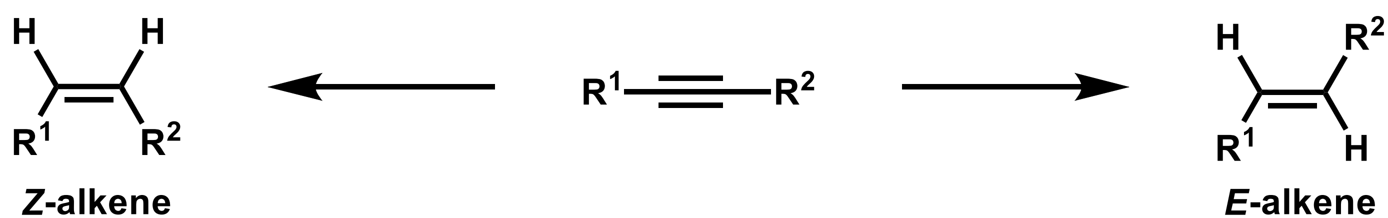
# Stereo-selective Transfer Hydrogenation of Alkynes into Alkene





LS 170715
M2 Shinsuke Shimizu

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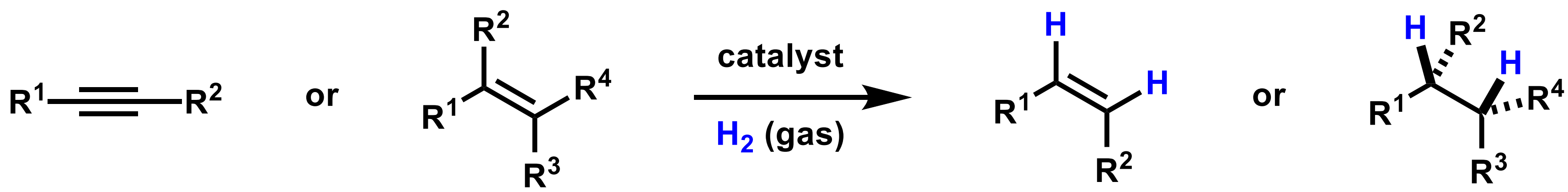
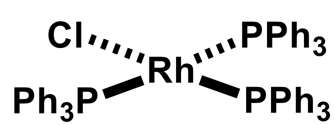
# Introduction of hydrogenation (1)

***direct hydrogenation*** **transfer hydrogenation**

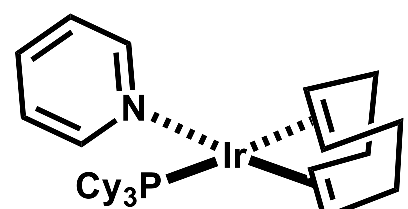
***direct hydrogenation (with $H_2$ gas as hydrogen source)***




**catalyst...** **Pd/C**
**$Pd/CaCO_3/Pb(OAc)_2$ (Lindlar cat)**
**$Pd/BaSO_4$ (Rosenmunt reduction)**
**$Pd/(OH)_2$ (Pearlman cat.)**
**Wilkinson cat**
**Crabtree cat, etc...**




**Wilkinson's cat**




**Crabtree's cat**

Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. Han, L.-B. et. al. *J. Am. Chem. Soc.* **2011**, *133*, 17037.

# Introduction of hydrogenation (2)

direct hydrogenation | ***transfer hydrogenation***

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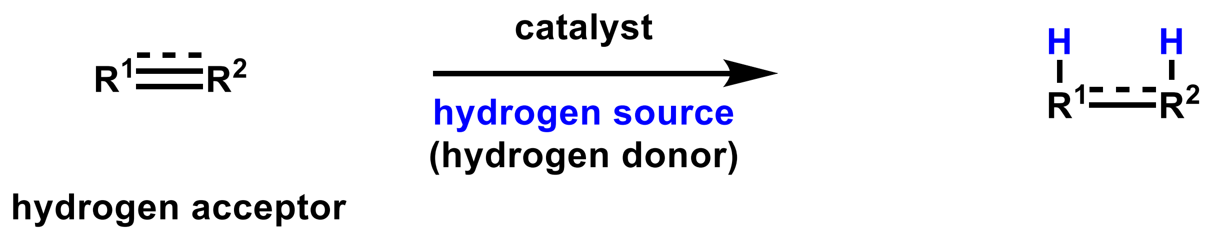
***<u>transfer hydrogenation (non-$H_2$ hydrogen source)</u>***




**catalyst...** **Pd, Ni, Co, Ir, Au, etc...**

**hydrogen source...** **$HCO_2H$, MeOH, EtOH, *i*-PrOH**
**$NH_3BH_3$**

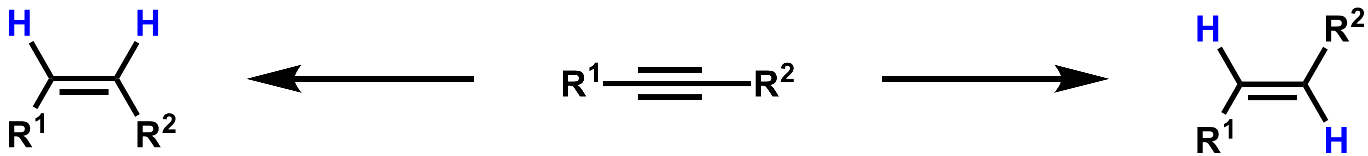
***convenient and powerful method***

- ***Not*** **require pressurized $H_2$ gas,** ***nor*** **elaborate experimental setups.**
- **hydrogen source are readily available, inexpensive, and easy to handle.**

Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. Han, L.-B. et. al. *J. Am. Chem. Soc.* **2011**, *133*, 17037.

# Stereoselective semi-reduction of alkyne

- semi-reduction




*Z*-alkene alkyne *E*-alkene

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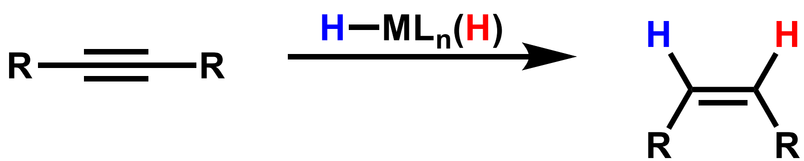
- *Z*-alkene
  - Lindlar cat -> see also 121208_LS_Yuki_Nakagawa_Semihydrogeantion_with_Pd.BN
  - *cis*-hydrometalation/reductive-elimination




- *E*-alkene
  - Birch reduction -> traditional an powerful method,
    but low functional-group tolerance because of the harsh condition.

-> ***remaining a major challenge***

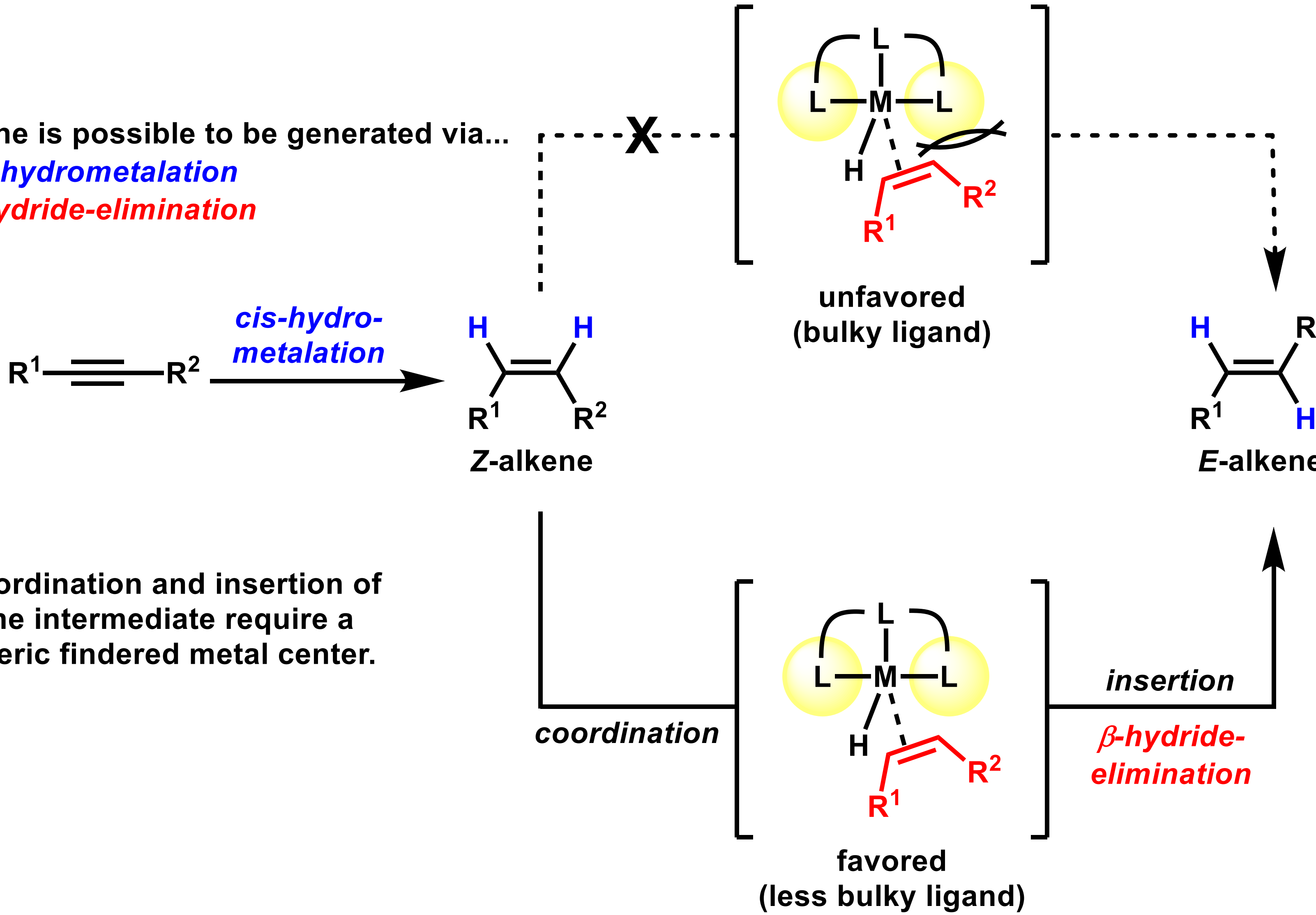


Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. Milstein, D. et. al. *Angew. Chem. Int. Ed.* **2013**, *52*, 14131.

# Contents

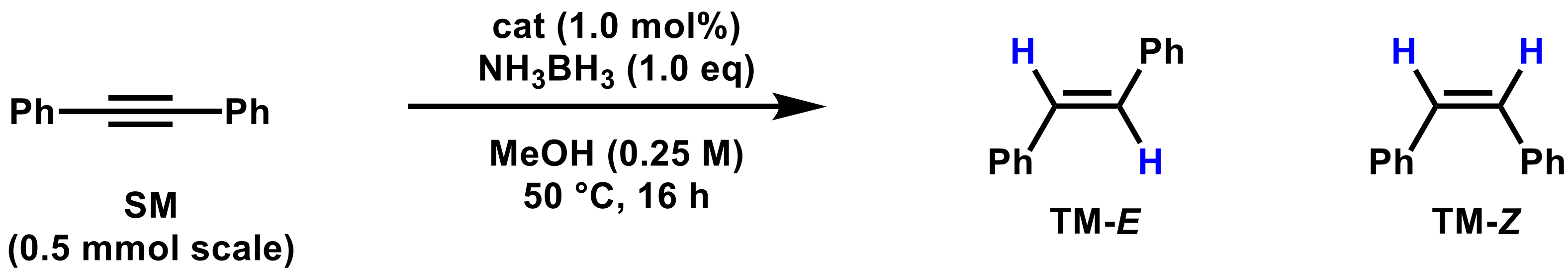
# Concept of this research

- E-alkene is possible to be generated via...
  (1) *cis-hydrometalation*
  (2) *β-hydride-elimination*



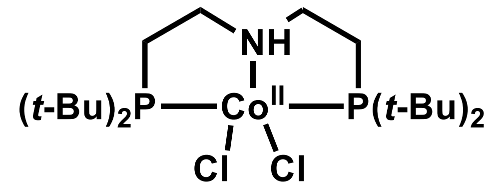

- the coordination and insertion of Z-alkene intermediate require a less steric findered metal center.

