

Metal-Catalyzed Enantioselective Cross-Couplings through Carbene Migratory Insertion

LSPN

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Sep. 26th, 2019

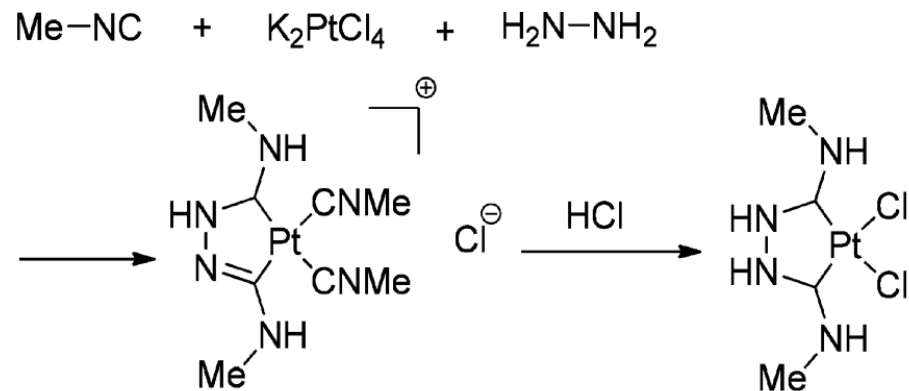
Content

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- 2. Metal-Catalyzed Enantioselective Cross-Couplings through Carbene Migratory Insertion
 - 2.1 Oxidative addition
 - 2.2 C-H activation
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- 3. Outlook

1. Brief Introduction to Metal Carbene

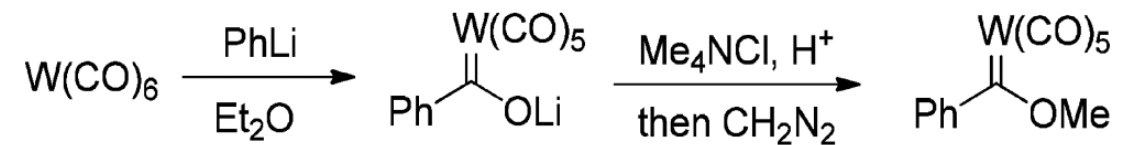
1.1 History

Chugaev's Synthesis of Platinum(II) Complex



Tschugajeff, L.; Skanawy-Grigorjewa, M.; Posnjak, A. *Z. Anorg. Allg. Chem.* **1925**, 148, 37.

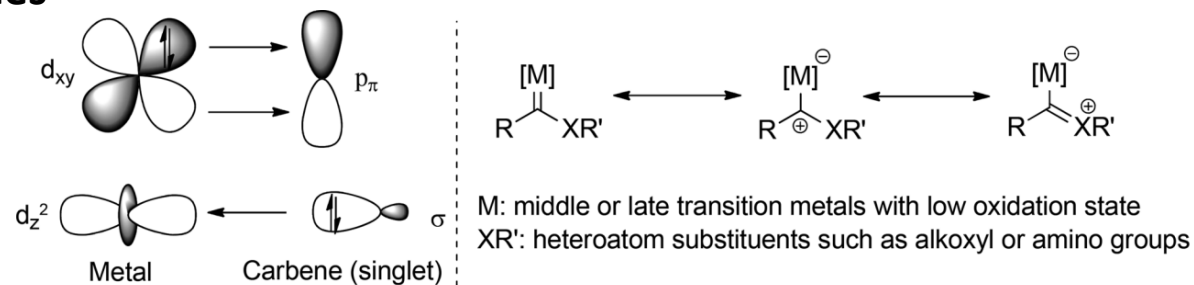
Fischer's Synthesis of Metal Carbene Complex



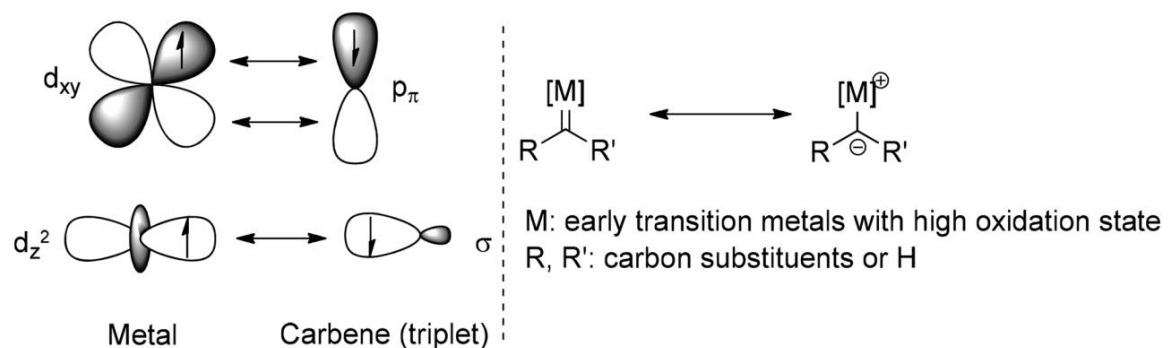
Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed.* **1964**, 3, 580.

