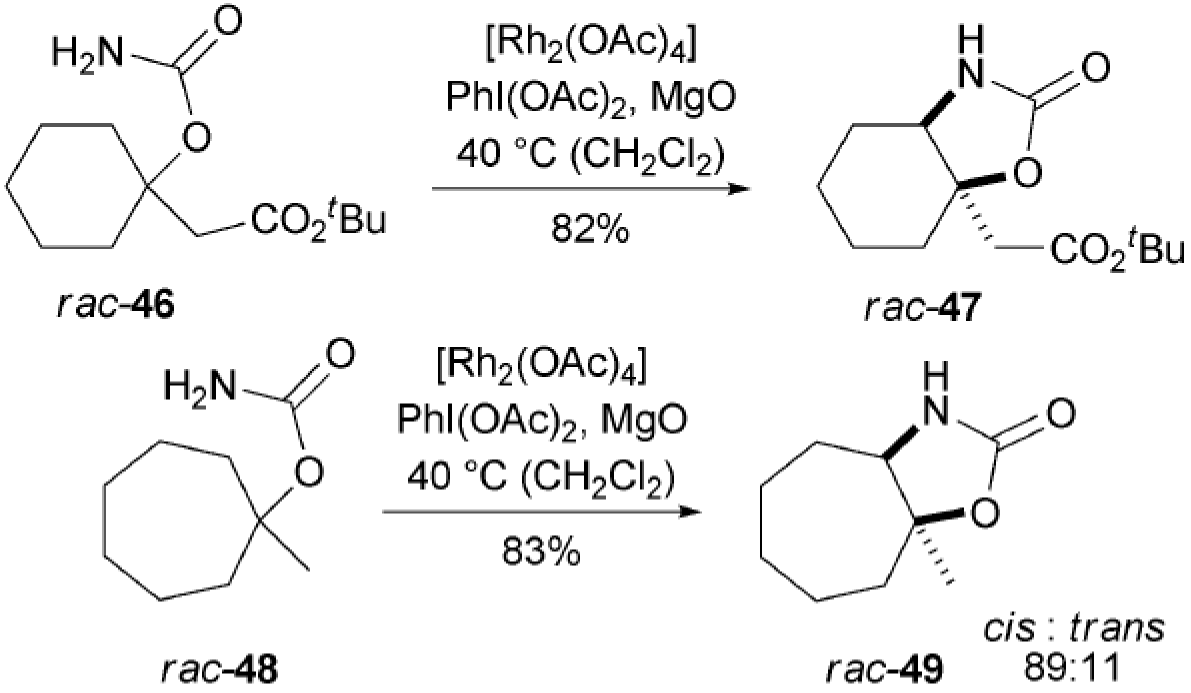
Metal nitrenoid insertions



Scheme 6

There is a question on next slide!

Reactions of Carbamates

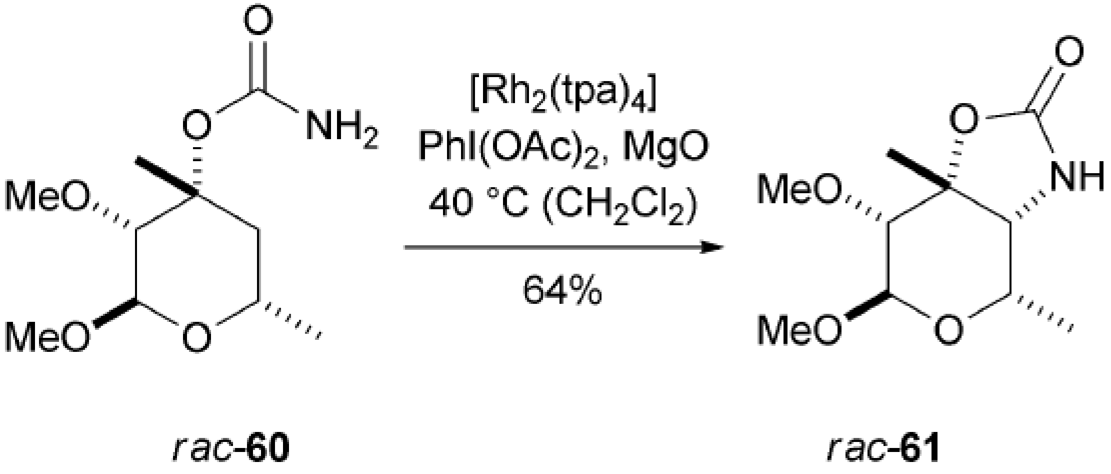


Scheme 7

What is the purpose of the MgO?

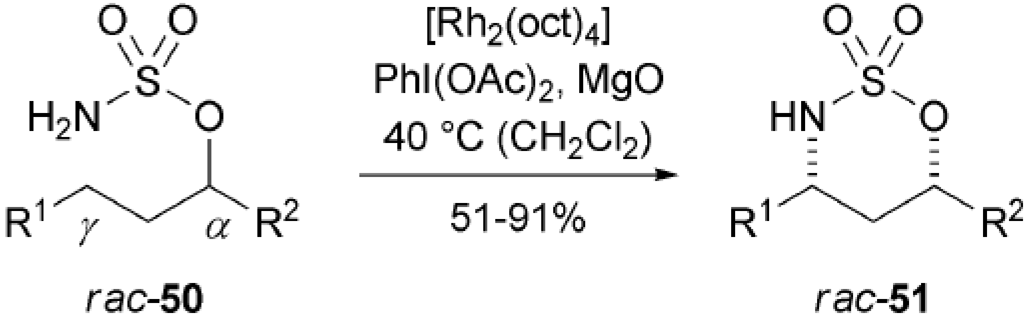
Solvent

- Changing the solvent to benzene and heated up to 80 degree led to complete conversion.

