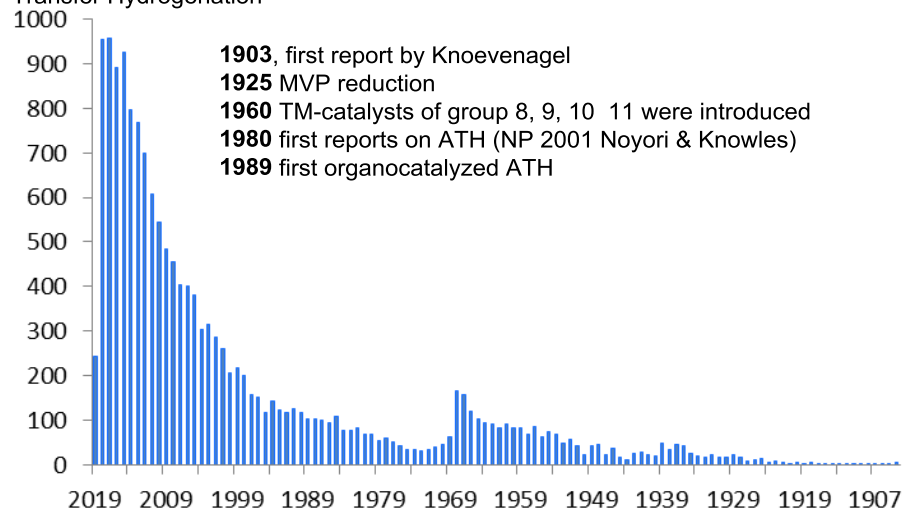
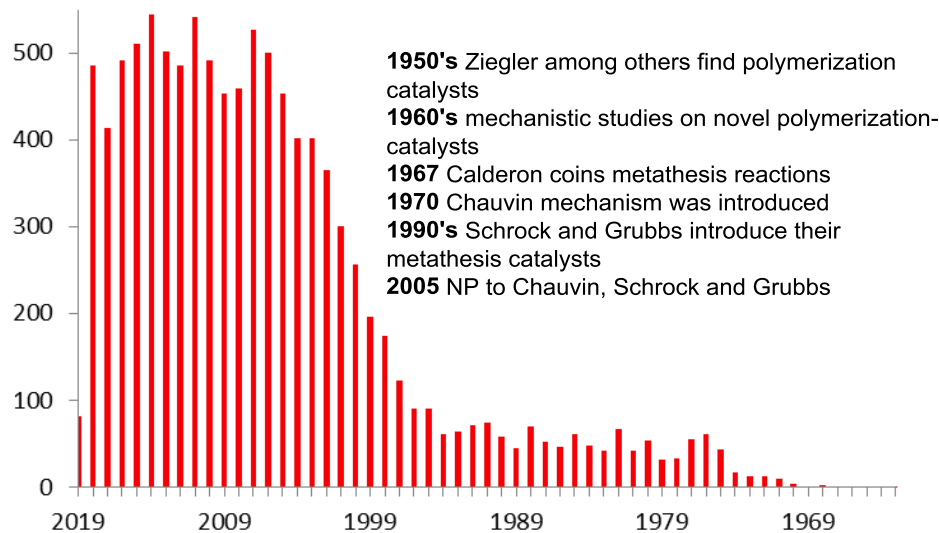


Beyond this presentation

Transfer Hydrogenation



Alkene Metathesis

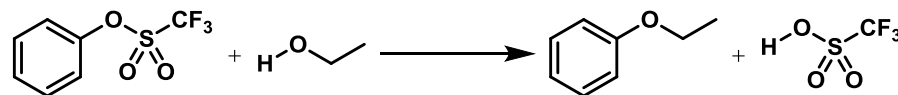


Rearrangements, Isomerizations and Alkyne Metathesis as well as heterogeneous and Enzyme mediated reactions are not covered in this topic

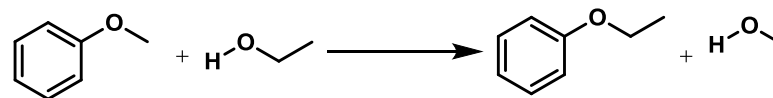
Background

ISODESMIC Reactions:

"...are bond separation reactions in which there is retention of the number of bonds of a given formal type, but with a change in their relation to one another. Such processes in general may be termed isodesmic" (*JACS*, 1970, 92, 4796.)

ISOFUNCTIONAL (subclass of isodesmic reactions)

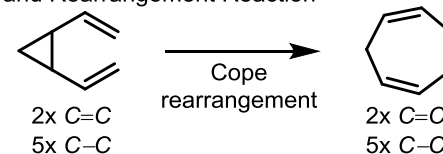
"...the number and type of functional groups is conserved throughout the reaction. This can be considered a subclass of isodesmic reactions..."

ERGONEUTRALITY

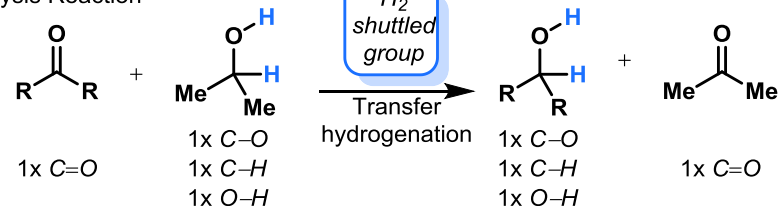
The energy of starting materials and products should have negligible ΔG° values. This vindicates that **isofunctional reactions are inherently reversible**.