1.2 Classification of Metal Carbenes

1). Fischer carbenes



2). Schrock carbenes

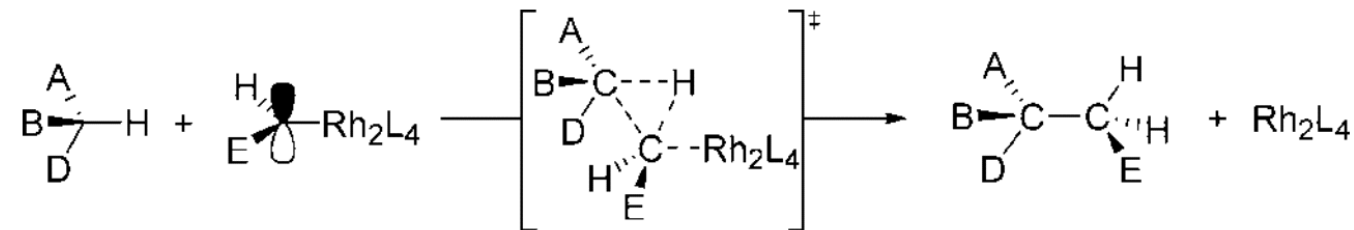


3). N-Heterocyclic carbenes

4). Carbene radicals

1.3 Modern Organic Chemistry involving Metal Carbene

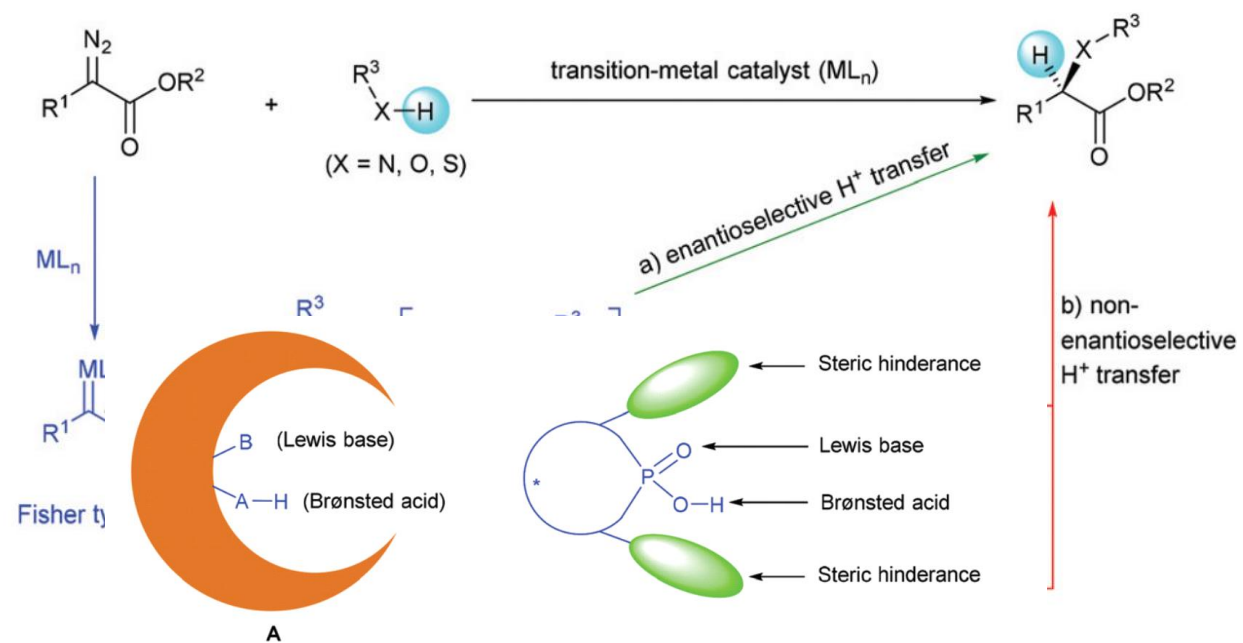
1. Cyclopropanation



2. X-H insertion

C(Si)-H insertion

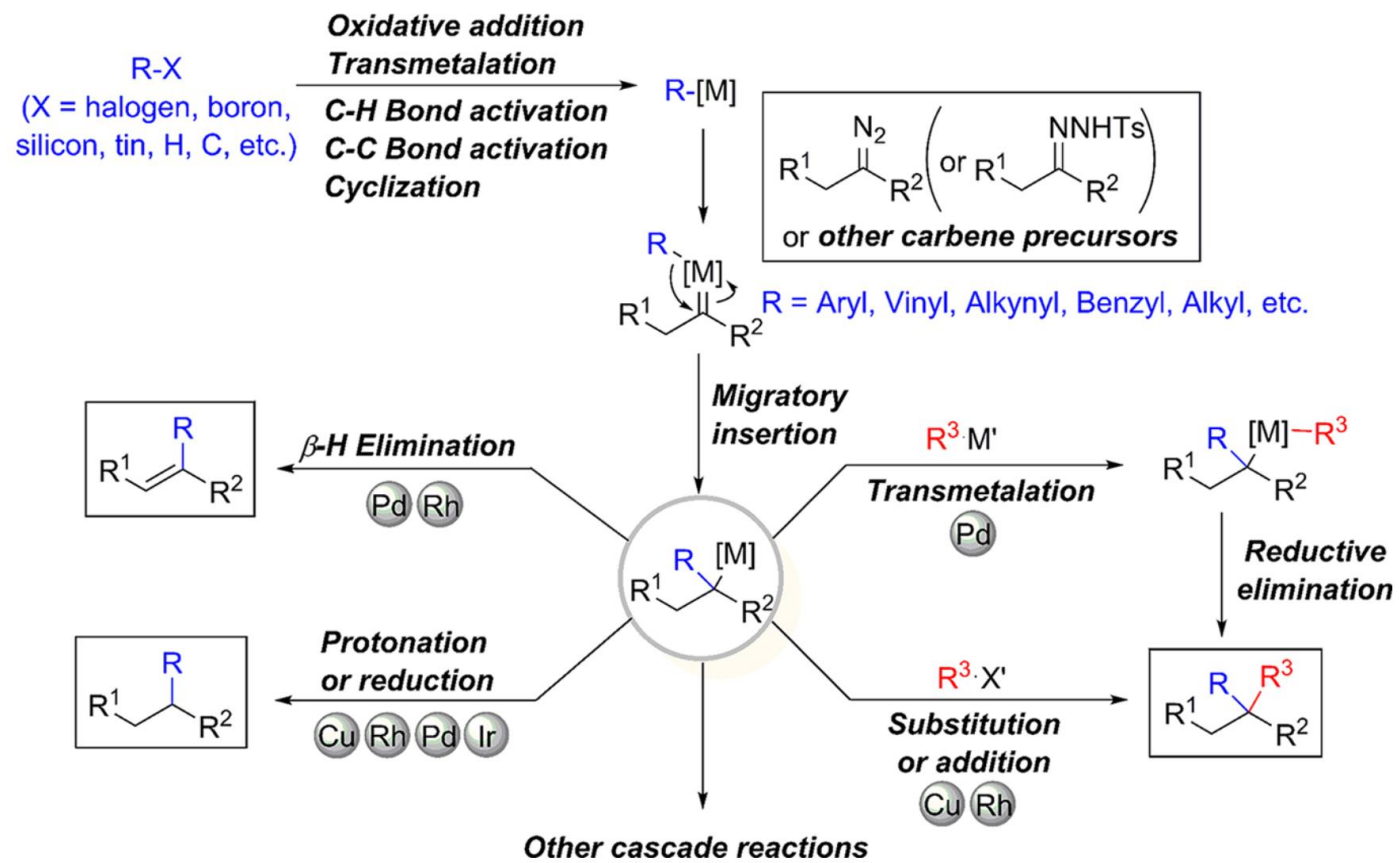
X-H insertion (O, S, N...)



3. Coupling reaction

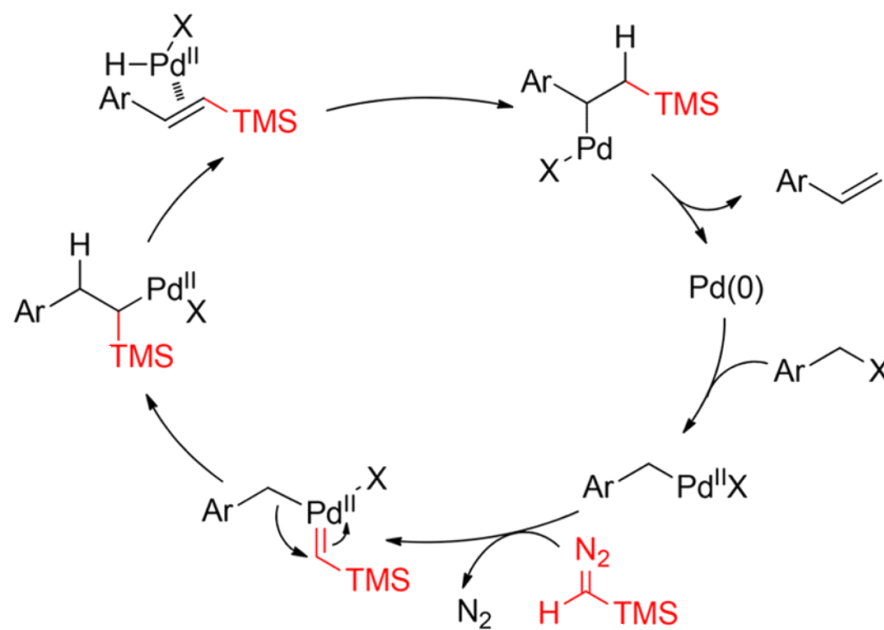
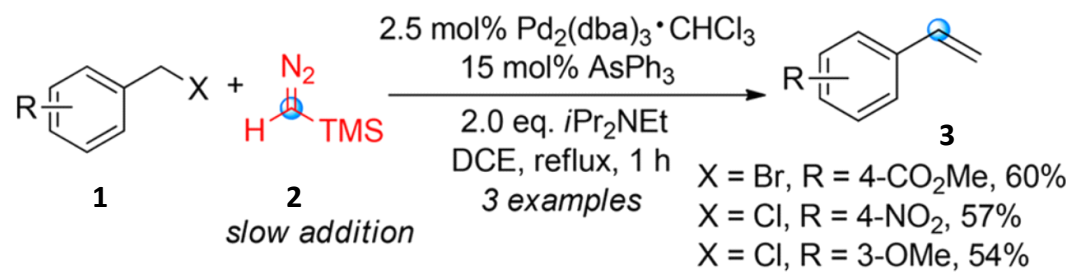
4. Ylide reaction