# Co-Catalyzed TH of Alkyne

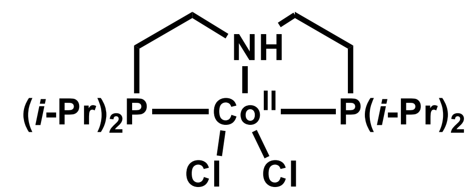



| entry | catalyst | yield / %[a] | | conv. SM / % |
|---|---|---|---|---|
| | | TM-*E* | TM-*Z* | |
| 1 | none | ND[b] | ND | 100 |
| 2 | $CoCl_2$ | 2 | 24 | 30 |
| 3 | cat A | 5 | 94 | 99 |
| 4 | cat B | 92 | 8 | 100 |
| 5 | cat C | 100 | ND | 100 |

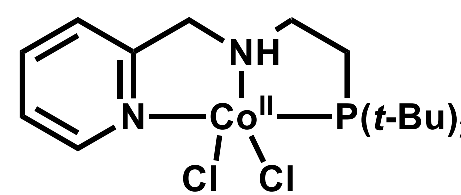
*a*: determined by GC analysis using biphenyl as the internal standard.
*b*: ND means "not detected".




cat A



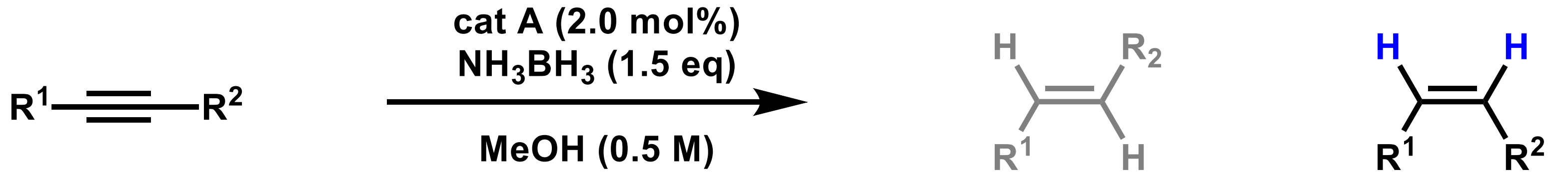

cat B




cat C

Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

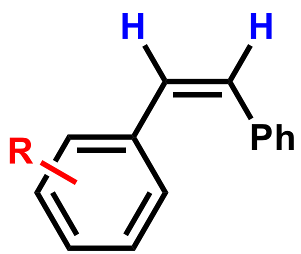
# Scope of the *Z*-selective hydrogenation



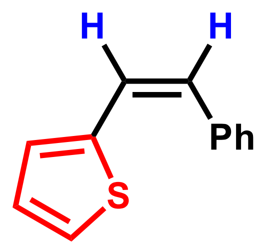

**SM**
**(0.5 mmol scale)**

**TM-*E*** **TM-*Z***

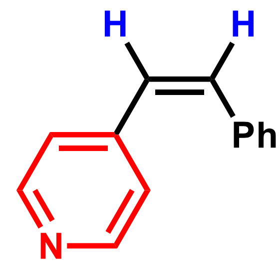
**yield (*E*/*Z*)[a]**



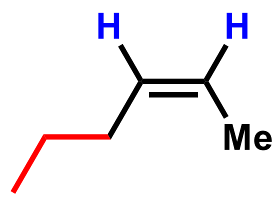

**R = H: 94% (1/18)[b]**
**R = *p*-$CH_3$: 86% (1/8)[c]**
**R = *m*-$CH_3$: 94% (1/13)[c]**
**R = *p*-MeO: 85% (1/8)**
**R = *p*-$CF_3$: 86% (1/15)[c, d]**
**R = *p*-CN: 48% (1/16)[d, e]**
**R = *p*-$CO_2Me$: 91% (1/14)[c]**
**R = *p*-$NH_2$: 67% (1/4)[f]**



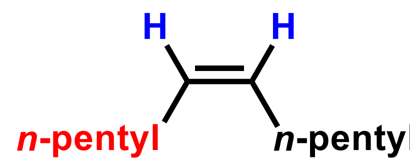

**72% (1/6)**




**63% (1/2)[g]**




**94% (1/17)[d]**

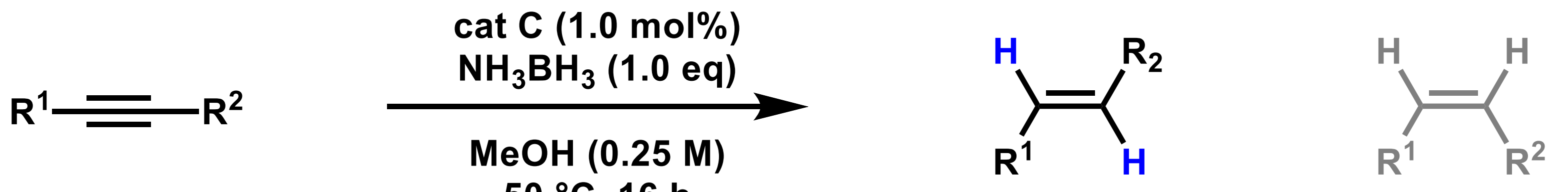



**99% (1/>99)**

***a*: isolated yield. *b*: $NH_3BH_3$ (1.2 eq), cat A (1.0 mol%). *c*: 60 °C. *d*: GC yield. *e*: $NH_3BH_3$ (2.6 eq). *f*: $NH_3BH_3$ (2.4 eq), cat A (3.0 mol%). *g*: $NH_3BH_3$ (1.0 eq), cat A (1.5 mol%).**


Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

# Scope of the *E*-selective hydrogenation

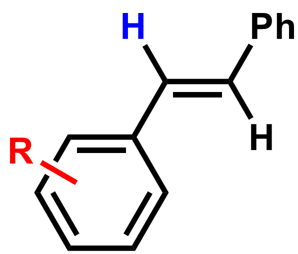



SM
(0.5 mmol scale)

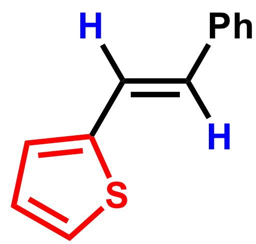
TM-*E*

TM-*Z*

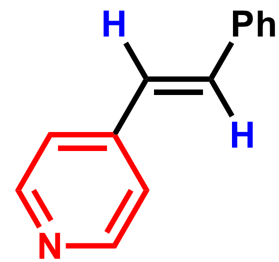
yield (*E*/*Z*)[a]



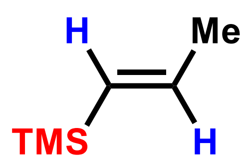
R = H: 92% (>99/1)[b]
R = *p*-$CH_3$: 91% (>99/1)
R = *m*-$CH_3$: 96% (>99/1)
R = *p*-MeO: 98% (>99/1)
R = *p*-$CF_3$: 97% (>99/1)
R = *p*-$CO_2$Me: 90% (>99/1)[c]
R = *p*-$NH_2$: 93% (>99/1)[d]
R = *p*-$NO_2$: 52% (4/1)



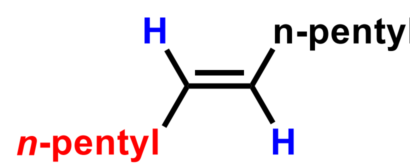
93% (>99/1)[e]



70% (6/1)[f]



90% (>99/1)

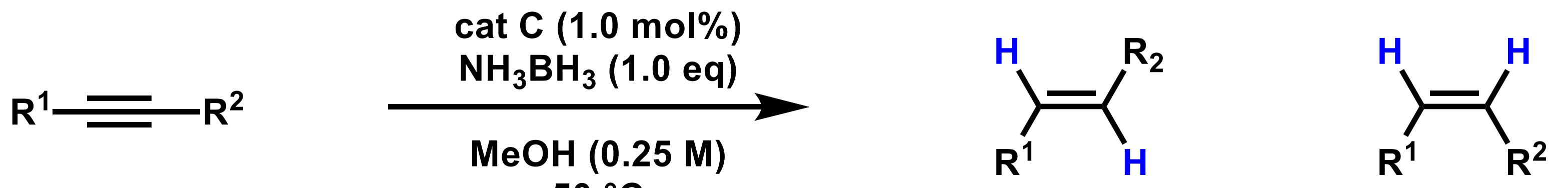


96% (1/1)[g]

*a*: isolated yield. *b*: 5 mmol scale, cat C (0.2 mol%), MeOH (0.1 M). *c*: GC yield. *d*: $NH_3BH_3$ (0.8 eq), cat C (3.0 mol%), MeOH/THF (0.25 M, 3/1), 36 h. *e*: $NH_3BH_3$ (1.5 eq), cat C (2.0 mol%), 36 h. *f*: $NH_3BH_3$ (0.7 eq), 36 h. *g*: $NH_3BH_3$ (0.5 eq), cat B (4.0 mol%), MeOH (0.5 M), 40 h.

Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

# Time-course study of the *E*-selective semireduction



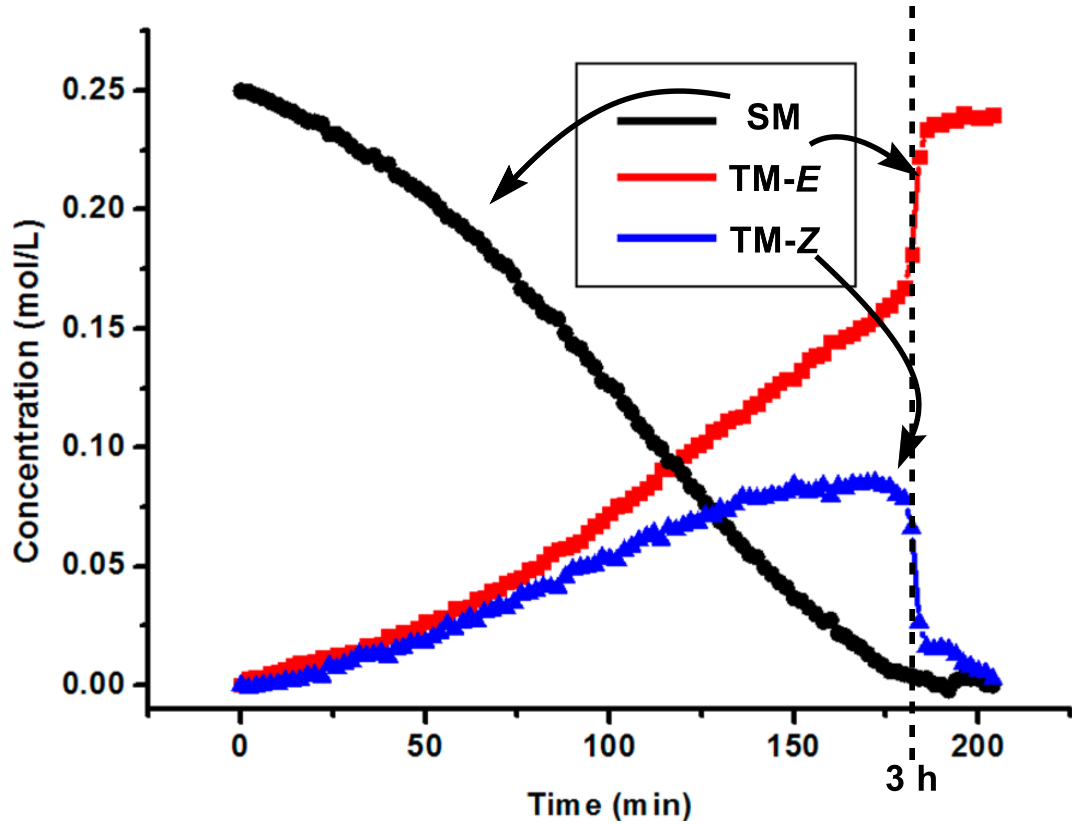

SM (0.5 mmol scale)

TM-*E* (95%)

TM-*Z*

- *Z*-alkene intermediate (TM-*Z*) was generated in the first 3 h.
- TM-*Z* was further converted to the *E*-alkene (TM-*E*) via a isomerization.
- Decrease in the concentration of SM led to a dramatic increase in the rate of the isomerization step (Time: 3 h).