Isofunctional reactions

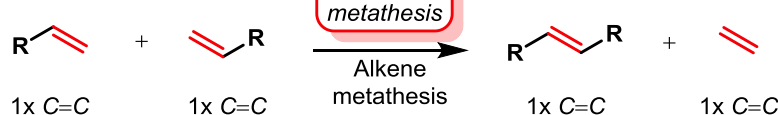
Unimolecular Isomerization and Rearrangement Reaction



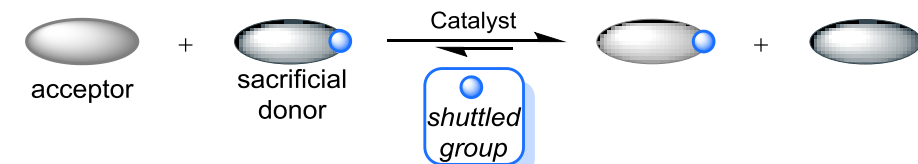
Shuttle Catalysis Reaction



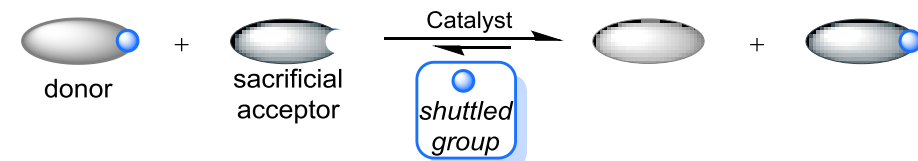
Metathesis Reaction



Forward Reaction: Functionalization



Reverse Reaction: Defunctionalization



A Shuttle Catalysis process provides a platform for performing functionalization/defunctionalization under similar conditions

Particular attractive if the use of the bare shuttled group should be avoided due to toxicity or instability

The Equilibrium

Key challenge is to shift the equilibrium to afford synthetically useful yields of the desired product. Thermodynamic strategies can be employed to drive the reaction forward.

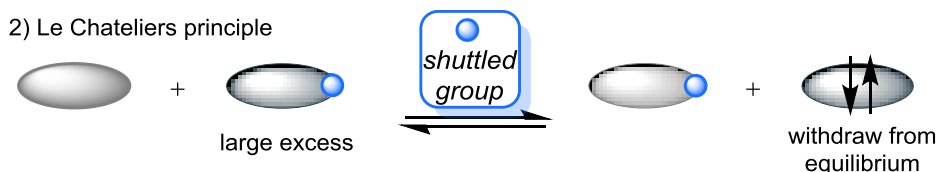
1) Ring strain release:

Experimentally determined heats of formation (ΔH_f) and calculated strain energies (SE), and entropies (S°) olefinic strain release (OS)

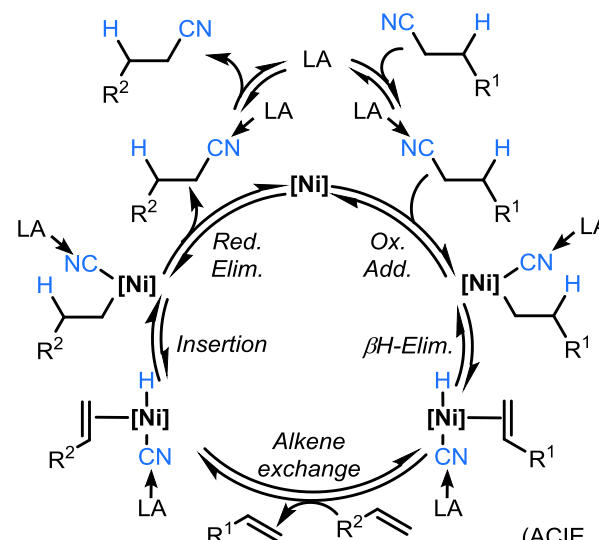
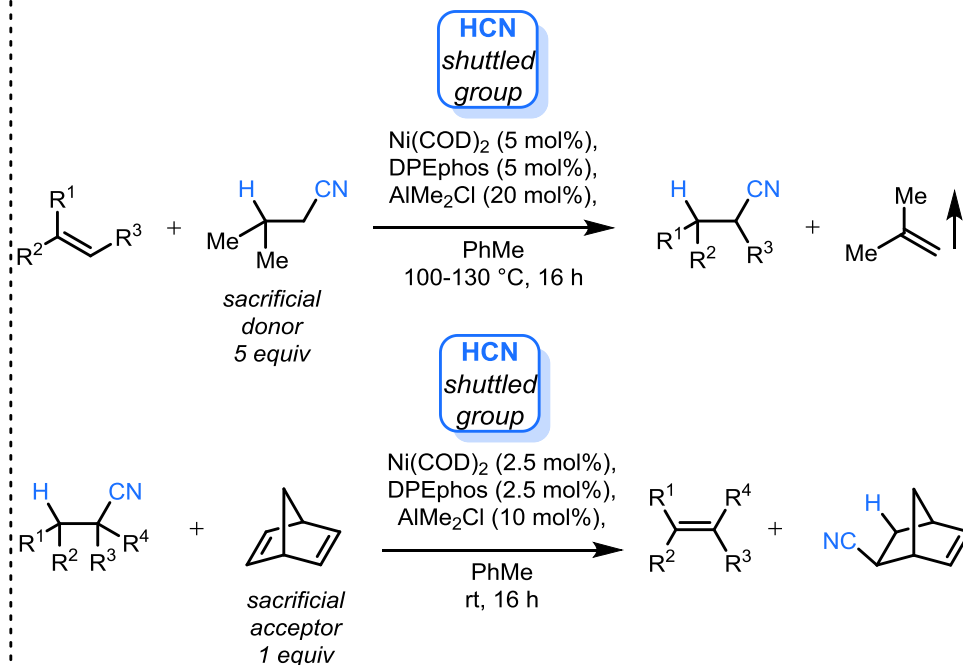
ΔH_f 12.73	ΔH_f 6.78	ΔH_f -18.44	ΔH_f -29.5	ΔH_f 21.1	ΔH_f -1.08
SE 27.5	SE 26.5	SE 6.2	SE 0	SE 19.2	OS -0.3
S° 56.8	S° 63.4	S° 70.0	S° 71.3	OS 4.8	S° 74.3

ACIE, 1986, 25, 312.