5. Other reactions

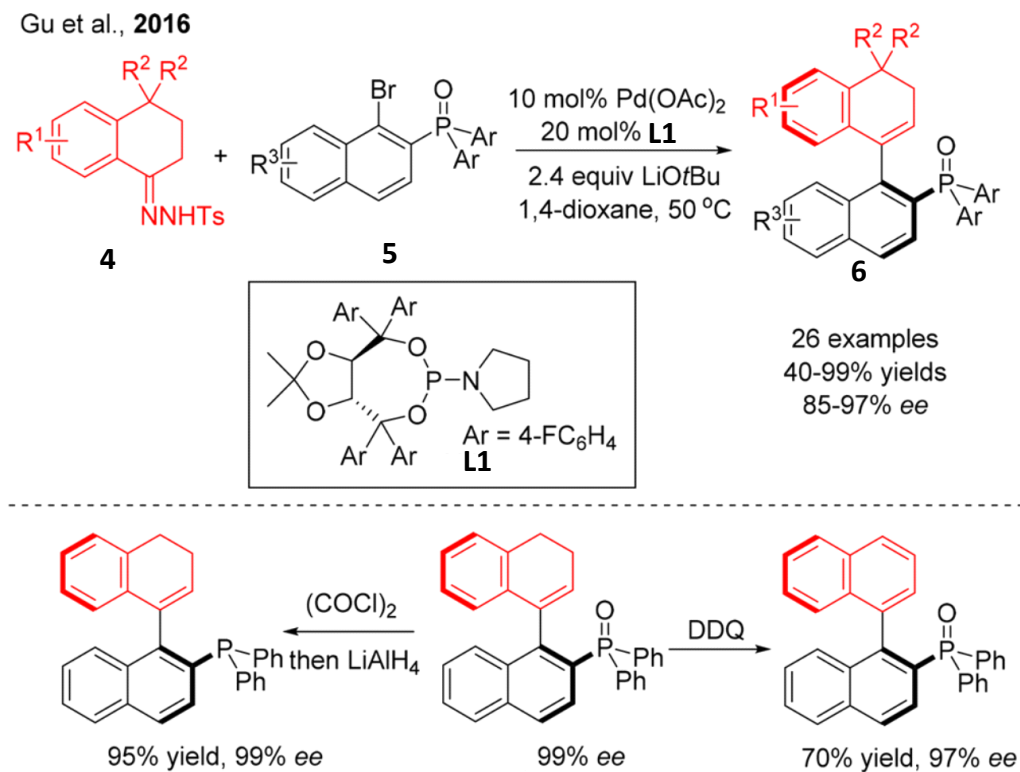


2. Metal-Catalyzed Enantioselective Cross-Couplings through Carbene Migratory Insertion

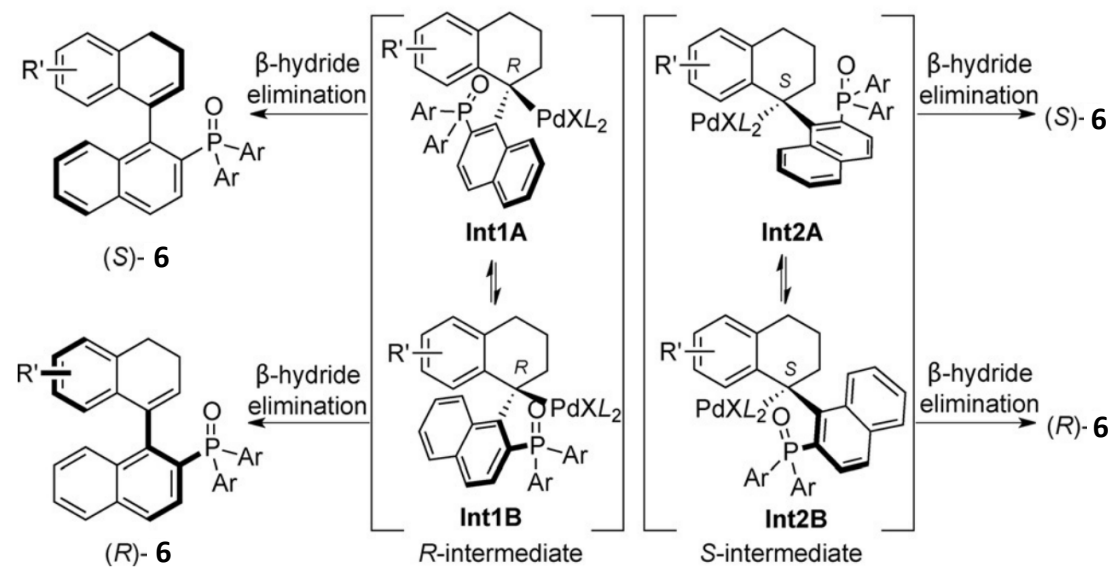
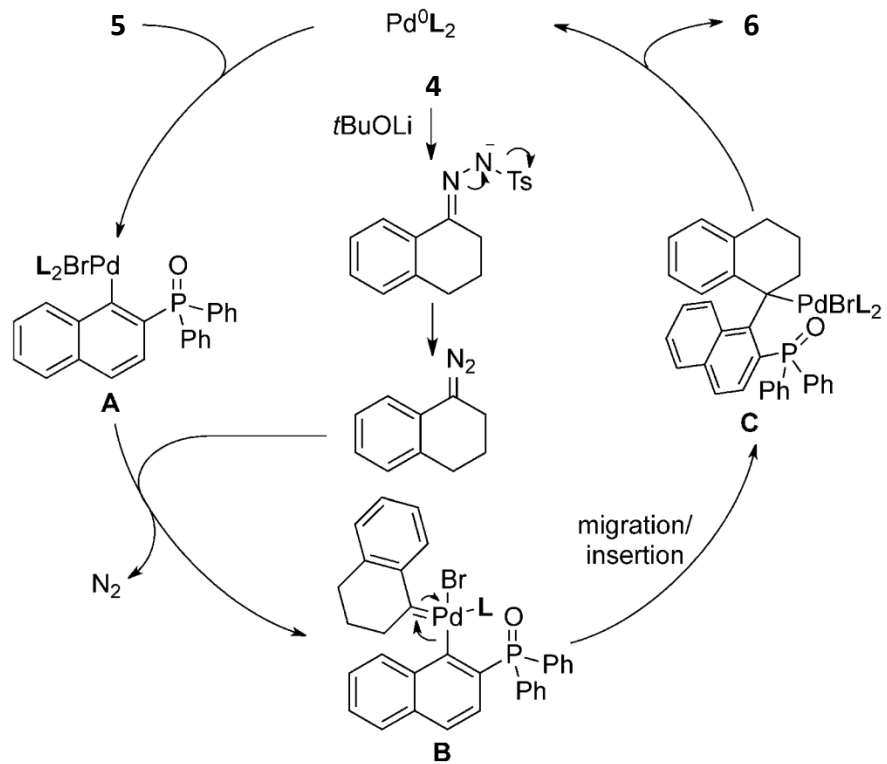
First catalytic cross-coupling reaction through carbene insertion



2.1 Oxidative addition Prior to Carbene Migratory insertion



Feng, J.; Li, B.; He, Y.; Gu, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 2186.

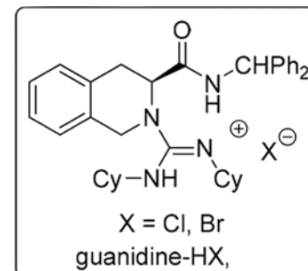
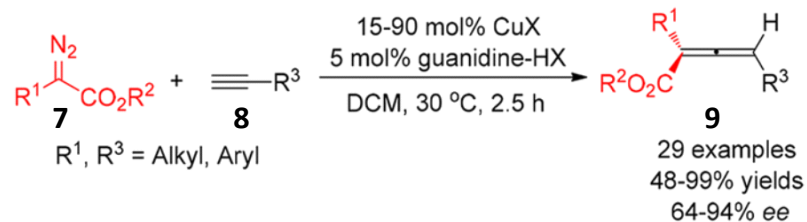


Feng, J.; Li, B.; He, Y.; Gu, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 2186.

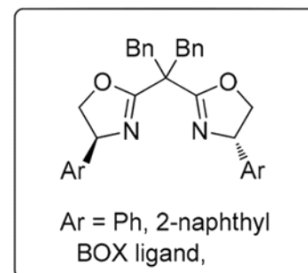
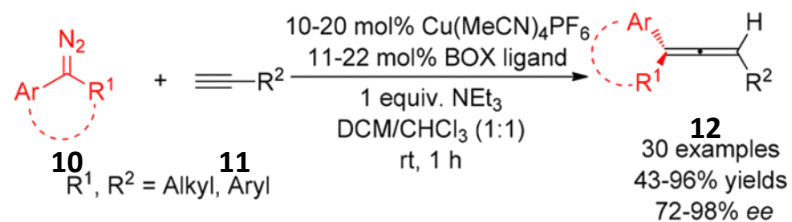
2.2 C-H activation Prior to Carbene Migratory insertion