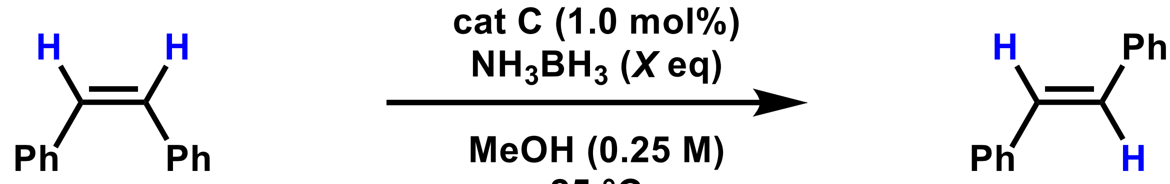
***isomerization process was inhibited by the SM?***




**The course of the reaction could be recorded from the characteristic IR absorption of SM, TM-*E* and TM-*Z*.**

Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

# Co-catalyzed isomerization of *Z*-alkene




**A** (0.5 mmol scale) → **TM-*E***

| entry | time | $NH_3BH_3$ (eq) | conv. A[a] (%) | yield TM-*E*[a] (%) |
|---|---|---|---|---|
| 1 | 1 h | 1.0 | 100 | 100 |
| 2 | 1 h | 0.1 | 100 | 100 |
| 3 | 16 h | 0 | 0 | ND[c] |
| 4[b] | 16 h | 1.0 | – | 8 |

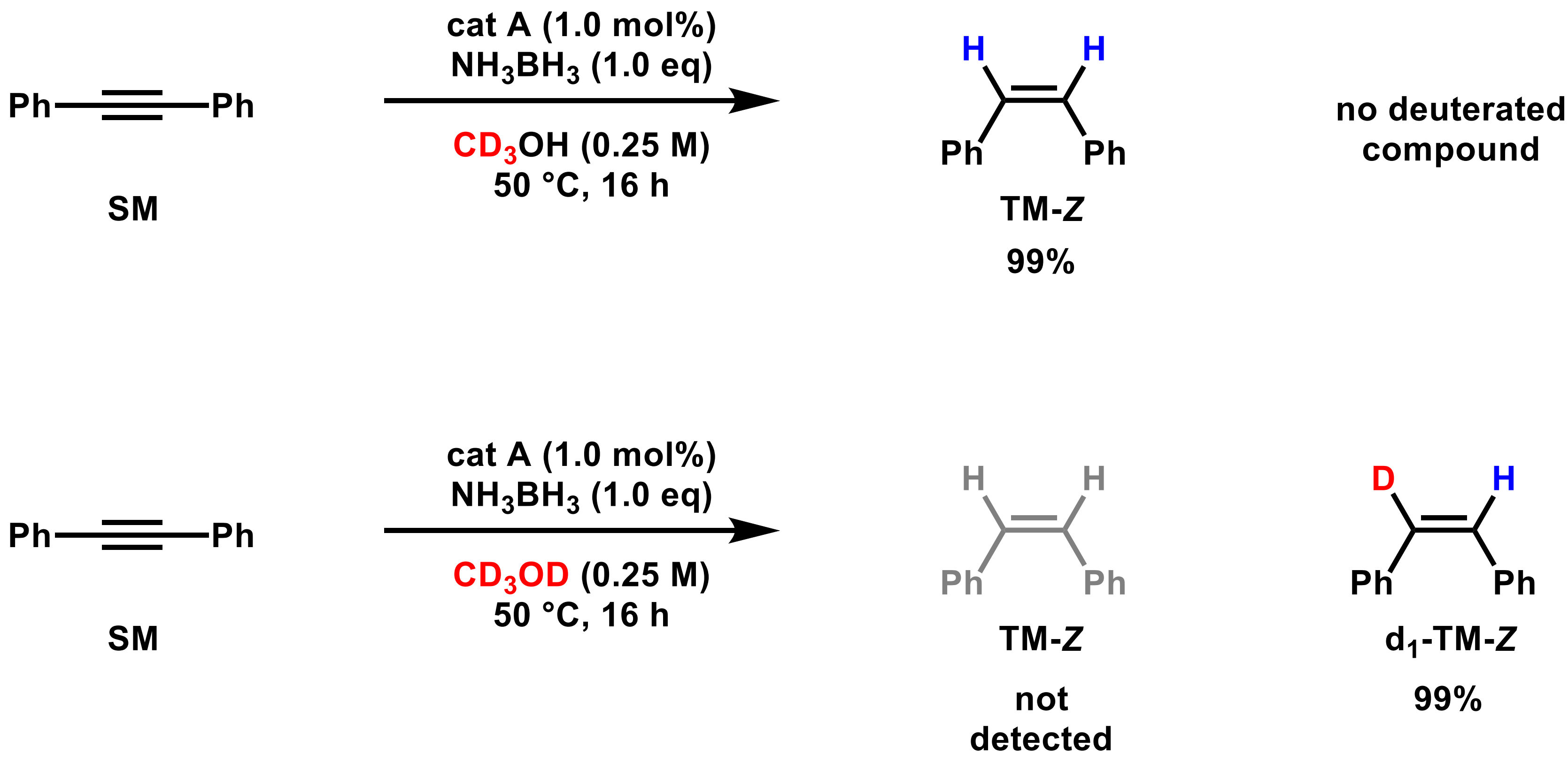
*a*: GC yields. *b*: B (1.0 eq) was added. *c*: ND means "not detected".


**B**

TM-*E* —*same comdition*→ no reaction

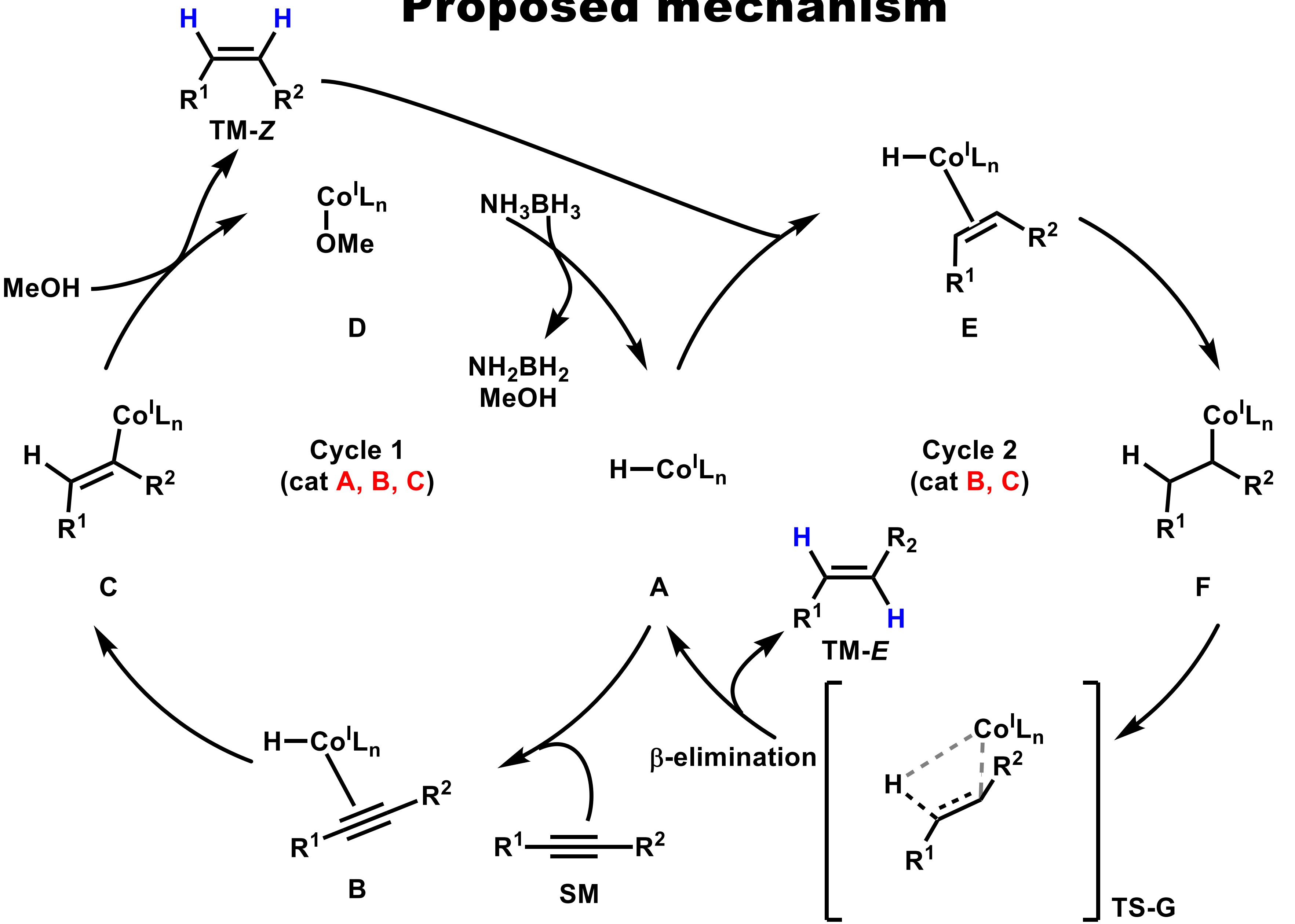
Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

# Deuterium-labeling experiments




Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

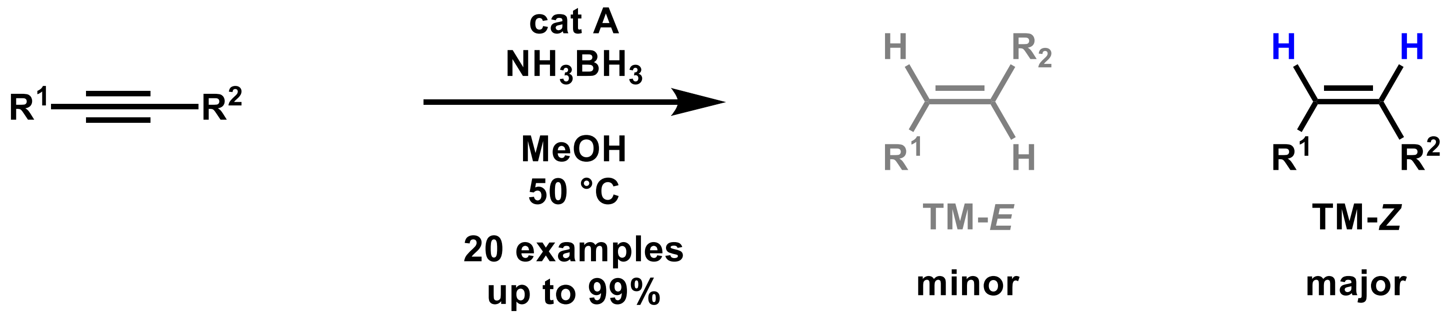
# Proposed mechanism



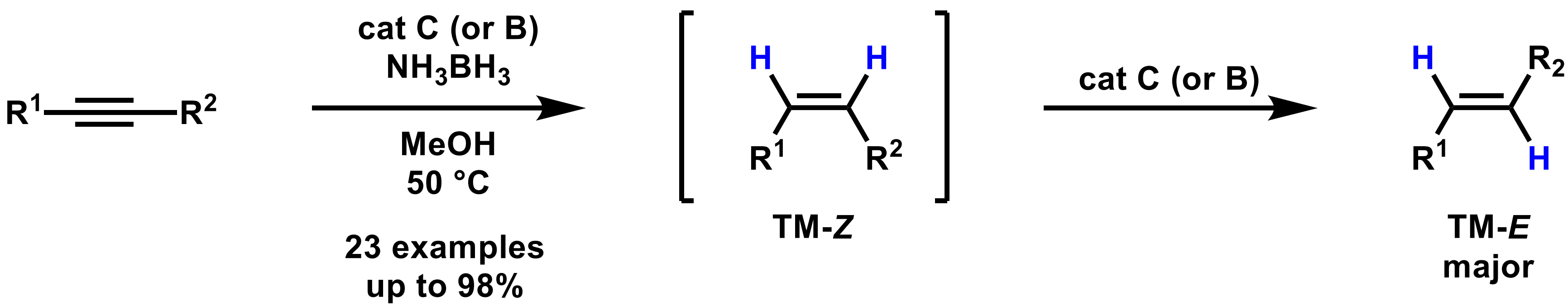

Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

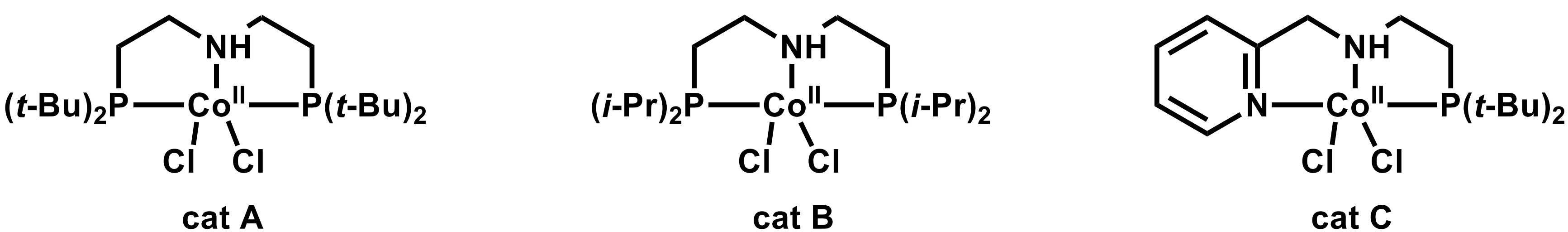
# Short summary

•*Z*-selective semi-hydrogenation




•*E*-selective semi-hydrogenation




Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

# Contents

# K. C. Kumara Swamy

| | |
|---|---|
| 1957 | Born in Kalasa (India) |
| 19XX | Ph.D from Indian Institute of Science (Bangalore) with Prof. S. S. Krishnamurthy |
| 1986-89 | P.D. at University of Massachusetts (Amherst, USA) with Prof. Robert R. Holmes. |
| now | Professor at the University of Hyderabad, School of Chemistry. |

