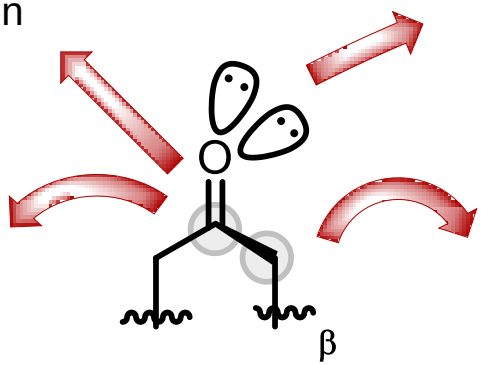
C-H Functionalization Directed by Ketone

Zhongxing Huang
Oct 29st, 2014

- **What characters of ketone can we use to functionalize C-H bonds?**

C=O system
- Photo-activation

Lewis Basicity
- Directing group for metal
- Hydrogen bond acceptors



Electrophilicity
- Enamine catalysis
- Imine catalysis
- Bifunctional catalysis

Acidity
- Alkylation
- Aldol reaction/condensation
- Halogenation
- Easy metallation

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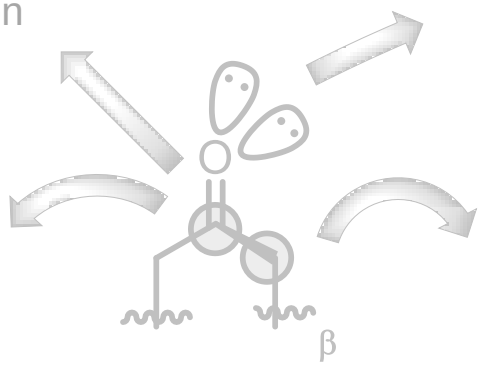

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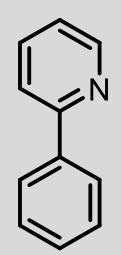
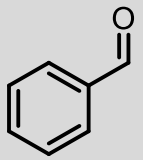
- **Scale of Lewis Basicity: BF_3 affinity**

BF_3 (gas) + LB (DCM solution) ⇌ LB-BF_3 (DCM solution) (Eq. 1)

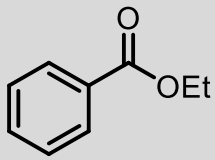
BF_3 affinity = $-\Delta H°$ (Eq. 1) (KJ/mol)



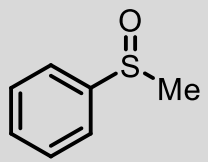
103.35



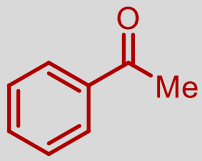
74.88



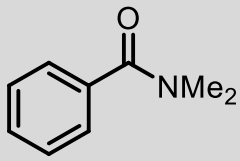
61.2



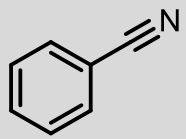
97.37



74.52



101.75



55.44

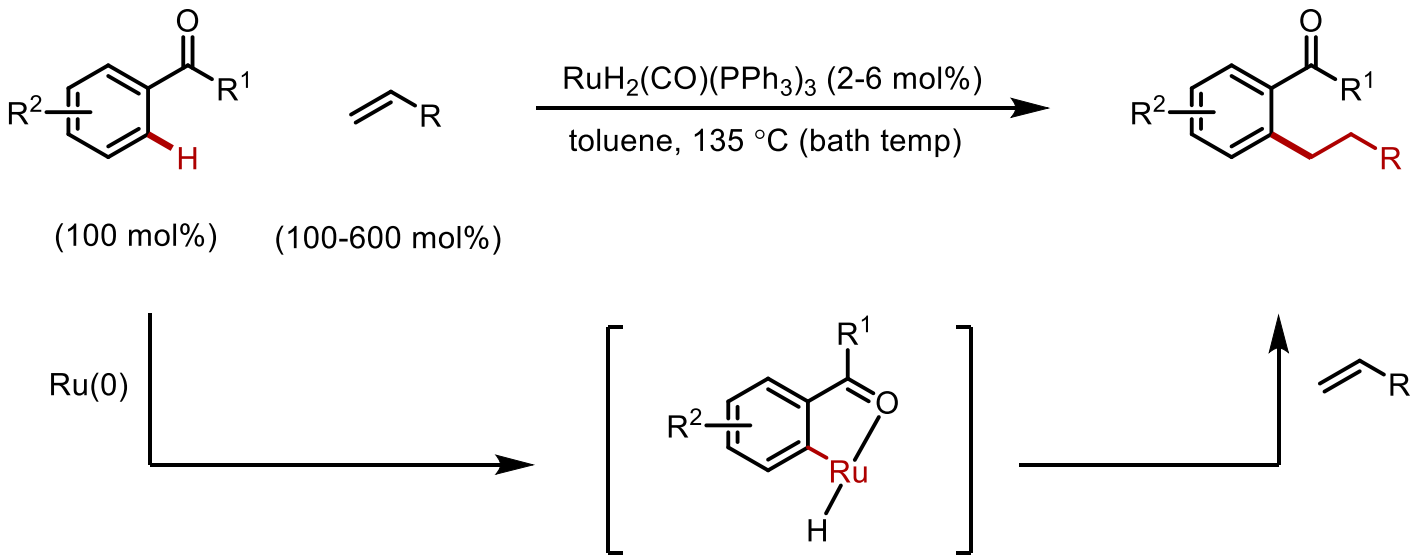
Team Solvent

1,4-dioxane	74.09	acetone	76.03	benzene	2.9
THF	90.40	cyclohexanone	76.36	toluene	3.3
2-MeTHF	92.83	ethyl acetate	75.55	DCM	10.0

Laurence, C.; Gal, J. Lewis Basicity and Affinity Scales, Wiley

Ketone as Directing Group

- **First report**



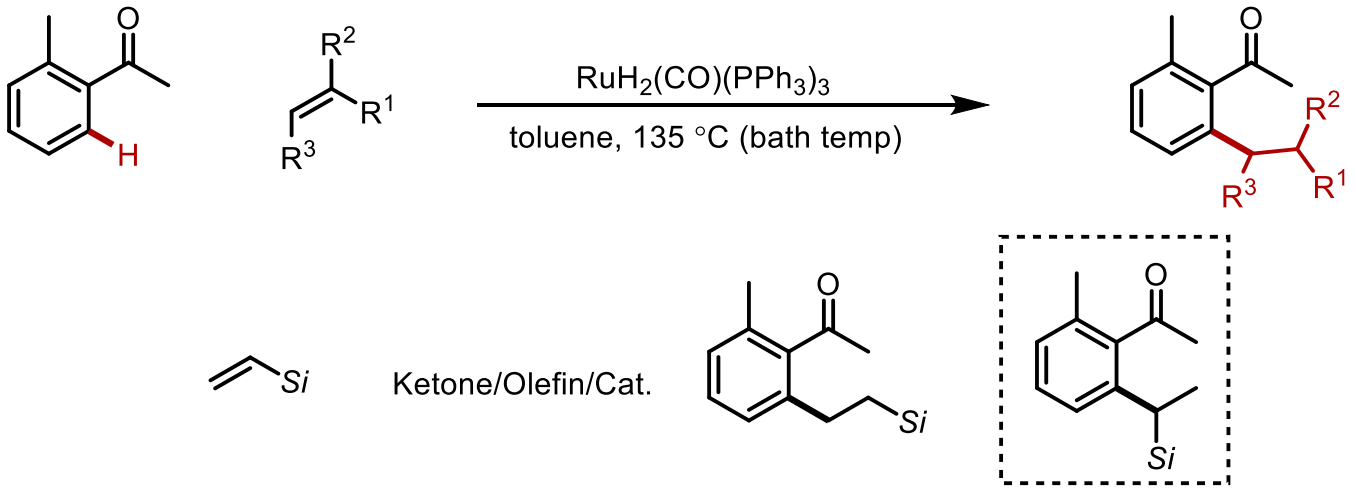
- Catalytic C-H functionalization (activation)
- Excessive substrate not necessary
- High efficiency and generality
- High selectivity enabled by directing group

'It may prove to be the first synthetically useful example of an organometallic-catalyzed transformation of a C-H bond.'

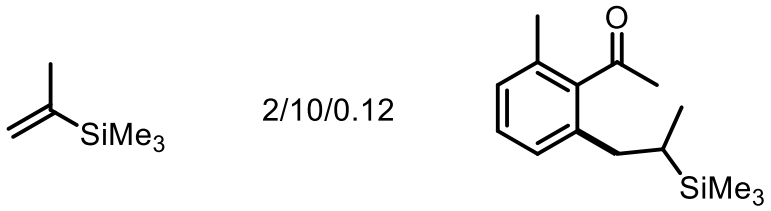
'More broadly, for either this Ru catalyst or other organometallic complexes, it remains to be seen what other functional groups will act to 'direct ' the functionalization of specific C-H bonds'

Murai, S. et al *Nature*, **1993**, *366*, 529
Goldman, A. D. *Nature*, **1993**, *366*, 514

- **Substrate scope**



Si =	$Si(OEt)_3$	2/2/0.04	2h, 93%
	$Si(OMe)_3$	2/2/0.04	4h, 91%
	$SiMe_2(OEt)$	2/2/0.04	2h, Quant.
	$SiMe_3$	2/2/0.04	4h, 72%
	$SiMe_2Ph$	2/2/0.04	1h, 90%



Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

Ketone as Directing Group

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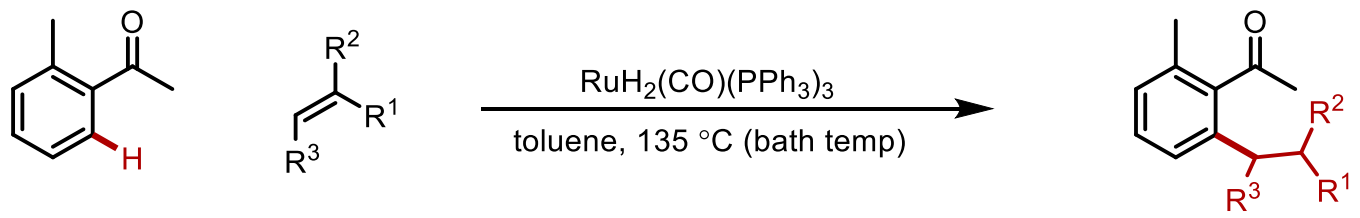
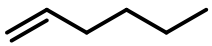
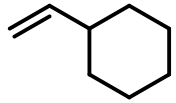
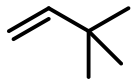
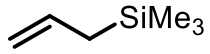
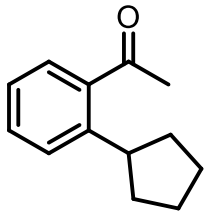
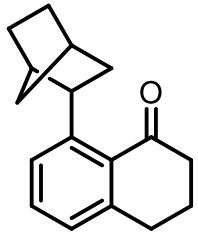


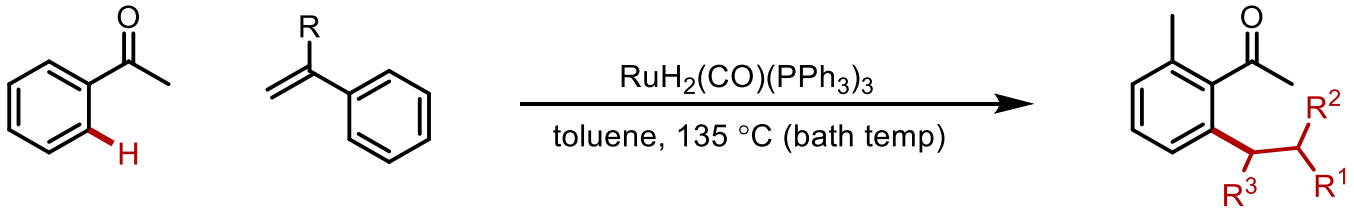
Olefin	Ketone/Olefin/Cat.	Product
	2/12/0.04	24h, Quant.
	2/10/0.04	5h, 23%
	2/2/0.04	24h, 19%
	2/10/0.04	8h, 99%
	2/10/0.12	4h, Quant.
	2/10/0.12	Trace
	2/10/0.12 48h, 36% Yield	
	2/4/0.04 1h, 86% Yield	

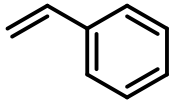
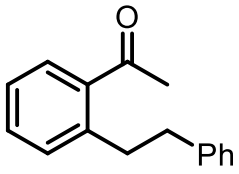
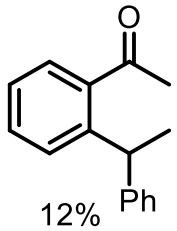
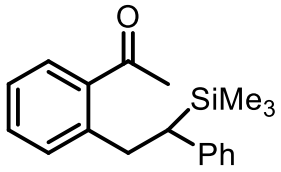
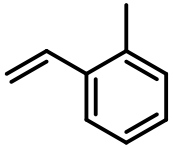
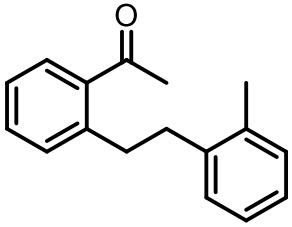
- Electronic property of olefin important
- e-deficient olefin not working (Michael)

Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

Ketone as Directing Group

- **Substrate scope**

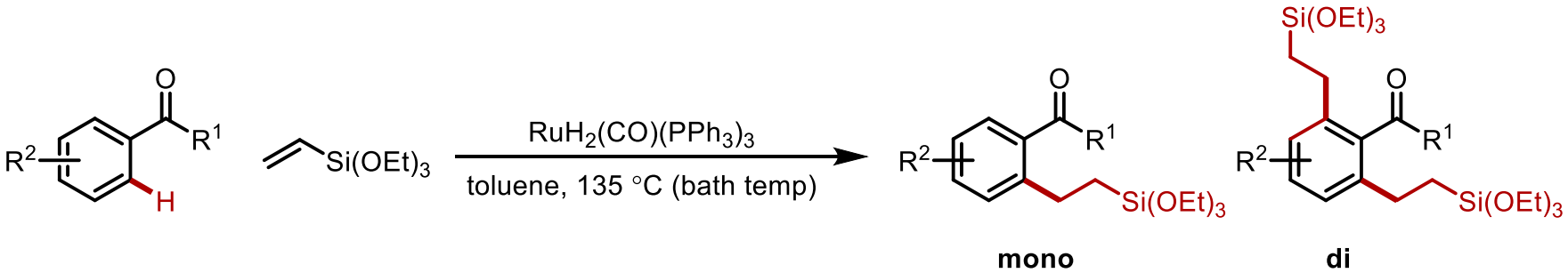


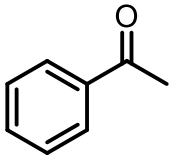
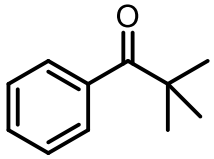
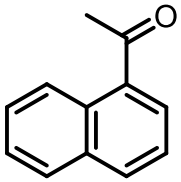
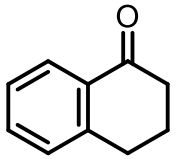
Olefin	Ketone/Olefin/Cat.	Time/h	Product		
	2/4/0.04	1	 72%	 12%	
	2/4/0.04	44		45%	**no other isomer**
	2/4/0.04	4		89%	**no other isomer**

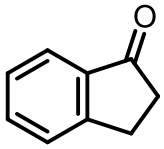
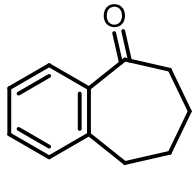
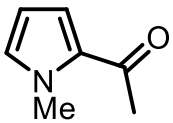
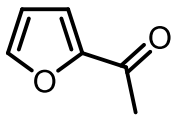
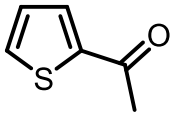
Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

Ketone as Directing Group

- **Substrate scope**



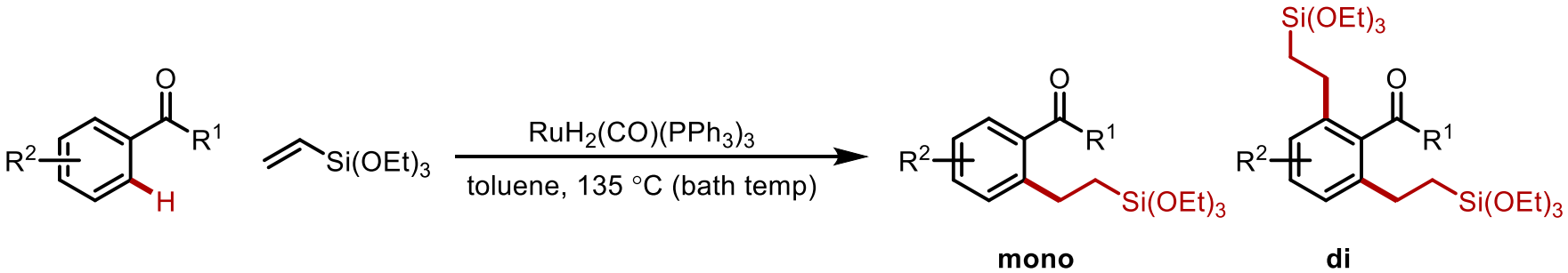
substrate				
Ketone/Olefin/Cat.	2/2/0.04	2/6/0.04	2/8/0.04	2/2/0.04	2/2/0.04
Time/h	0.23	90	24	6	0.5
Yield/%	83 (mono:di 9:1)	94 (only di)	Quant. (only mono)	Quant.	Quant. **95% on a 22g-scale**

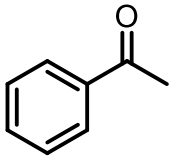
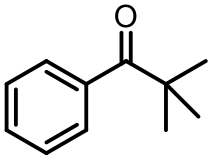
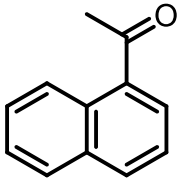
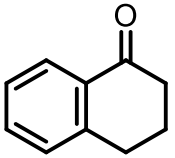
substrate					
Ketone/Olefin/Cat.	2/4/0.04	2/2/0.04	2/10/0.12	2/2/0.04	2/2/0.04
Time/h	22	20	48	4	1
Yield/%	**No reaction**	88	99	Quant.	Quant.

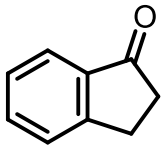
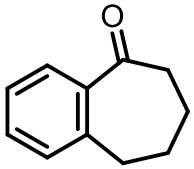
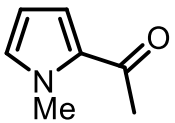
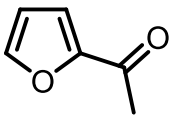
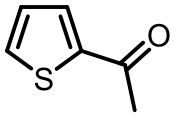
Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

Ketone as Directing Group

- **Substrate scope**



substrate				
Ketone/Olefin/Cat.	2/2/0.04	2/6/0.04	2/8/0.04	2/2/0.04	2/2/0.04
Time/h	0.23	90	24	6	0.5
Yield/%	83 (mono:di 9:1)	94 (only di)	Quant. (only mono)	Quant.	Quant. **95% on a 22g-scale**

substrate					
Ketone/Olefin/Cat.	2/4/0.04	2/2/0.04	2/10/0.12	2/2/0.04	2/2/0.04
Time/h	22	20	48	4	1
Yield/%	**No reaction**	88	99	Quant.	Quant.

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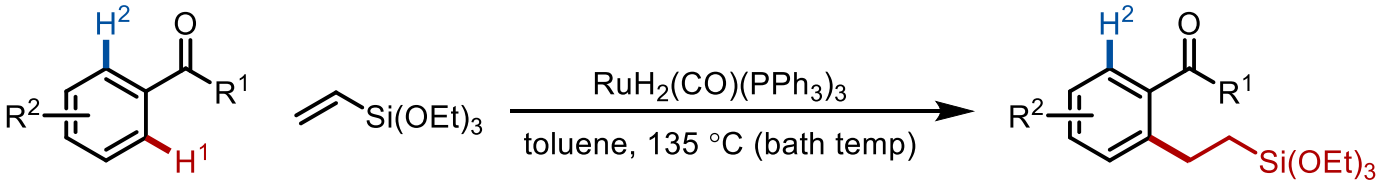
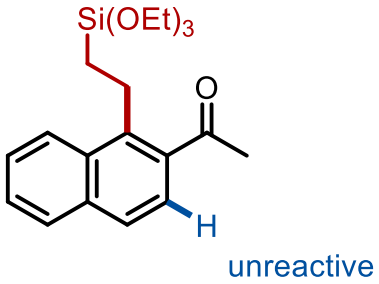
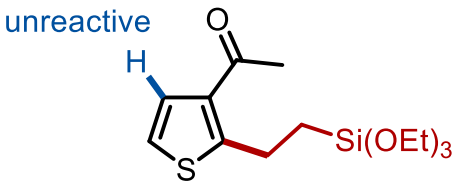
Ketone as Directing Group

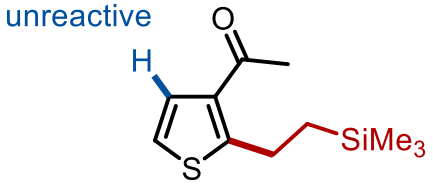
- **Substrate scope**



product



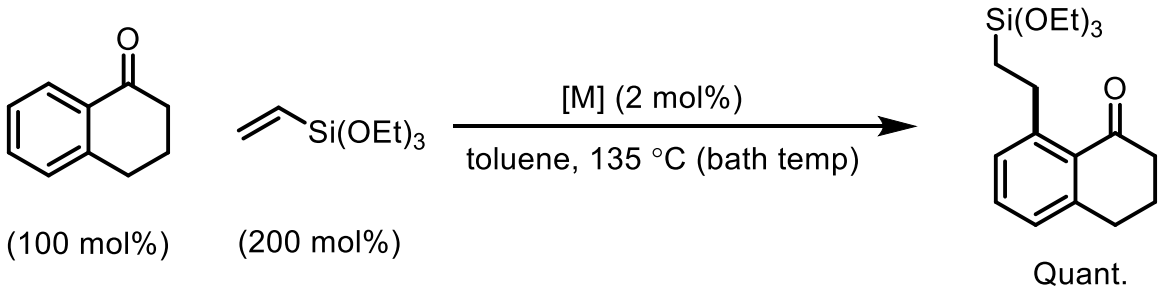




Ketone/Olefin/Cat.	2/2/0.04	2/2/0.04	2/2/0.04
Time/h	6	1	24
Yield/%	Quant.	Quant.	87

Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

- **Choice of catalyst**



(100 mol%) (200 mol%) Quant.