2.2.1 Functional C-H-Alkyn

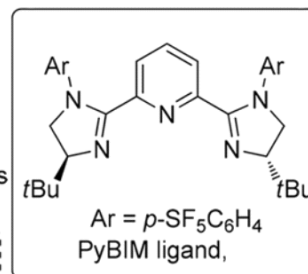
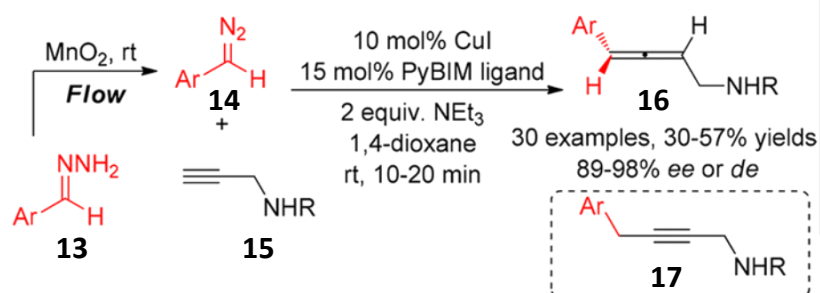
a) Liu, Feng et al., 2015



b) Wang et al., 2016



c) Ley et al., 2017

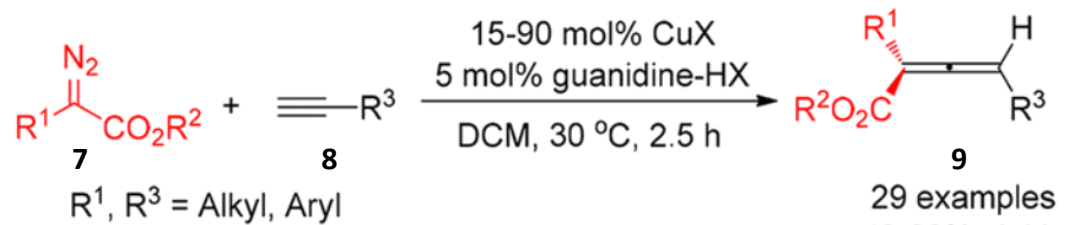


a) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512.

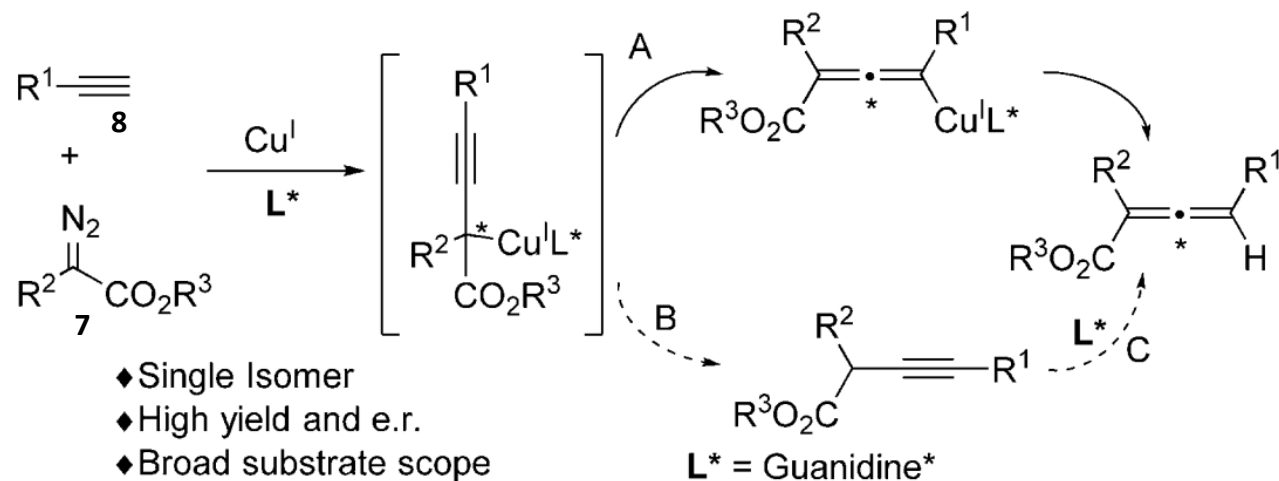
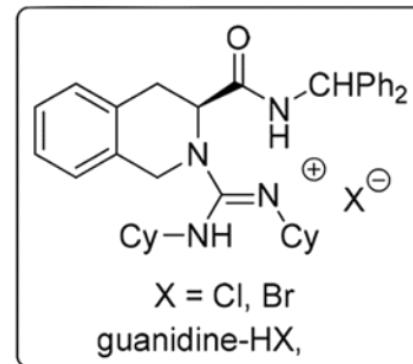
b) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2016**, *138*, 14558.

c) Poh, J. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2017**, *56*, 1864.

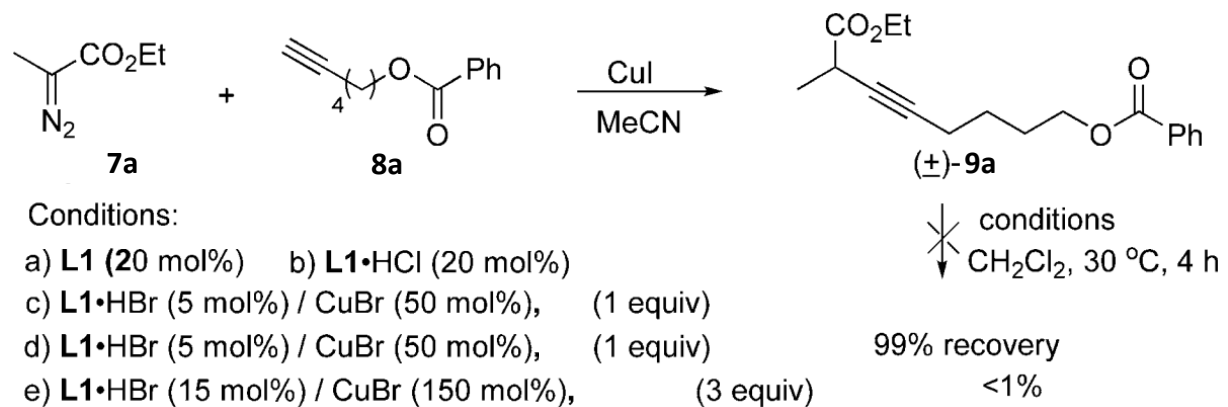
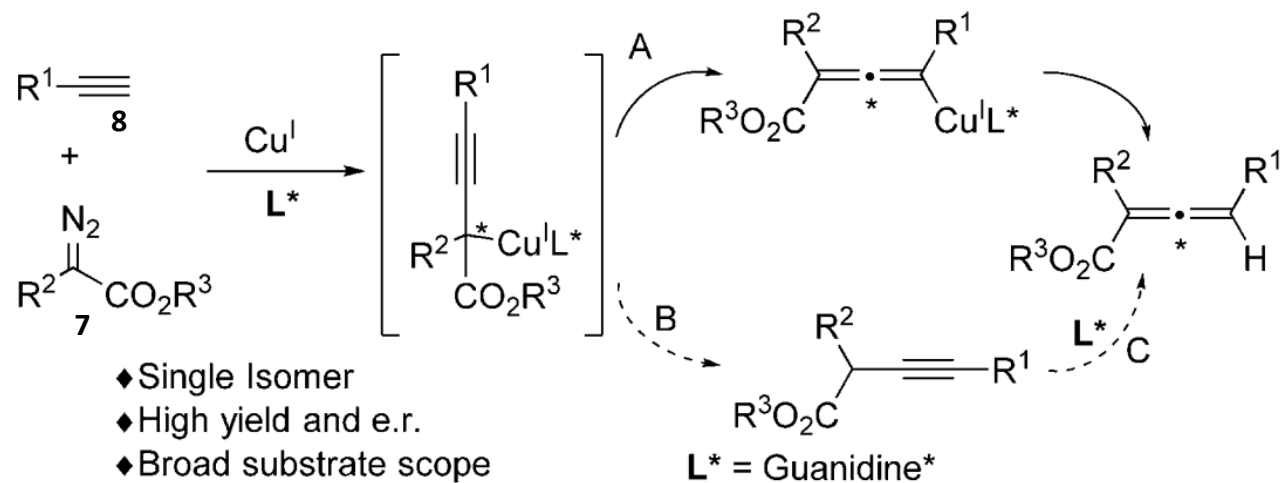
a) Liu, Feng et al., 2015



29 examples
48-99% yields
64-94% ee

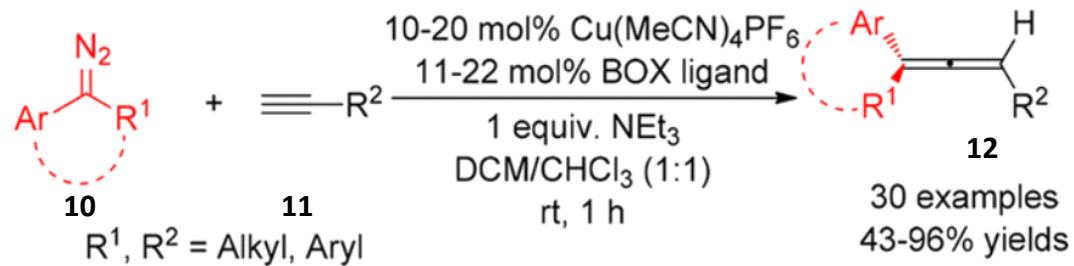


a) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512.