***Current research interests***

(i) Chiral phosphorus compounds- Utility as chiral ligands for transition metals

(ii) Phosphonates in Organic Synthesis

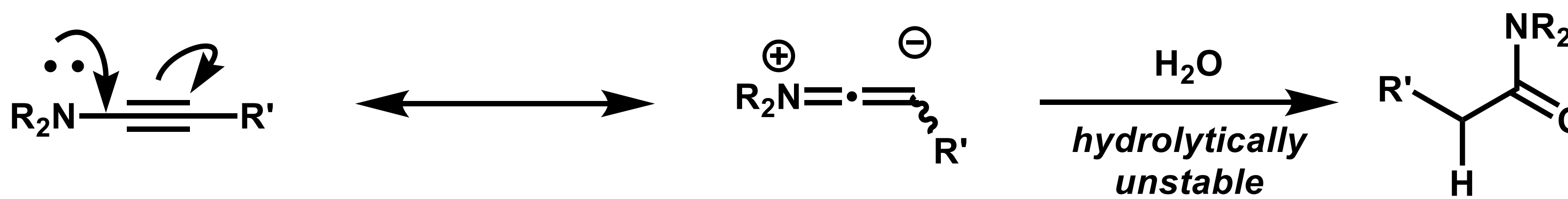
(iii) Unusual Phosphorus Compounds

(iV) Allene chemistry and palladium catalysis

http://chemistry.uohyd.ac.in/~kcks/profile.htm

# Background of ynamides (1)

- **ynamine (1958~)**




***difficult in the experimental preparation and general handling of ynamine.***

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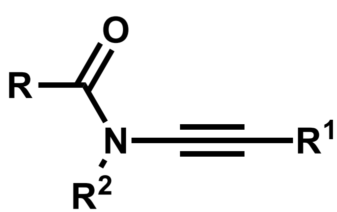
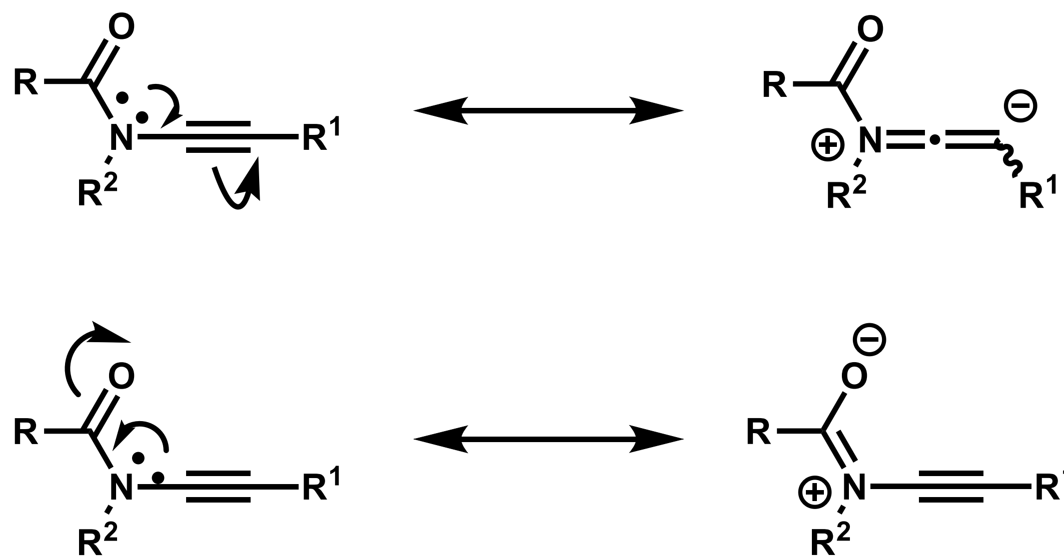
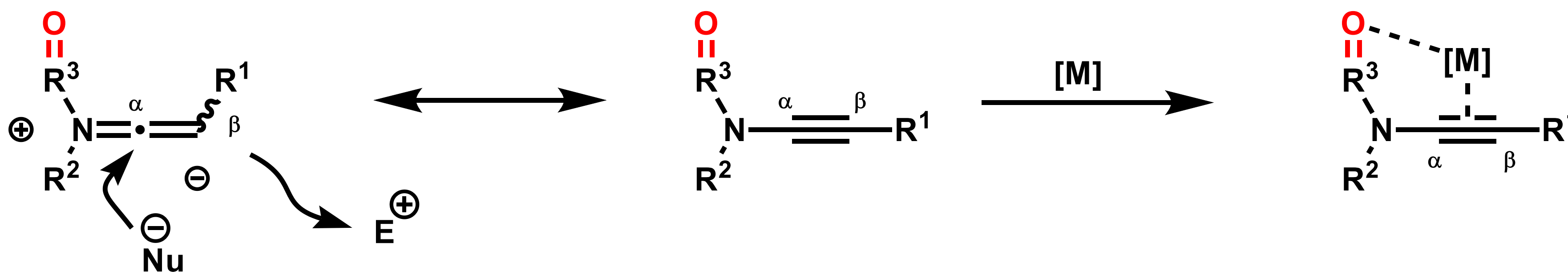
- **ynamide (1972~)**

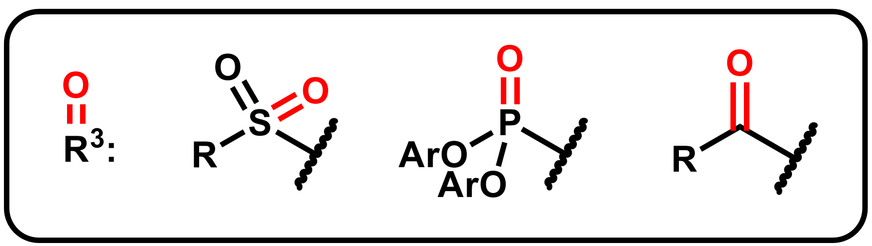


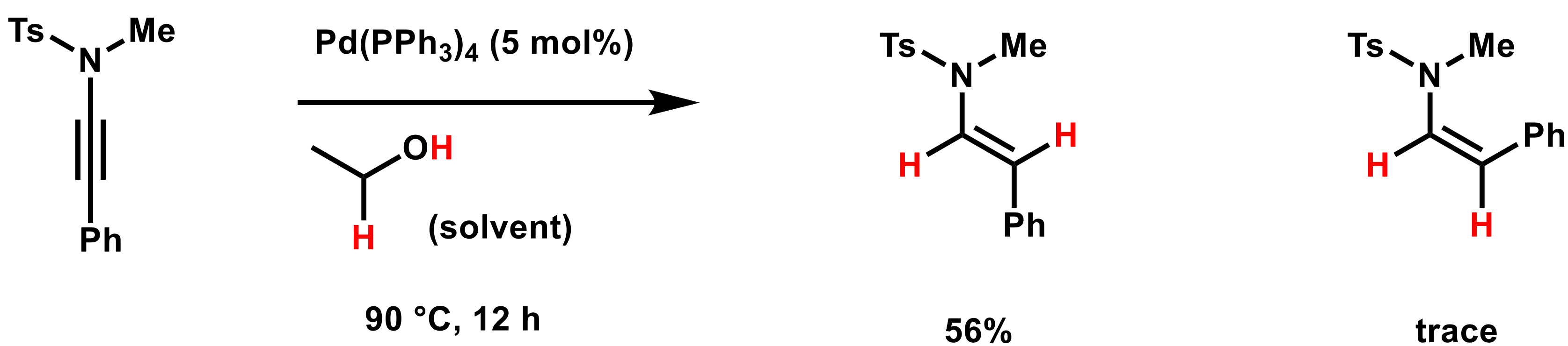

**EWG**
- **stabilization**
- **directing group**
- **chiral auxiliary**

# Background of ynamides (2)



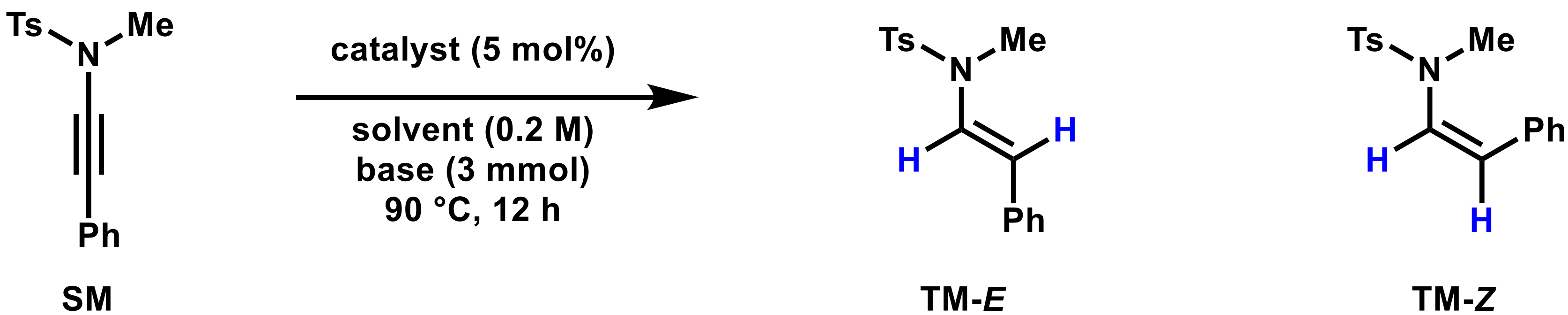




-> see 120707_Answer_Tomomi_GOTO_Ynamide




Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984. *Chem. Rev.* **2010**. *110*. 5064.

# Pd-catalyzed hydrogenation of ynamide with ethanol

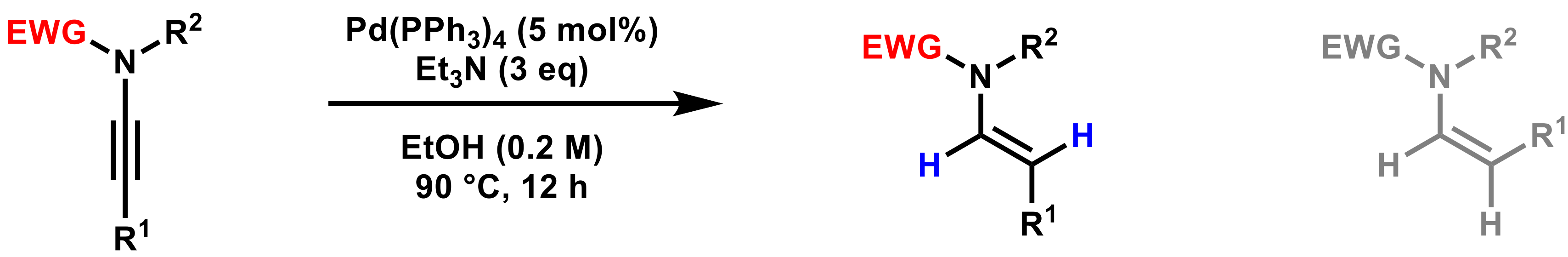


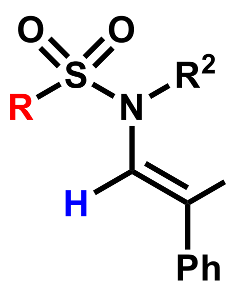

| entry | catalyst | solvent | base | ratio | | | yield[a] |
|---|---|---|---|---|---|---|---|
| | | | | TM-*E* | TM-*Z* | SM | |
| 1 | $Pd(PPh_3)_4$ | EtOH | — | 60 | 0 | 40 | 56% |
| 2 | $Pd(PPh_3)_4$ | tol (or THF, DMSO) | — | no reaction | | | 0 |
| 3 | — | EtOH | — | no reaction | | | 0 |
| 4 | $Pd(PPh_3)_4$ | *i*-PrOH | — | 36 | 0 | 64 | 33% |
| 5 | $Pd(PPh_3)_4$ | *n*-PrOH | — | 54 | 0 | 46 | 52% |
| 6 | $Pd(PPh_3)_4$ | *t*-BuOH | — | no reaction | | | 0 |
| 7 | $Pd(PPh_3)_4$ | EtOH | NaOH | 42 | 0 | 58 | 36% |
| 8 | $Pd(PPh_3)_4$ | EtOH | $Et_3N$ | 100 | 0 | 0 | 92% |

*a*: isolated yield.