Catalyst	*Time required*
$RuH_2(CO)(PPh_3)_3$	10 min
$Ru(CO)_2(PPh_3)_3$	1 h
$RuH_2(PPh_3)_4$	2 h
$Ru(CO)_3(PPh_3)_2$	6.5 h

Ineffective catalysts
$RuHCl(CO)(PPh_3)_3$
$RuCl(OAc)(CO)(PPh_3)_2$
$RuCl_2(PPh_3)_3$
$Ru_3(CO)_{12}$

No reactivity
$IrCl(CO)(PPh_3)_2$
$[IrH_2(acetone)_2(PPh_3)_2]BF_4$

- Neither H nor CO necessary
- Ru(0) with at least $2PPh_3$

Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

Ketone as Directing Group

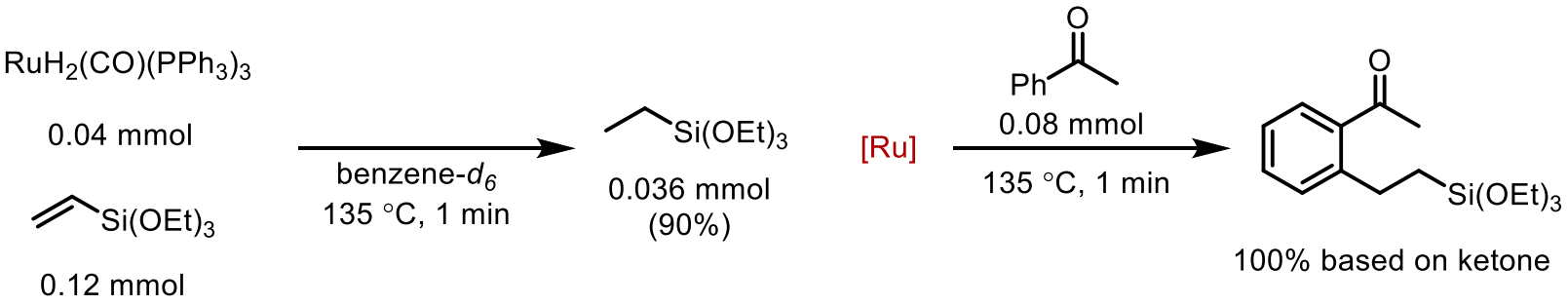
- **Generation of active catalyst**
  - Reductive elimination of H_2

    $RuH_2(CO)(PPh_3)_3$ stable under thermal conditions

  - Reduction of ketones

    No ketone reduced in the reaction between Ru and ketones

  - Reduction of olefins

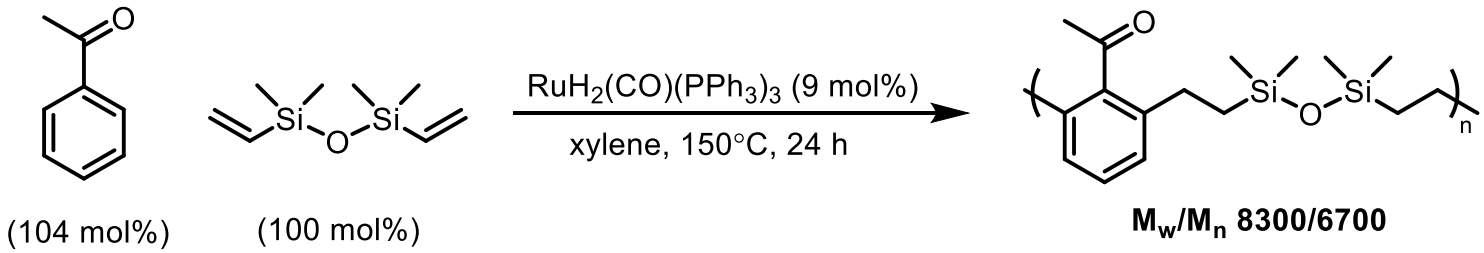


- Active catalyst
- Structure not established

Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

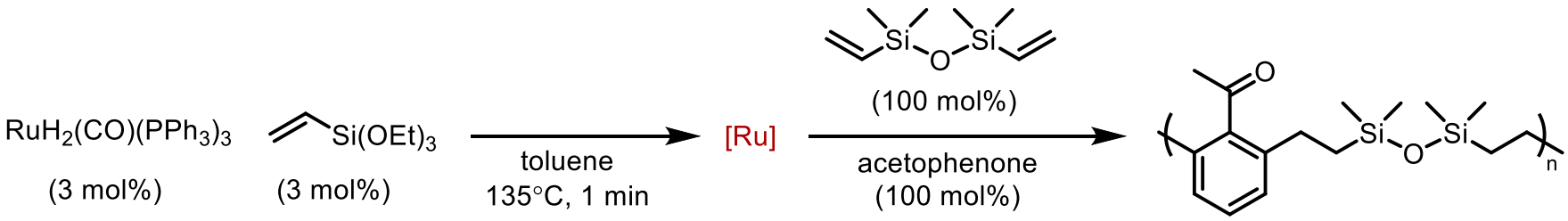
Ketone as Directing Group

- **Generation of active catalyst**



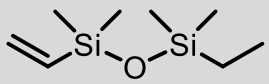
(104 mol%) (100 mol%)

M_w/M_n 8300/6700



M_w/M_n 40600/14800

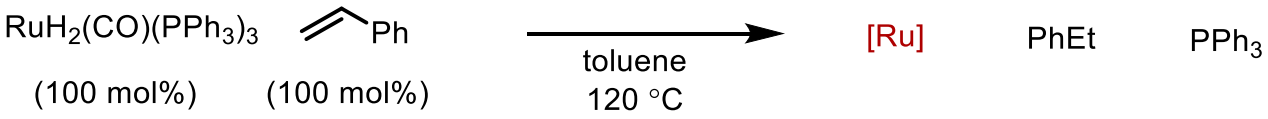
- Pre-generation of active catalyst avoids



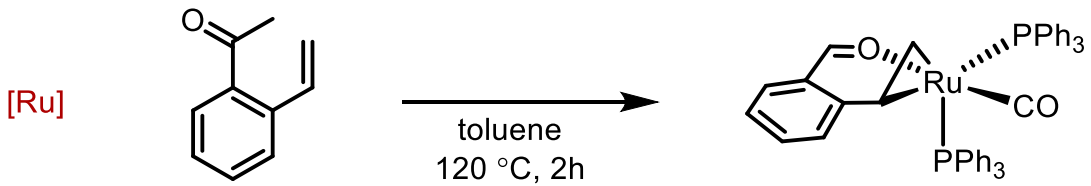
terminator

Weber, W. P. et al *Macromolecules* **1995**, *28*, 5686

- **Generation of active catalyst**



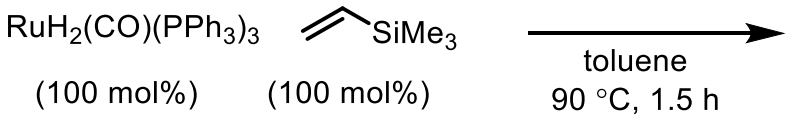
- A free PPh_3 released
- Hydride peaks disappeared
- 'Tempting' to propose $RuCO(PPh_3)_2$
- P-peaks non-consistent with $RuCO(PPh_3)_2$
- May be dimer or trimer

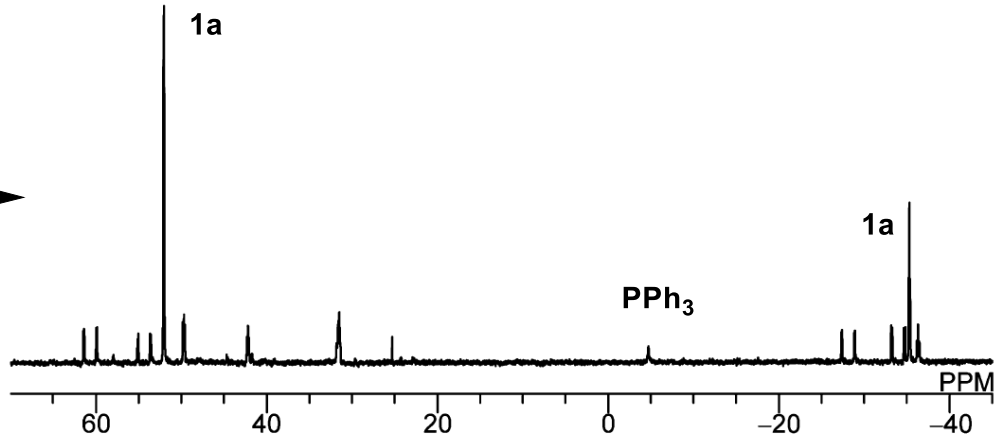


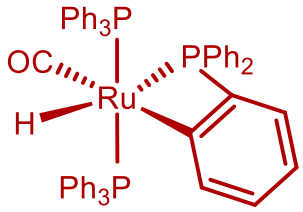
- Active catalyst for co-polymerization
- [Ru]=$RuCO(PPh_3)_2$?

Weber, W. P. et al *Organometallics* **1998**, 17, 584

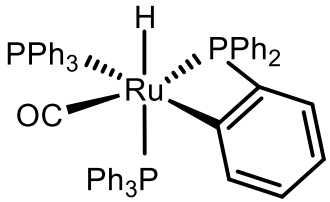
- **Generation of active catalyst**



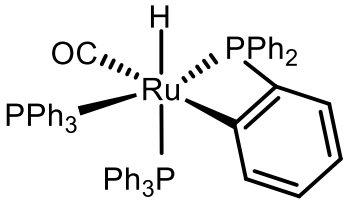




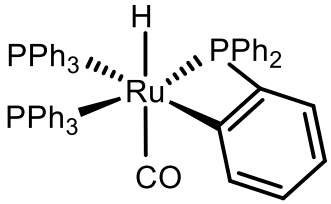
1a
major isomer



1b



1c

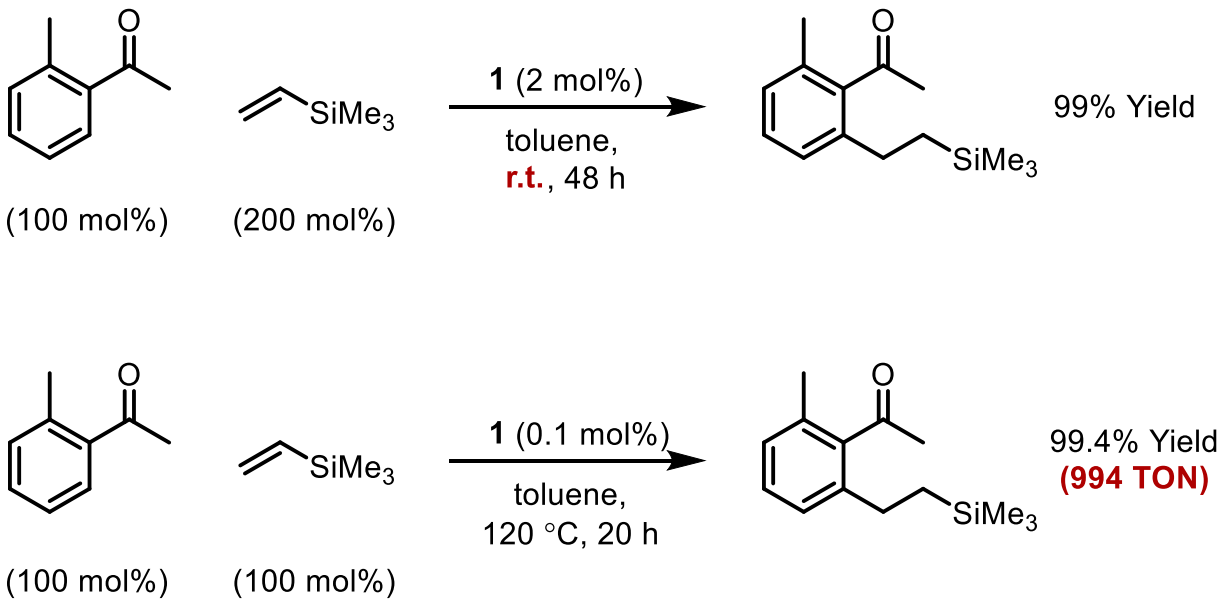


1d

- X-ray crystals unacceessible
- All assigned by NMR
- Can be considered as resting state of Ru(0)

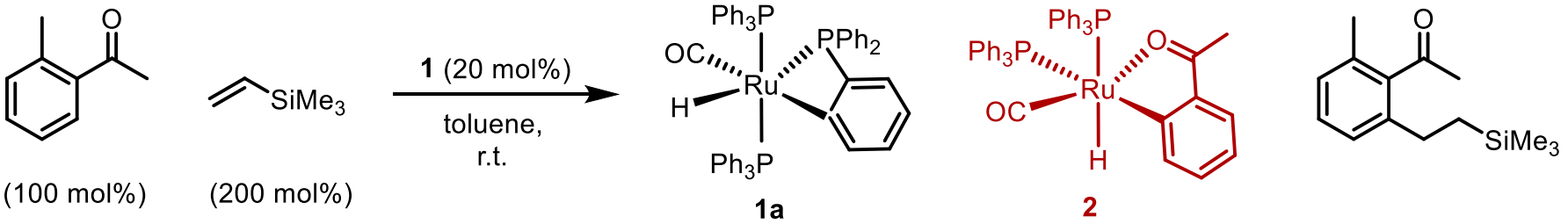
Kakiuchi, F.; Murai, S. et al *J. Am. Chem. Soc.* **2010**, *132*, 17741

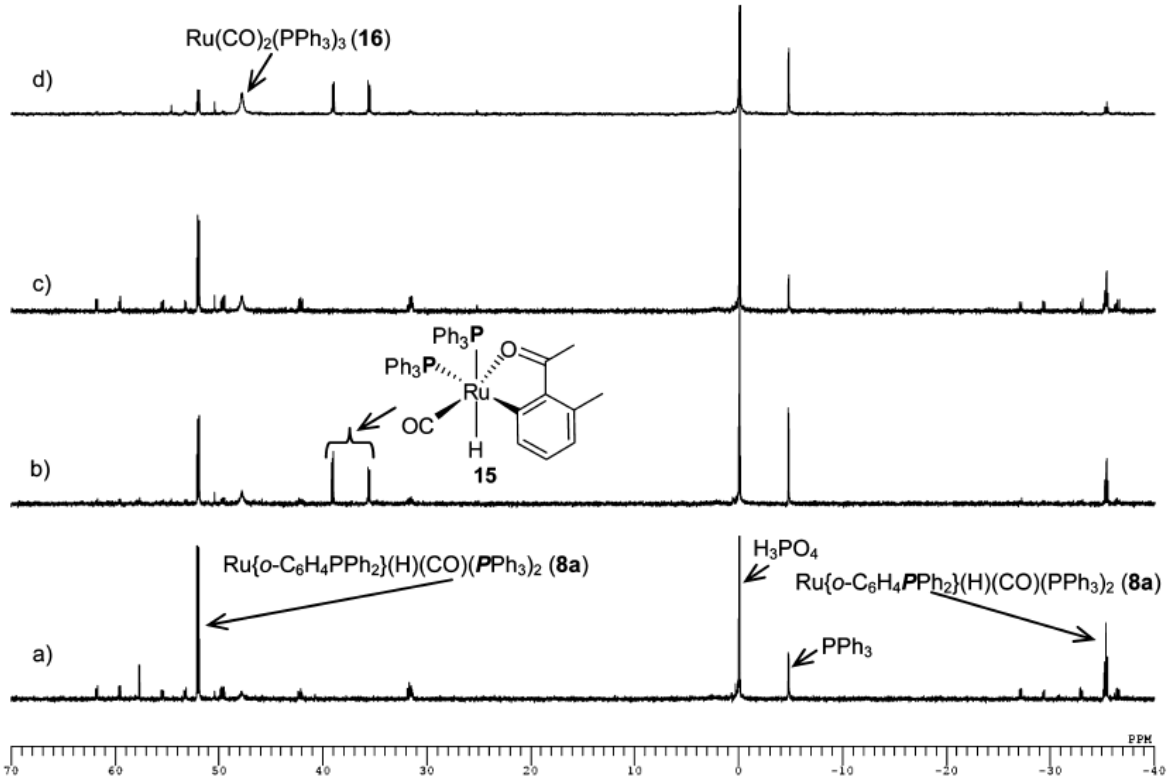
- **Reactivity of active catalyst**



Kakiuchi, F.; Murai, S. et al *J. Am. Chem. Soc.* **2010**, *132*, 17741

- **Dynamic of active catalyst**





3h after more ketone

5 days

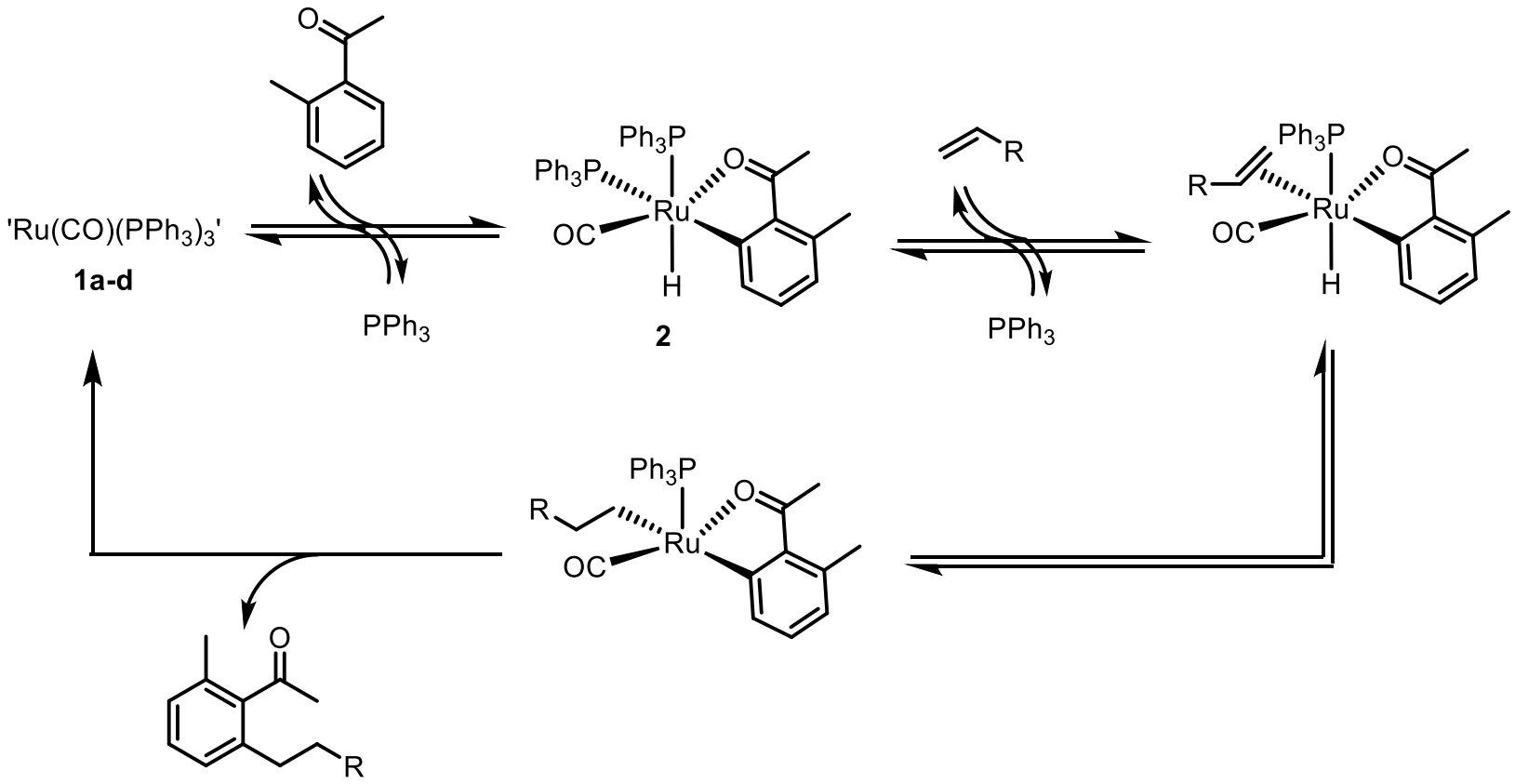
6h

- **1** disappear and re-emerge
- **2** disappeared after rxn
- CO stays
- $Ru(CO)_2(PPh_3)_3$ unreactive