2) Le Chateliers principle



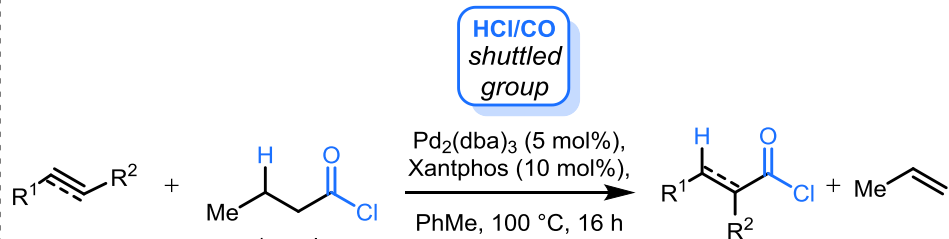
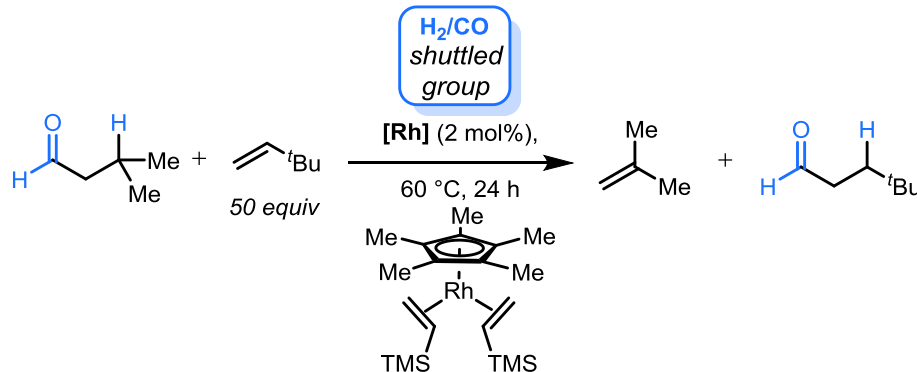
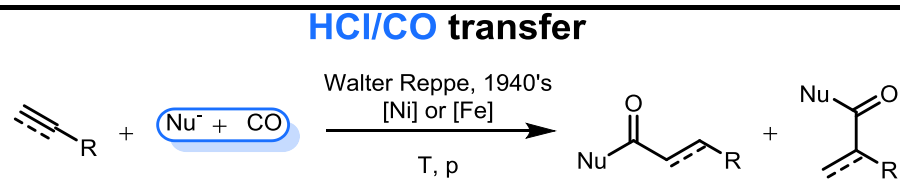
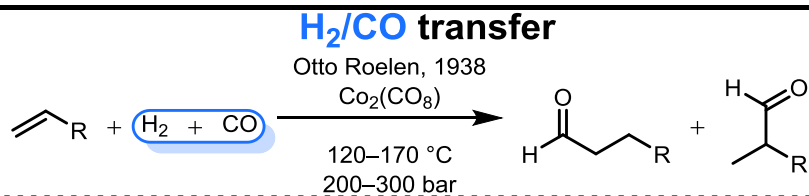
HCN transfer



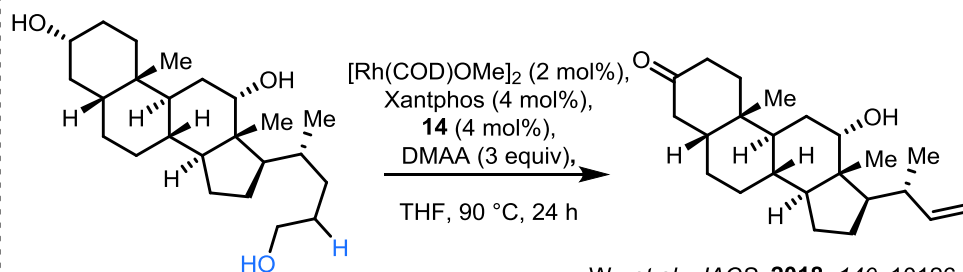
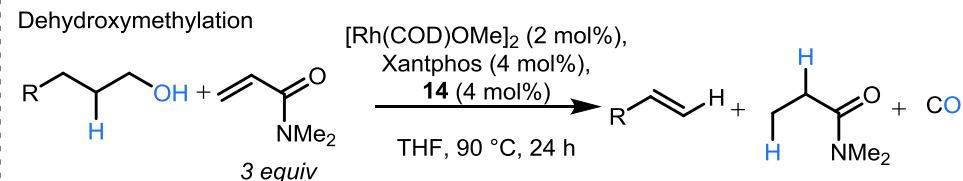
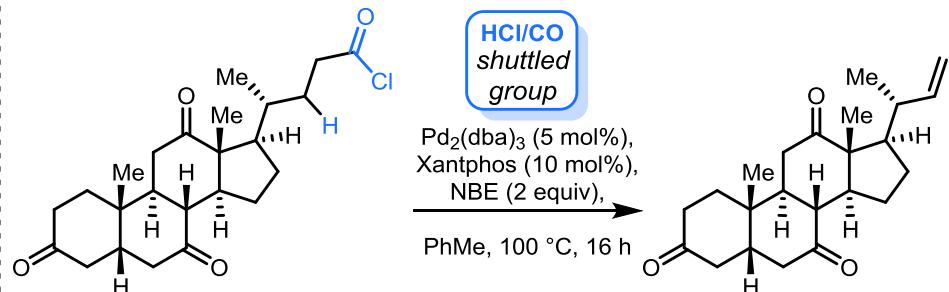
The role of the Lewis acid co-catalyst was corroborated by computational studies.

Every step is intrinsically reversible.

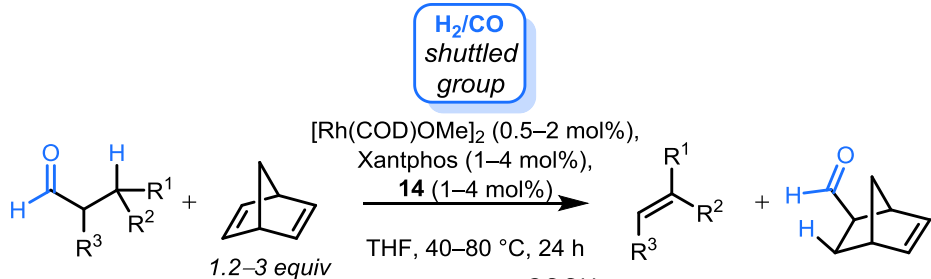
For every essential mechanistic step a microscopic reverse exists



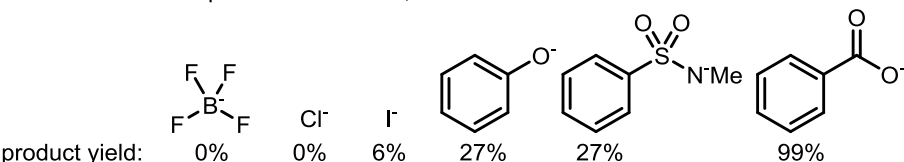
Reaction is more feasible with alkynes as compared to alkene



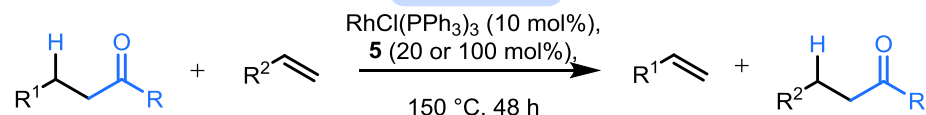
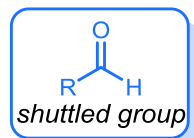
Lenges *et al.*, *ACIE*, **1999**, 38, 3533.
isolated example of the forward reaction/ Hydroformylation