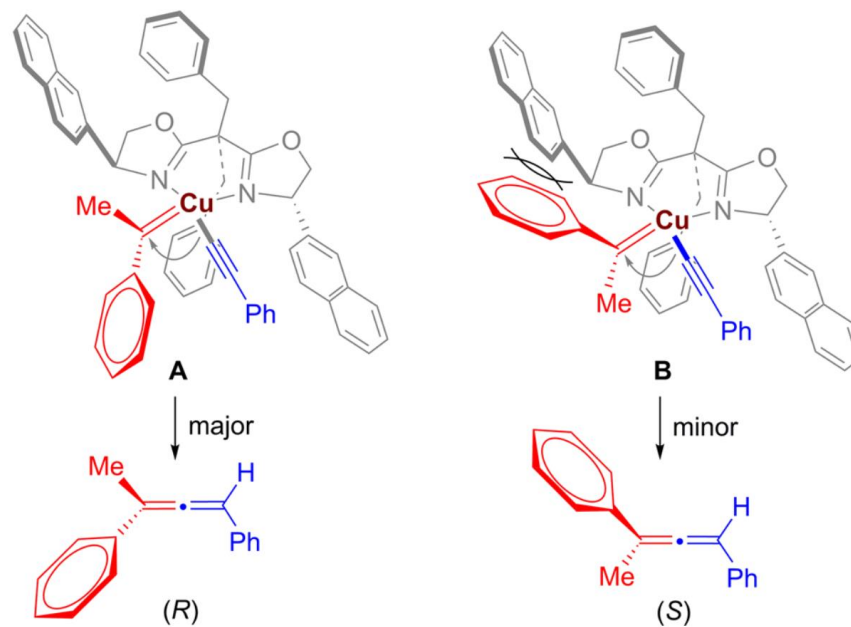
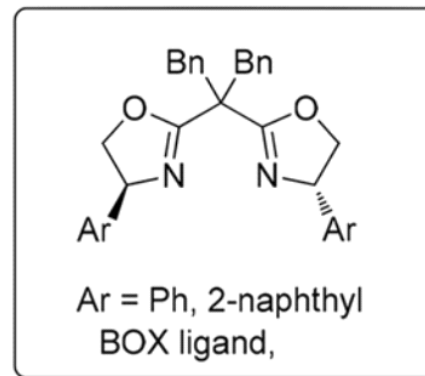


a) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512.

b) Wang et al., 2016

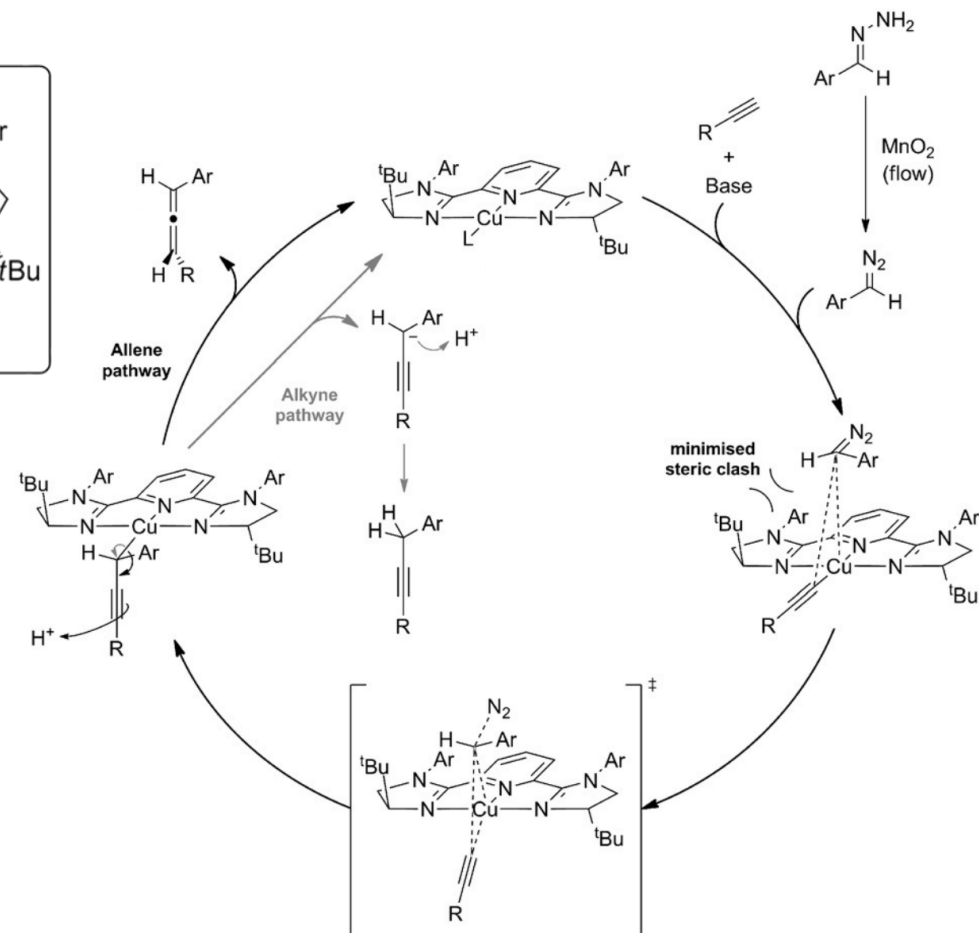
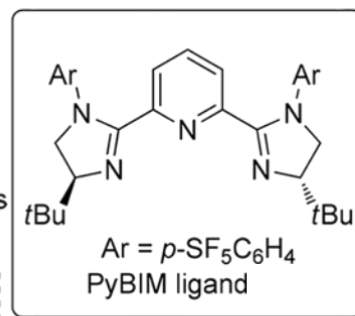
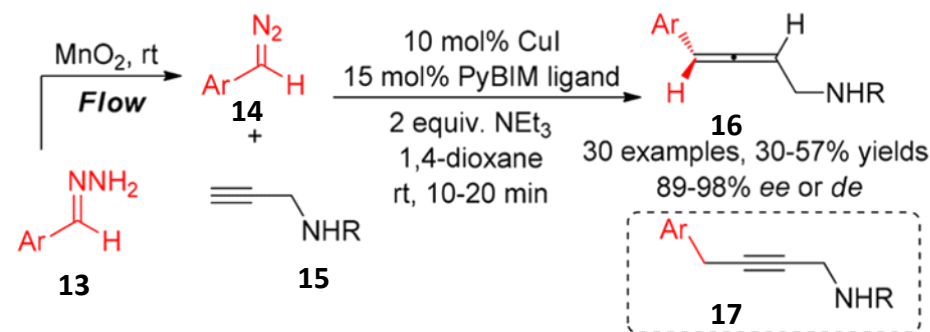


30 examples
43-96% yields
72-98% ee



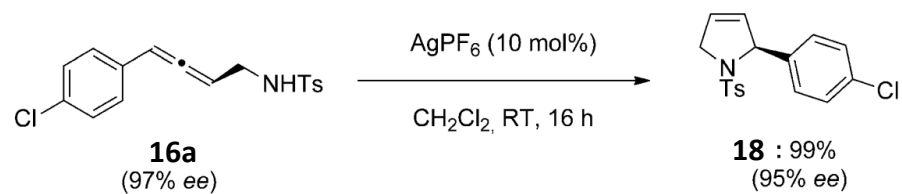
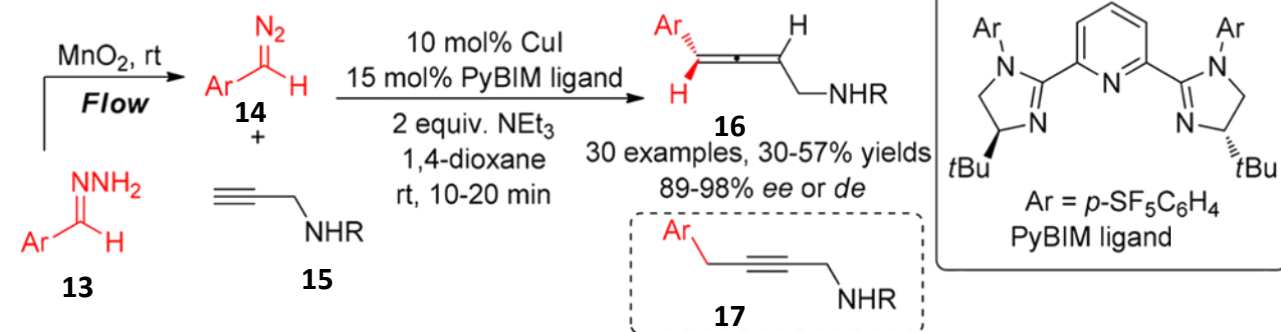
b) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2016**, *138*, 14558.