Active catalyst

Kakiuchi, F.; Murai, S. et al *J. Am. Chem. Soc.* **2010**, *132*, 17741

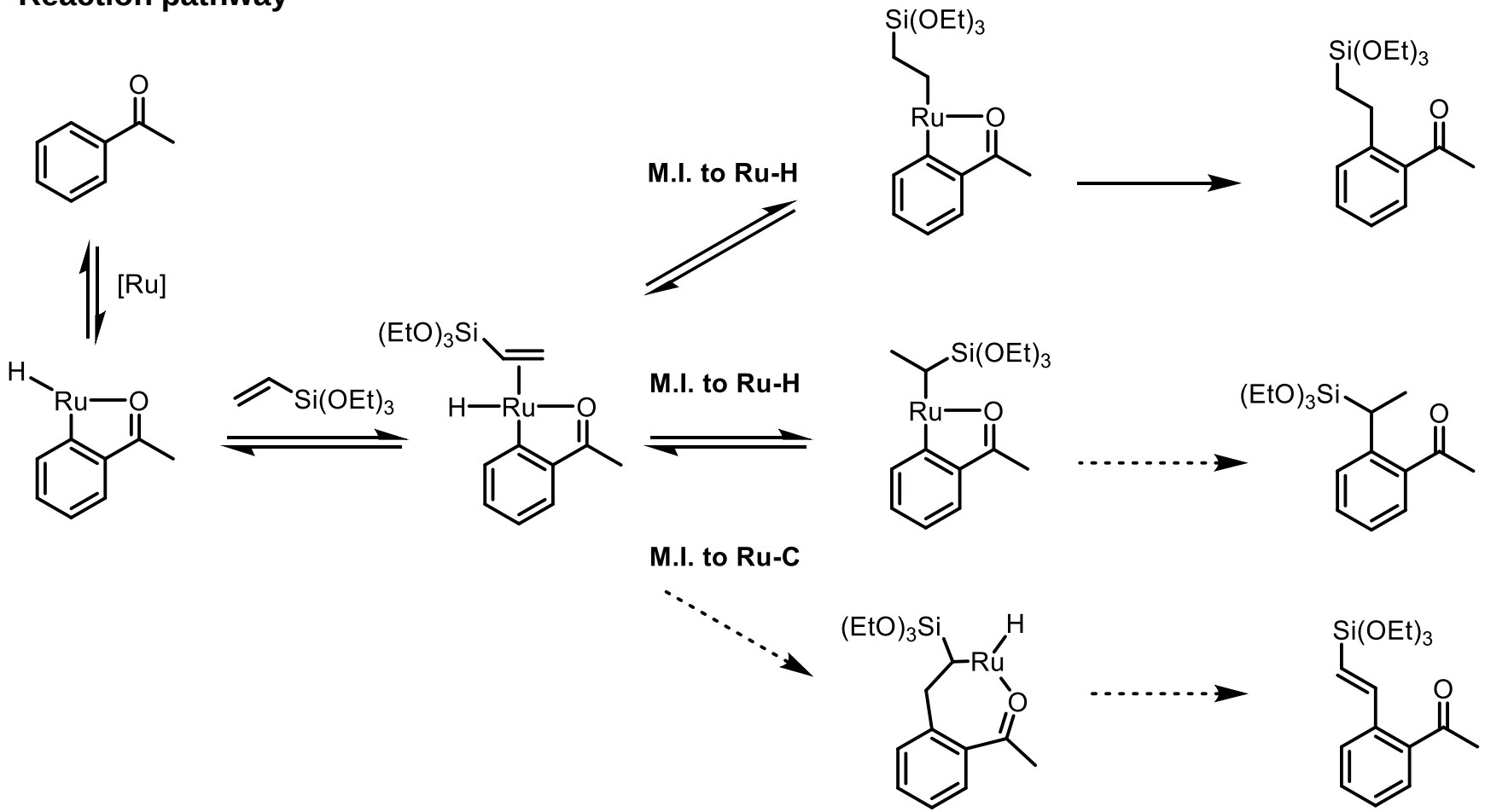
- **Proposed mechanism**



Kakiuchi, F.; Murai, S. et al *J. Am. Chem. Soc.* **2010**, *132*, 17741

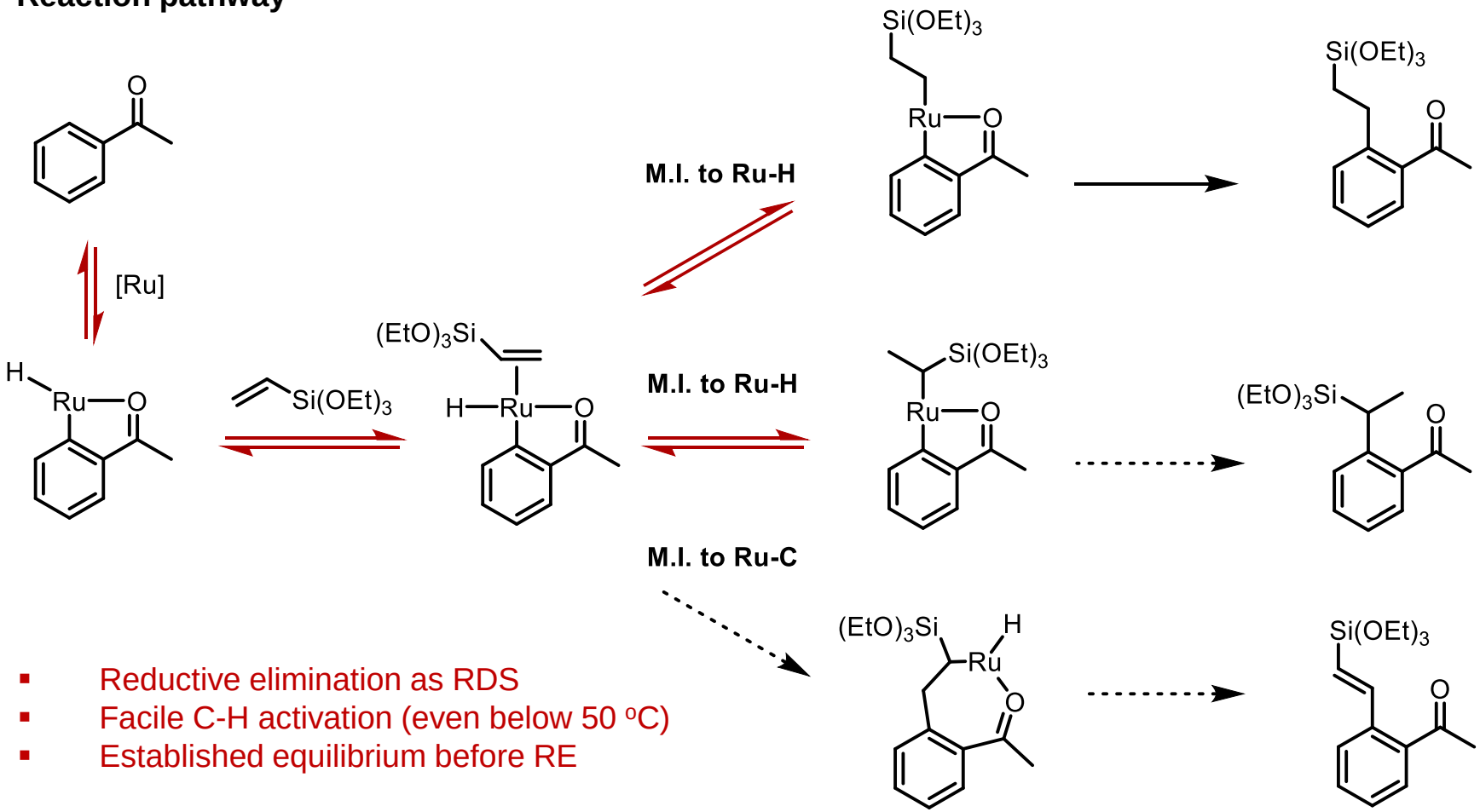
Ketone as Directing Group

- **Reaction pathway**



Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

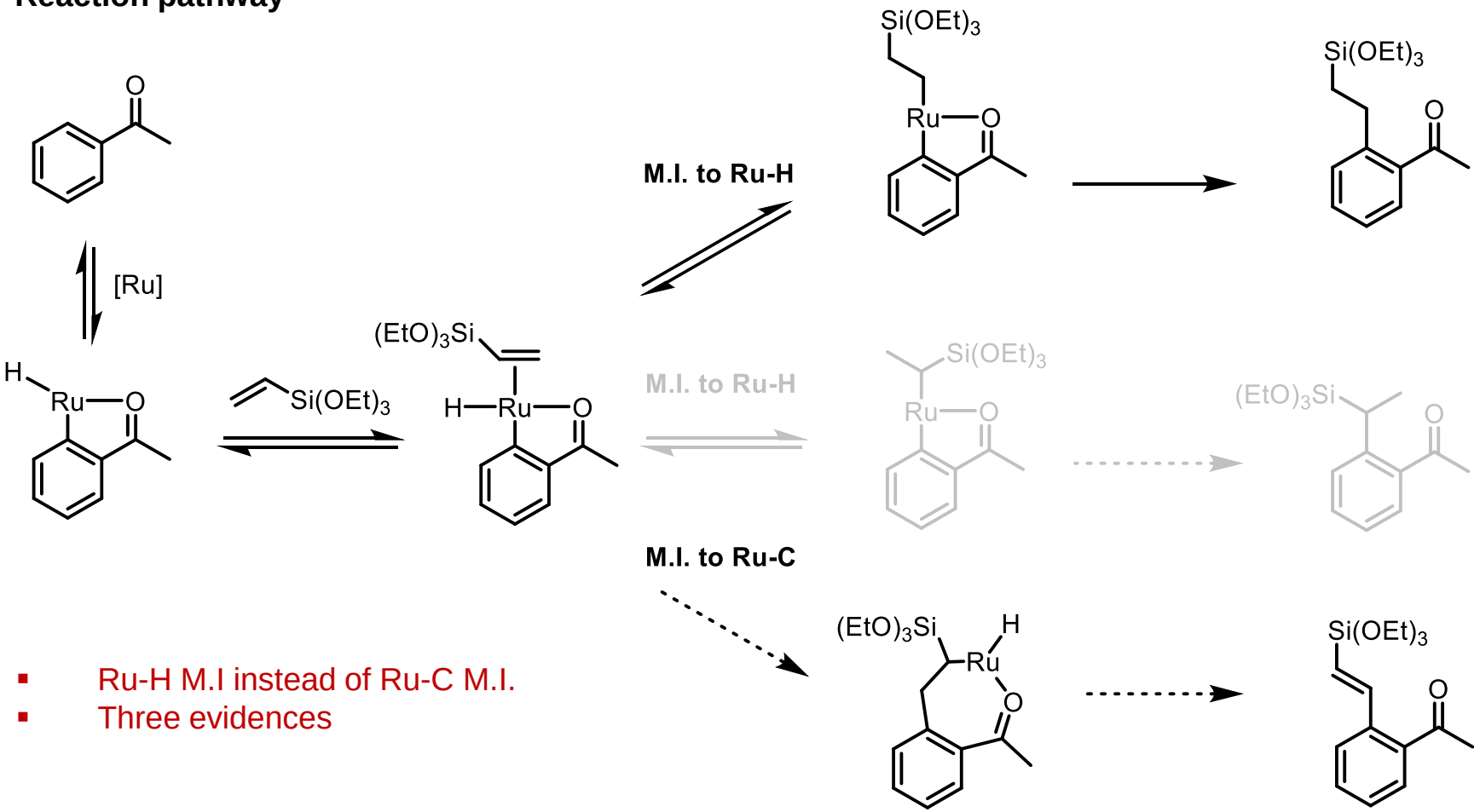
- **Reaction pathway**



- Reductive elimination as RDS
- Facile C-H activation (even below 50 °C)
- Established equilibrium before RE

Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

- **Reaction pathway**



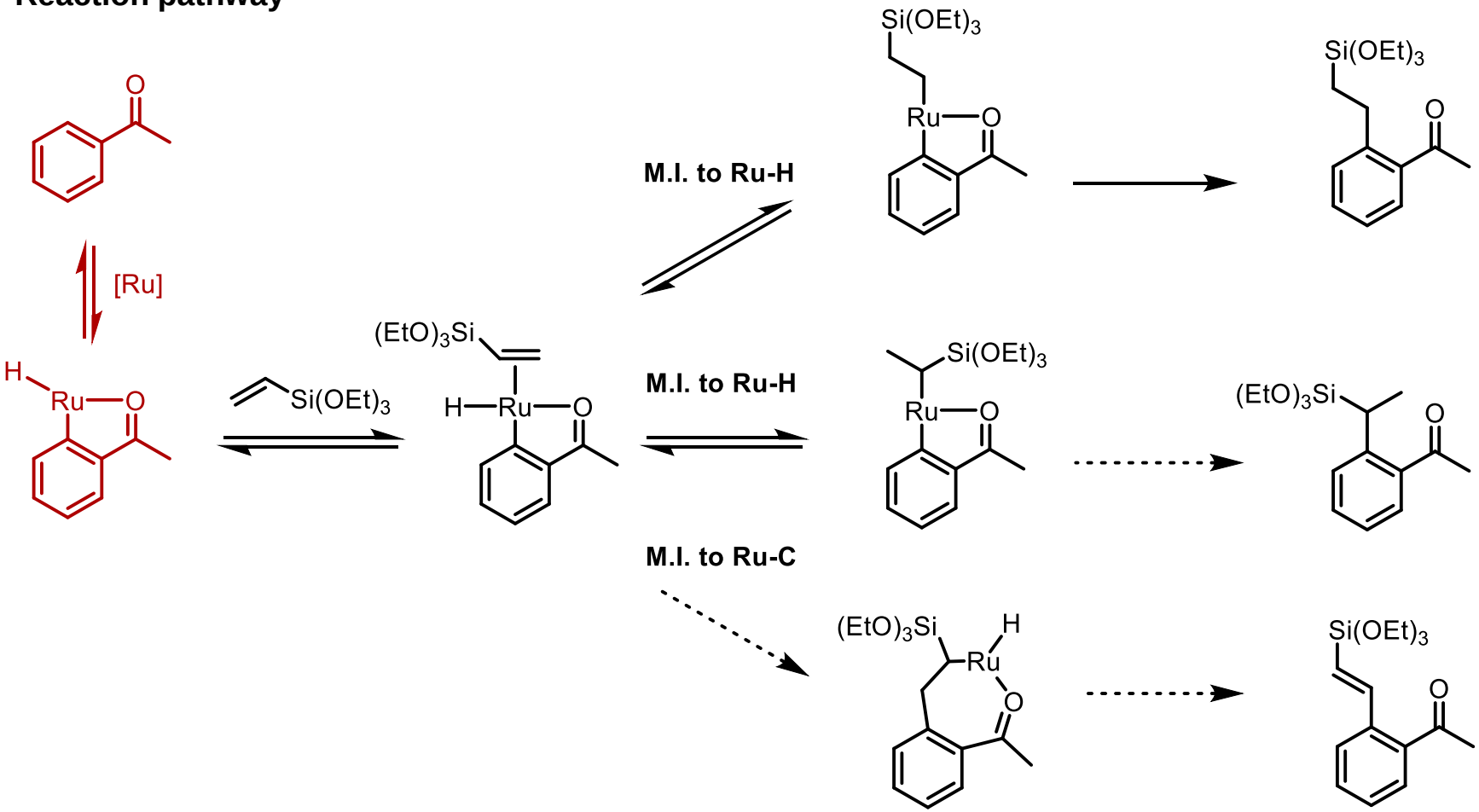
- Ru-H M.I instead of Ru-C M.I.
- Three evidences

Evidence No.1

Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

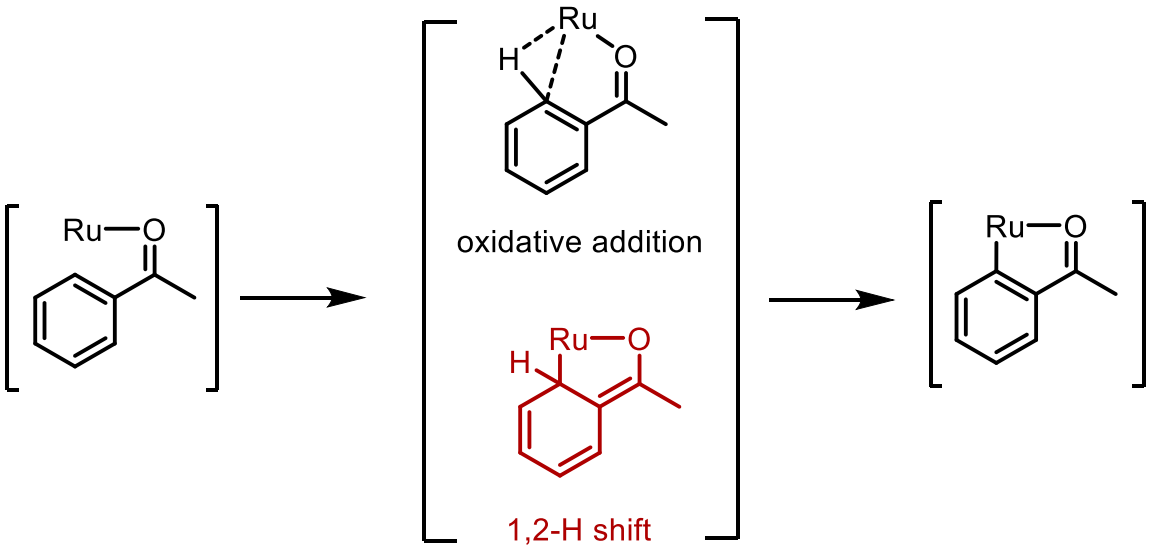
Ketone as Directing Group

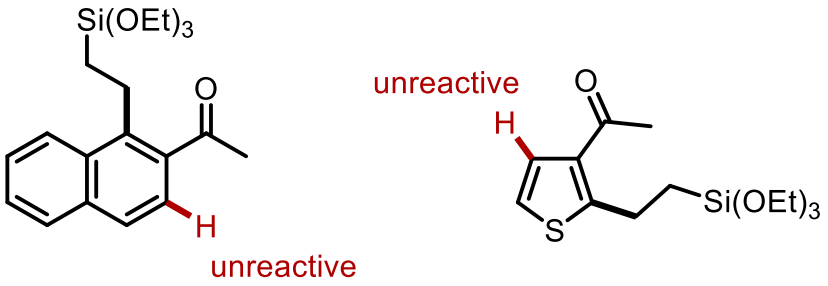
- **Reaction pathway**



Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

- **Reaction pathway**



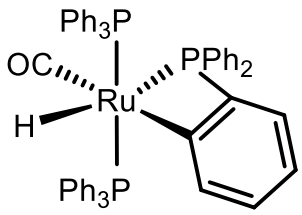


Murai, S. et al *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62

- ***Catalyst Modification and Improvement***
- ***C-C Bond Formation***
- ***C-X Bond Formation***

- ***Catalyst Modification and Improvement***
- *C-C Bond Formation*
- *C-X Bond Formation*

- **Ruthenium precursors**



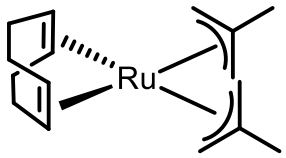
1a

≡ Ru(0) $3PPh_3$ CO

strong σ-donor π-acid

Criteria for active catalyst

- Easy to generate Ru(0)
- Coordinately unsaturated Ru(0)
- Electron-rich Ru(0)

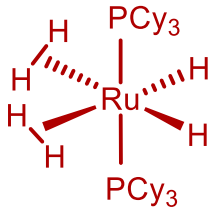


(100 mol%)

PCy_3

(200 mol%)

H_2 (6 bar)

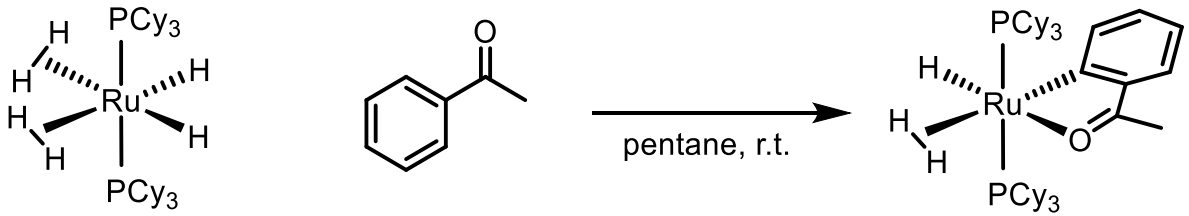


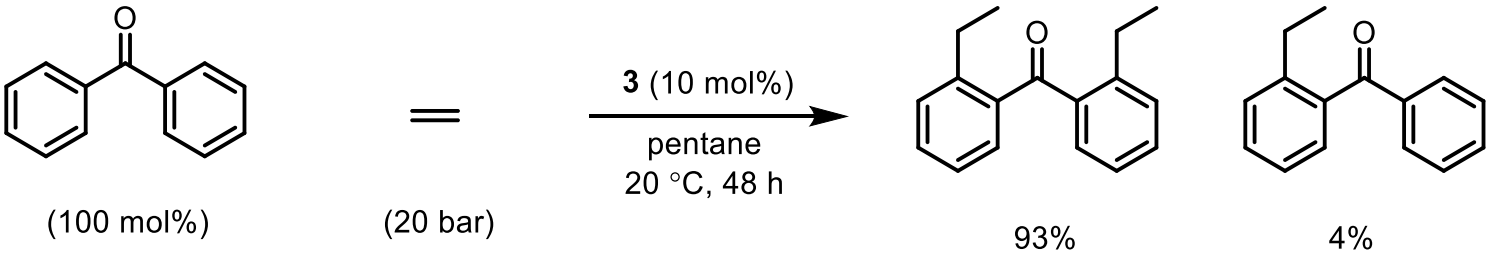
3

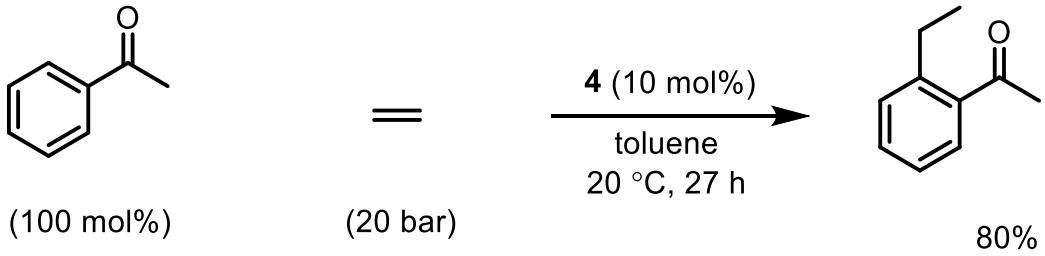
- Two dihydrogen ligands
- Two e-donating P-ligands
- Cy-H hard to insert
- Higher concentration of Ru(0)

Busch, S.; Leitner, W. *Chem. Commun.* **1999**, 2305

- **Ruthenium precursors**



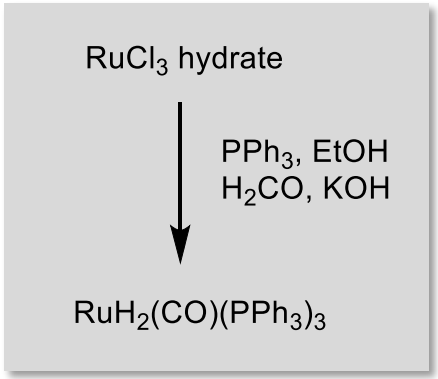




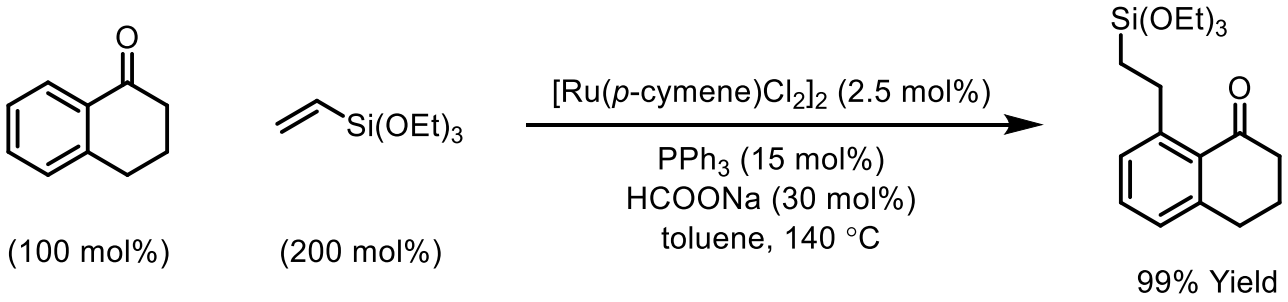
- Only ethylene works
- Bad solubility of **3** in pentane
- Bad stability of **3** in toluene

Busch, S.; Leitner, W. *Adv. Synth. Catal* **2001**, *343*, 192
Chaudret, B. et al *J. Am. Chem. Soc.* **1998**, *120*, 4228

- **In-situ generation of active catalyst**



- Air- and moisture-sensitive
- Tedious preparation
- Complexation with various ligand not allowed

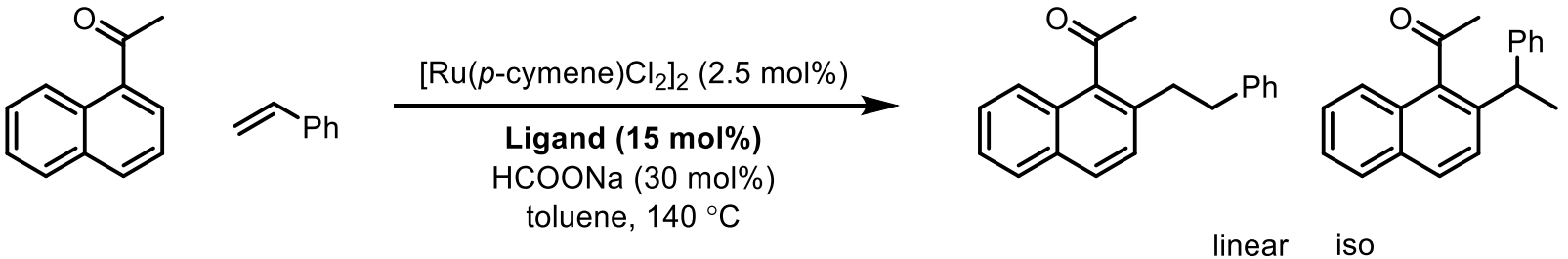


- 3 equiv. of ligand optimal
- PPh_3 as best ligand
- Thallium salt also works as reductant