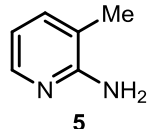
Murphy *et al.*, *Science*, **2016**, 347, 56.
no isomerization of products observed, reaction runs under kinetic control



RCHO transfer

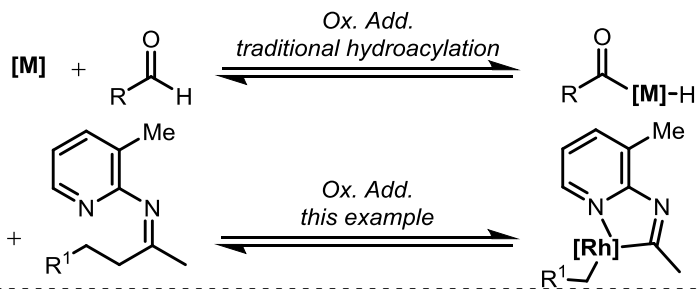


10 equiv

R¹: Ph, (aliphatic, H)R²: aliphaticJun *et al.*, JACS, 1999, 121, 880.

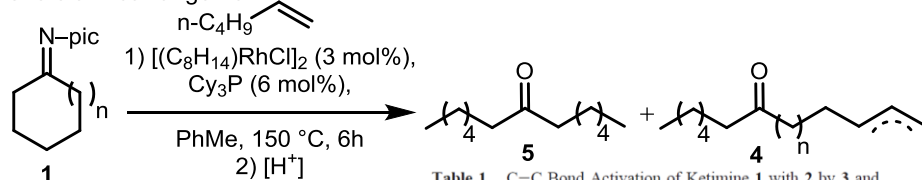
Polymerization of styrene products as additional driving force

Reaction proceeds via an oxidative addition step into an unstrained C–C bond. It is in complement with the traditional hydroacylation processes.

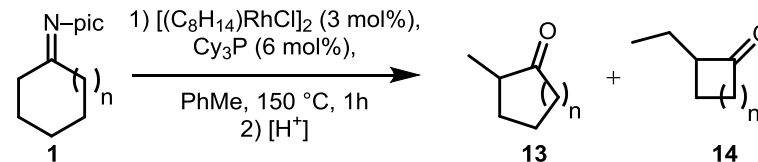


Extension of the methodology

Skeletal Rearrangement

Table 1. C–C Bond Activation of Ketimine 1 with 2 by 3 and Cy₃P

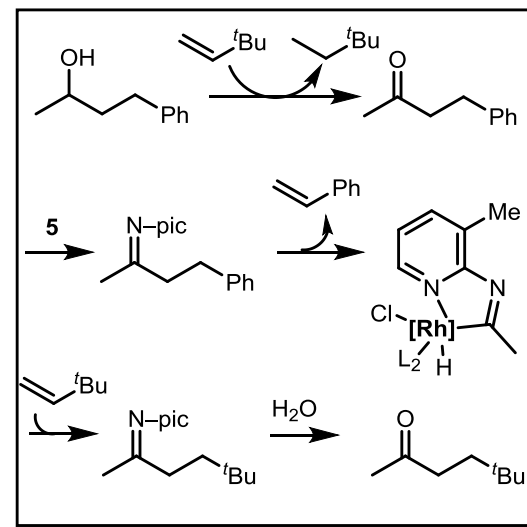
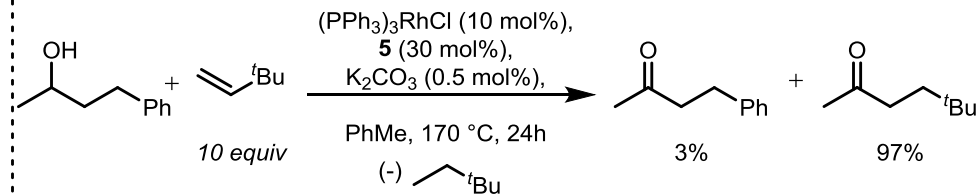
entry	reactant 1 (n)	product(s)	ratio of 4:5 (ter:int of 4) ^a	overall yield, ^b %
1	1a (n = 0)	5	0:100	9
2	1b (n = 1)	5	0:100	5
3	1c (n = 2)	4c + 5	23:77 (52:48)	76
4	1d (n = 3)	4d + 5	39:61 (13:87)	89
5	1e (n = 5)	4e + 5	38:62 (15:85)	83
6	1f (n = 7)	4f + 5	39:61 (22:78)	86
7	1g (n = 10)	4g + 5	37:63 (16:84)	79

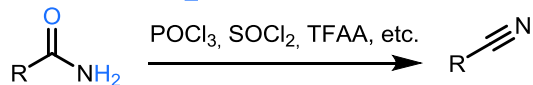
Jun *et al.*, JACS, 2001, 123, 751.Table 2. Skeletal Rearrangement of Ketimine 1 by 3 and Cy₃P

entry	reactant 1 (n)	products	ratio of 13:14	overall yield, ^a %
1	1a (n = 0)			0
2	1b (n = 1)	13b	100:0	21
3	1c (n = 2)	13c + 14c	76:24	82
4	1d (n = 3)	13d + 14d	33:67	12
5	1h (n = 4)			0

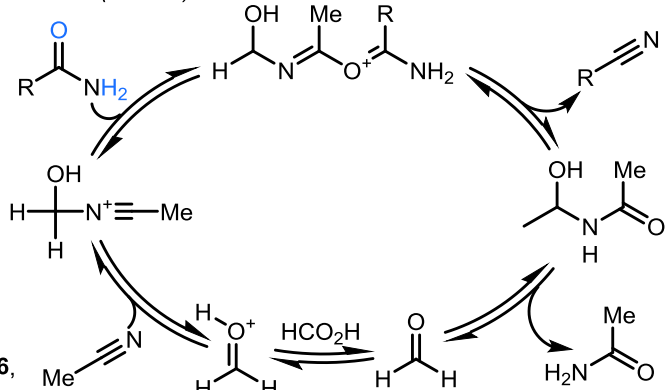
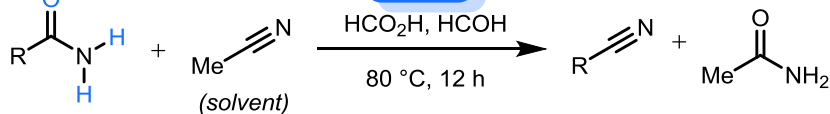
^a Yields and the ratio of 13 and 14 were determined by GCD.Jun *et al.*, JACS, 2001, 123, 751.