c) Ley et al., 2017



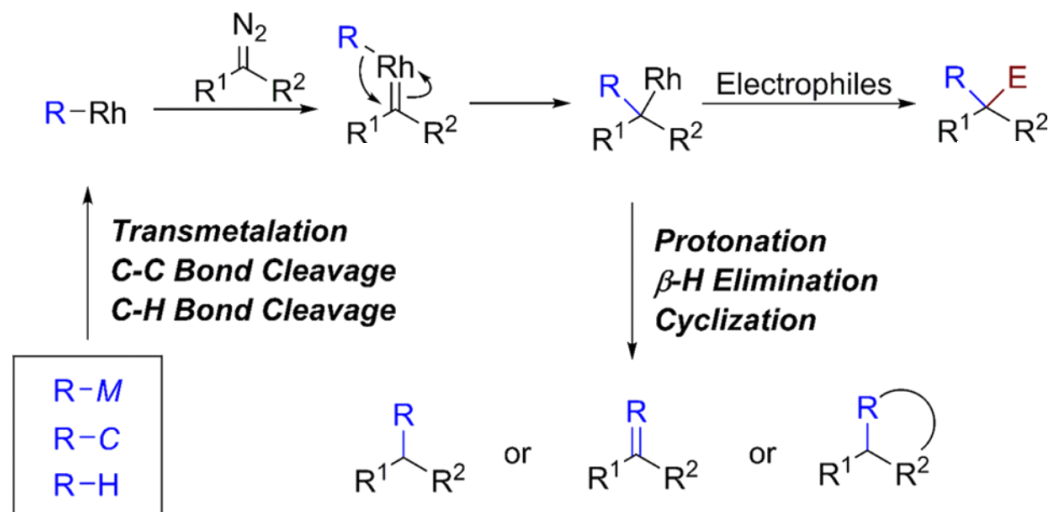
c) Poh, J. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. *Angew. Chem., Int. Ed.* 2017, 56, 1864.

c) Ley et al., 2017



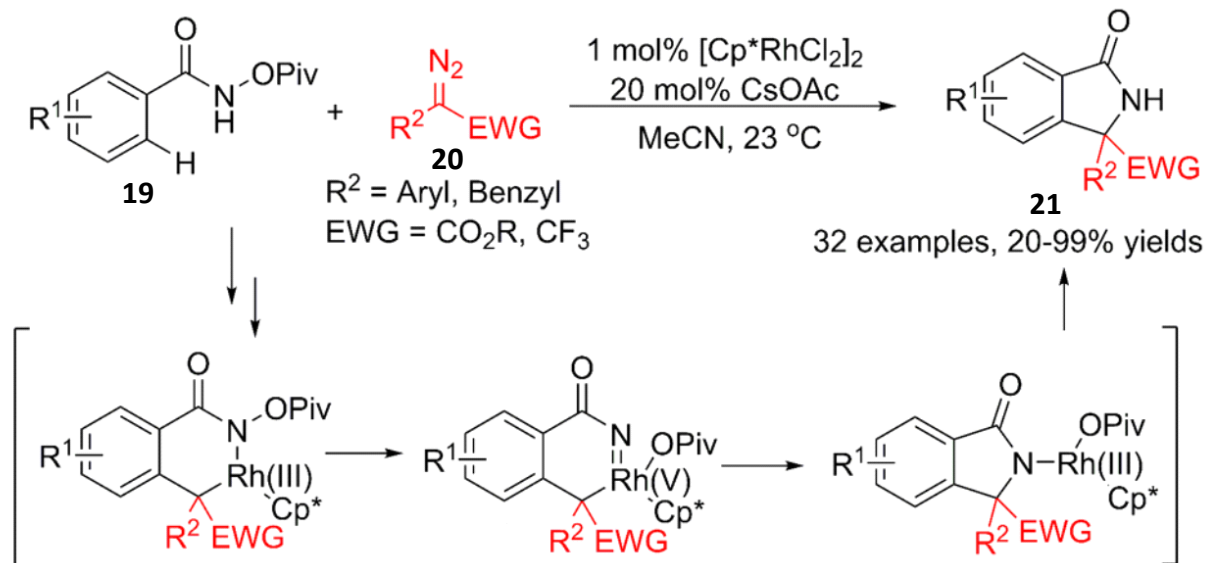
c) Poh, J. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. *Angew. Chem., Int. Ed.* 2017, 56, 1864.

2.2.2 C-H activation with directing group



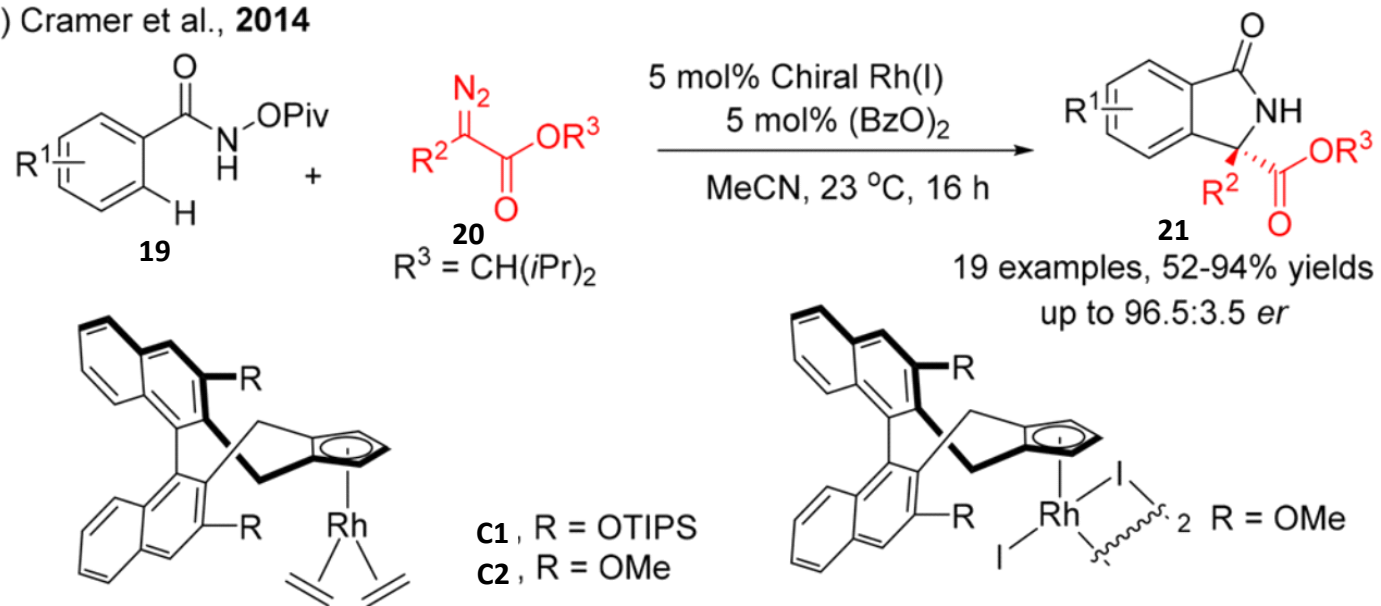
2.2.2.1 C-H activation with cyclization

Rovis et al., **2013**; Xia et al., **2015** (DFT calculations)