- Comparable yield and scope as Murai's
- Higher catalyst loading

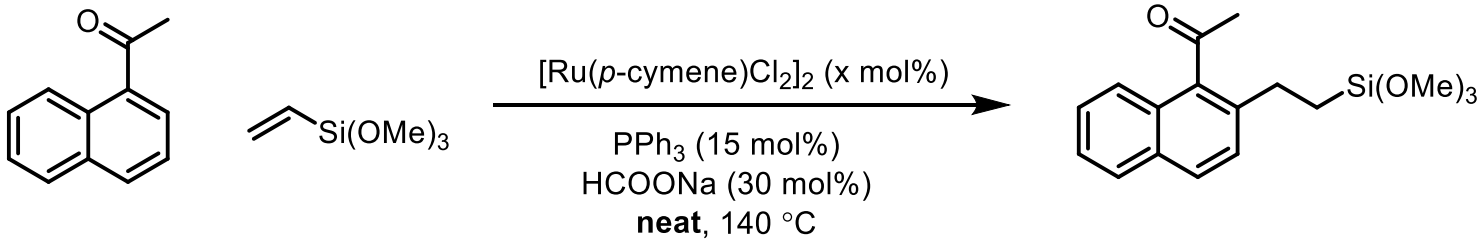
Darse, S.; Genet, J.-P. et al *Angew. Chem. Int. ed.* **2006**, *45*, 8232

- **In-situ generation of active catalyst**
  - Ligand-controlled selectivity



	linear	iso
PPh_3	60	40
$PPhCy_2$	95	5

  - High catalyst turnover



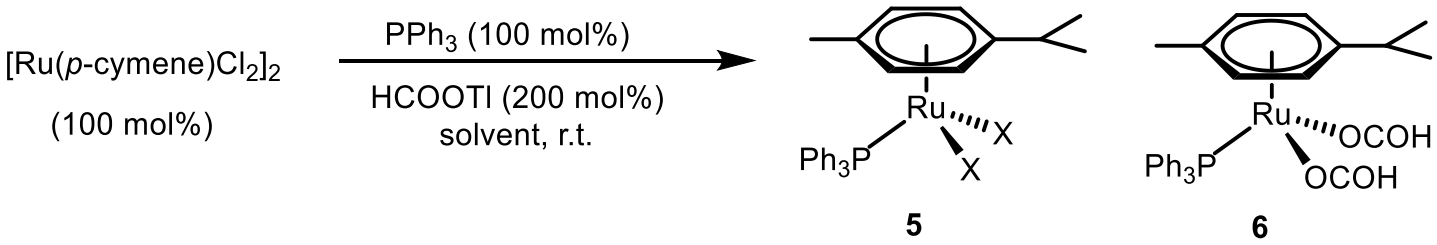
(50 mmol) (150 mmol)

% cat.	Yield(%)	TON
0.2	89	445
0.04	45	1125

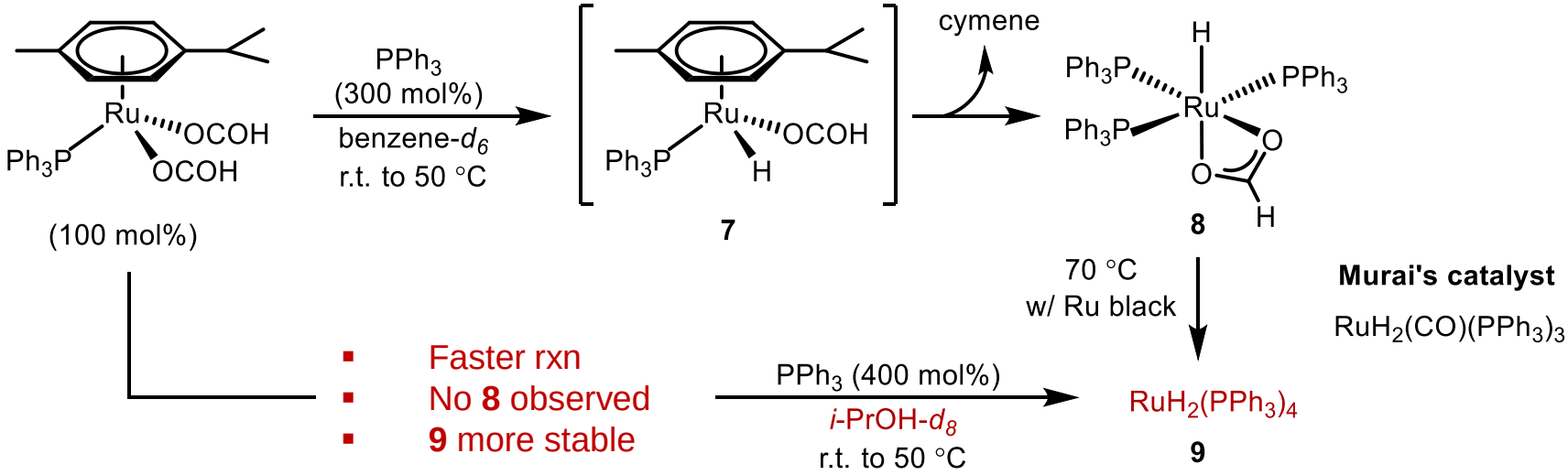
  - Low conversion though

Darse, S.; Genet, J.-P. et al *Angew. Chem. Int. ed.* **2006**, *45*, 8232

- **Mechanism elucidation**



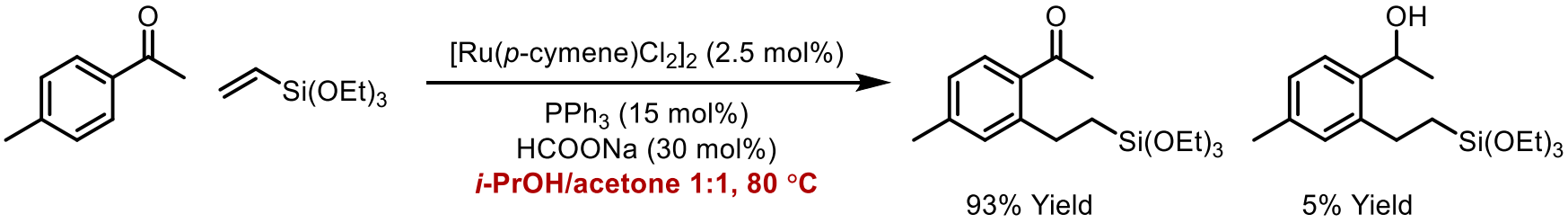
X = I	benzene-d_6	22h	51	49
	MeOH-d_4	2h	51	100
X = Cl	MeOH-d_4	2h	51	100



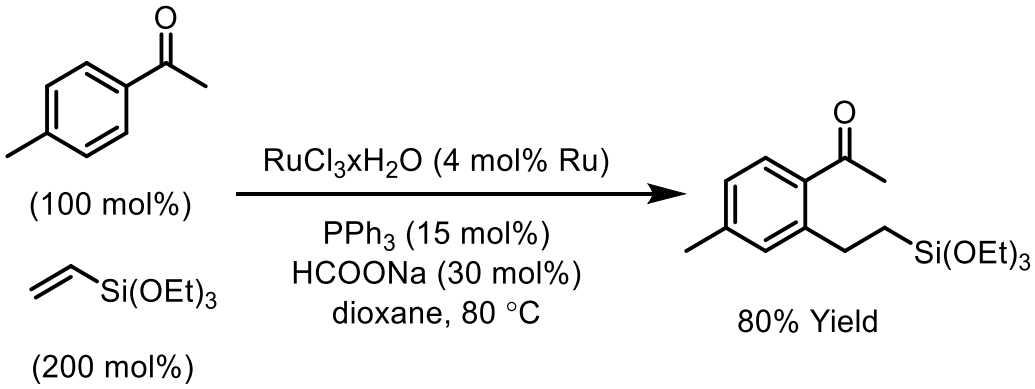
Darse, S. et al *J. Am. Chem. Soc.* **2009**, *131*, 7887

Catalyst Modification and Improvement

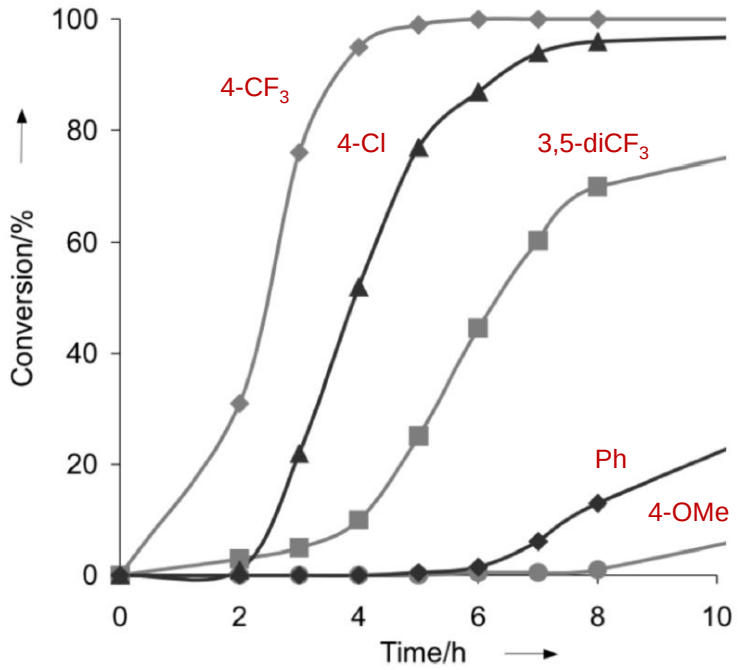
- **In-situ generation of active catalyst**
  - *i*-PrOH as solvent



  - $RuCl_3$ as precursor



Precursor	price(euro/mmol)
$RuCl_3$	2.7
$RuH_2(CO)(PPh_3)_3$	87
$RuH_2(PPh_3)_4$	160
$Ru_3(CO)_{12}$	38
$[RuCl_2(p\text{-cymene})]_2$	21

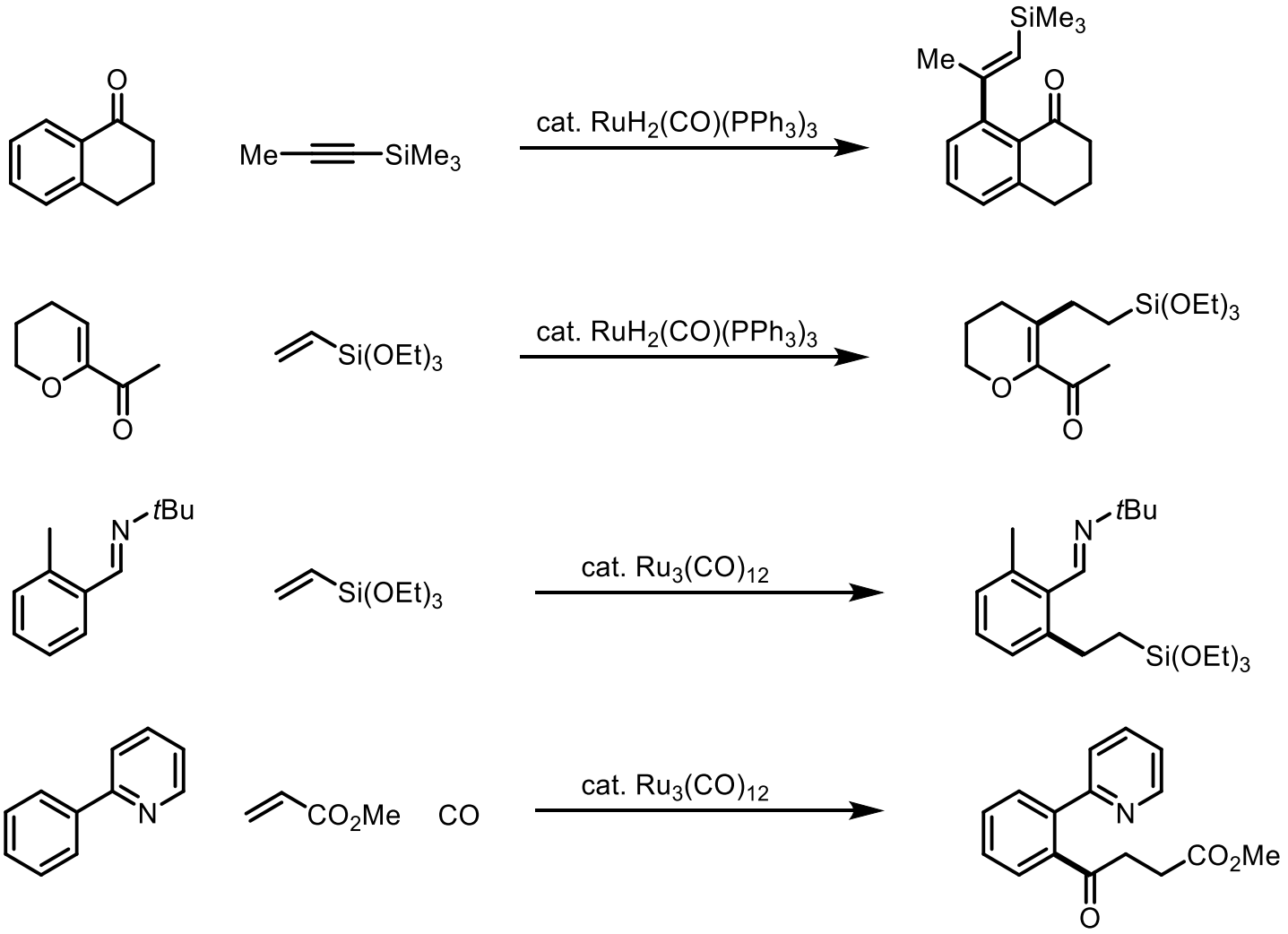


performances of PAr_3

Darse, S. et al *J. Org. Chem.* **2010**, *75*, 208
Darse, S. et al *Org. Lett.* **2010**, *12*, 3038

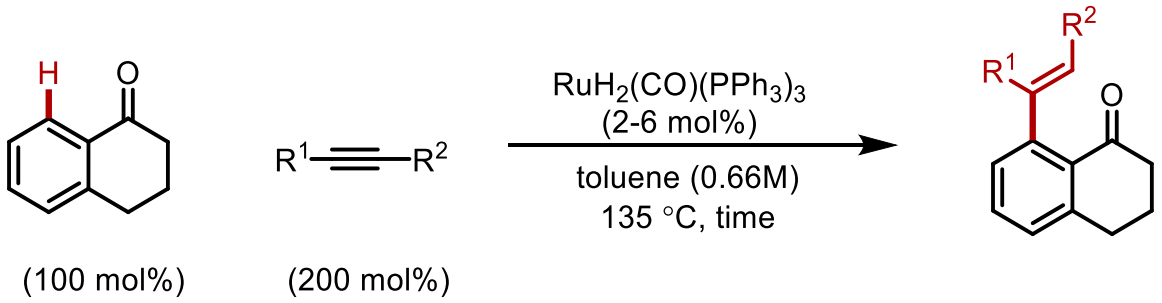
- *Catalyst Modification and Improvement*
- ***C-C Bond Formation***
- *C-X Bond Formation*

- **Murai's preliminary results**



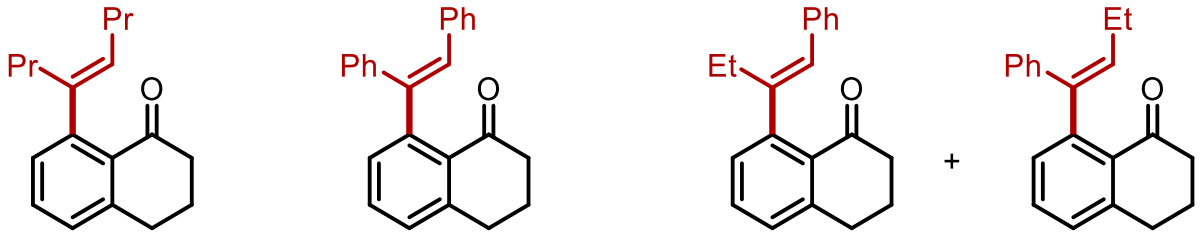
Murai, S. et al *J. Syn. Org. Chem. Jpn.* **1994**, *52*, 992

- **Addition to alkynes**

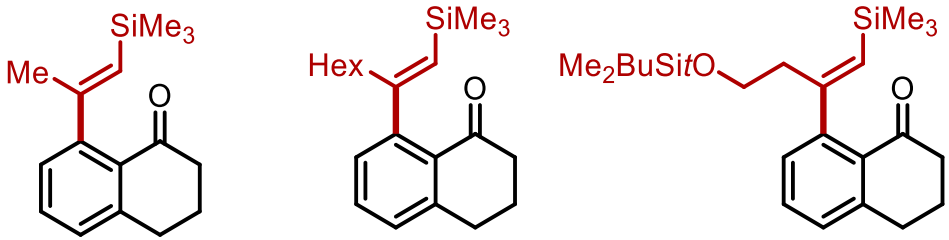


(100 mol%) (200 mol%)

selected examples



4h, 72% (*E/Z* 16/1) | 1h, 85% (*E/Z* 9/1) | 4h, 73% (5/1) | 27% (*5*/1)



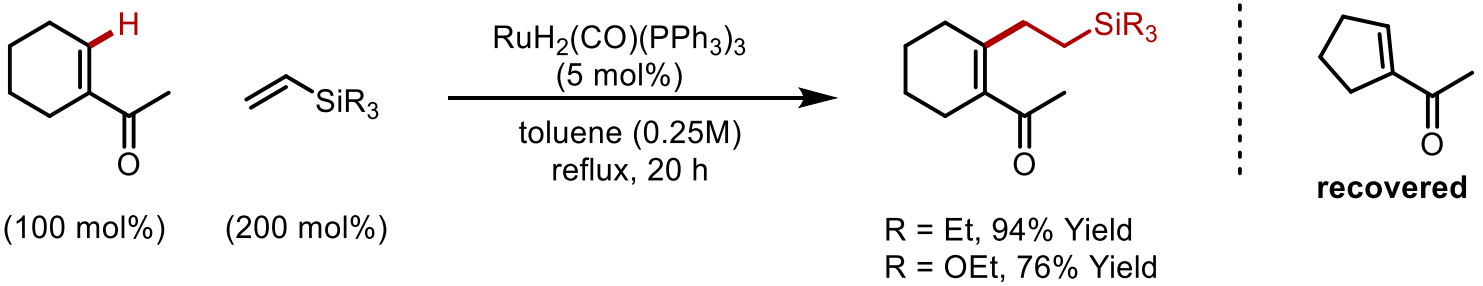
3h, 83% (only *E* isomer) | 2h, Quant. (*E/Z* 11/1) | 21h, 55% (*E/Z* 11/1)

- Terminal alkyne not working
- Internal olefin not working

Murai, S. et al *Chem. Lett.* **1995**, 681

- **Functionalization of olefinic C-H bond**
  - Addition to alkenes

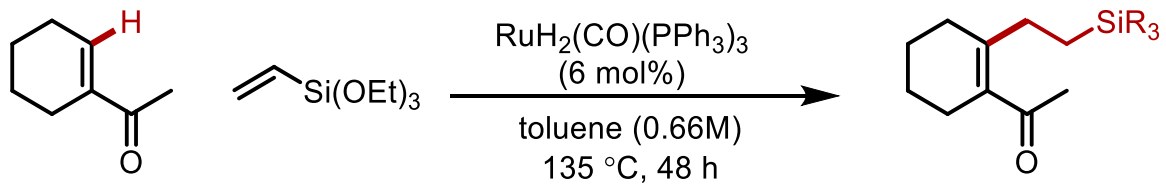
Trost



(100 mol%) (200 mol%)

R = Et, 94% Yield
R = OEt, 76% Yield

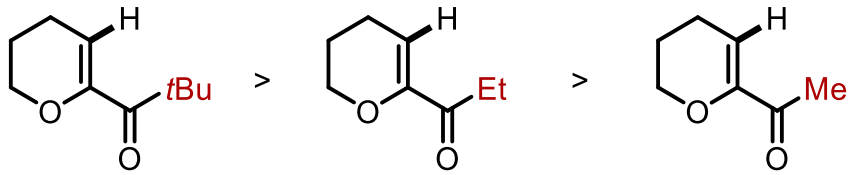
Murai



(100 mol%) (200 mol%)

ca. 50% Yield

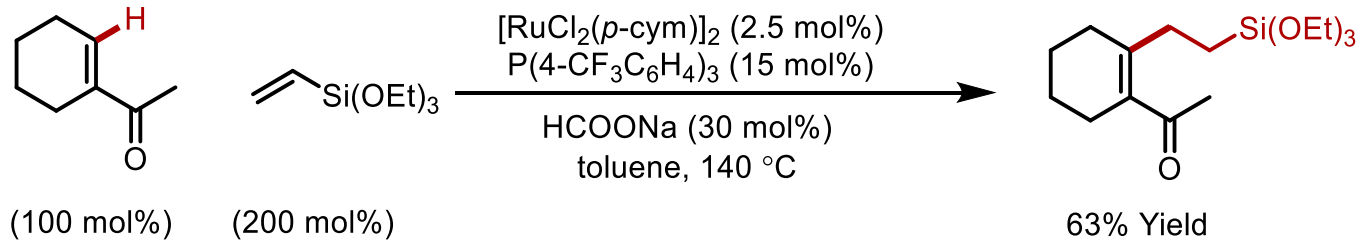
reaction rate



Trost, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 5371
Murai, S. et al *Chem. Lett.* **1995**, 679

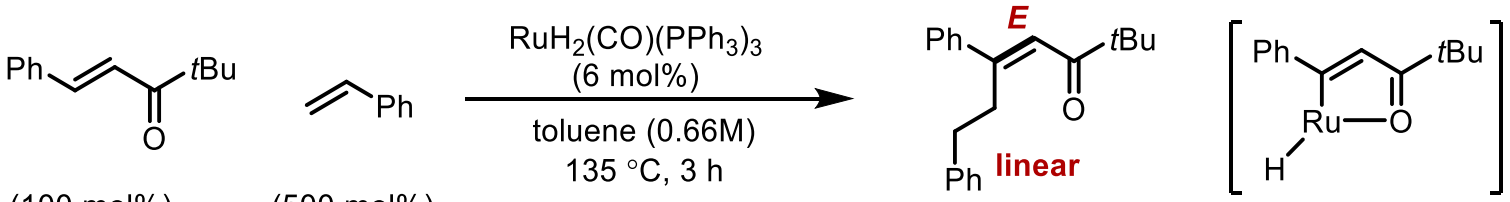
- **Functionalization of olefinic C-H bond**
  - Addition to alkenes