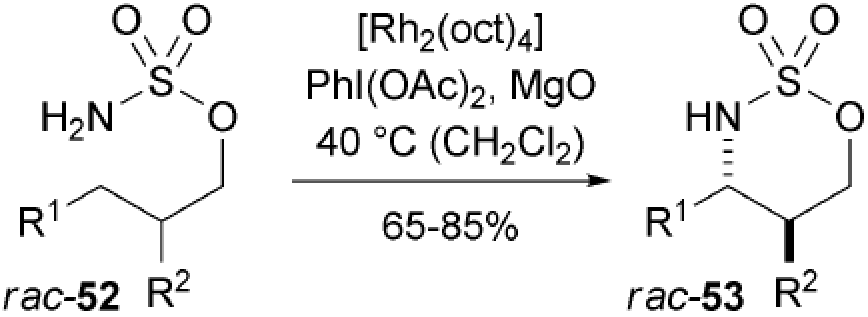


Reactions of Sulfamate esters

Reactions of α,γ-substituted sulfamate esters

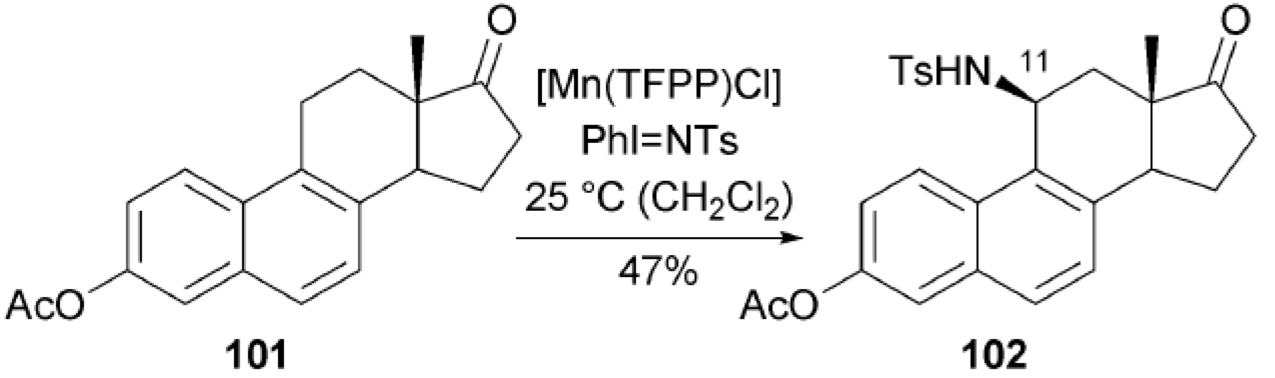


Reactions of β,γ-substituted sulfamate esters



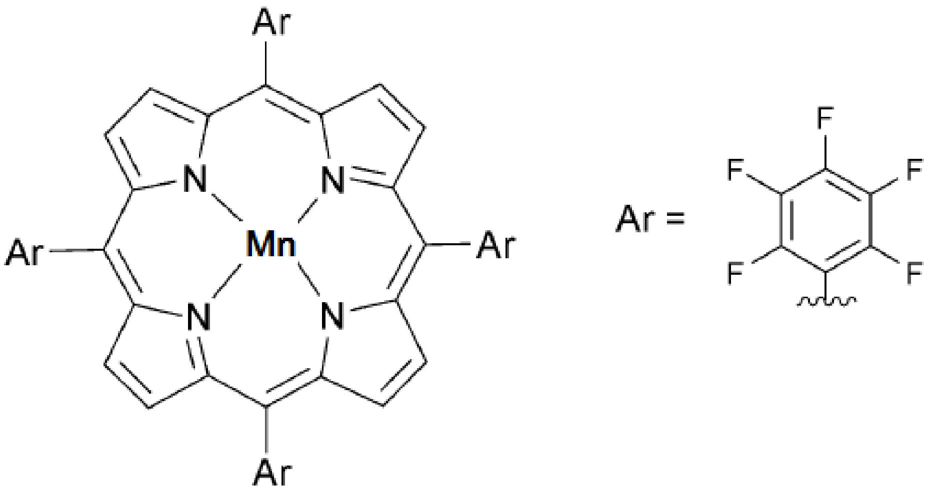
a rough reaction rate scale was drawn: 3° > ethereal ≈ benzylic > 2° ≫ 1°.

Intermolecular nitrene



101 **102**

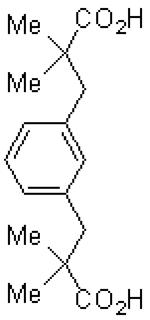
(16)

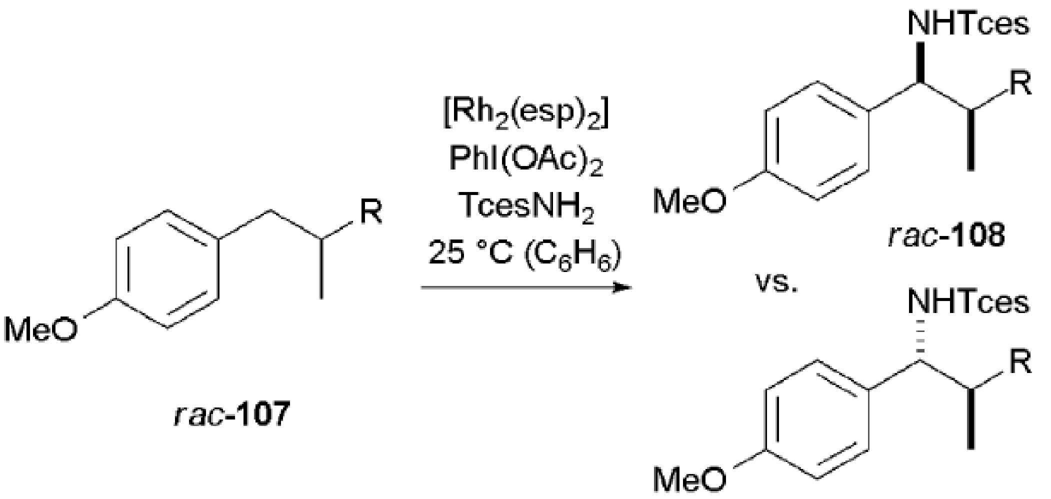


Intermolecular nitrene

Tces=1,1,1-trichloroethoxysulfamate

bis[rhodium(α,α,α′,α′- tetramethyl-1,3-benzenedipropionic acid)]