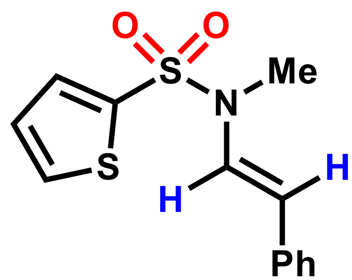
Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984.

# Substrate Scope (1)

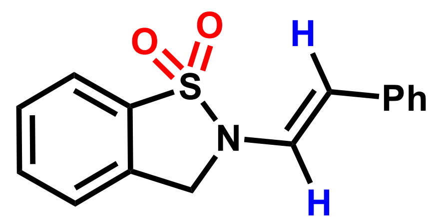


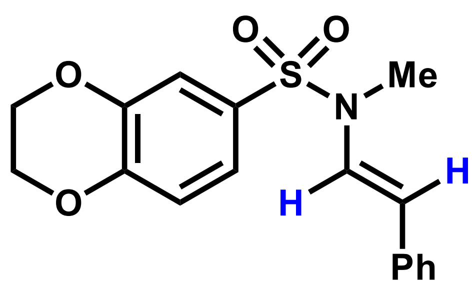

**R = Tol: 92% ($R^2$ = Me)**
**R = (*p*-MeO)Ph: 94% ($R^2$ = Me)**
**R = 4-biphenyl: 86% ($R^2$ = Me)**
**R = naphthyl: 90% ($R^2$ = Me)**
**R = Tol: 88% ($R^2$ = Bn)**
**R = Tol: 86% ($R^2$ = Ph)**



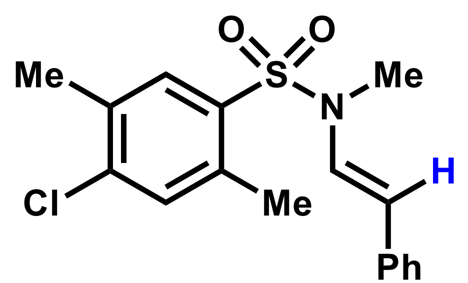

**93%**




**96%**



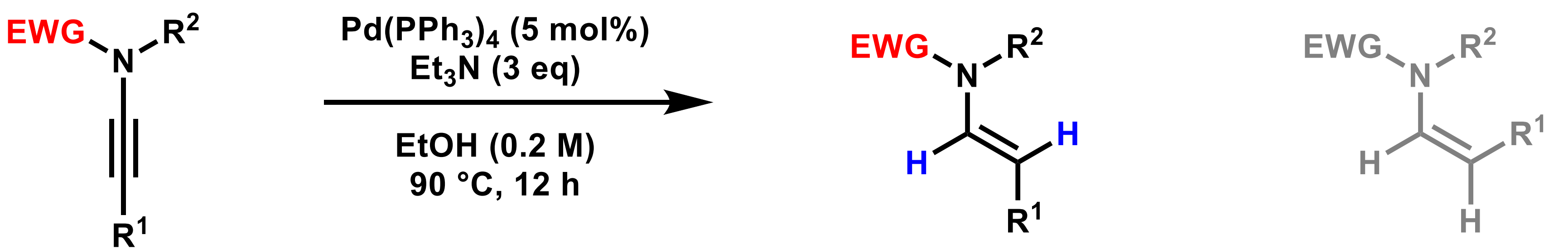

**82%**

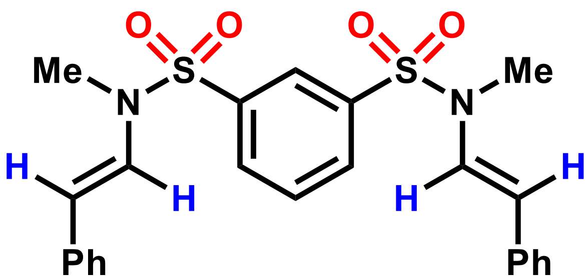



**76%**

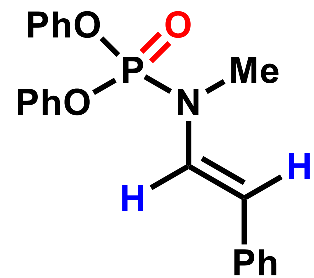
Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984. **isolated yield**

# Substrate Scope (2)

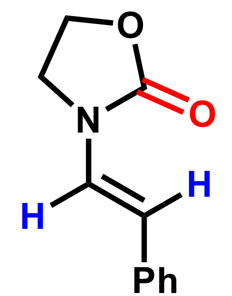


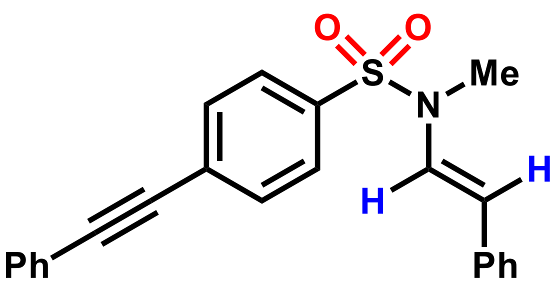
82%



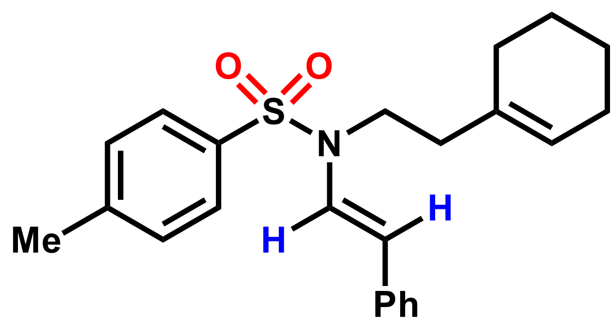
95%



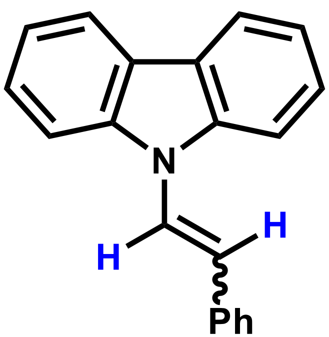
74% (*E*/*Z*: 6/1)



80%



87%

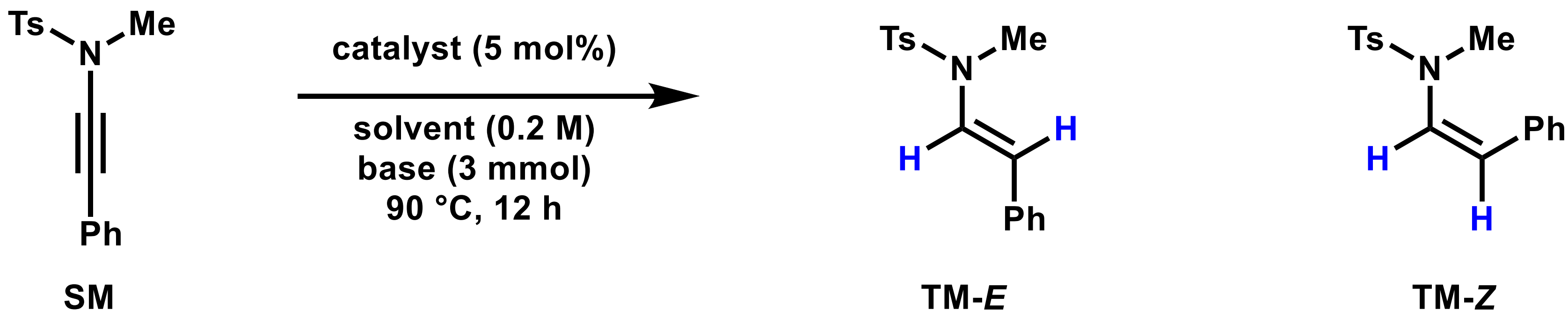


96% (*E*/*Z*: 5/1)

Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984.

**isolated yield**

# Optimization of Pd catalyst

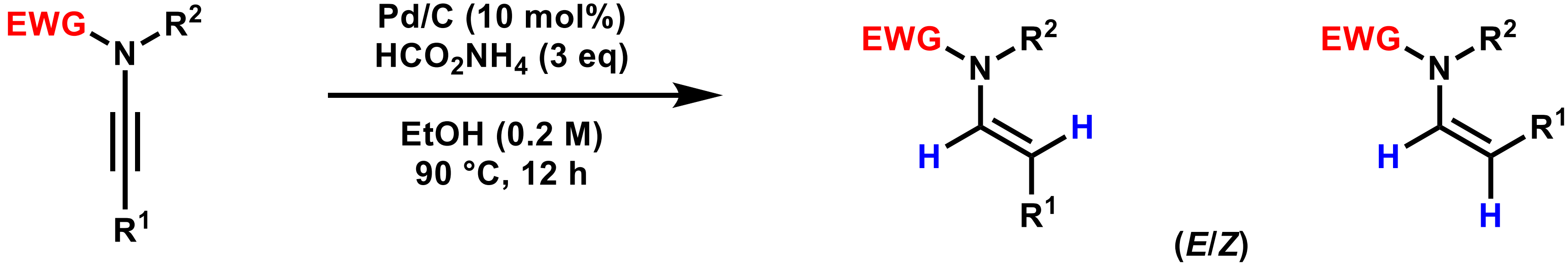


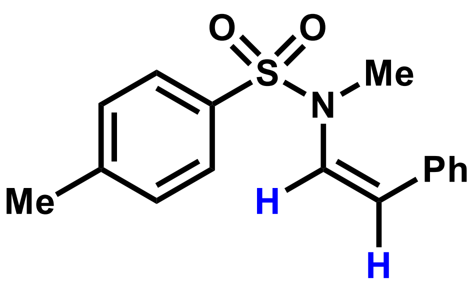

| entry | catalyst | solvent | base | ratio (yield) | | | yield of TM-*E*[a] |
|---|---|---|---|---|---|---|---|
| | | | | TM-*E* | TM-*Z* | SM | |
| 1 | $PdCl_2(PPh_3)_2$ | EtOH | $Et_3N$ | 96 | 4 | 0 | 90%[b] |
| 2 | $Pd(OAc)_2(PPh_3)_2$ | EtOH | $Et_3N$ | 90 | 10 | 0 | 84%[b] |
| 3 | Pd/C | EtOH | $Et_3N$ | 0 | 6 | 94 | 0 |
| 4 | $Pd_2(dba)_3$ | EtOH | $Et_3N$ | 0 | 20 | 80 | 0 |
| 5[c] | $Pd(PPh_3)_4$ | EtOH | $Et_3N$ | no reaction | | | 0 |
| 6[d] | $Pd(PPh_3)_4$ | EtOH | $Et_3N$ | 76 | 0 | 24 | 72% |
| 7 | $Pd(PPh_3)_4$ | EtOH | $Et_3N$ | 100 | 0 | 0 | 92 |

*a*: isolated yield. *b*: total (TM-*E* + TM-*Z*) yield. *c*: reaction perfoemed at room temperature.
*d*: 3 mol% [Pd]-catalyst used.