Transfer hydrogen strategy

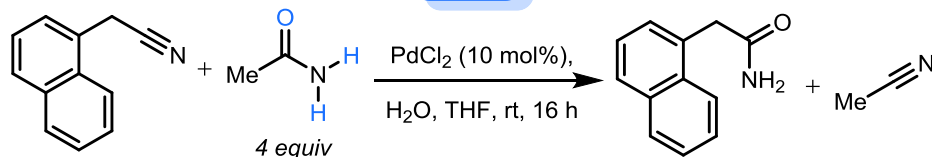
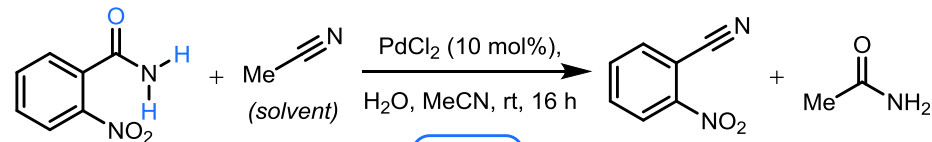
Jun *et al.*, Organometallics, 2001, 20, 2928.

H₂O transfer

Traditional approach required harsh conditions, which are poorly compatible with polar functional groups and causes epimerization

**H₂O
shuttled
group**

Heck et al., *JOC*, **1996**, 61, 6486.

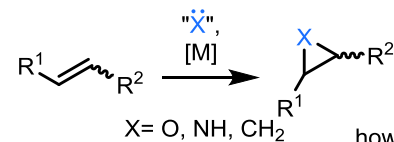
**H₂O
shuttled
group**

Maffioli et al., *Org. Lett.*, **2005**, 7, 5237.

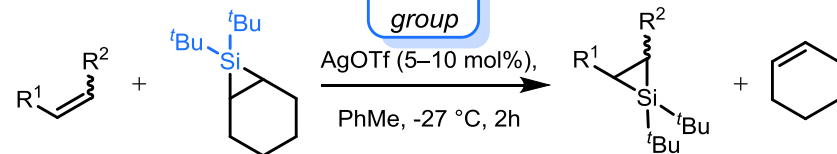
How about H₂S transfer? Until know only one report (Zoltewicz, **1960**)

:X - transfer

3-membered cyclic compounds are well-documented intermediates in organic synthesis

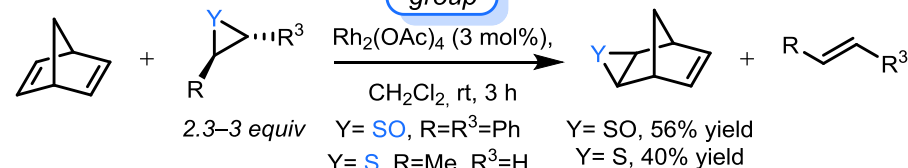


Cirakovic, *JACS*, **2002**, 124, 6524.

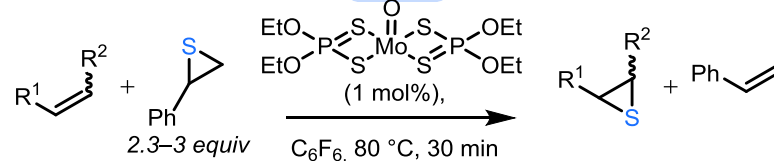
**:Si^tBu₂
shuttled
group**

The reaction proceeds via σ -bond metathesis of the Ag-cat. into the strained Si-C bond, followed by a β -silyl elimination

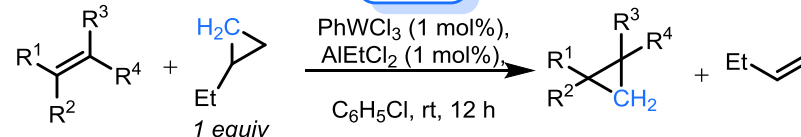
Kendall, *Synlett*, **1998**, 4, 391.

**:Y
shuttled
group**

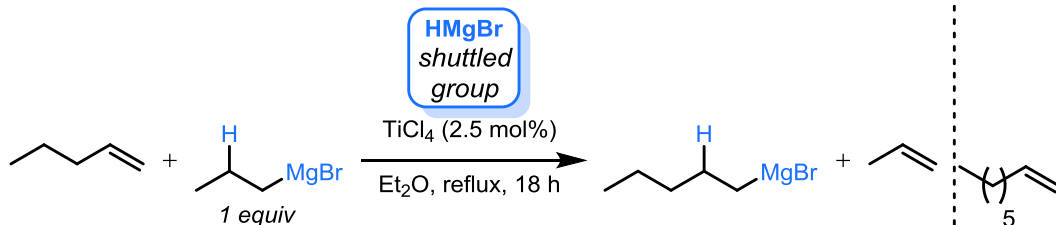
Adam, *JACS*, **2003**, 125, 3871.

**:S
shuttled
group**

Gassman, *JACS*, **1976**, 98, 6058.

**:CH₂
shuttled
group**

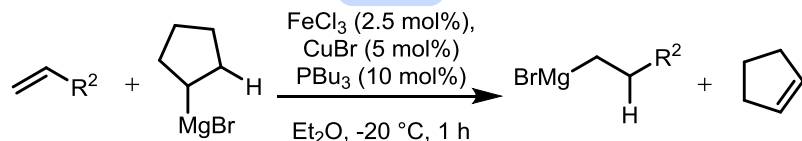
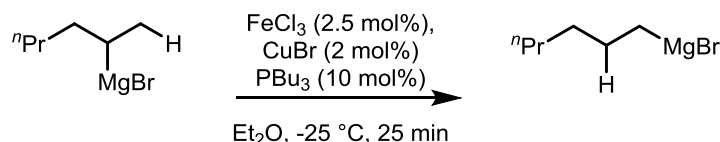
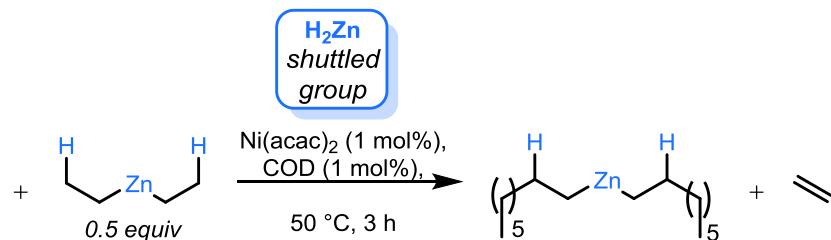
HMgBr transfer