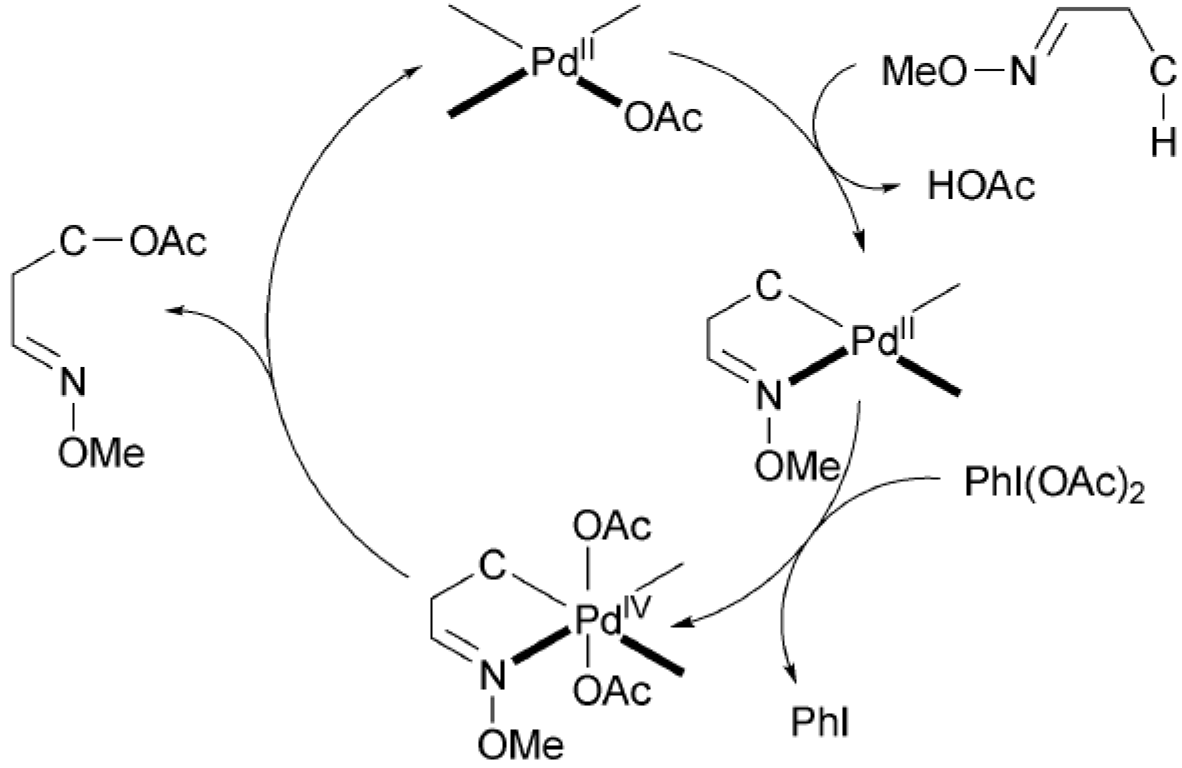
rac-**107**

rac-**108**

rac-**109**

Substrate	R	*rac*-**108**/*rac*-**109**	Yield (%)
rac-**107a**	COOMe	82 : 18	81
rac-**107b**	$PO(OEt)_2$	> 95 : 5	65
rac-**107c**	SO_2Ph	> 95 : 5	56
rac-**107d**	NO_2	91 : 9	63
rac-**107e**	CN	80 : 20	86
rac-**107f**	OAc	86 : 14	40

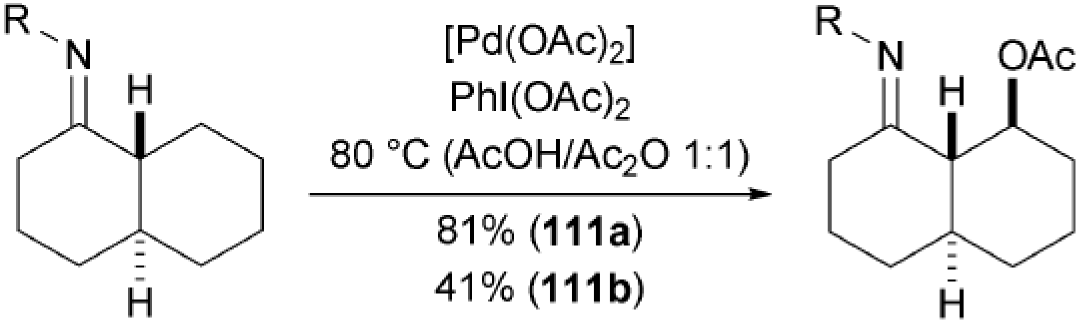
Directed metal C-H insertions



Scheme 18

Sp3-CH2-activation

- Sanford



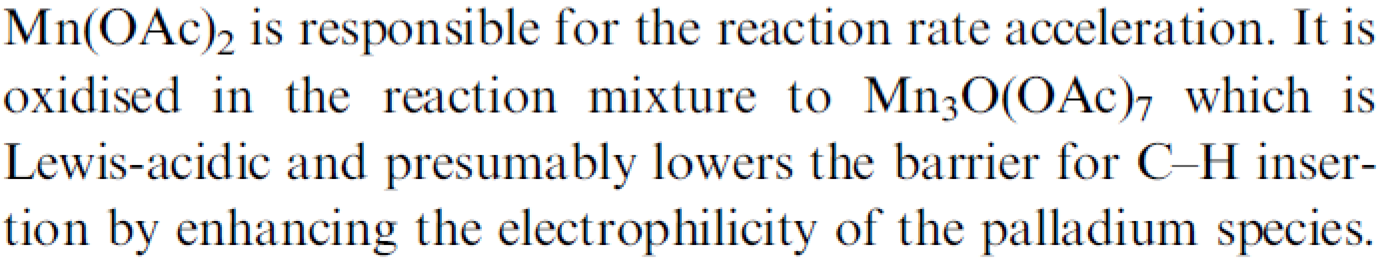
rac-**110a** R = OMe
rac-**110b** R = OH

rac-**111a** R = OMe
rac-**111b** R = OAc

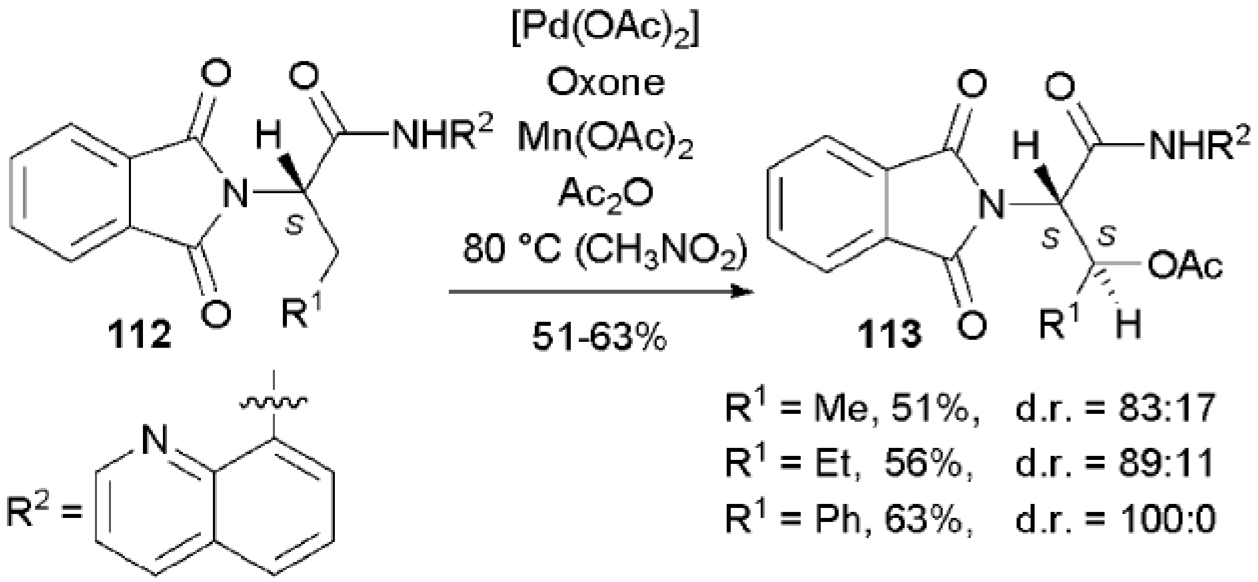
(19)

Sp3-CH2-activation

- Corey



$Mn(OAc)_2$ is responsible for the reaction rate acceleration. It is oxidised in the reaction mixture to $Mn_3O(OAc)_7$ which is Lewis-acidic and presumably lowers the barrier for C–H insertion by enhancing the electrophilicity of the palladium species.