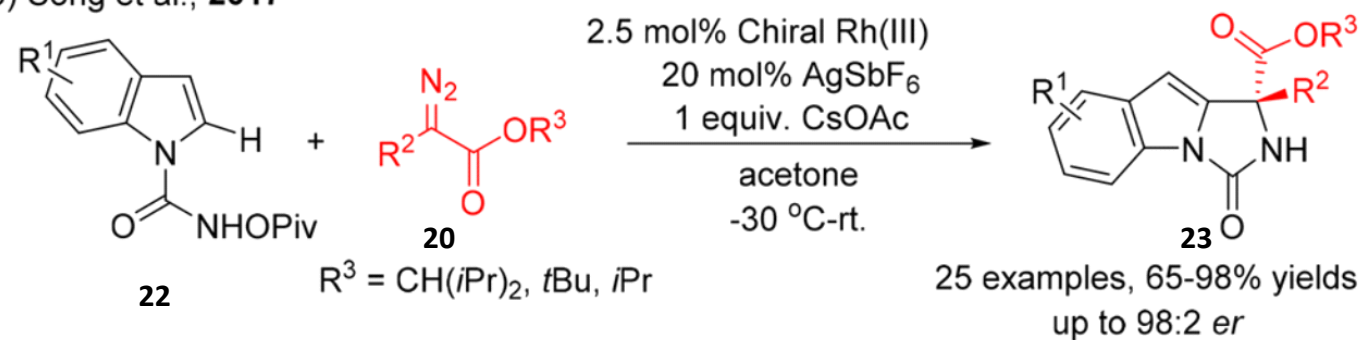


- Hyster, T. K.; Ruhl, K. E.; Rovis, T. J. *Am. Chem. Soc.* **2013**, *135*, 5364.
- Zhou, T.; Guo, W.; Xia, Y. *Chem.-Eur. J.* **2015**, *21*, 9209.

a) Cramer et al., 2014

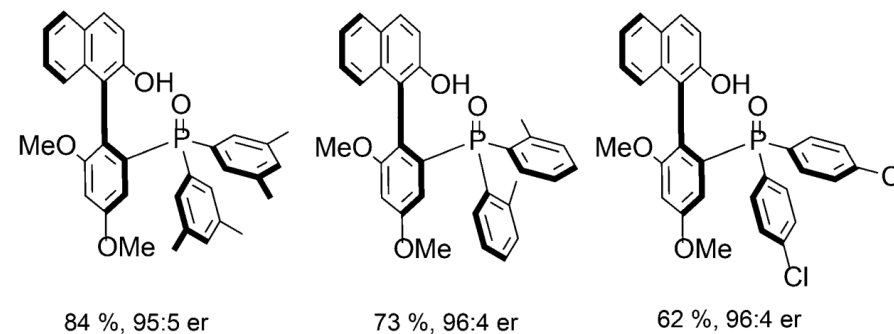
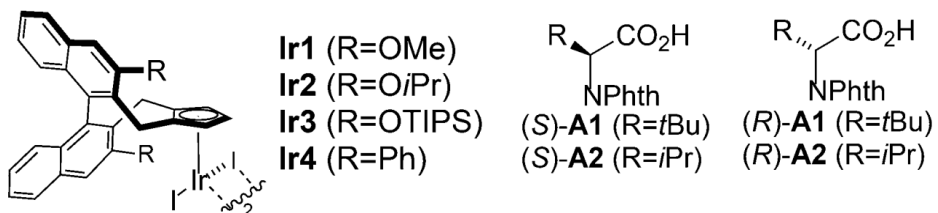
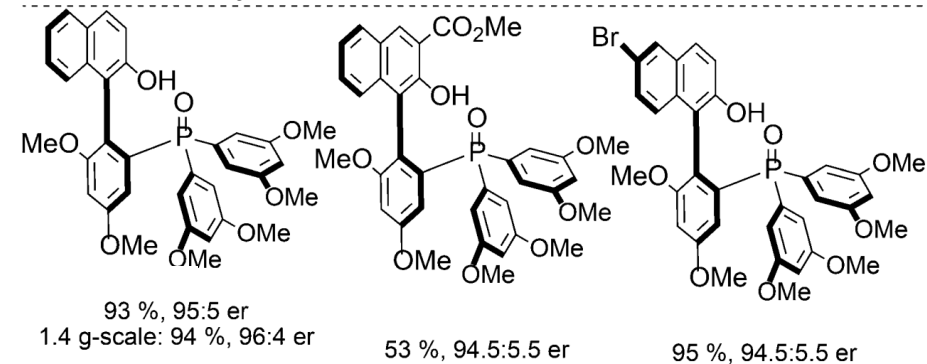
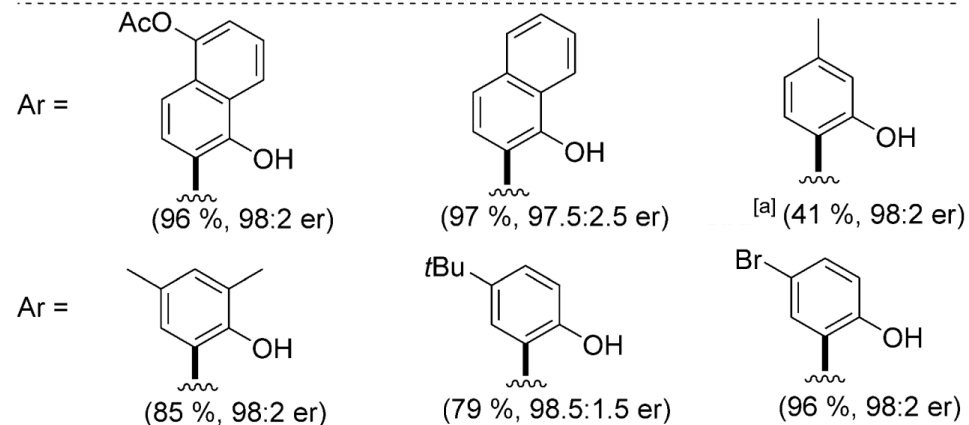
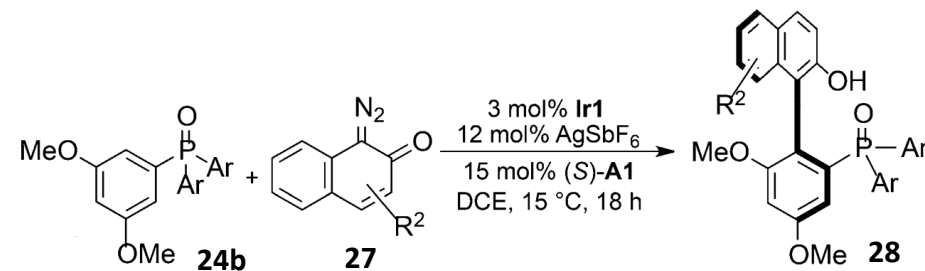
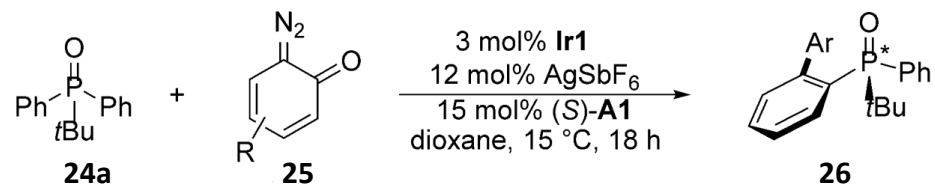