Darses

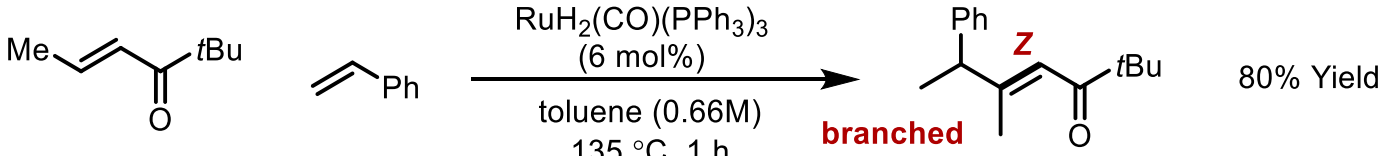


(100 mol%) (200 mol%) 63% Yield

Murai



(100 mol%) (500 mol%) 64% Yield
not isomerized from Z

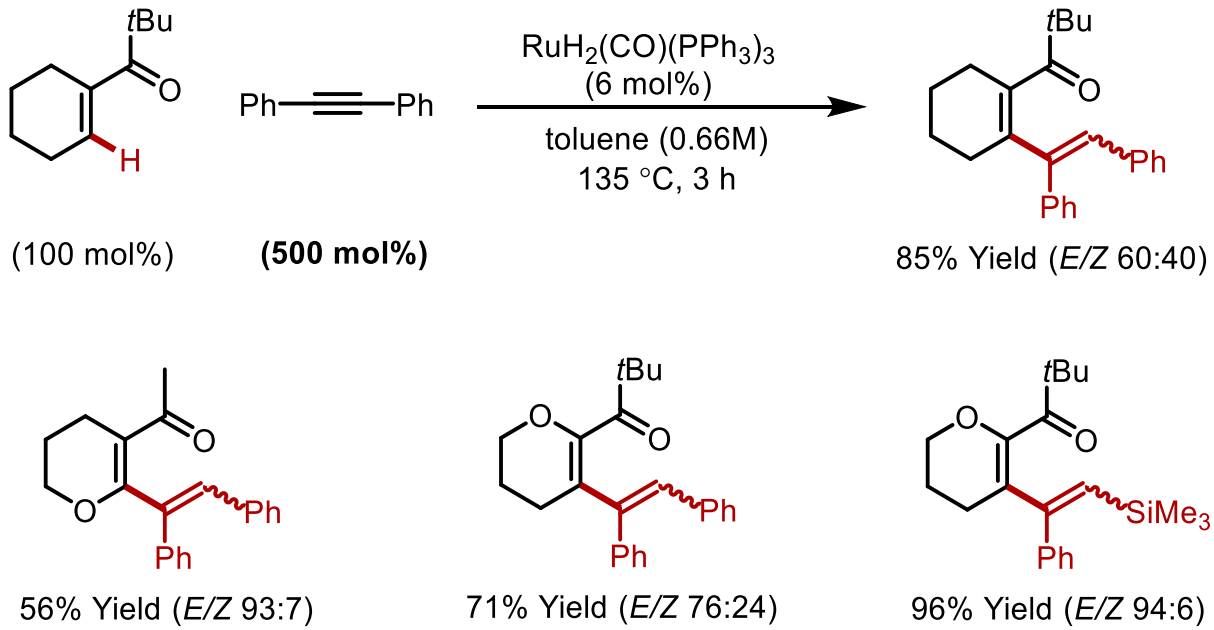


(100 mol%) (500 mol%) 80% Yield

Darse, S. et al *Adv. Synth. Catal.* **2009**, 351, 153
Murai, S. et al *Chem. Lett.* **1998**, 893

- **Functionalization of olefinic C-H bond**
  - Addition to alkynes

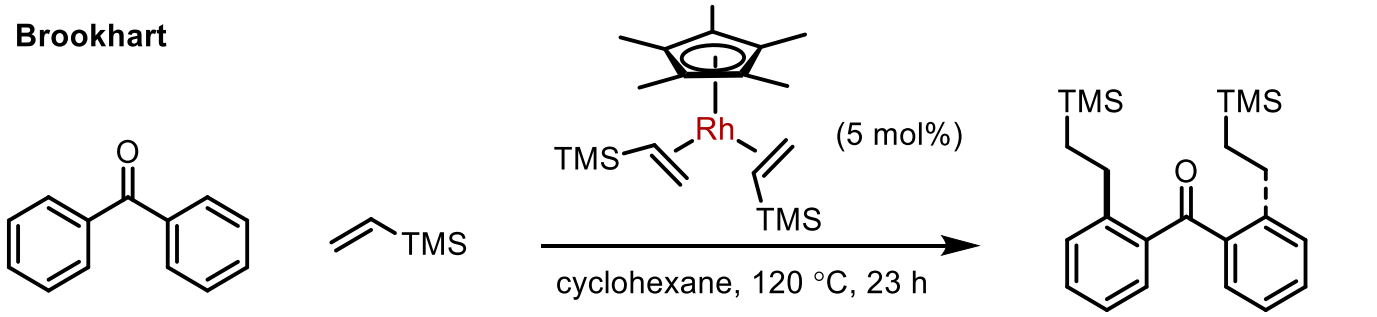
Murai



Murai, S. et al *J. Mol. Cat. A.* **2002**, *182*, 511

- **Addition to olefin or alkyne using other metals**

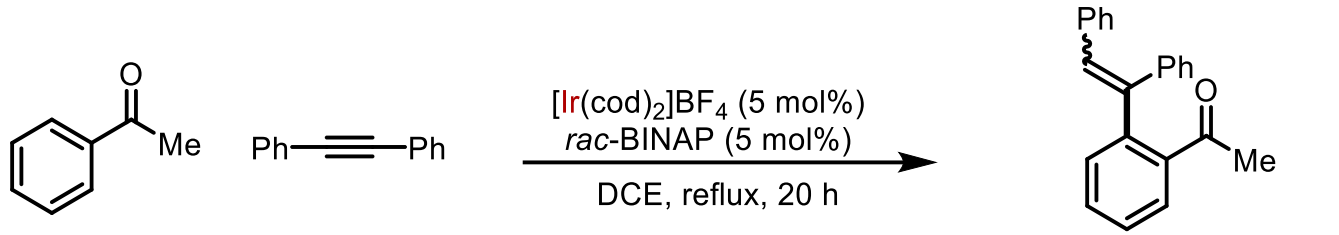
Brookhart



(100 mol%) (100 mol%)

99% Yield (mono:di 8:1)

Shibata



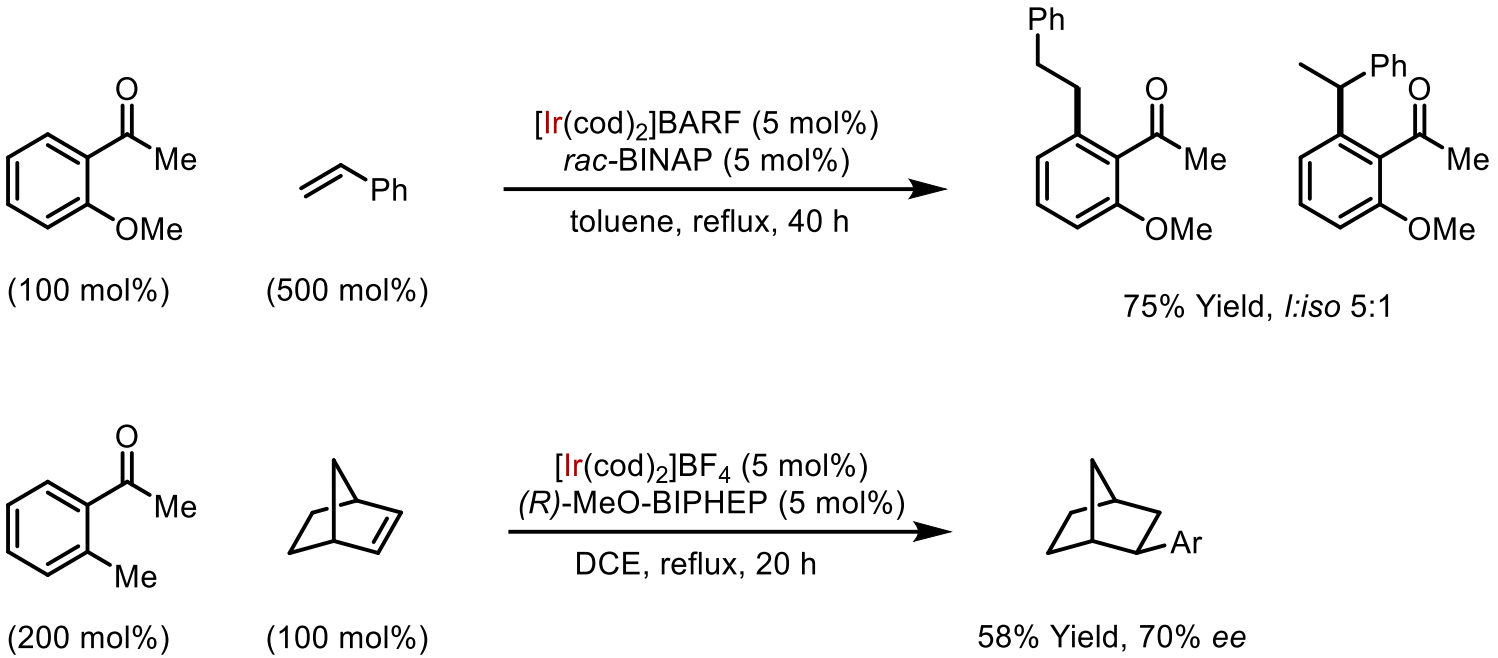
(200 mol%) (100 mol%)

83% Yield (*E/Z* > 20:1)
15% di

Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616
Shibata, T. et al *J. Organomet. Chem.* **2008**, *693*, 3939

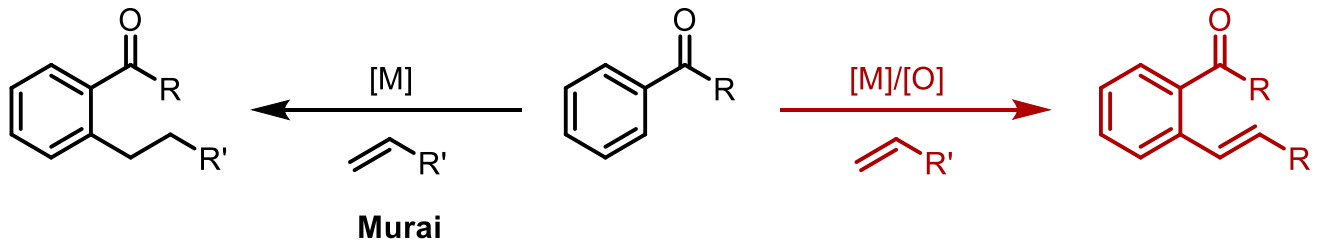
- **Addition to olefin or alkyne using other metals**

Shibata

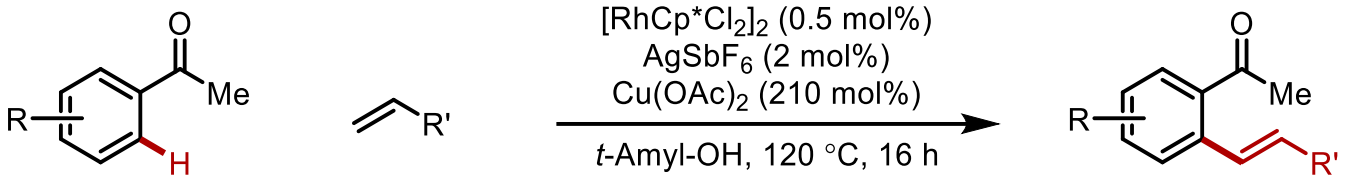


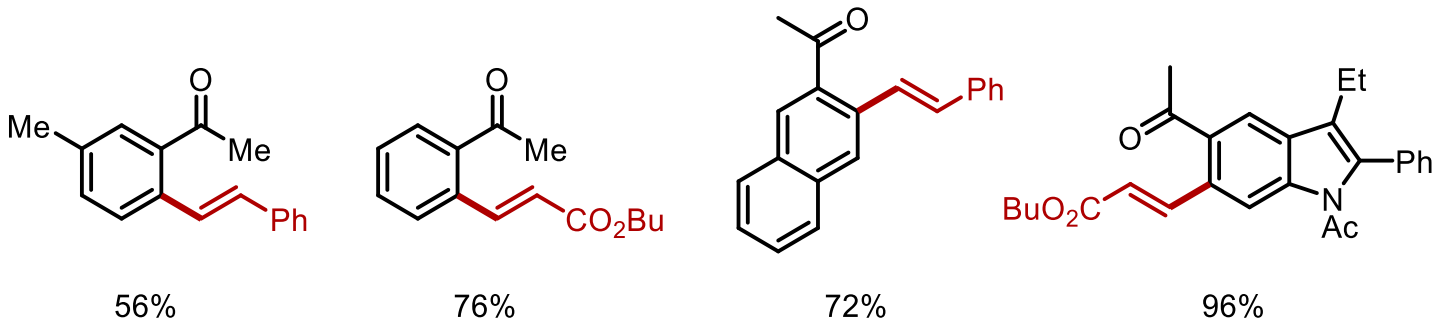
Shibata, T. et al *J. Organomet. Chem.* **2008**, *693*, 3939

- **Oxidative Murai chemistry**



Glorius

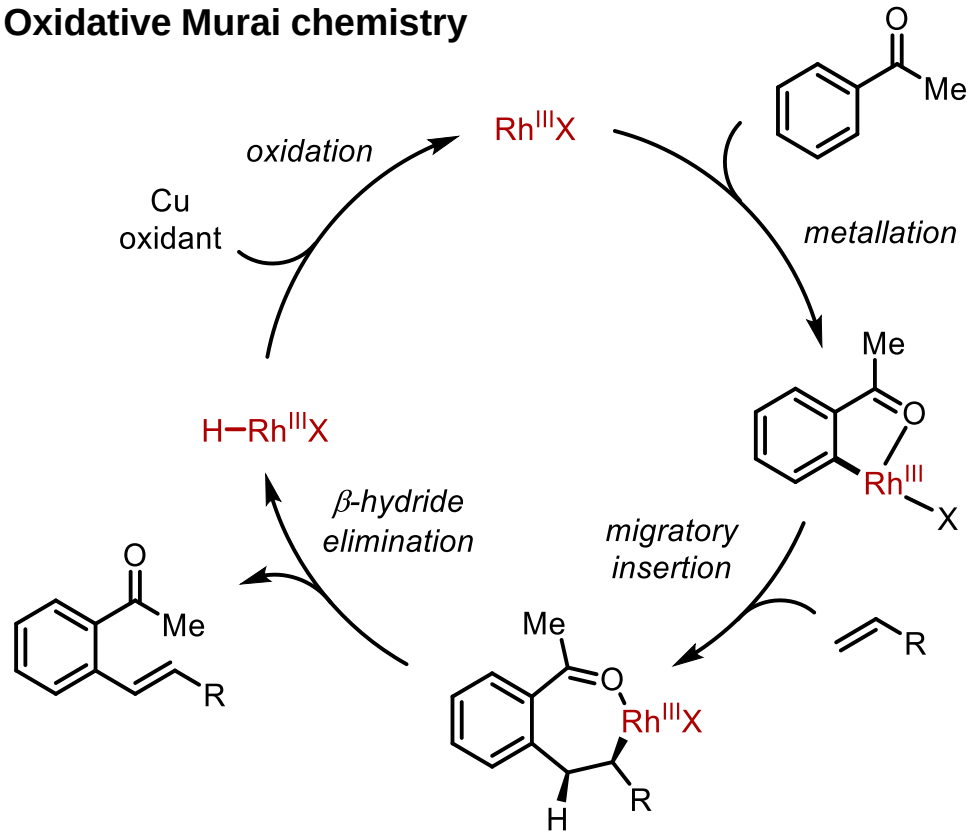




- Michael acceptor
- Regioselectivity

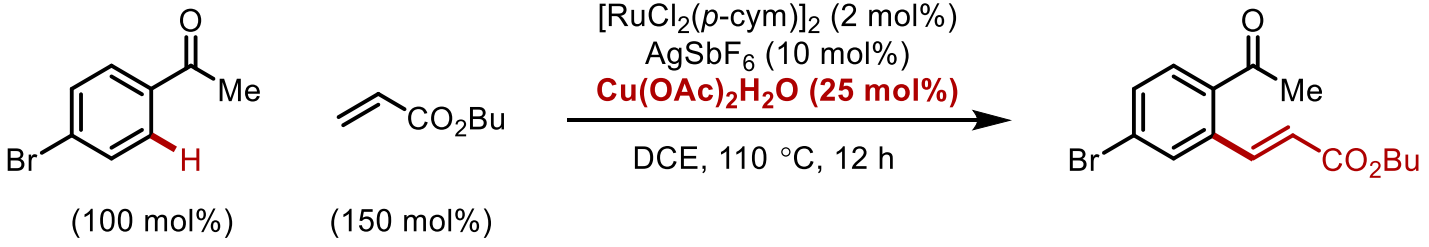
Glorius, F. et al *Angew. Chem. Int. Ed.* **2011**, *50*, 1064

- **Oxidative Murai chemistry**



- Different metallation
- Different M.I.
- Different product-forming step

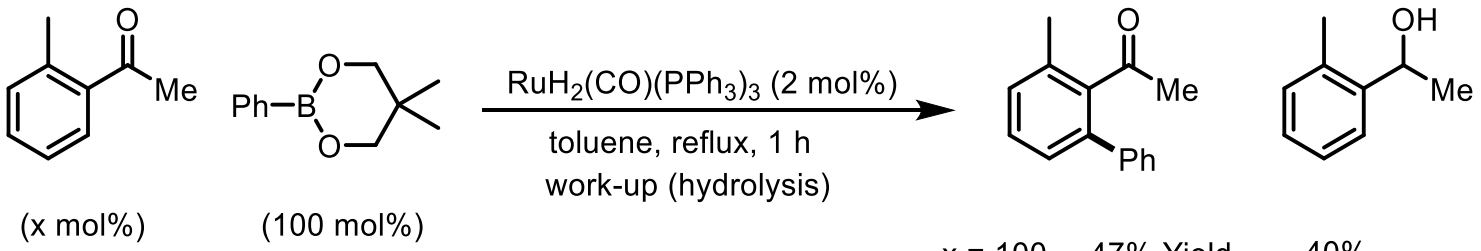
Jeganmohan

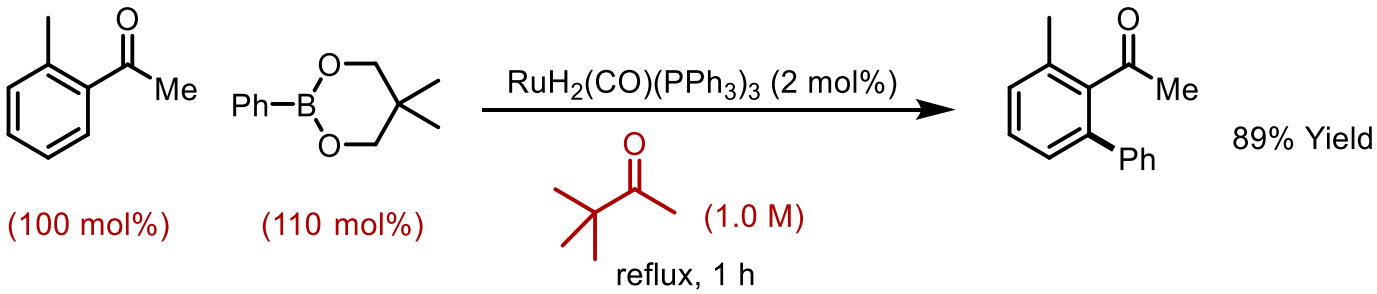


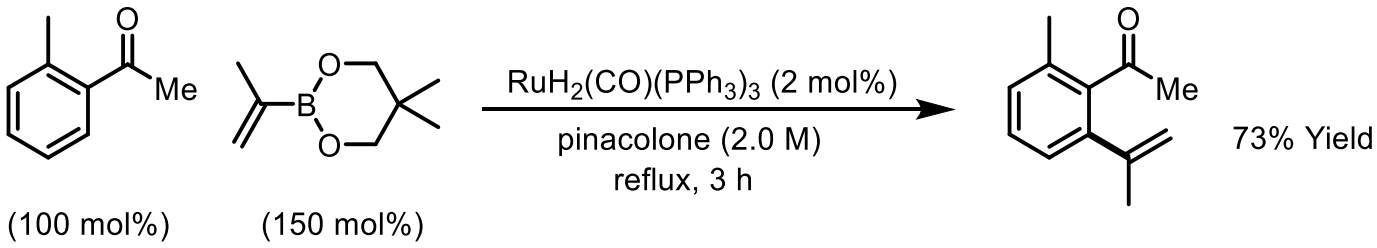
(100 mol%) (150 mol%)

Glorius, F. et al *Angew. Chem. Int. Ed.* **2011**, *50*, 1064
Jeganmohan, M. et al *Org. Lett.* **2011**, *13*, 6144

- **Arylation and alkenylation using boron reagents**



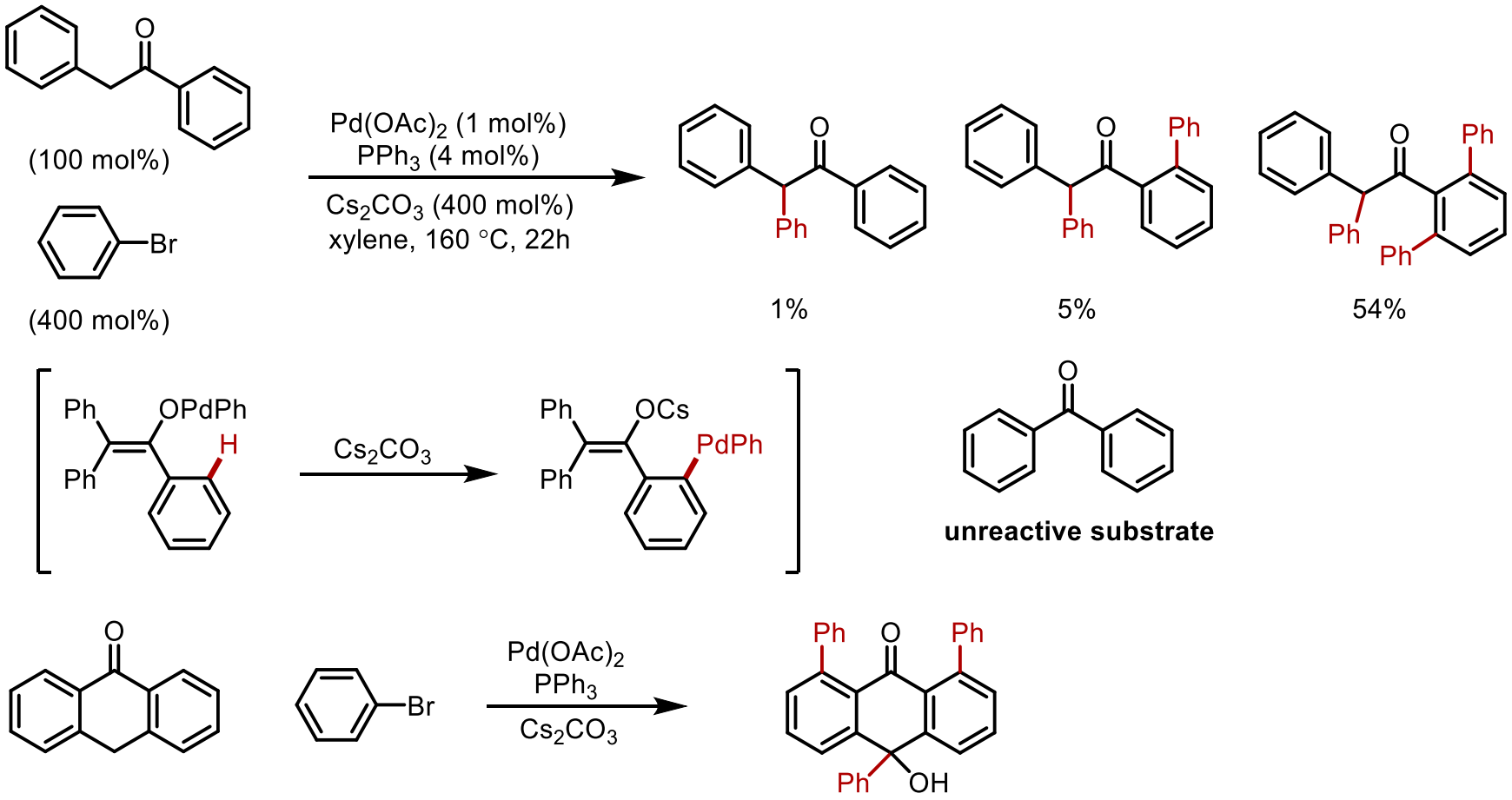




- Complimentary to alkyne addition

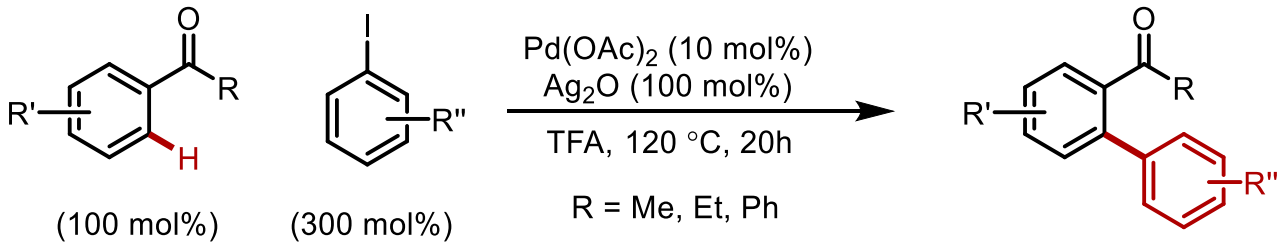
Kakiuchi, F. *J. Am. Chem. Soc.* **2003**, *125*, 1698
Kakiuchi, F. *J. Am. Chem. Soc.* **2005**, *127*, 5936
Kakiuchi, F. *J. Org. Chem.* **2007**, *72*, 3600