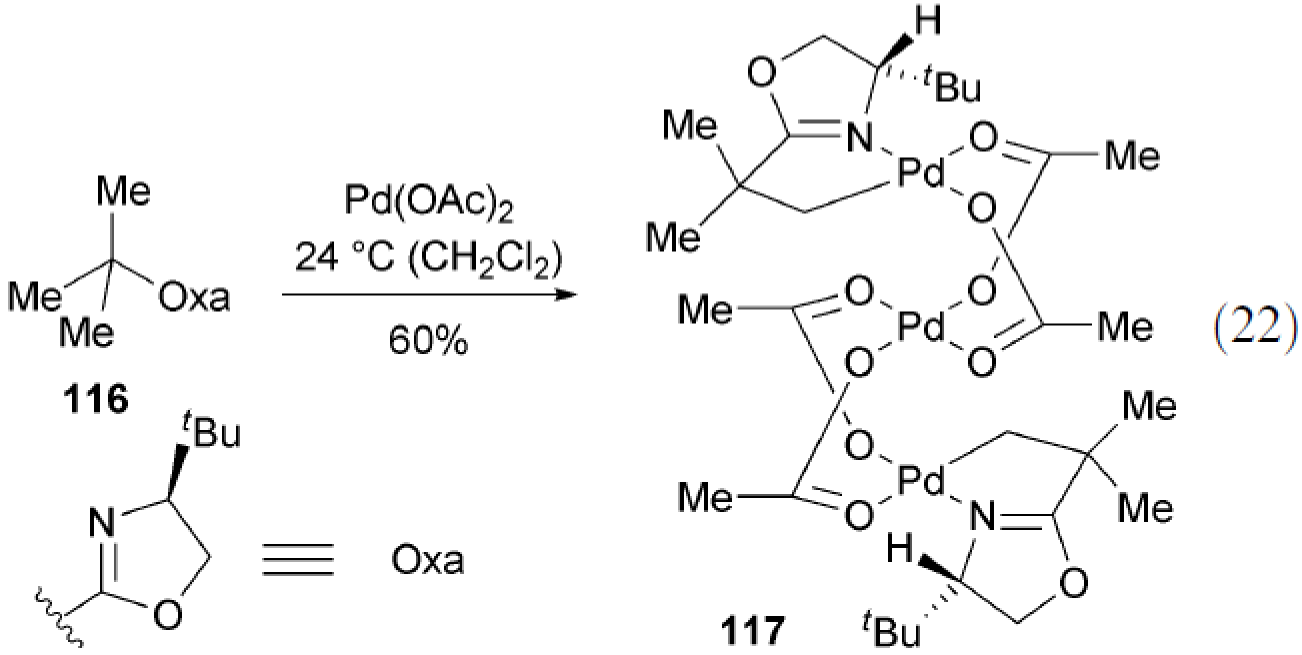


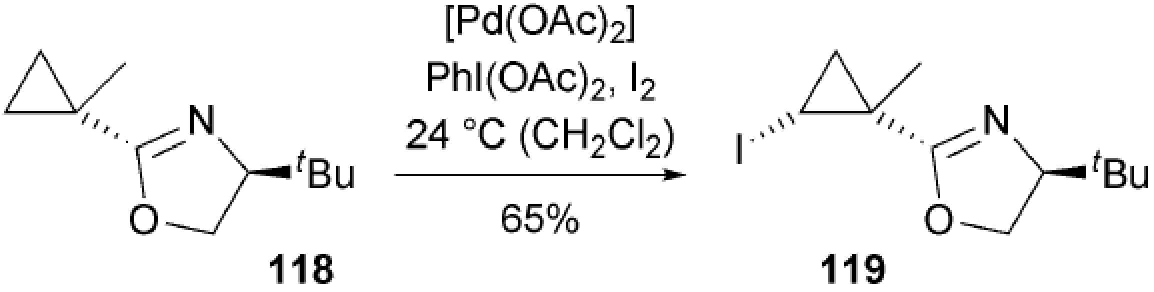
R^1 = Me, 51%, d.r. = 83:17
R^1 = Et, 56%, d.r. = 89:11
R^1 = Ph, 63%, d.r. = 100:0