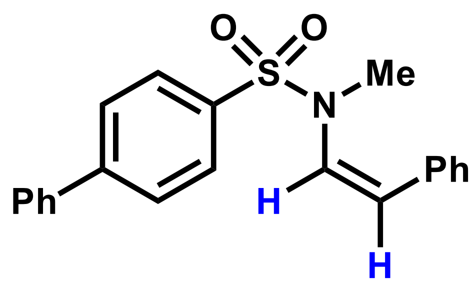
Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984. **isolated yield**

# Scope of the *Z*-selective hydrogenation (1)

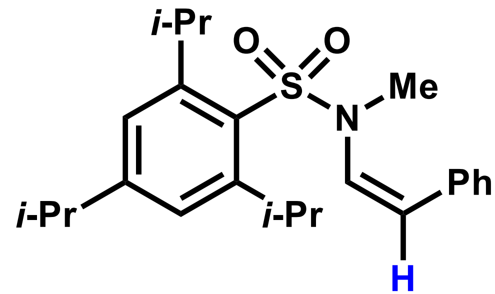


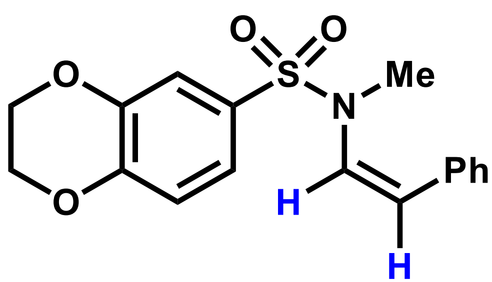

82%
(4/96)



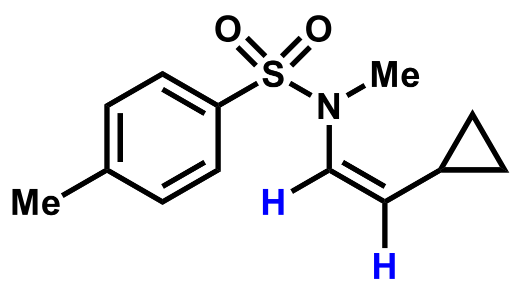

74%
(9/91)



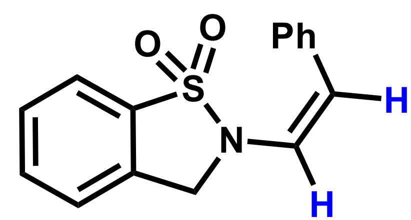

76%
(11/89)




80%
(7/93)



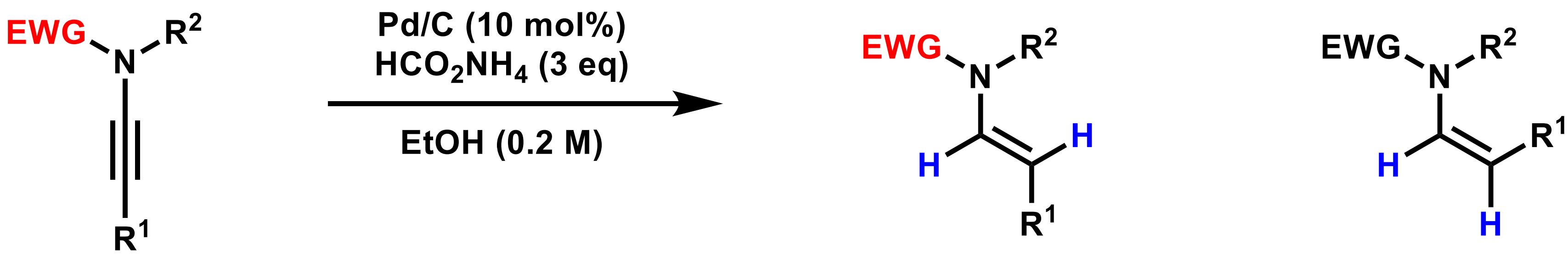

74%
(2/98)

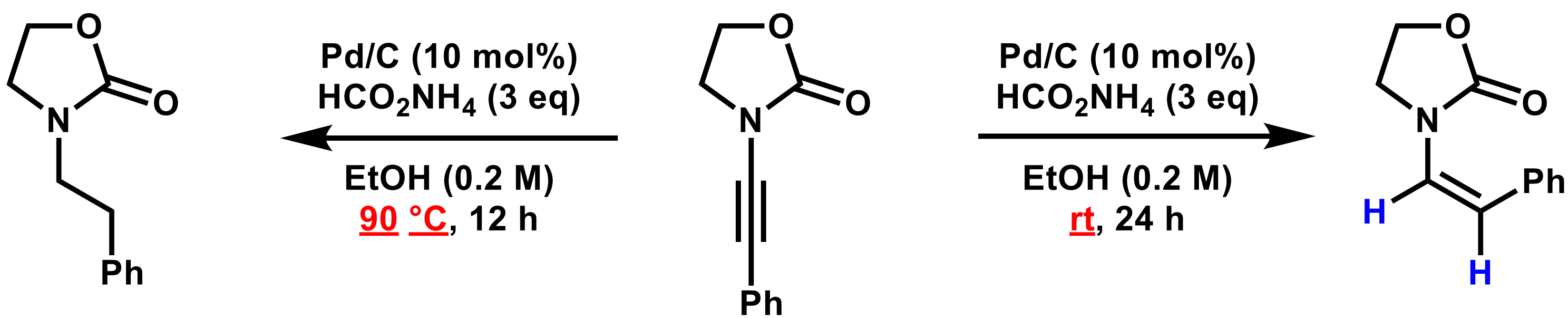



86%
(7/93)

Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984. **isolated yield**

# Scope of the *Z*-selective hydrogenation (2)

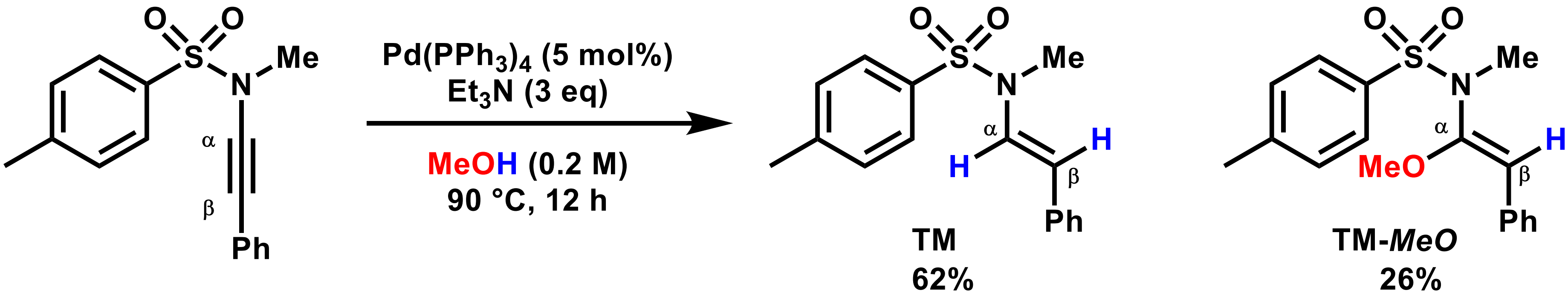


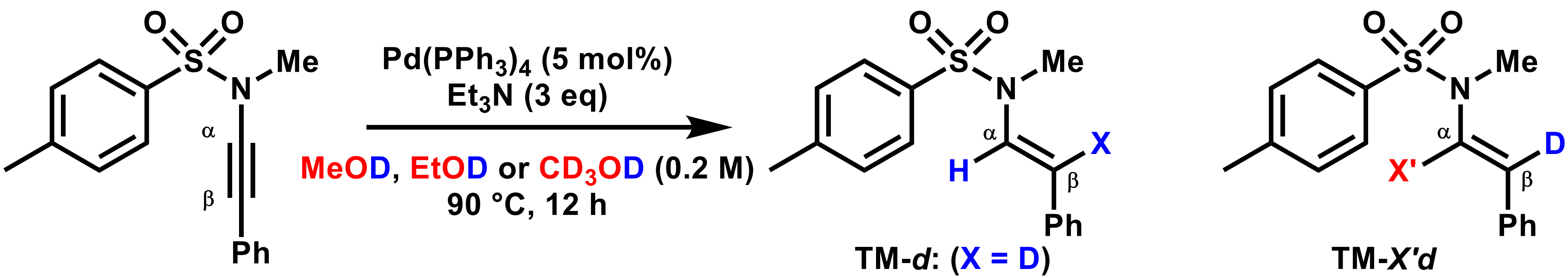



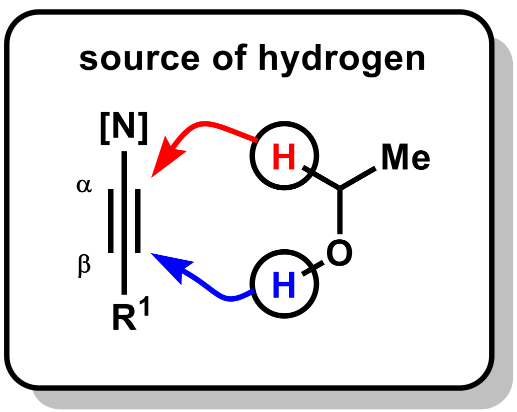

94% 76%

Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984. **isolated yield**

# Control experiments



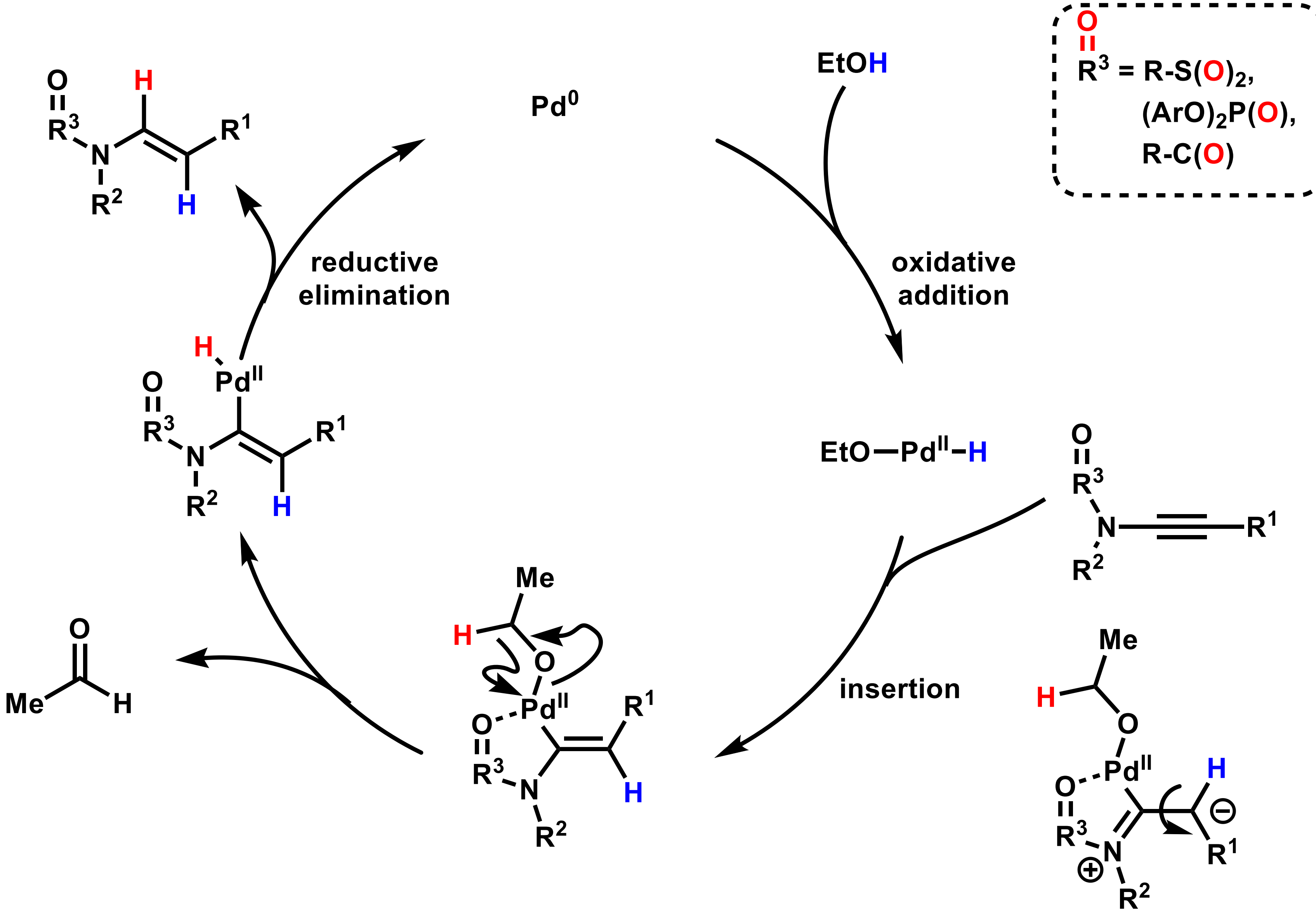




| | | |
|---|---|---|
| MeOD: | TM: 0%<br>TM-*d*: 56% | detected (not isolated)<br>X = OMe |
| EtOD[a]: | 90%<br>(TM/TM-*d* = 1/≥1) | NOT detected<br>X = OEt |
| $CD_3OD$ | no reaction | NOT detected<br>X = $OCD_3$ |

*a*: ca 60% deuterated EtOD was used (prepared by hydrolysis of $Si(OEt)_4$ with $D_2O$).

Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984.