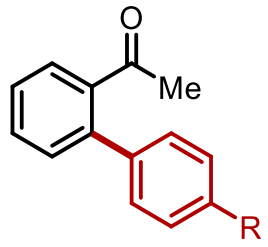
- **Global arylation using aryl bromide**



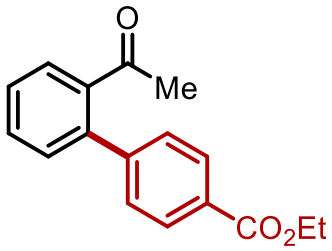
Miura, M. et al *Tetrahedron Lett.* **1999**, *40*, 5345
Miura, M. et al *Tetrahedron* **2001**, *57*, 5967

- **Arylation using aryl bromide**

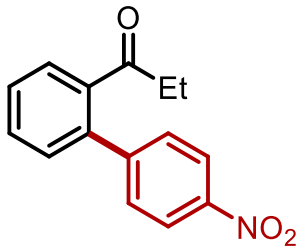




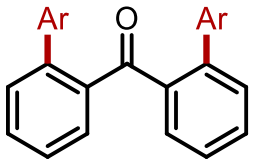
R = H, 23%
R = OMe, 20%



78% Yield



68% Yield



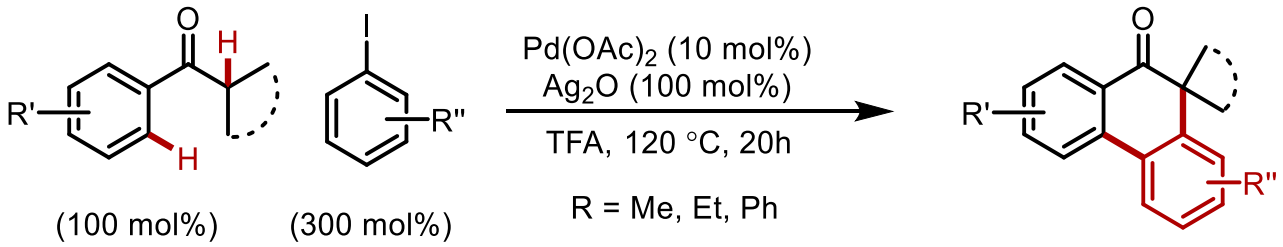
Ar = 4-$NO_2C_6H_4$

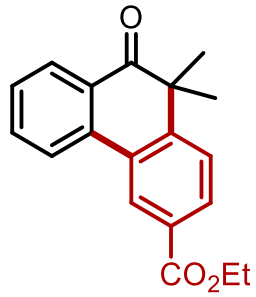
82% Yield

- Acidic conditions
- Only electron-poor aryl iodides work well
- Non-enolizable ketone works

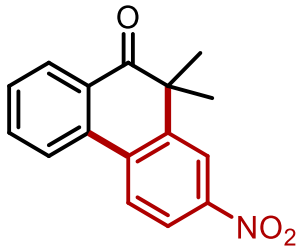
Cheng, C.-H. et al *J. Am. Chem. Soc.* **2010**, *132*, 8569

- **Arylation using aryl bromide**

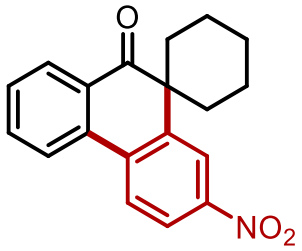




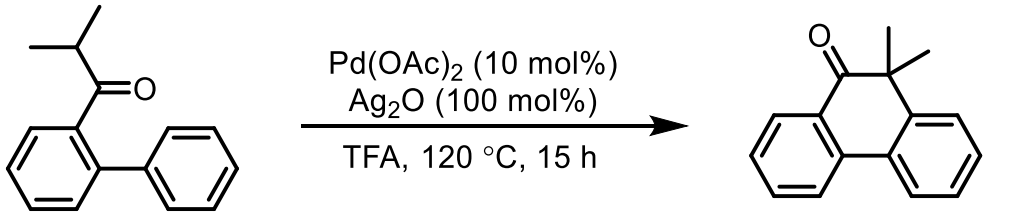
68% Yield



69% Yield



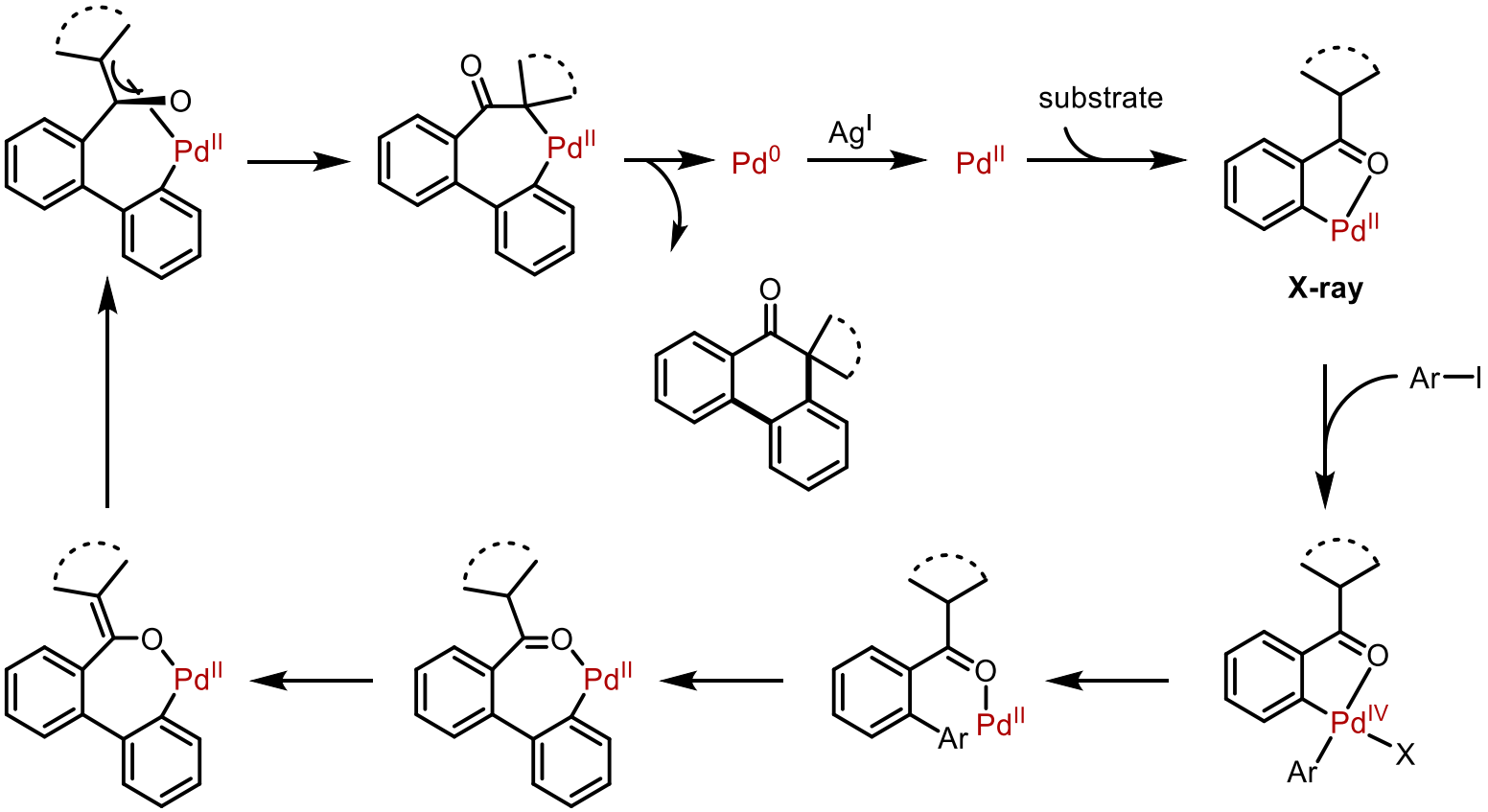
72% Yield



94% Yield

Cheng, C.-H. et al *J. Am. Chem. Soc.* **2010**, *132*, 8569

- **Arylation using aryl bromide**

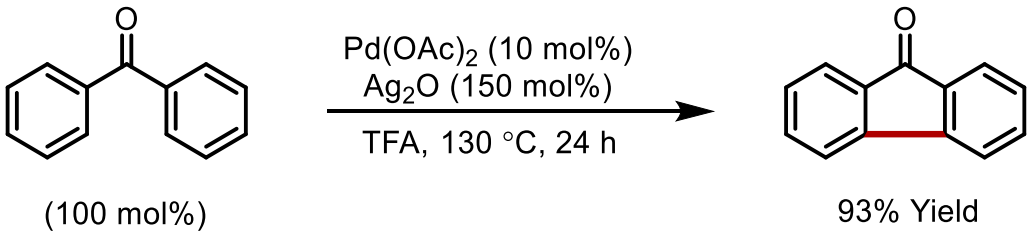


- Weaker C-H bond
- More stable enolate

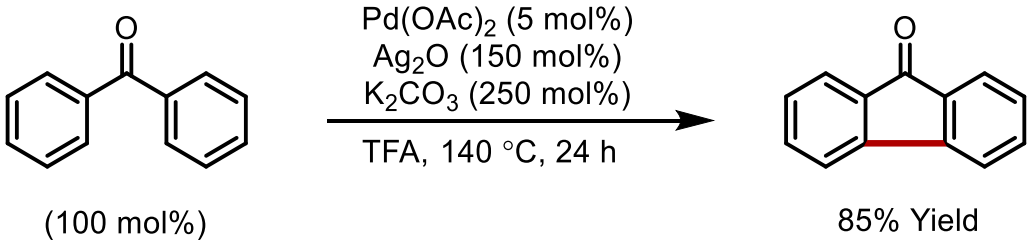
Cheng, C.-H. et al *J. Am. Chem. Soc.* **2010**, *132*, 8569

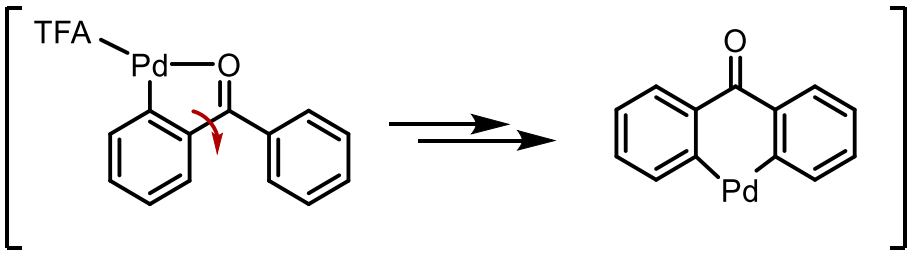
- **Fluorenone Synthesis**

Cheng



Shi



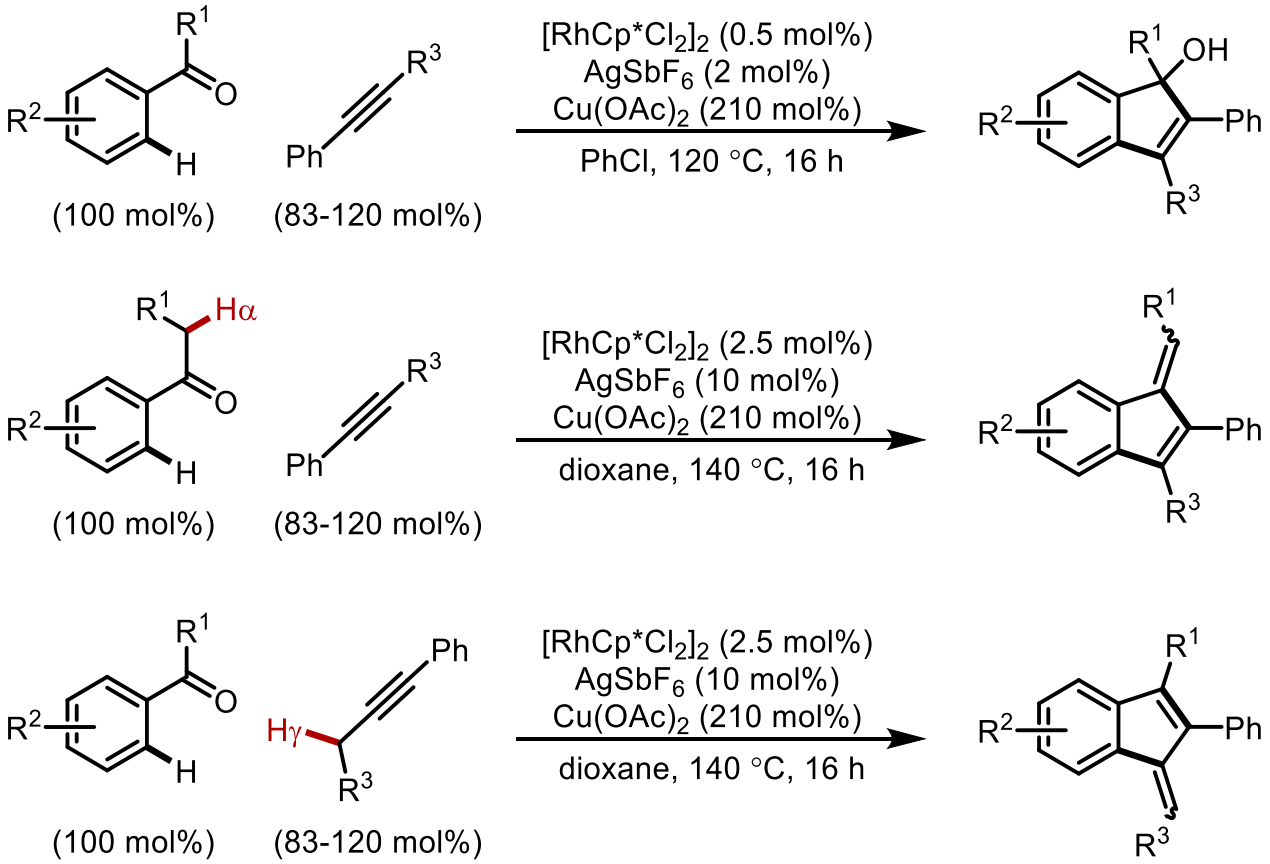


- Benzophenone imine, oxime, and hydrazone not working

Shi, Z. et al *Org. Lett.* **2012**, *14*, 4850.
Cheng, C.-H. et al *Chem. Commun.* **2012**, *48*, 9379

- **Indenol and fulvene synthesis**

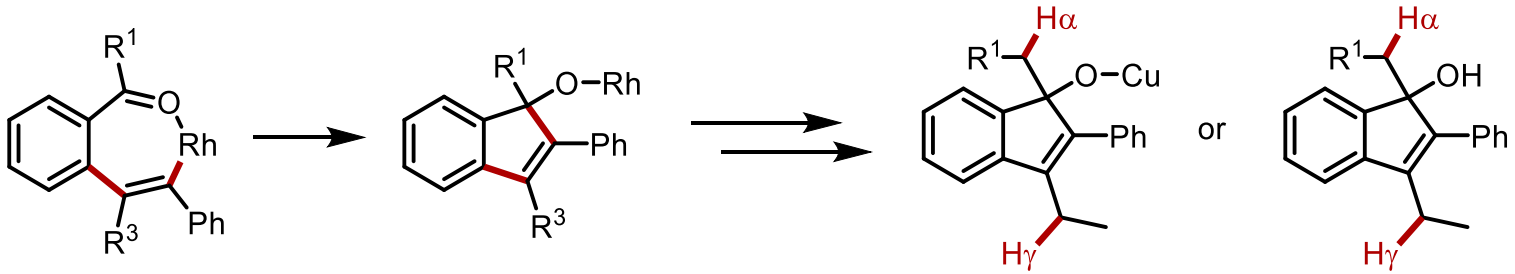
Glorius

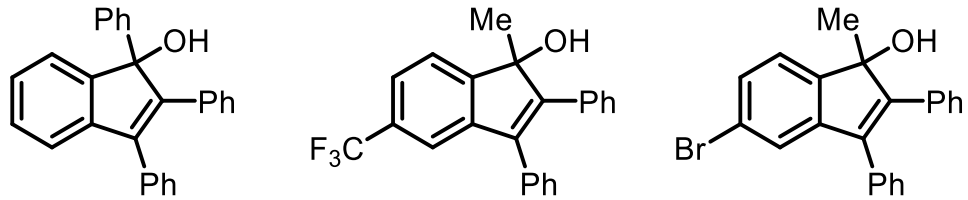


- Redox-neutral but stoichiometric Cu needed

Glorius, F. et al *J. Am. Chem. Soc.* **2011**, *133*, 2154

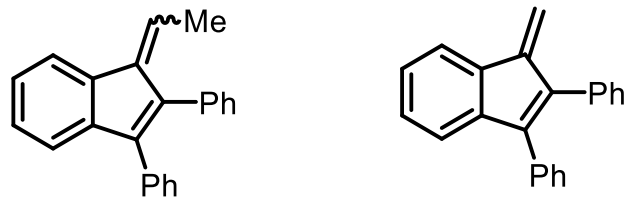
- **Indenol and fulvene synthesis**





66% 66% 66%

- Electron-neutral and rich arenes favor dehydration



α: 69% (*E/Z* 2.3:1)
γ: 80% (*E/Z* 2.8:1)

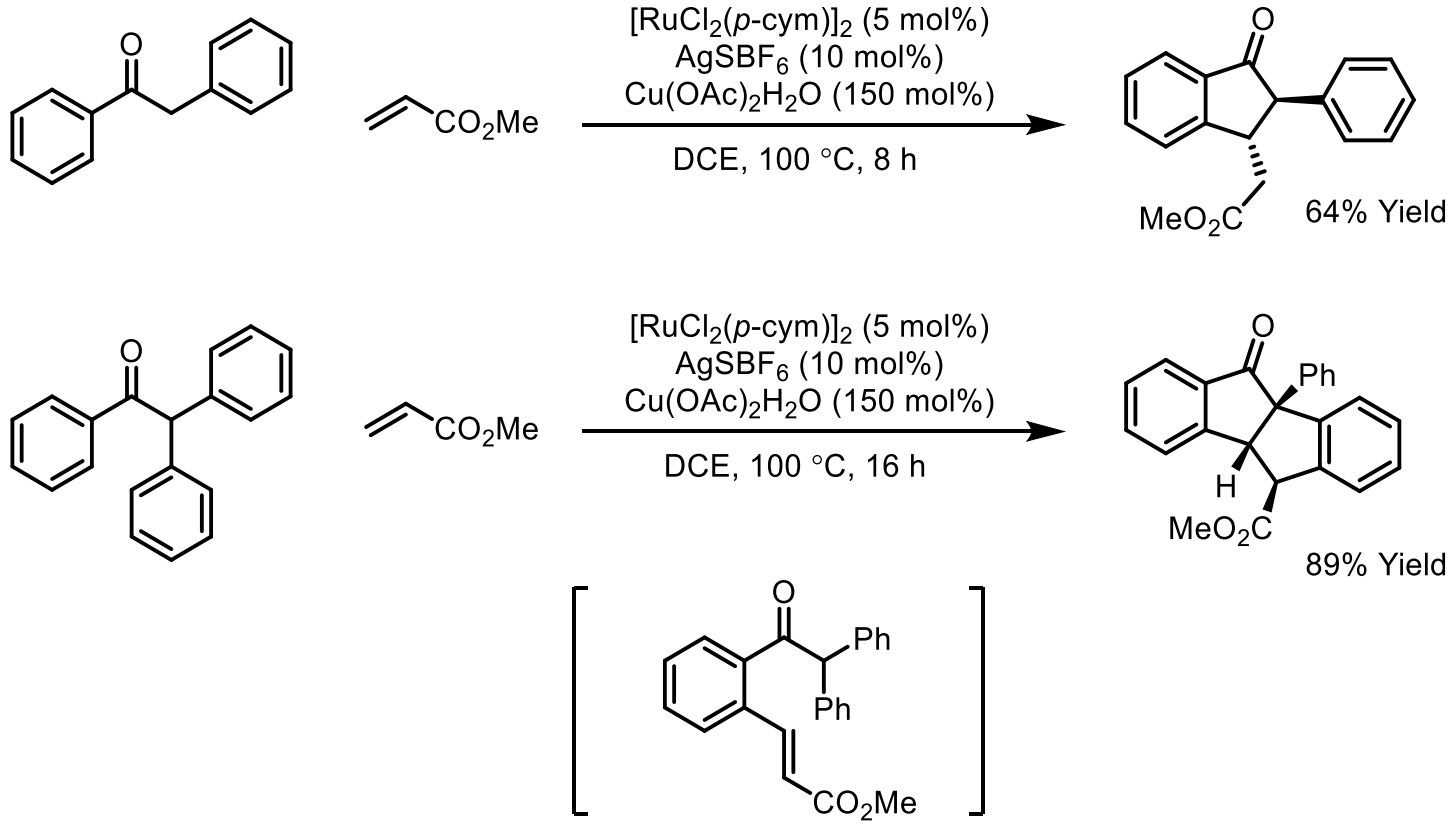
α: 70%
γ: 77%

- Cationic Ir: Shibata
- Rh w/ Cu: Cheng
- Ru w/ cat. Cu: Jeganmohan

Shibata, T. et al *Synlett*. **2010**, *1*, 97
Cheng, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 4169
Jeganmohan, M. *Eur. J. Org. Chem.* **2012**, 417