potassium peroxymonosulfate, $KHSO_5$

Sp3-CH2-activation

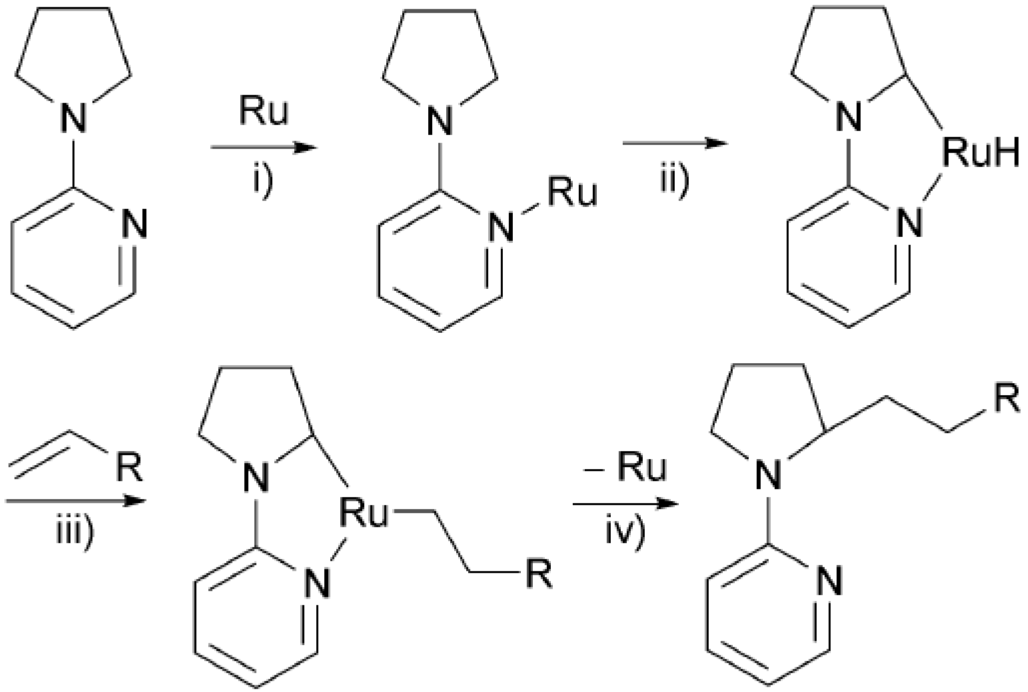
- Yu





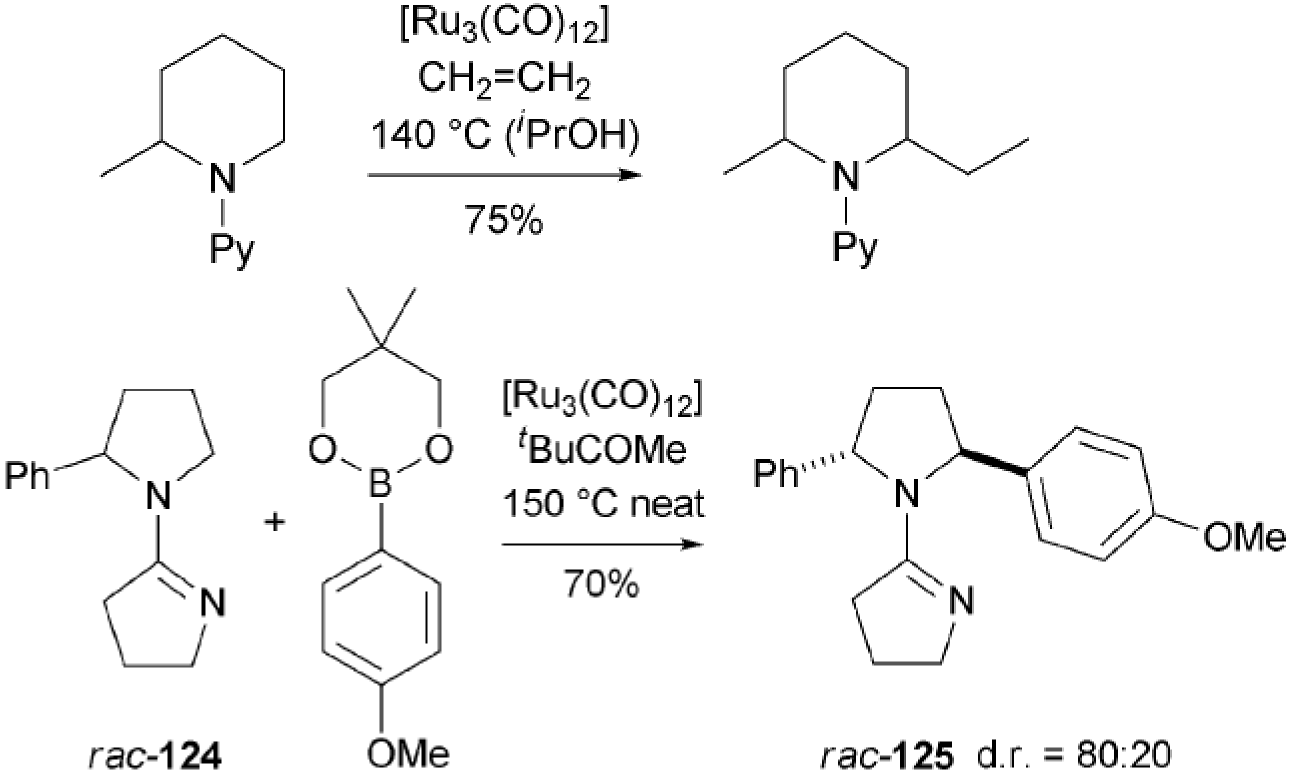
Sp3-CH2-activation

- Murai



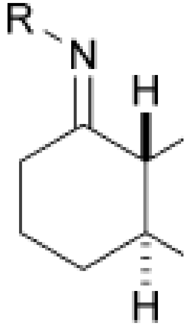
Sp3-CH2-activation

- Murai

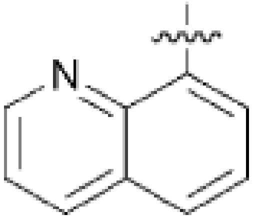


Summary

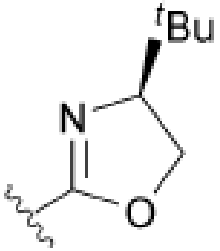
- Directing group



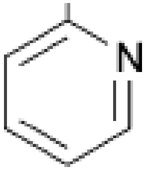
Sanford



Corey



Yu

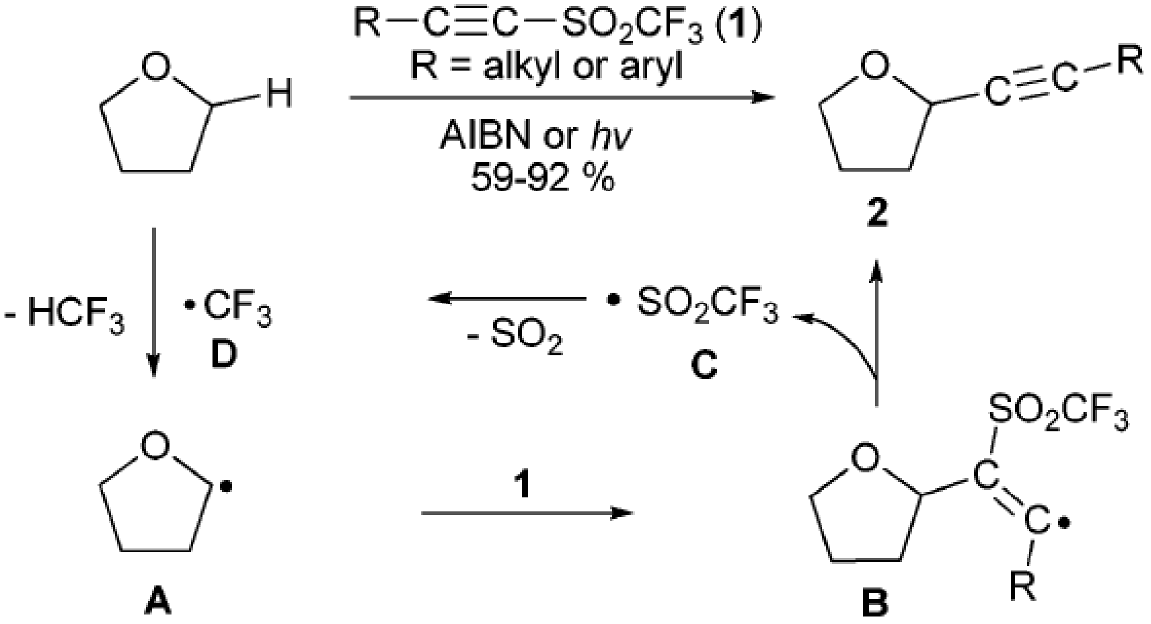


Murai

alpha-C–H functionalization of ethers and alcohols

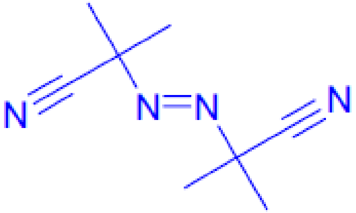
- Radical-mediated C-H functionalization
- Metal mediated carbenoid insertion
- cross-dehydrogenative coupling (CDC)
- Intramolecular annulation
- Transfer hydrogenative coupling (THC)
- Transition metal-catalyzed coupling