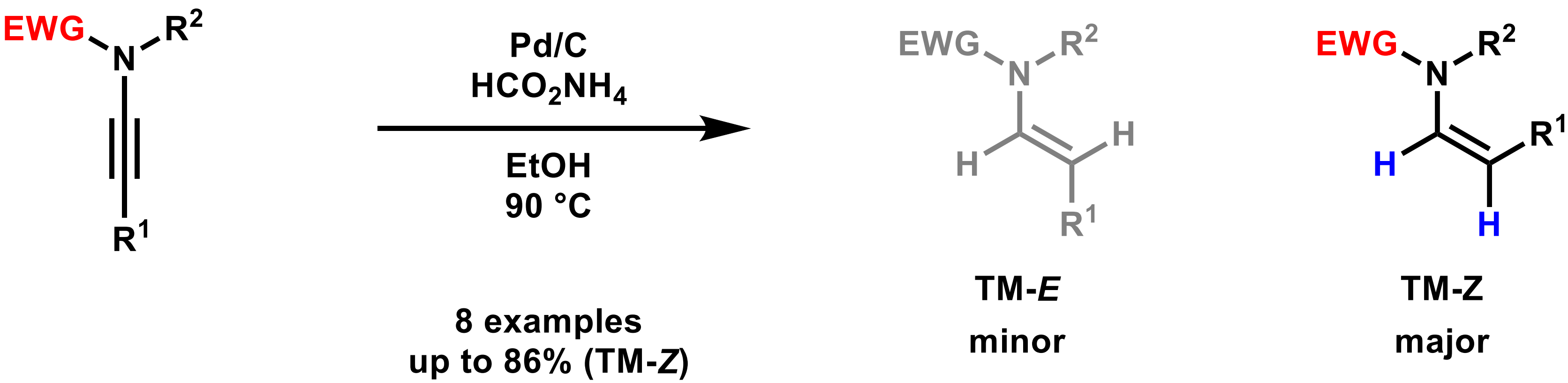
# Proposed methanism



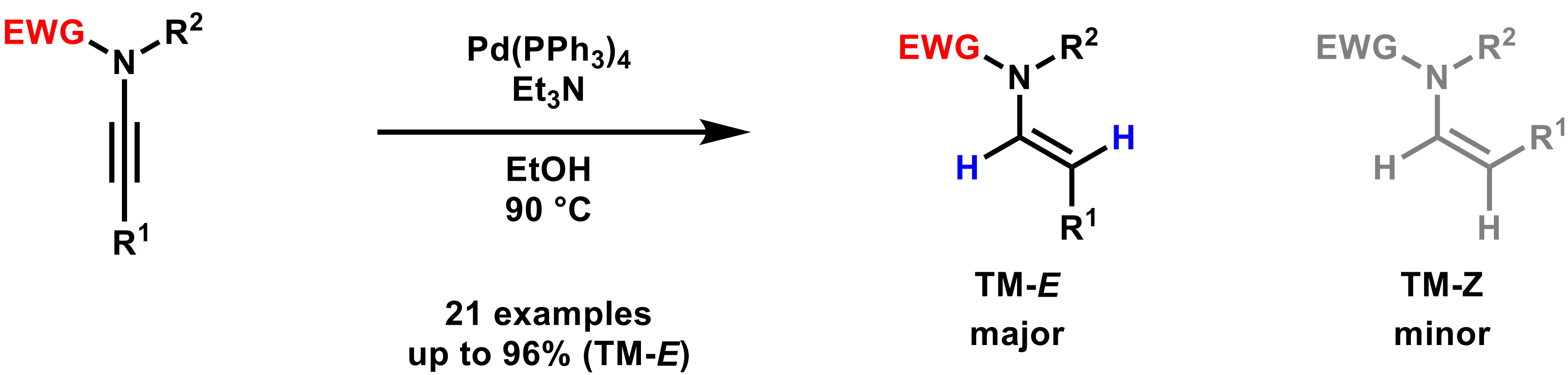

Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984.

# Summary

•*Z*-selective semi-hydrogenation



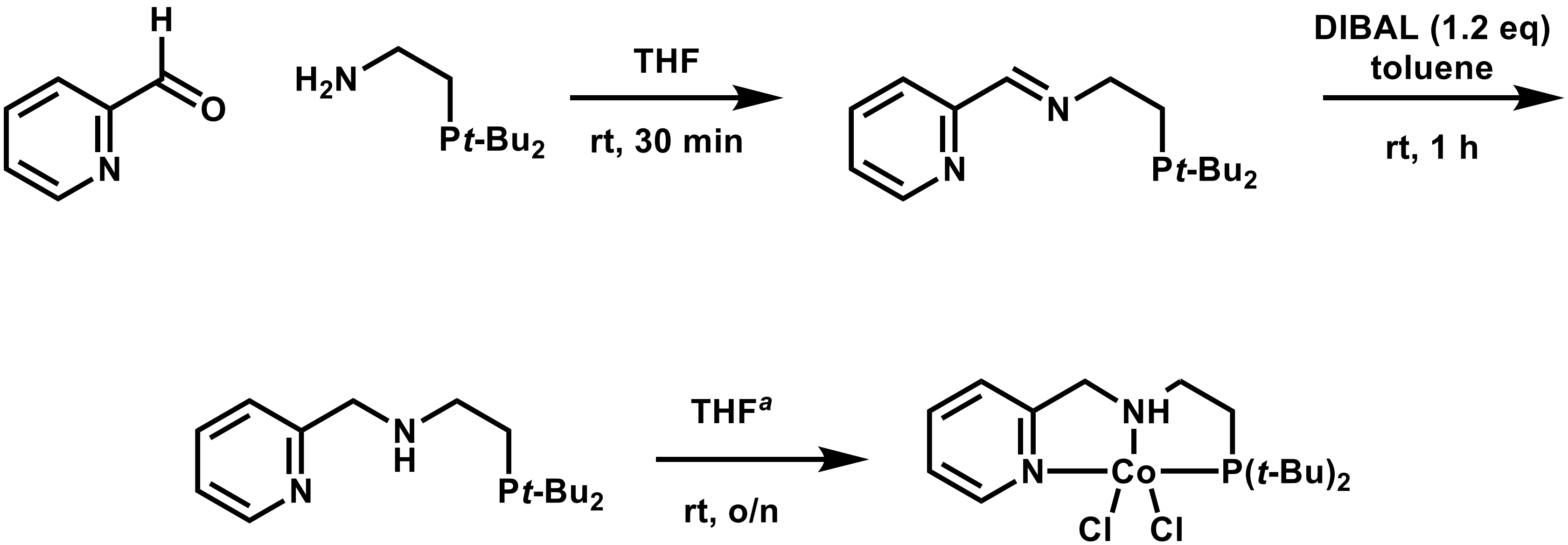

•*E*-selective semi-hydrogenation




Reddy, A. S.; Swamy, K. C. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984.

# Appendix

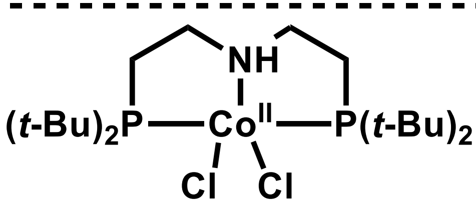
# Preparation of catalyst



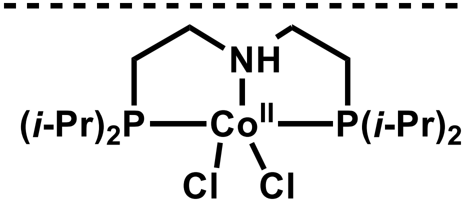

cat C

*a*: cat A and cat B were prepared under same condition

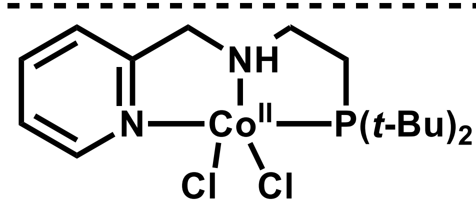
---




cat A




cat B

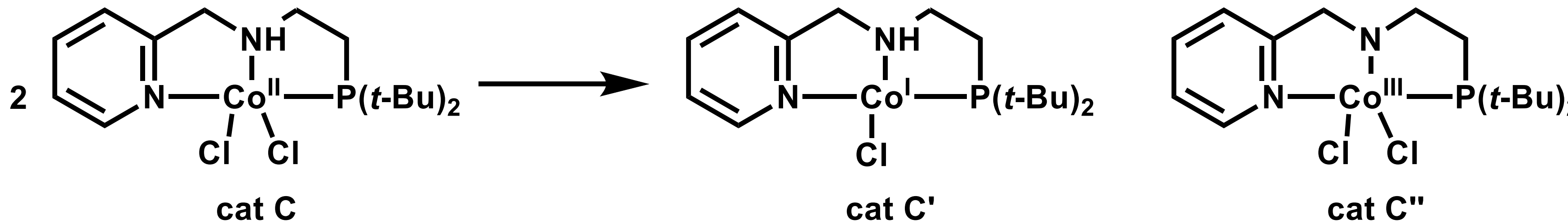


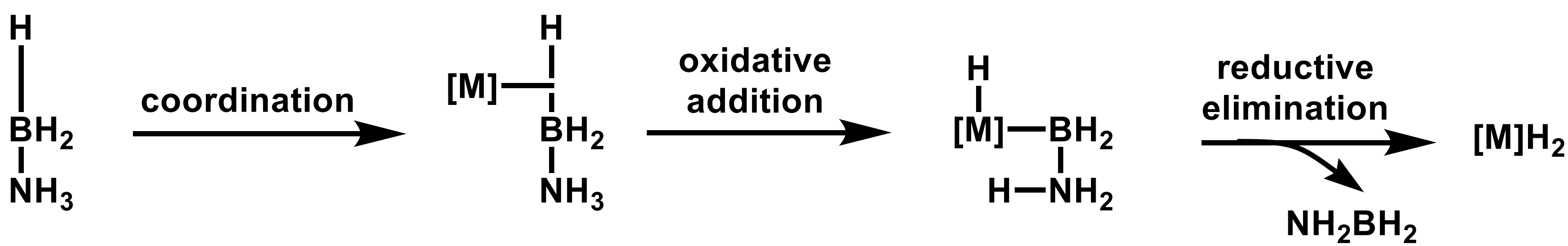

cat C

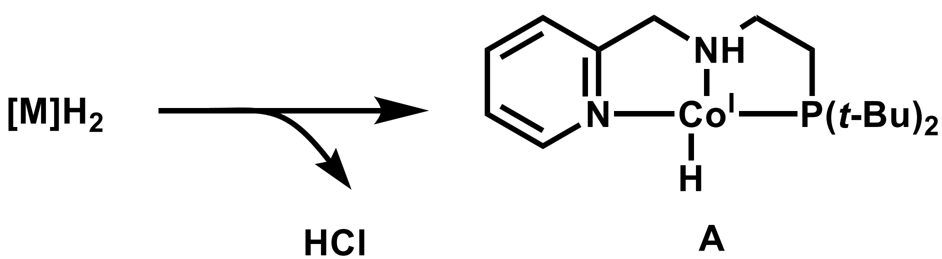

Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

# Activation of catalyst

disproportionation of Co(II)

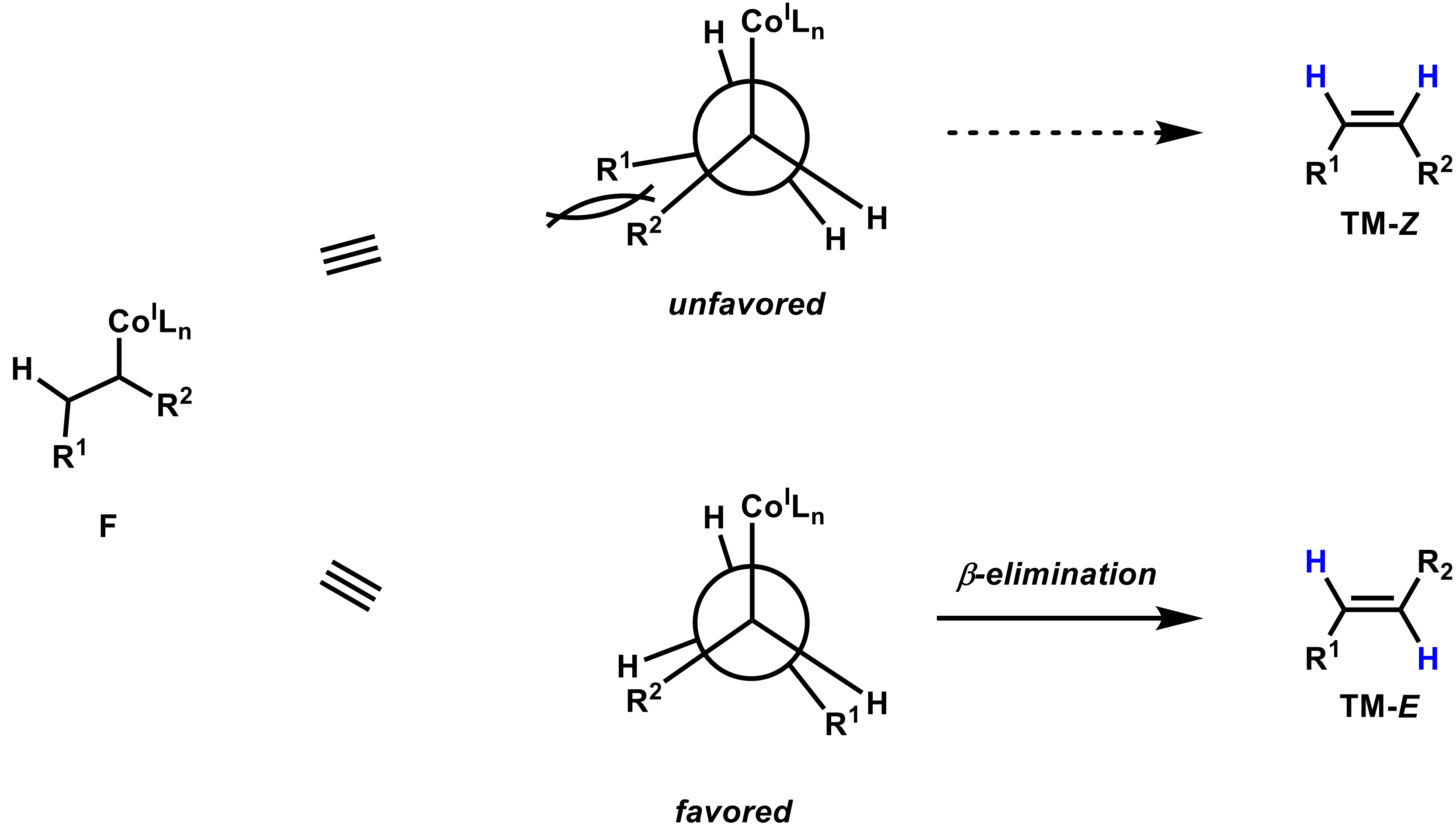



*J. Am. Chem. Soc.* **2016**, *138*, 8588. *J. Am. Chem. Soc.* **2007**, *129*, 1845.