- **Some cascade examples**

Greaney

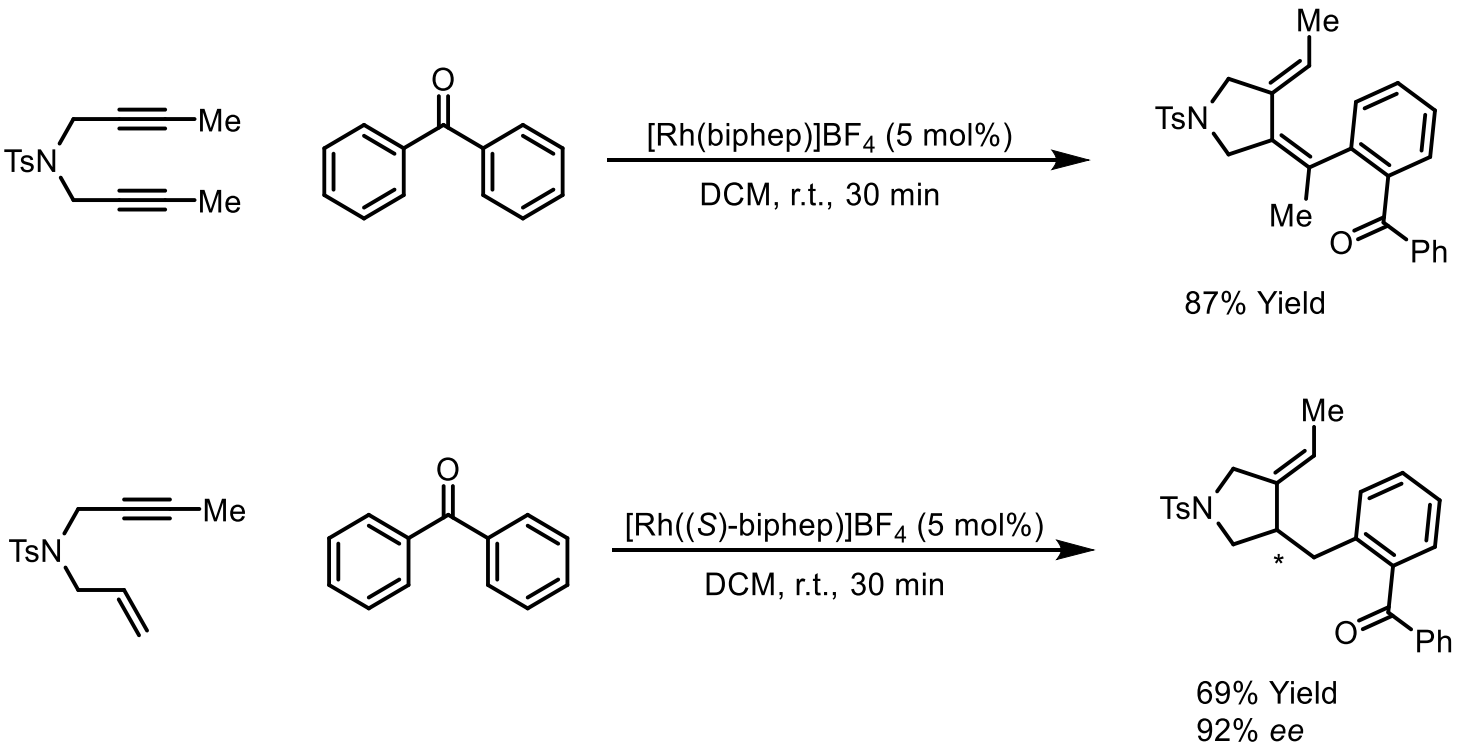


- Ru is necessary for alkenylation
- Cyclization can be mediated by Cu alone

Greaney, M. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 1529

- **Some cascade examples**

Shibata

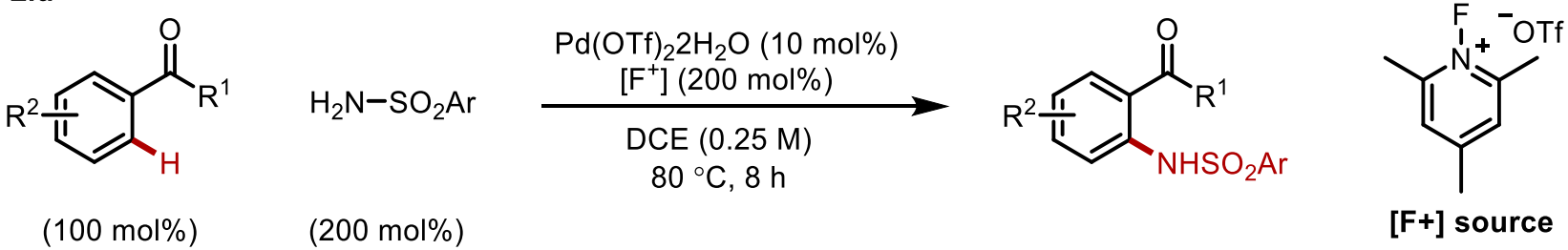


Shibata, T. et al *Org. Lett*. **2007**, *9*, 3097
Tanaka, K. et al *Org. Lett*. **2007**, *9*, 2203
Tanaka, K. et al *Angew. Chem. Int. Ed.*. **2008**, *47*, 1312

- *Catalyst Modification and Improvement*
- *C-C Bond Formation*
- ***C-X Bond Formation***

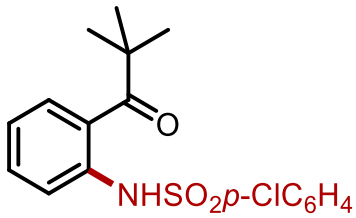
- **C-N bond formation**

Liu

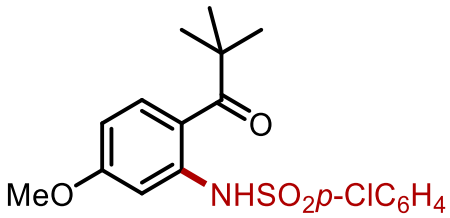


(100 mol%) (200 mol%)

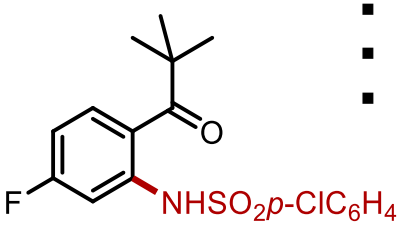
selected examples



82%

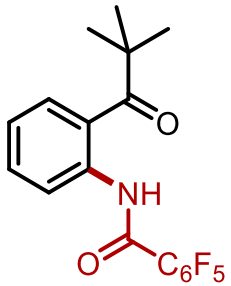


76%

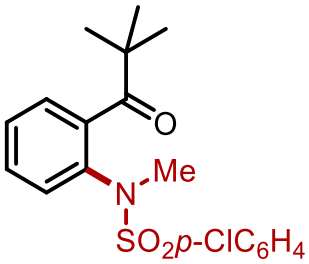


66%

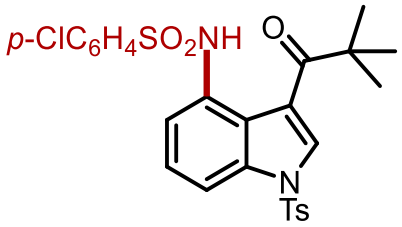
- Super-electronphilic Pd
- Non-enolizable ketones
- E-rich better than e-poor



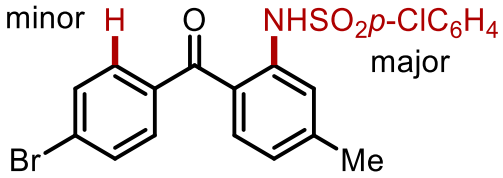
37%



34%



41%

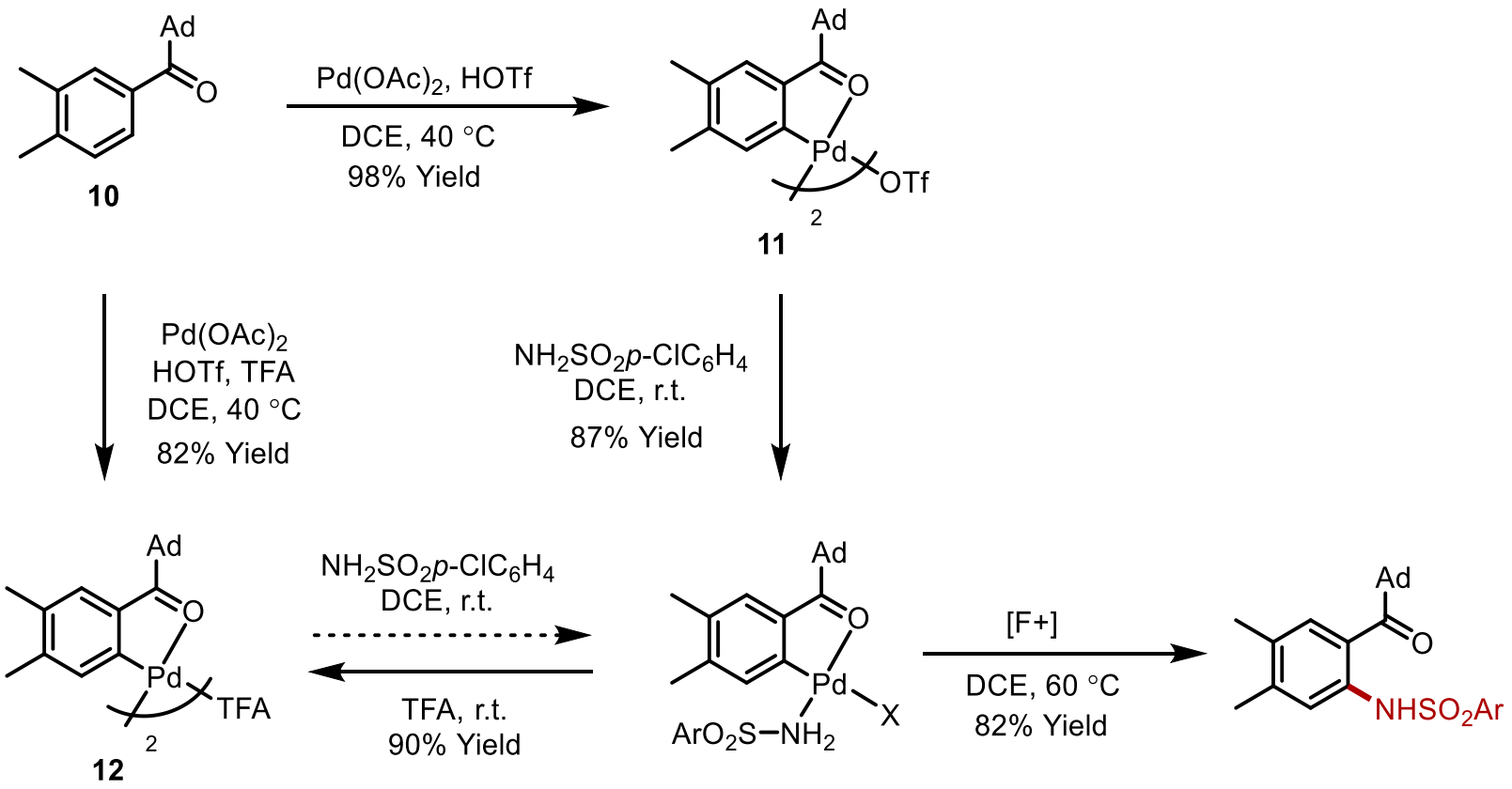


62% (major:minor 6.2:1)

Weak coordination => electrophilic catalyst

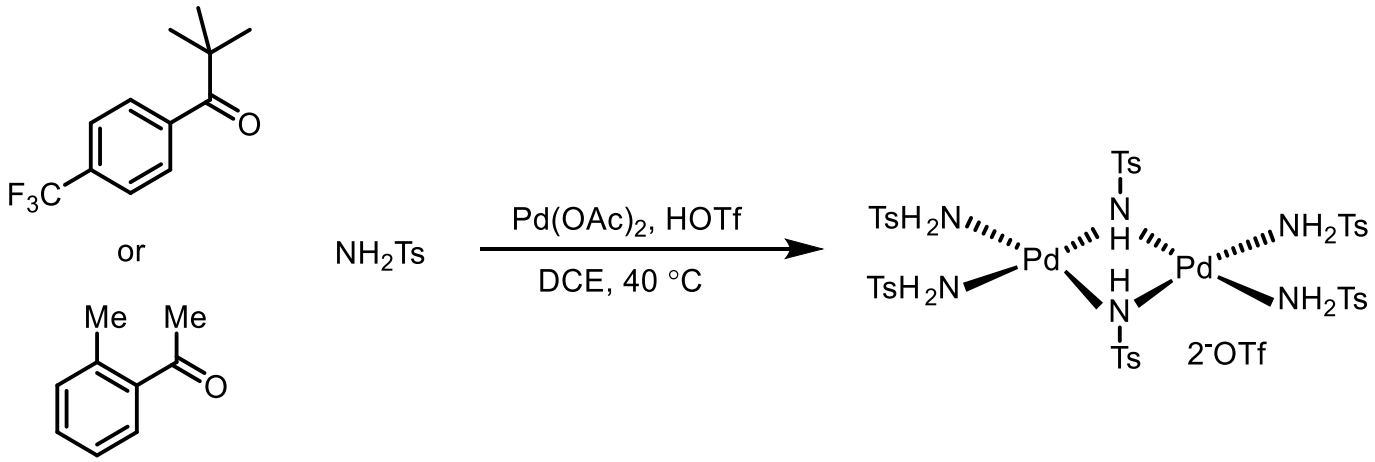
Liu, L. et al *J. Am. Chem. Soc.* **2011**, *133*, 1466

- **C-N bond formation**



Liu, L. et al *J. Am. Chem. Soc.* **2011**, *133*, 1466

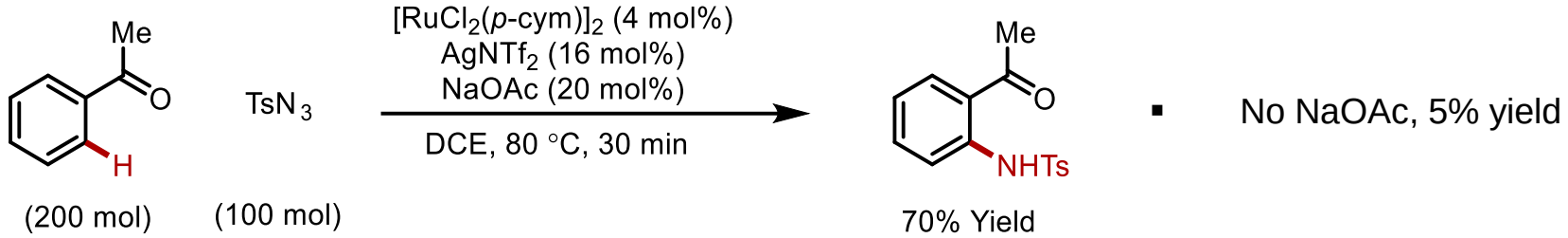
- **C-N bond formation**



Liu, L. et al *J. Am. Chem. Soc.* **2011**, *133*, 1466

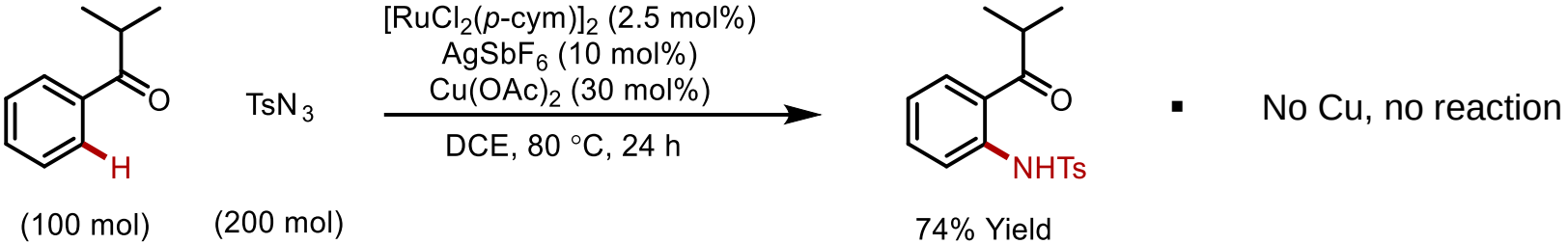
- **C-N bond formation**

Chang



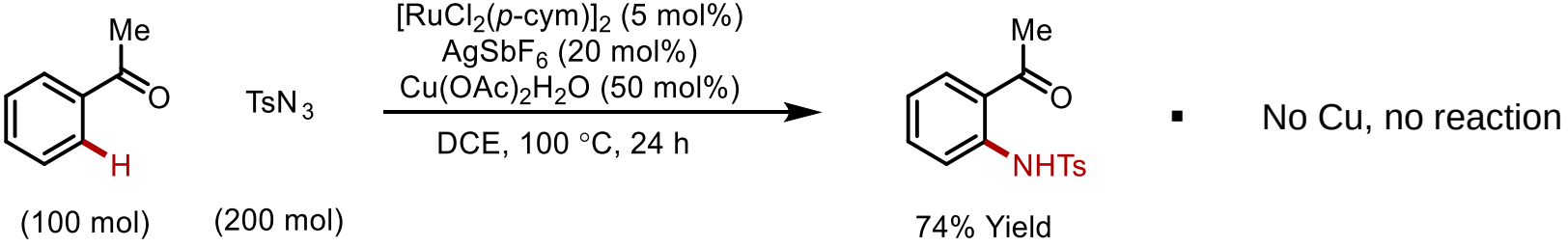
- No NaOAc, 5% yield

Jiao



- No Cu, no reaction

Sahoo



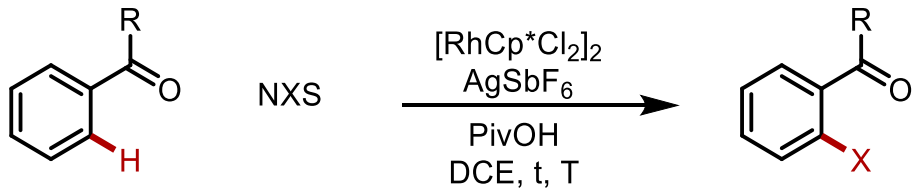
- No Cu, no reaction

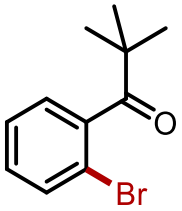
Weak coordination => electrophilic catalyst
=>cationic metal center=>ligand not basic enough
=>difficult C-H activation

Chang, S. et al *Chem. Eur. J.* **2013**, *19*, 7328
Jiao, N. et al *Chem. Commun.* **2013**, *49*, 5654
Sahoo, A. K. et al *Chem. Commun.* **2013**, *49*, 5225

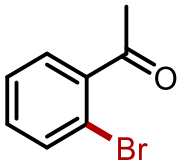
- **C-I, Br, Cl bond formation**

Glorius

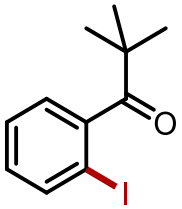




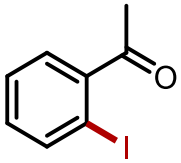
1 mol% Rh
110 mol% NBS
110 mol% PivOH
78%, 120 °C, 16h



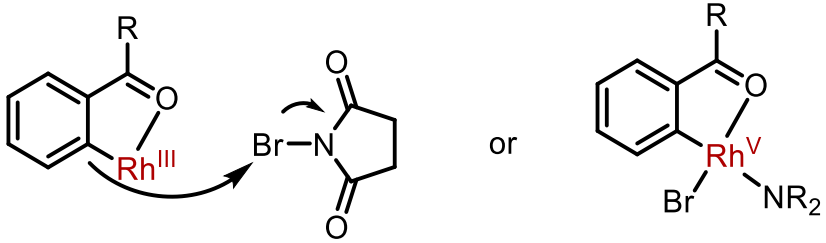
2.5 mol% Rh
220 mol% NBS
110 mol% $Cu(OAc)_2$/no PivOH
50%, 120 °C, 21h



1 mol% Rh
250 mol% NIS 5 portions
110 mol% PivOH
53%, 120 °C, 52h



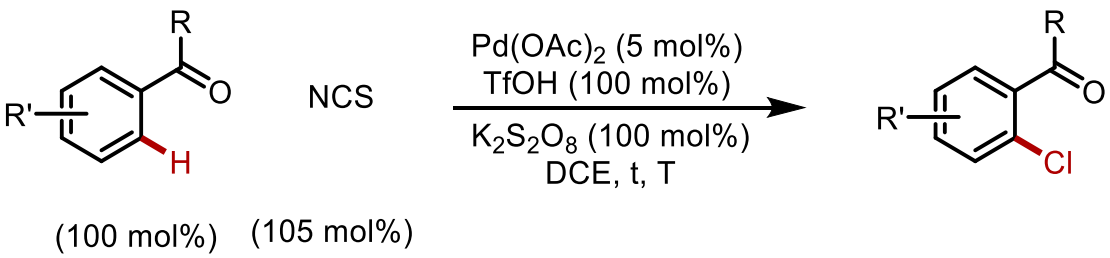
2.5 mol% Rh
140 mol% NIS
220 mol% $Cu(OAc)_2$/no PivOH
61%, 120 °C, 21h