Radical-mediated addition and elimination



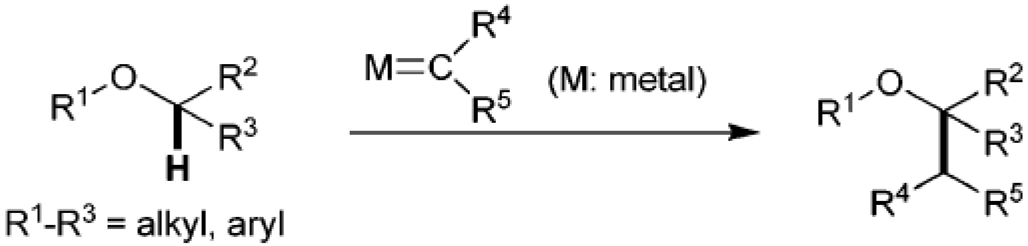
AIBN

2,2'-azo *bis*isobutyronitrile

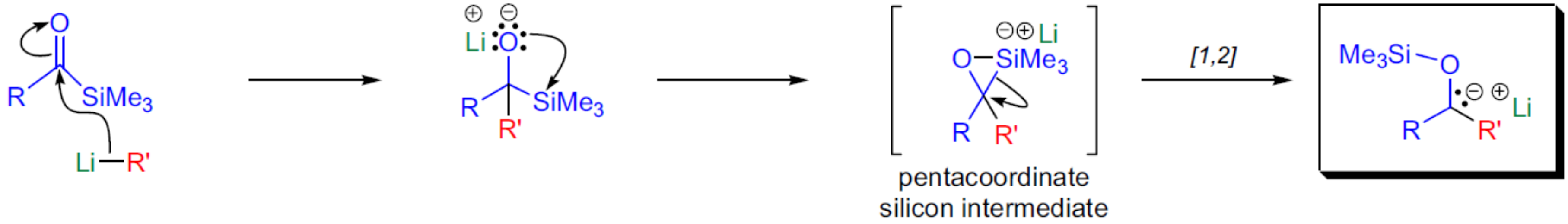


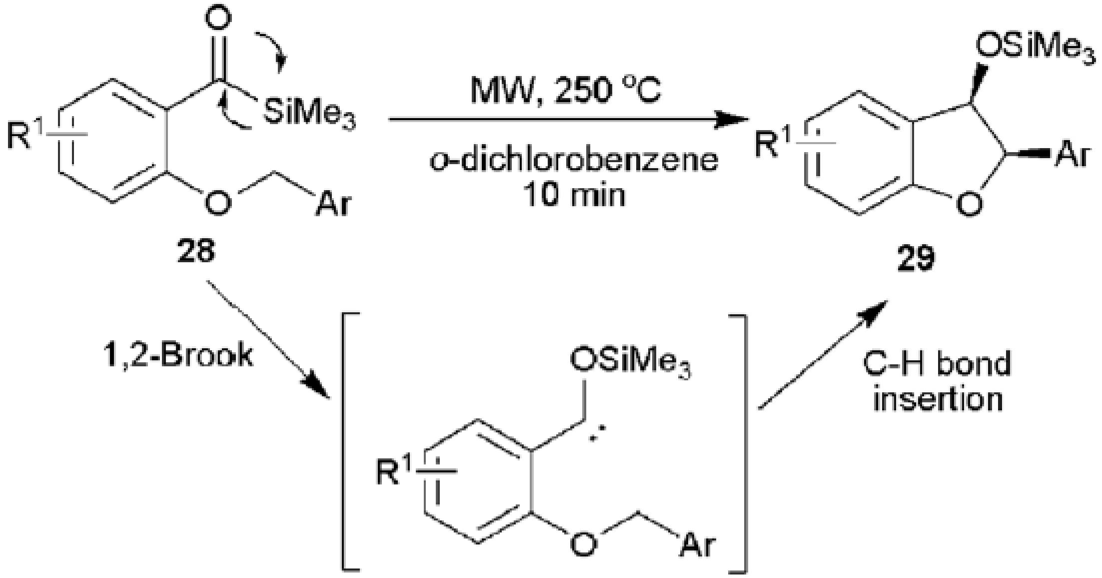
Metal mediated carbenoid insertion

- Stereoselective method

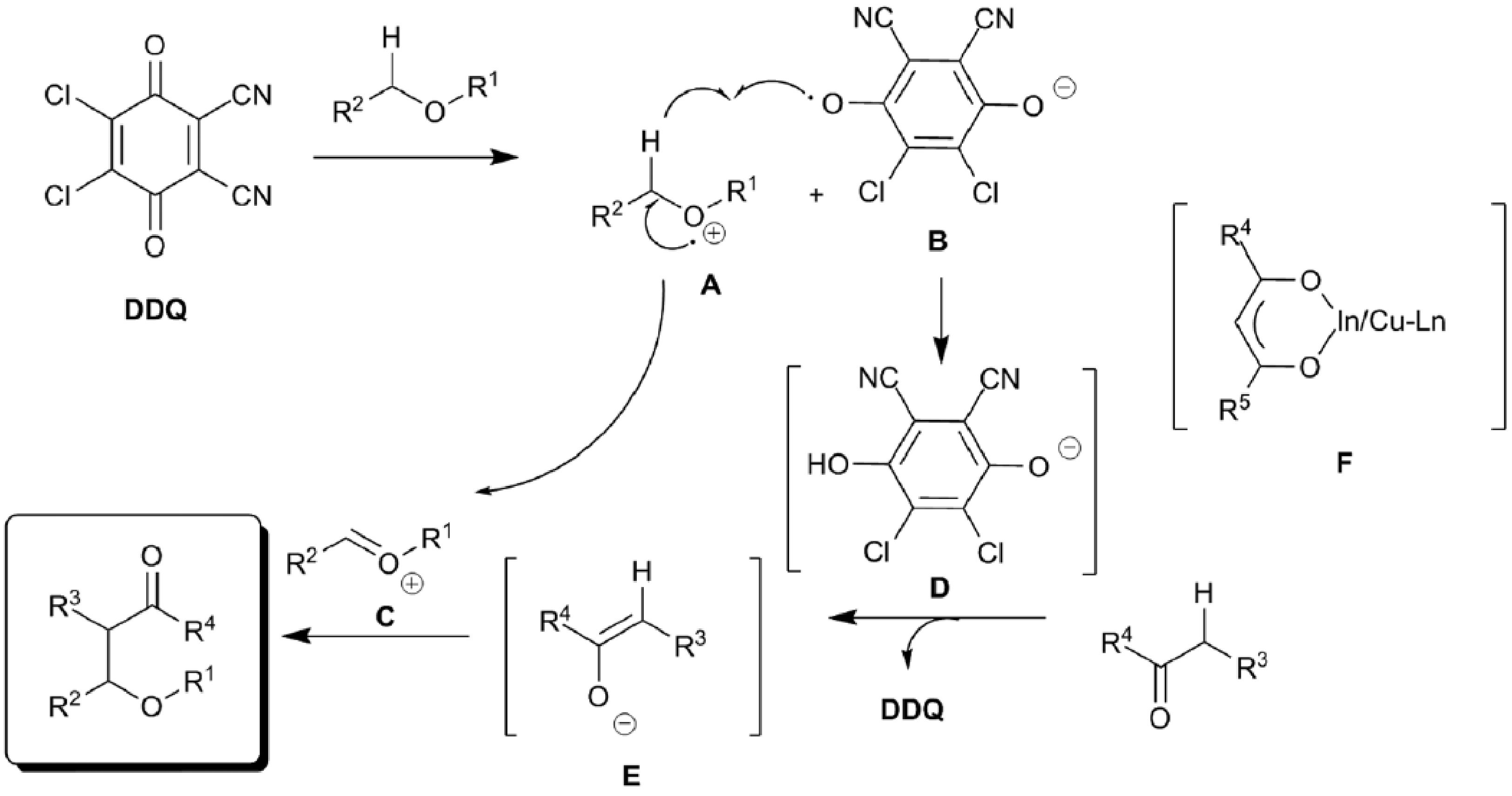


Brook rearrangement



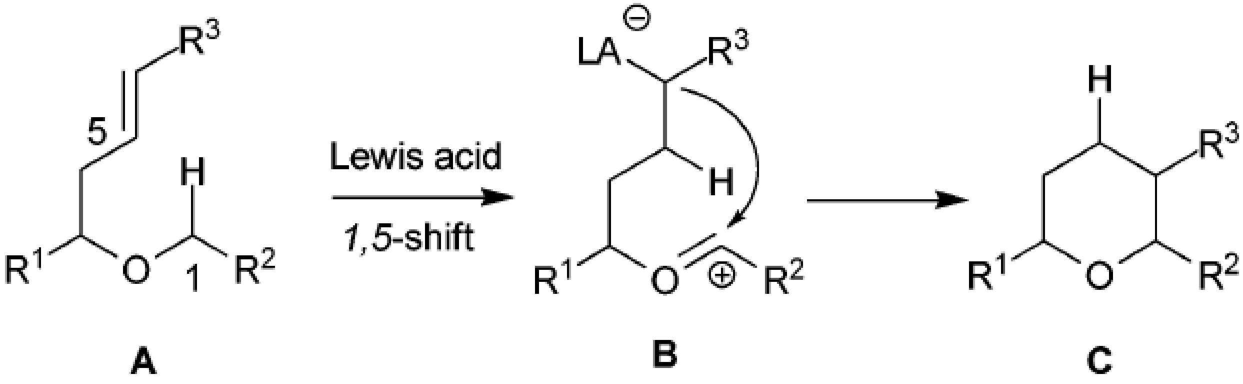