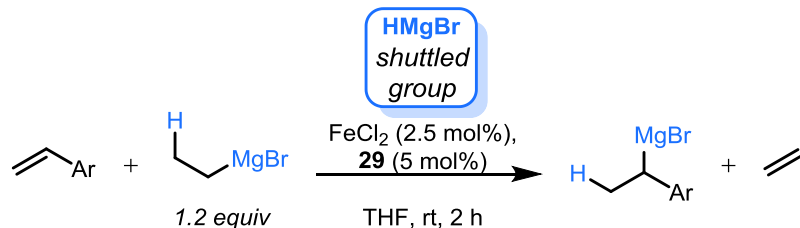
First report by Cooper and Finkbeiner in 1962.

It is shown that NiCl_2 and Cp_2TiCl_2 catalyze the homomagnesiation reaction as well.

HZnBr transfer

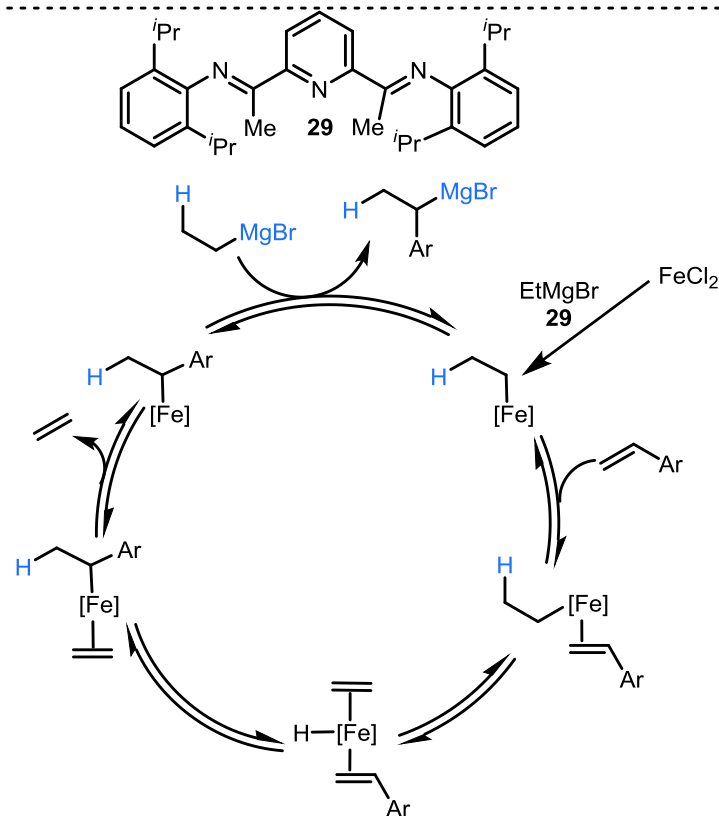


Shirakawa *et al.*, *JACS*, **2012**, 134, 272.

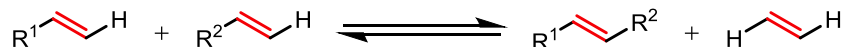
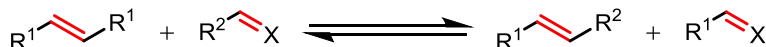


Greenhalgh *et al.*, *JACS*, **2012**, 134, 272.

Greenhalgh *et al.*, *Organometallics*, **2014**, 33, 5811.

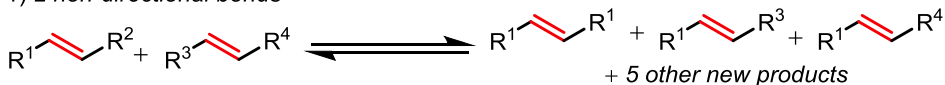


Further report on Hydromagnesiation-type reactions by the group of Xi (**2016**, Ti-catalyzed) trapping newly formed Grignard reagents with CO_2 and Nakamura (**2012**: Fe-cat., without ligands) utilizing alkynes is a non-isofunctional process.

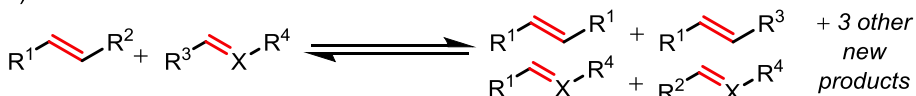
Differentiation between π bond and σ bond metathesis/ bond multiplicity**Classification**Type 1) Metathesis between two functionally *identical* bondsType 2) Metathesis between two functionally *different* bonds**Bond Distribution**

Depending on the directionality of a bond less products will be formed

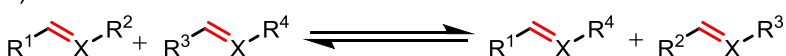
1) 2 non-directional bonds



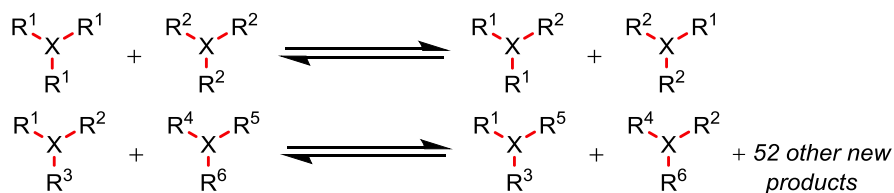
2) 1 non-directional and 1 directional bond