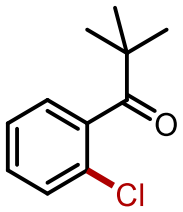


Glorius, F. et al *J. Am. Chem. Soc.* **2012**, *134*, 8298

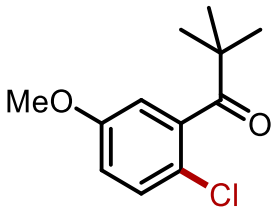
- **C-I, Br, Cl bond formation**

Rao

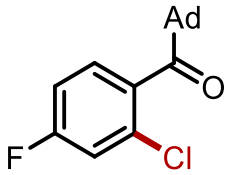




75%, 80 °C, 8h



71%, 80 °C, 3.7h



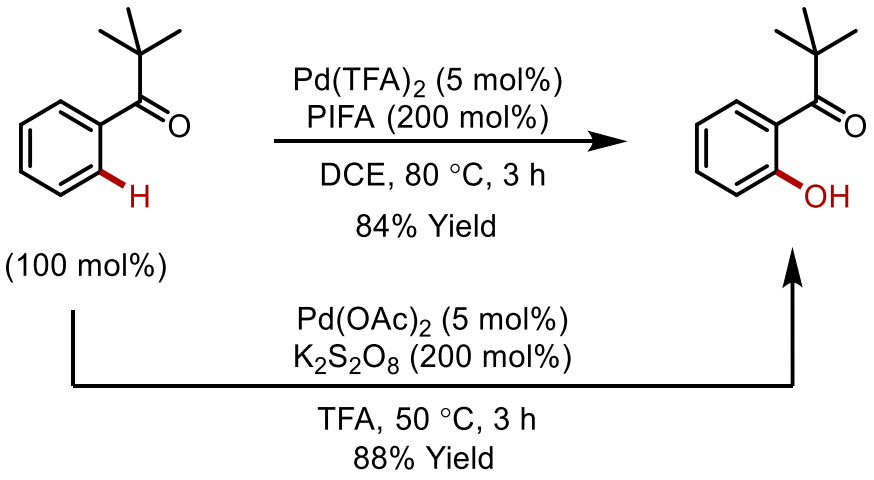
93%, 120 °C, 30h

- $K_2S_2O_8$ as necessary co-oxidant

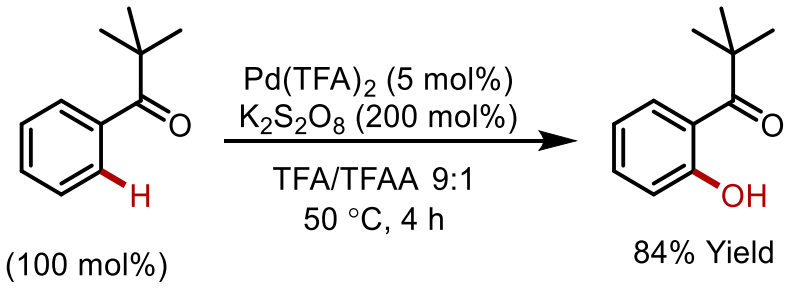
Rao, Y. et al *Angew. Chem. Int. Ed.* **2013**, *52*, 4440

- **C-O bond formation**

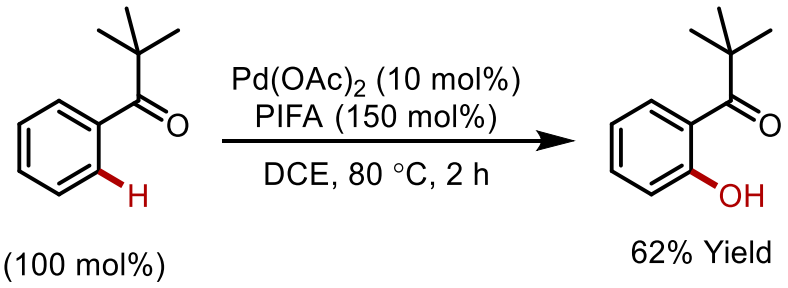
Momo



Rao



Kwong

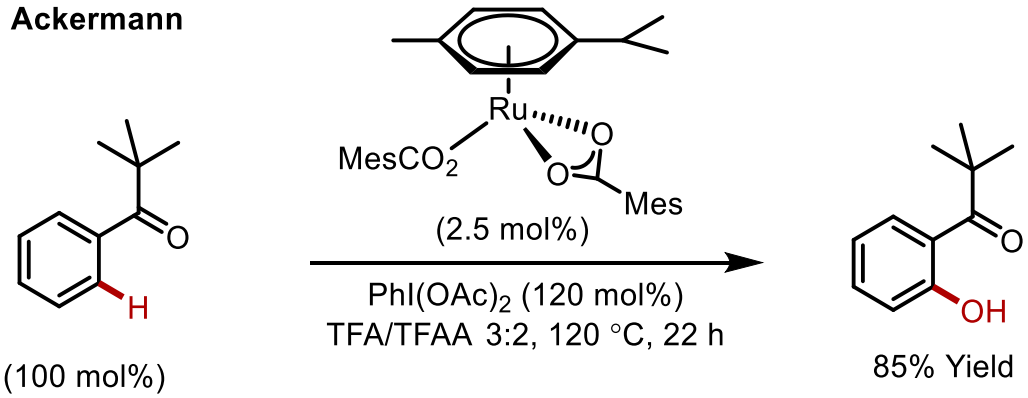


- Primary, secondary, tertiary and aryl aryl ketones all work
- e-rich arenes favored

Rao, Y. et al *Angew. Chem. Int. Ed.* **2012**, *51*, 13070
Dong, G. et al *Angew. Chem. Int. Ed.* **2012**, *51*, 13075
Kwong, F. Y. et al *Org. Lett.* **2013**, *15*, 270

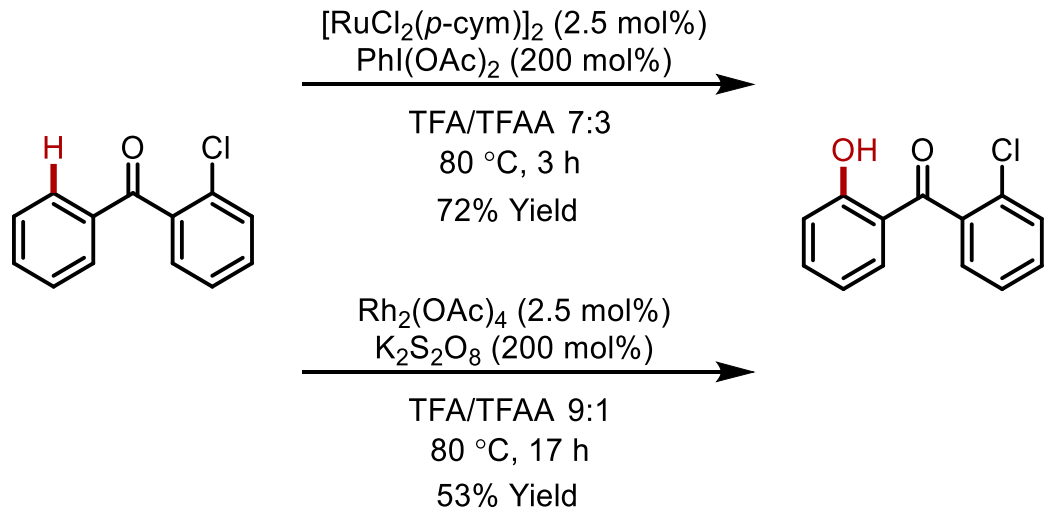
- **C-O bond formation**

Ackermann



- Neutral Ru precursor
- $RuCl_3$ also works
- Only tertiary or aryl ketones work
- Favor e-rich arenes

Rao



- Primary, secondary ketones work

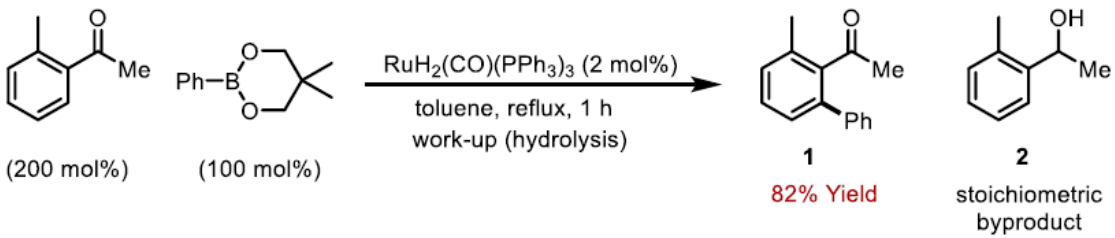
Rao, Y. et al *Org. Biomol. Chem.* **2013**, *11*, 2318
Ackermann, L. et al *Org. Lett.* **2012**, *14*, 6206

Summary

- First directing moiety in catalysis
- Common functional group, ‘natural directing group’
- Weak coordination, restricted scope
- Still versatile
- Sp3 C-H functionalization of ketones is a promising direction
- Not covered today: polymerization (10~20 literatures)


Thank
you!

1. Please draw the mechanism of the coupling between 2-methyl acetophenones and phenylboronates shown below. Note that the stoichiometric byproduct **2** is only generated after reaction work-up (hydrolysis).

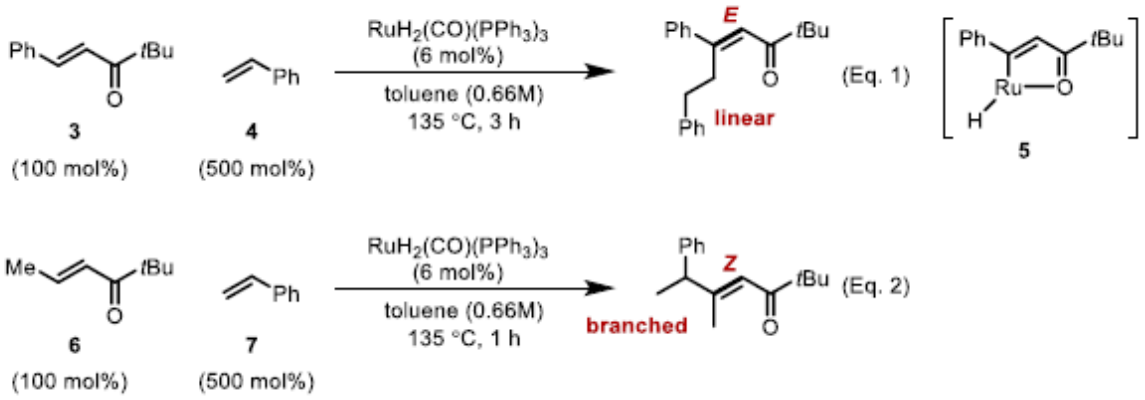


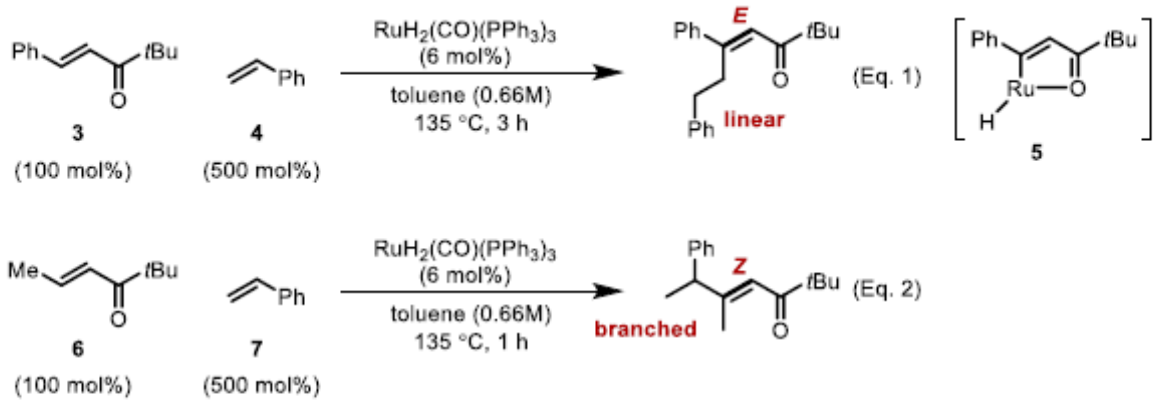
(200 mol%) (100 mol%)

1 82% Yield

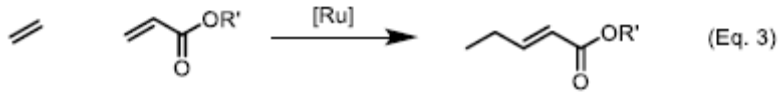
2 stoichiometric byproduct

2. During Murai's study of the addition of olefinic C-H bond to alkenes, two similar reactions (Eq. 1 and 2) gave totally different results in terms of regio- and stereoselectivity. The results (*E* and linear) in Eq. 1 can be explained by a mechanism involving direct oxidative addition of Ru(0) into olefinic C-H bond (**5**), followed by migratory insertion and reductive elimination. However, a different mechanism should be responsible for the selectivity (*Z* and branched) in Eq. 2.



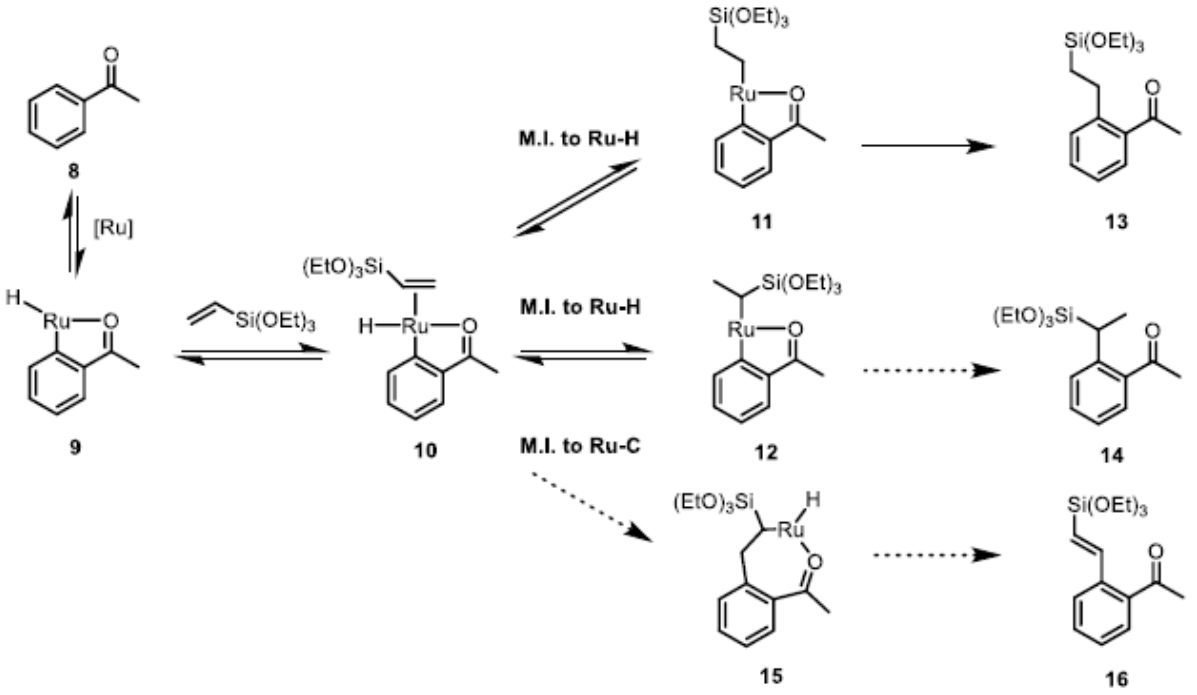


Now, let's start from a simplified system below. Except the pathway of direct oxidative addition, there are two other plausible mechanisms for the Eq. 3.

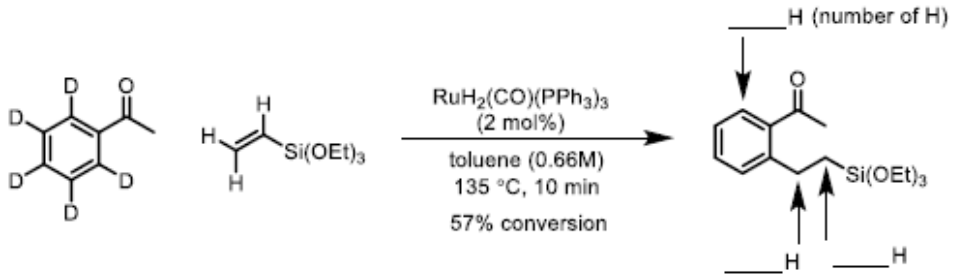


(a) Draw a possible mechanism of Eq. 3 starting from Ru-H species.
(b) Draw a possible mechanism of Eq. 3 starting from Ru(0) species.
(c) In terms of regio- (branched) and stereoselectivity (*Z*), which of the mechanism is more plausible for Eq. 2 and why?

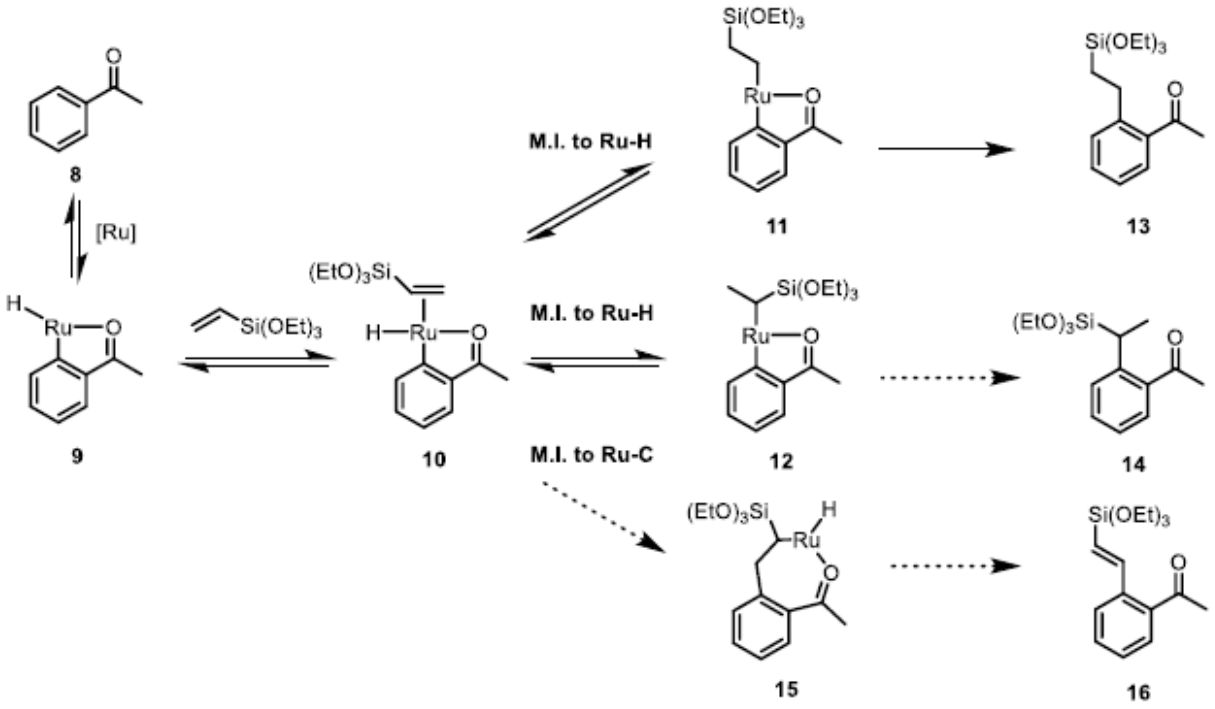
3. Drawn below is the proposed mechanism of the Ru-catalyzed C-H addition to olefin directed by ketones.



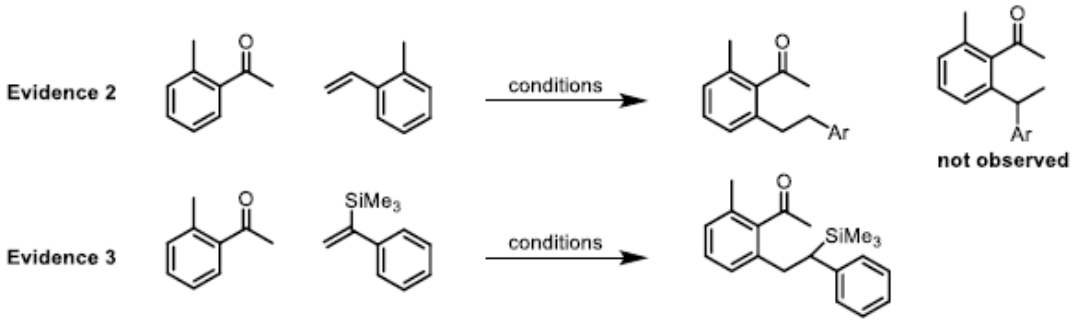
(a) Reductive elimination was proposed as the rate determining step in the reaction, which means, under the reaction conditions, species before the product-forming step (**8-12**) are in fast equilibrium with each other. Based on this, predict the theoretical result of the deuterium labeling reaction below.



3. Drawn below is the proposed mechanism of the Ru-catalyzed C-H addition to olefin directed by ketones.



(b) The authors proposed the migratory insertion into Ru-H bond instead of Ru-C bond based on three evidences. The first evidence is the absence of product **16**. The other two evidences are listed below. Explain why these two results support the authors' proposal.



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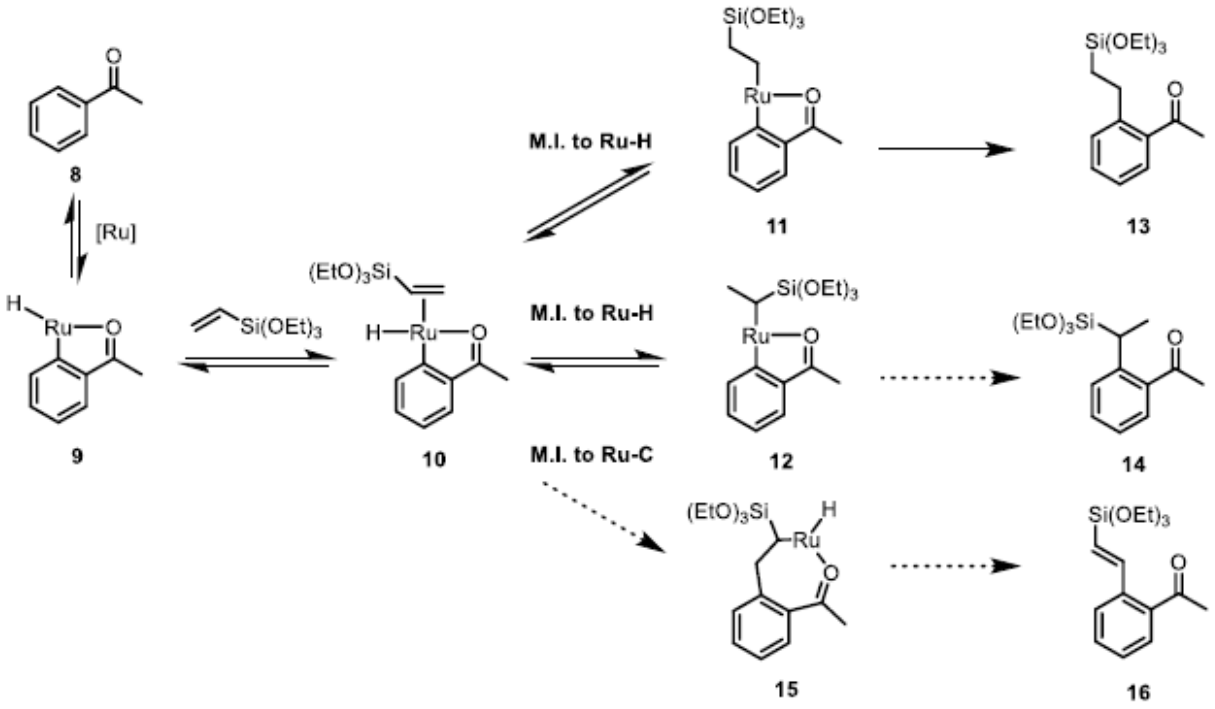

(a) For the formation of **9**, the author proposed a pathway to explain the regioselectivity of **17** and **18**. The pathway can be viewed as the '1,4-addition' of Ru(0) to an 'enone' shown below. Please explain the regioselectivity of **17** and **18** using this pathway.