Oxidative CDC reaction of ether with carbonyl compounds



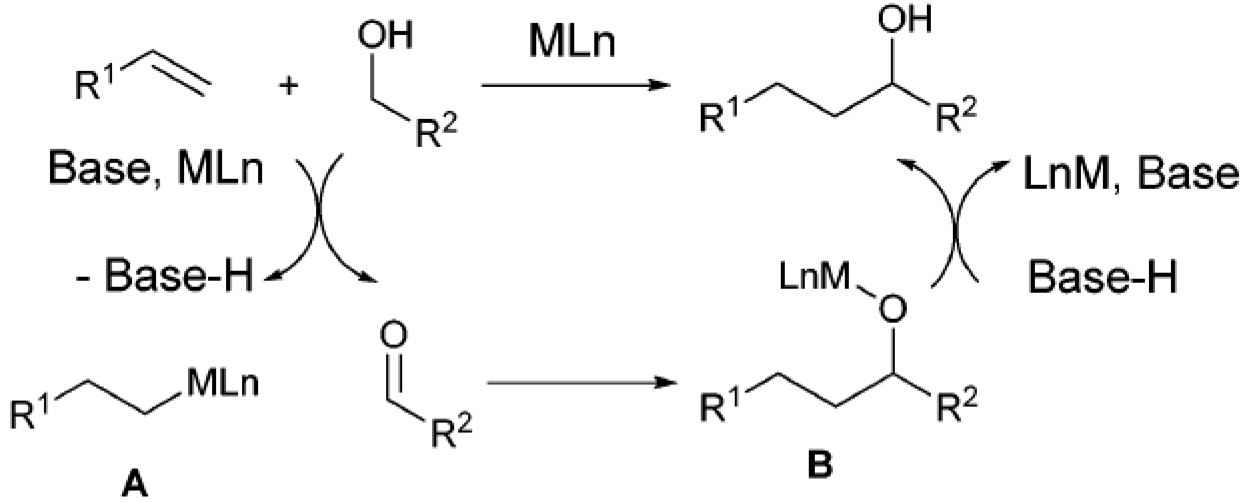
Scheme 16 Single-electron transfer mechanism for oxidative CDC reaction of ether with ketone.

Intramolecular annulation of ether via 1,5-hydride migration



Scheme 18 Intramolecular annulation process of ether with C=C moiety *via 1,5*-H migration.