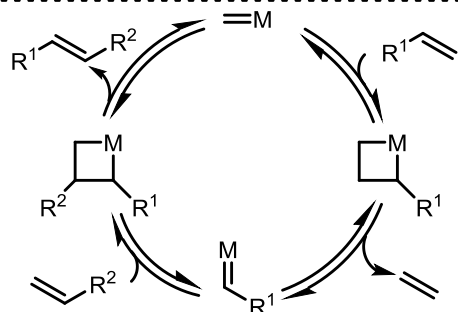
3) 2 directional bonds



Metathesis of more than one bond in the same starting material

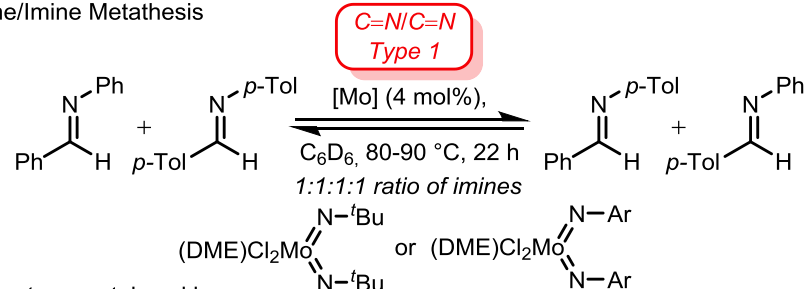
(mainly σ bond metathesis)**Chauvin Mechanism**

1971 proposed by Chauvin

 **π Bond Metathesis**

Additional to alkene and alkyne metathesis, four more are known

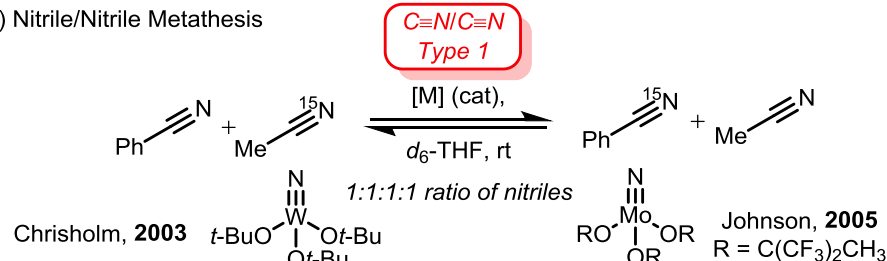
1) Imine/Imine Metathesis



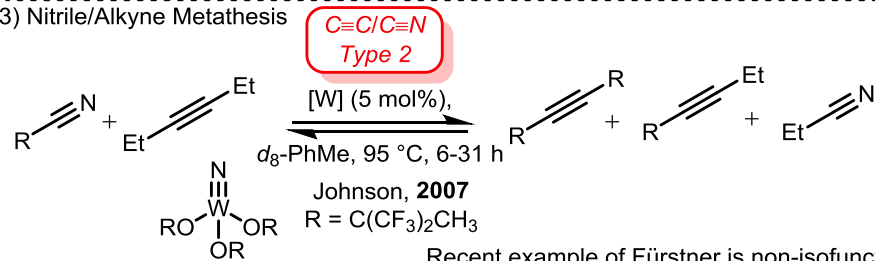
other systems catalyzed by

Zr, Ta, Ti, Re and Nb; reactivity via carbonyl intermediates were studied

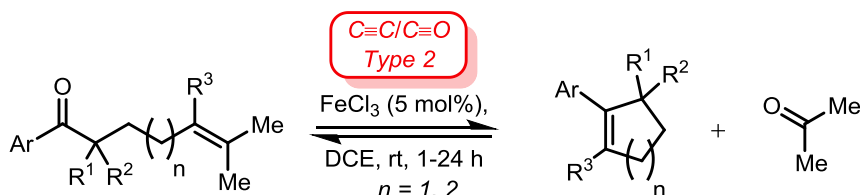
2) Nitrile/Nitrile Metathesis



3) Nitrile/Alkyne Metathesis



4) Carbonyl/Alkene Metathesis

Other report by Schindler, ROM with GaCl₃Organocatalytic examples by Lambert (ROM, tropylium) and Franzén (Ph₃CBF₄)

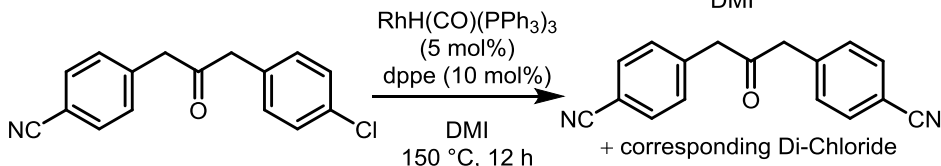
σ Bond Metathesis

C-C Metathesis Reaction

direct bond cleavage depends on:

ring strain release

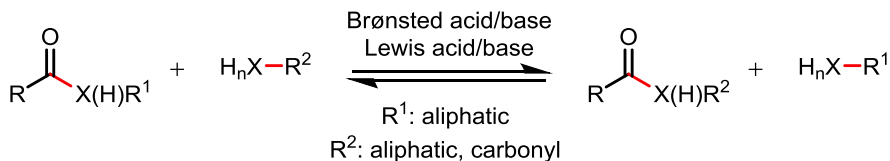
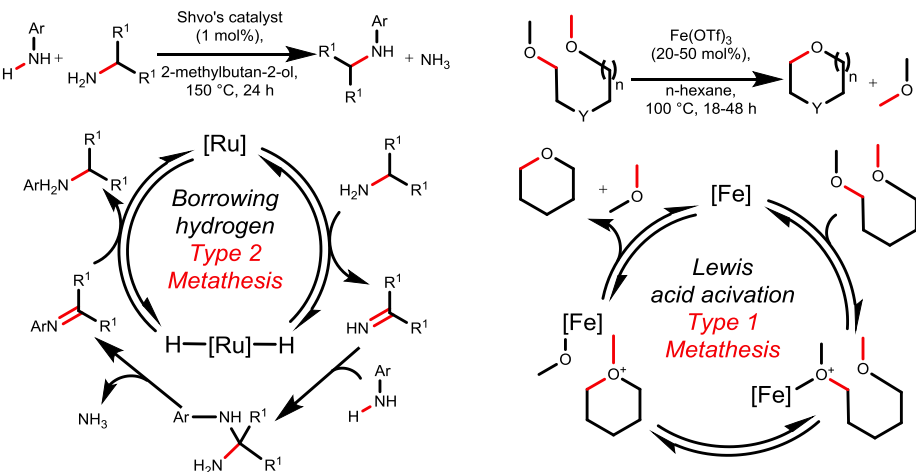
activation/ direction of the cleavable bond