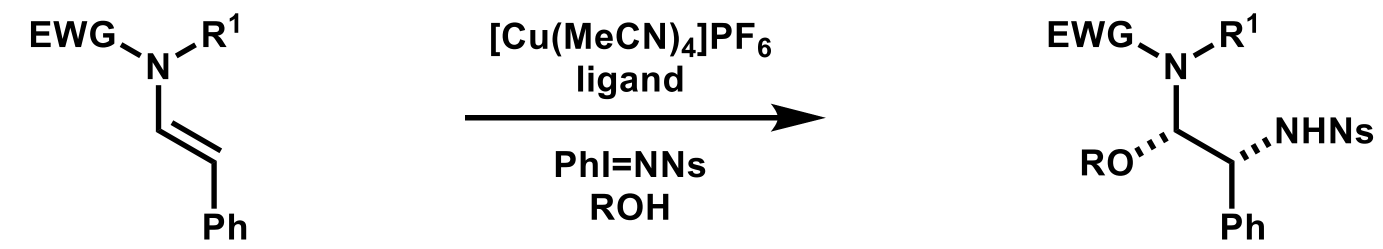
# E/Z-selectivity of β-elimination




Fu, S.; Chen, N.- Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

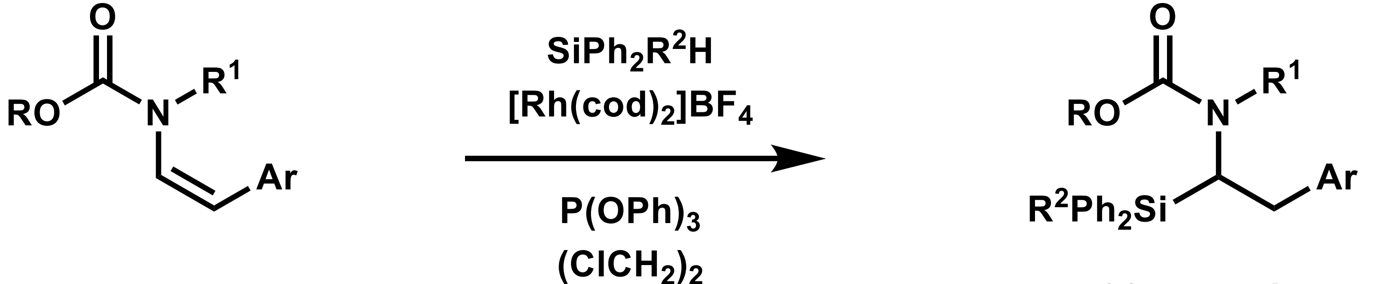
# Utilization of enamide

• **Direct intermolecular difunctionalization**




**23 examples**
**37-88%**
**(ee up to 94%)**

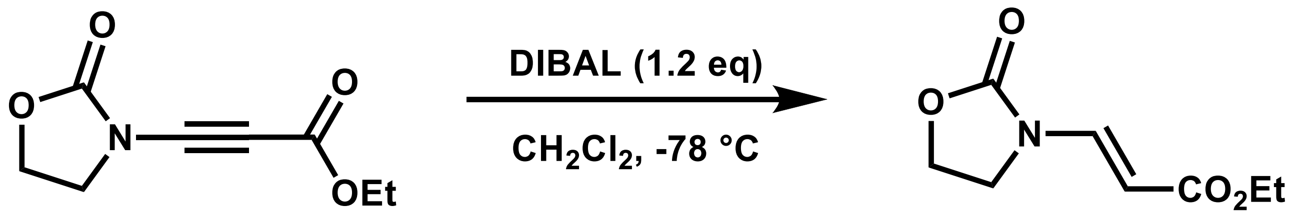
• **Hydrosilylation of enamides using silanes**



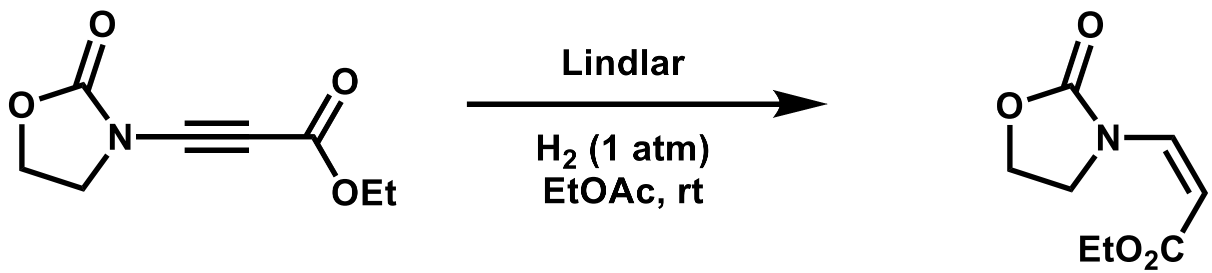

**36 examples**
**28-97%**

Gigant, N.; Chausset-Boissarie, L.; Gillaizeau, I. *Chem. Eur.* **2014**, *20*, 7548.

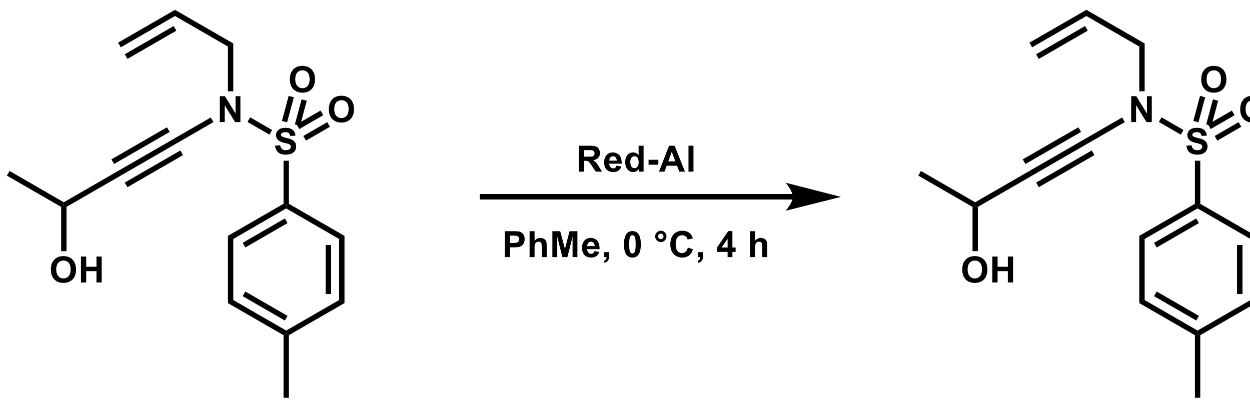
# Other reduction methods of ynamide




50% (*E*)




92% (*Z*)

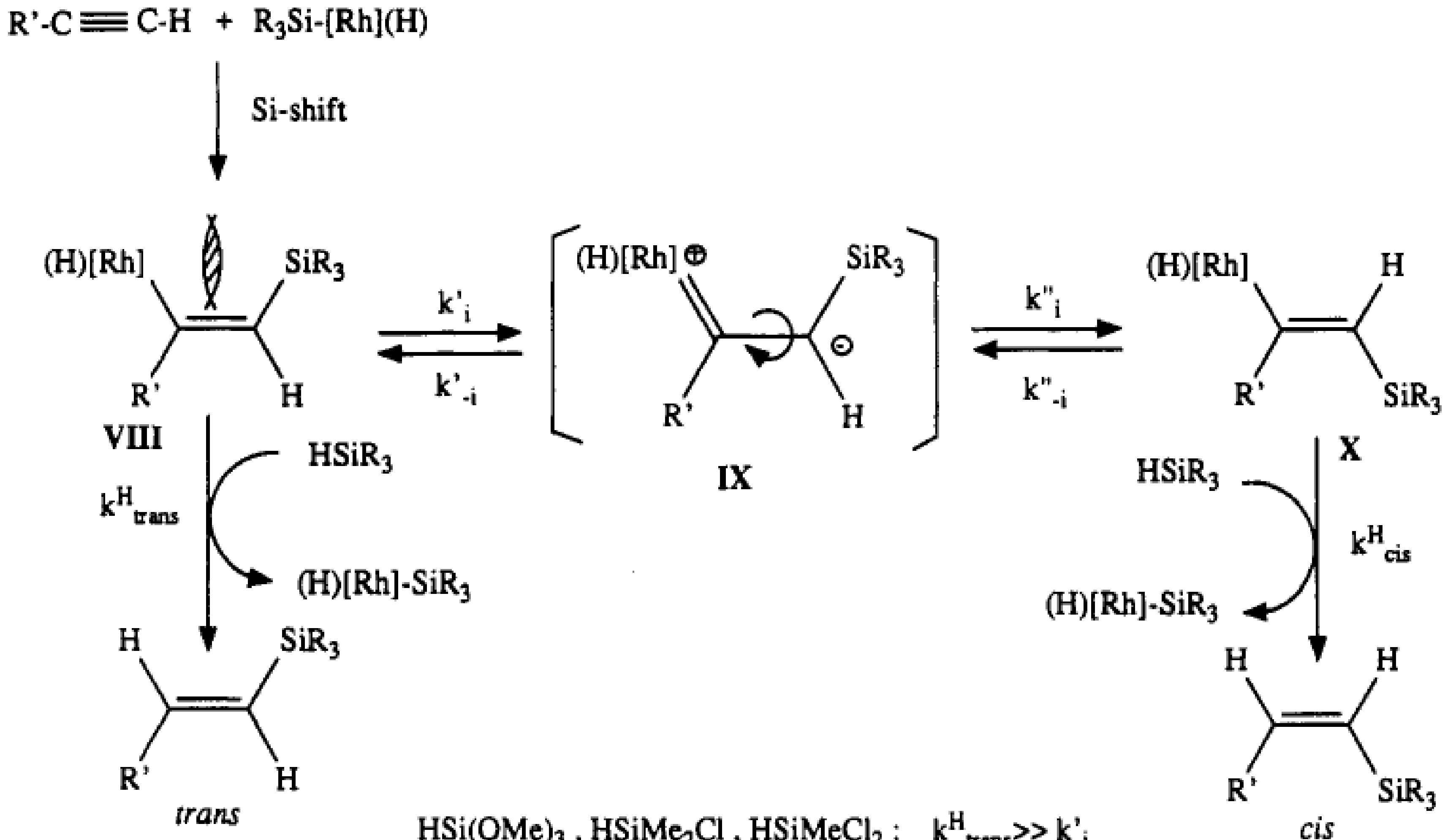



76% (*E*)

*JOC*. **2006**, *71*, 4170. *Org. Biomol. Chem.* **2012**, *10*, 1406.

# Proposed mechamism for the trans addition

**Scheme III. Proposed Mechanism for the Apparent Trans Addition**




$HSi(OMe)_3$, $HSiMe_2Cl$, $HSiMeCl_2$ : $k^{H}_{trans} \gg k'_{i}$

$HSiEt_3$, $HSiMe_2Et$, $HSiMe_2Ph$ : $k^{H}_{trans} < k'_{i}$