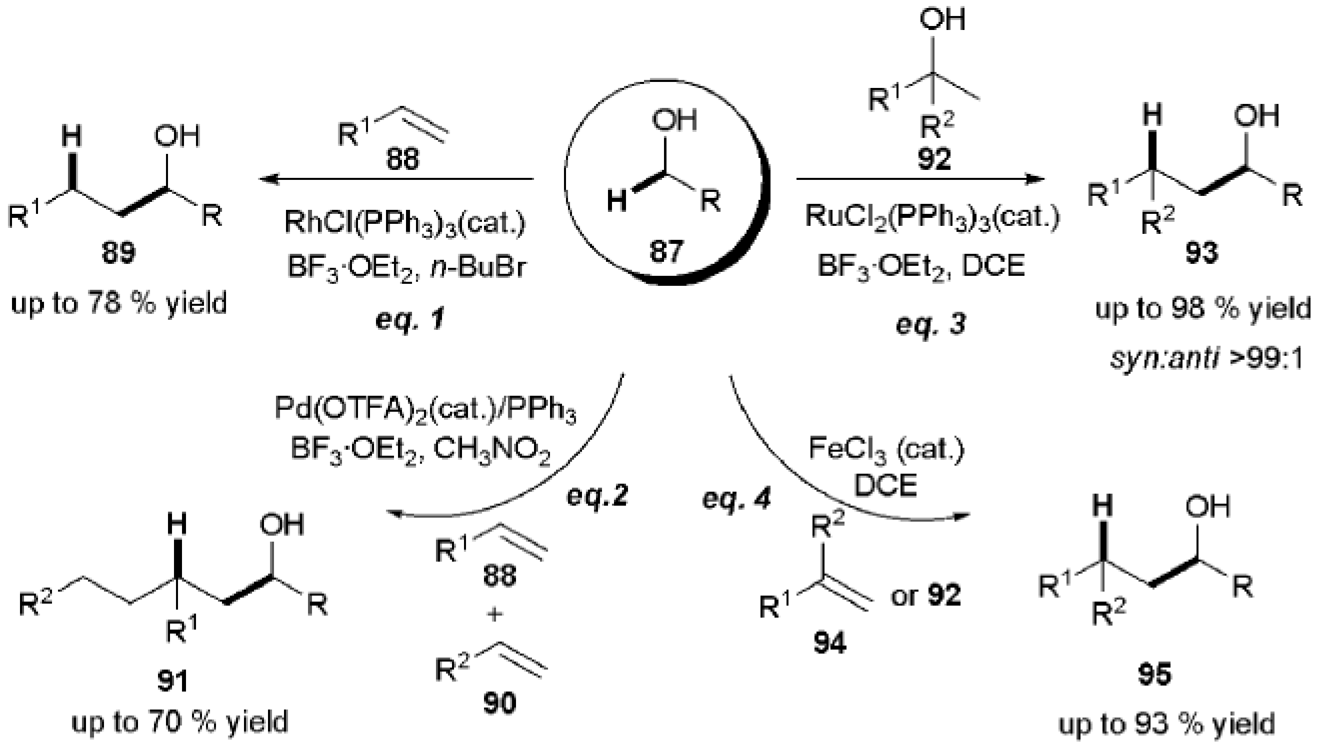
Transfer hydrogenative coupling (THC) of alcohols with alkene and alkyne



Scheme 25 General process of THC reactions of alcohol with unsaturated species.

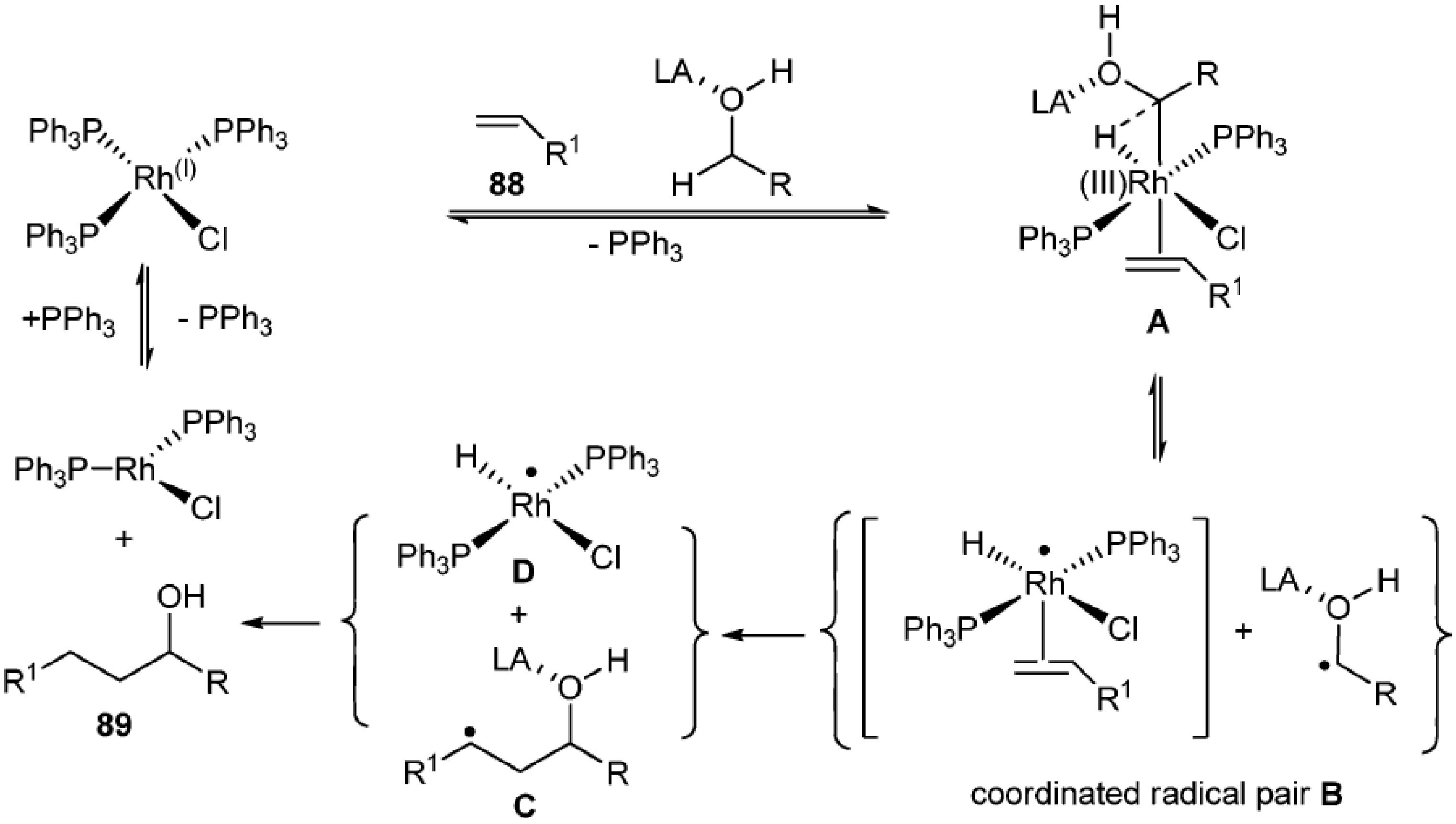
Feel familiar?

Transition metal-catalyzed coupling of alcohols with alkenes via C–H insertion



R= alkyl; R^1, R^2 = aryl, alkyl

Mechanism



X

Scheme 30 Mechanism of $RhCl(PPh_3)_3/BF_3{\cdot}OEt_2$-copromoted coupling of alcohol with alkene.

Summary for the second half

Type	Radical	Carbene	CDC	Annulation	THC	T. S. Metal coupling
Good at making	Sub-furan	2^{o}, 3^{o} ether	Conbonyl Beta-H	Pyran like	1,3 diol 2^{o} alcohol	2^{o} alcohol
Catalyst		Rh (Davies)	DDQ, In, Cu, Fe	BF3, Sc(oTf)3, LA	Ru, Ir	Rh, Ru, Pd, Fe
Difference	Radical	diazo	Dehydrogenative (oxidation)	Migration	Hydrogenative (reduction)	Radical