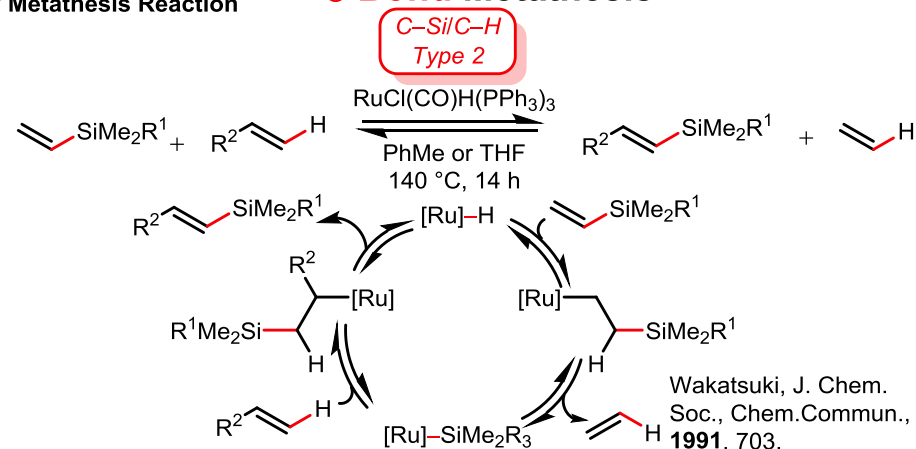
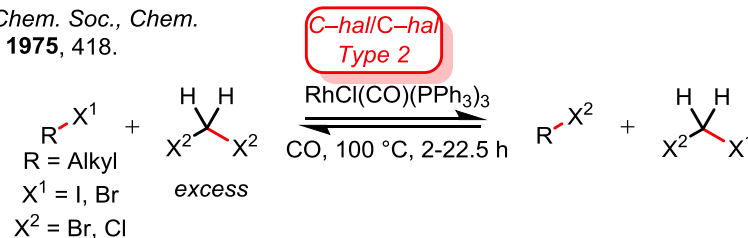
group of Goldman and Brookhart: tandem dehydrogenation/alkene metathesis, [Ir]/[Mo]-catalyzed system

group of Zhou alkynyl group exchange, [Lu]-catalyzed

C-N and C-O Metathesis Reaction

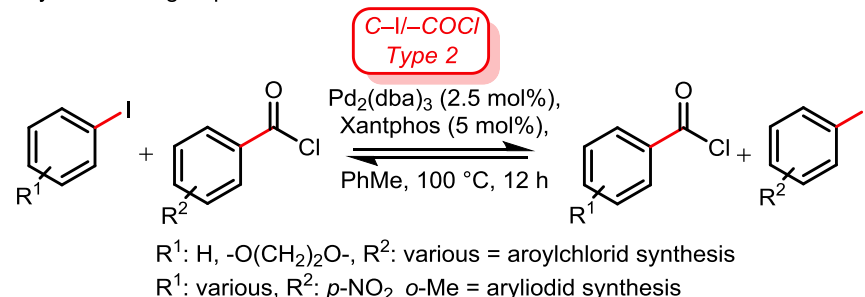
 $X \equiv O$. (Esterification) Transesterification is well known and broadly applied. $X \equiv N$. (Amidation) Transamidation poses challenges because of lower reactivity and an acidic NH bond:**Brønsted base catalyzed imine initiated approach** for sec. amides: Gellman and Stahl**Lewis acidic activation** (AlCl₃, Sc(OTf)₃, Ti(NMe₂)₄, Zr(NMe₂)₄) for tert. amides heavily investigated by Gellman and Stahl**Activation of the Amides** enabled Ni- or Pd-catalyzed reactions (Szostak, Garg)

C-Y Metathesis Reaction

 σ Bond MetathesisLyons, J. Chem. Soc., Chem. Commun., **1975**, 418.C-hal/C-H [Cu]-cat. metathesis on alkynes discovered by Hein (**2017**)

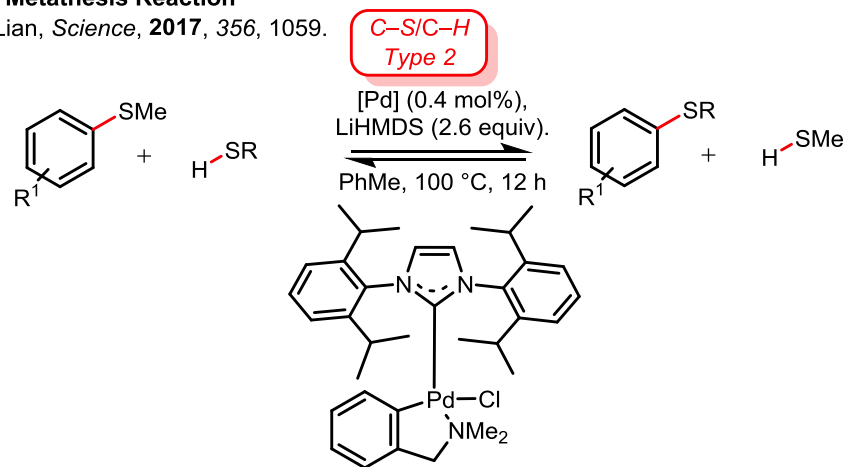
X-Y Metathesis Reaction

Traditionally functional group transformations are irreversible

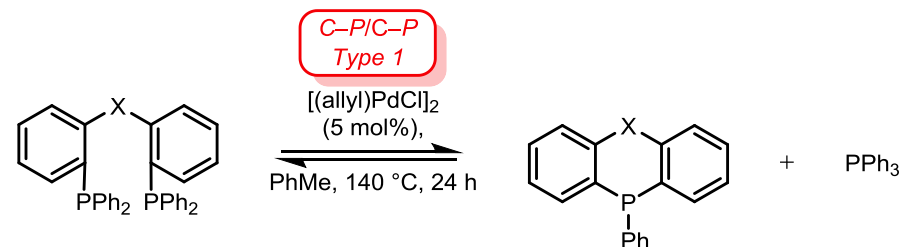
Driving forces:

Synthesis of Aryliodides: Sterically congested, or electron deficient aroyl chlorides were employed

Synthesis of Aroyl Chlorides: Iodobenzene was used in excess or an electron rich aryl iodide

σ Bond Metathesis**C–Y Metathesis Reaction**Dr. Lian, *Science*, **2017**, 356, 1059.

Similar as in C–O Metathesis the thioether exchange is scarce
LiHMDS withdraws the thiomethoxyide with is considered to drive the reaction

Chatani, *Chem. Lett.*, **2017**, 46, 1296.

Chelation assisted C(sp²)-P cleavage and Phosphonium ion formation is considered
mechanistically

Purification of products after oxidation