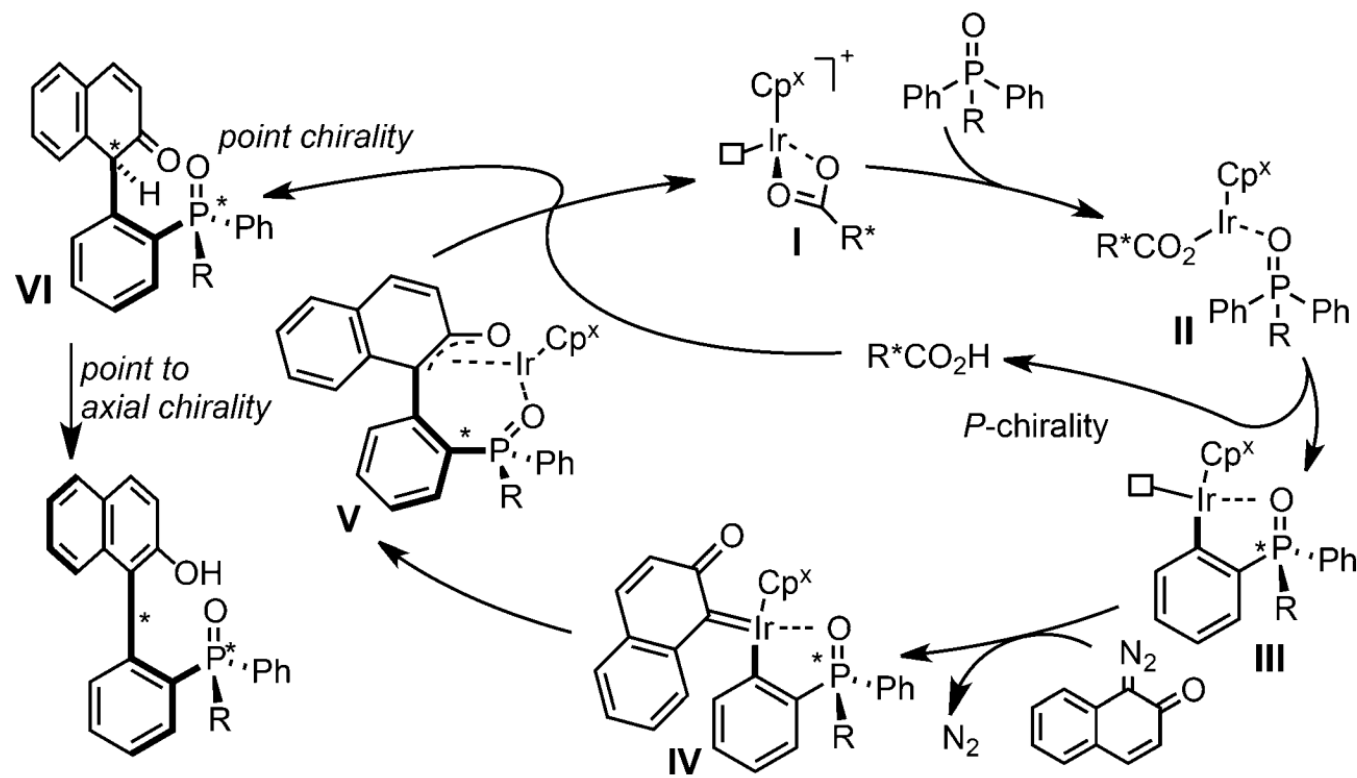
b) Song et al., 2017



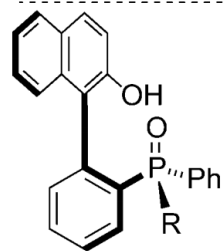
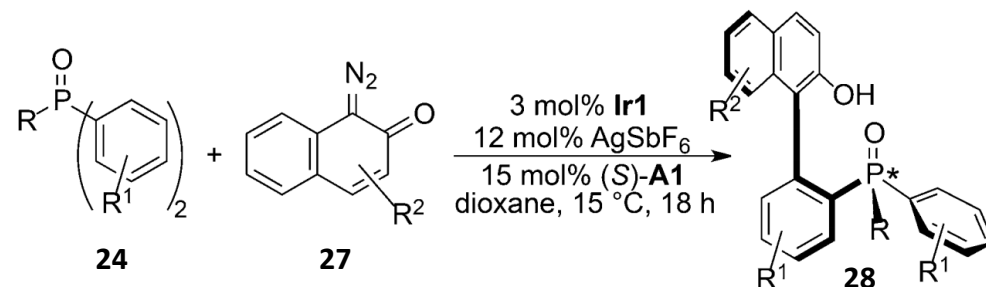
- a) Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896.
 b) Chen, X.; Yang, S.; Li, H.; Wang, B.; Song, G. *ACS Catal.* **2017**, *7*, 2392.

2.2.2.2 C-H activation without cyclization

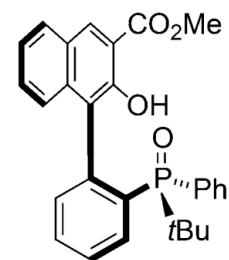
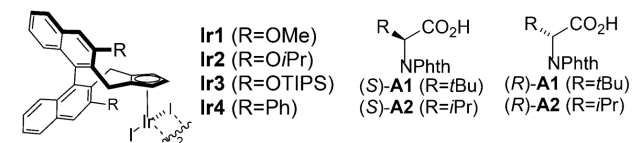




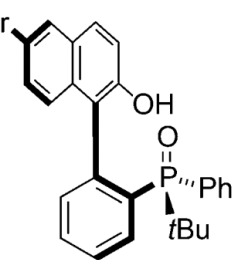
Jang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. *Angew. Chem. Inter. Ed.* **2018**, *57*, 12901.



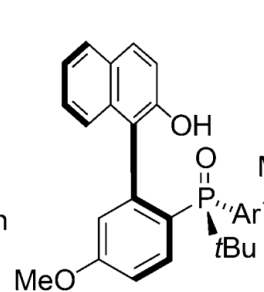
(R=*t*Bu): 85 %, >20:1 dr, 99:1 er
 (R=Ad): 70 %, >20:1 dr, 99:1 er
 (R=Cy): 59 %, 1.1:1 dr, 93.5:6.5 er (68:32 er)
 (R=*i*Pr): 67 %, 1.2:1 dr, 90.5:9.5 er (97:3 er)
 (R=N*i*Pr₂): 85 %, 1.1:1 dr, 97.5:2.5 er (77:23 er)



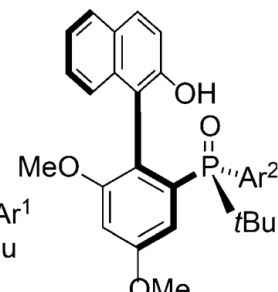
61 %, >20:1 dr
99.5:0.5 er



79 %, >20:1 dr
99.5:0.5 er



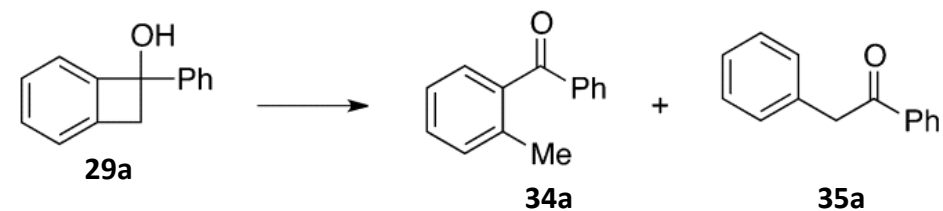
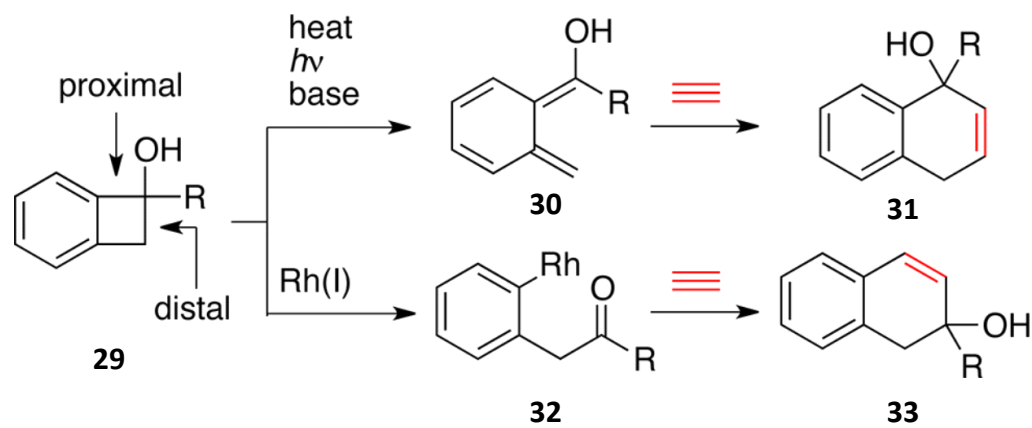
65 %, 20:1 dr
99.5:0.5 er



96 %, 2.8:1 dr
90.5:9.5 er
(80.5: 19.5 er)

Jang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. *Angew. Chem. Inter. Ed.* **2018**, *57*, 12901.

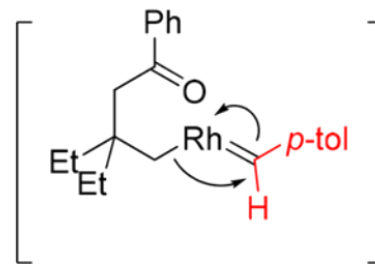
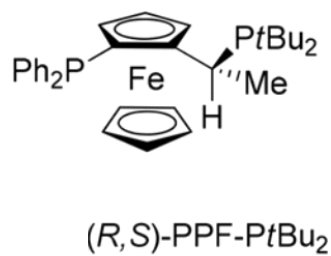
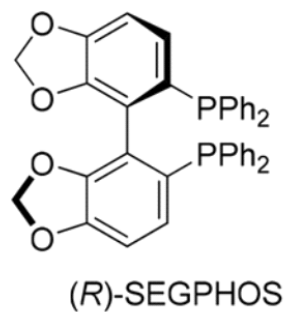
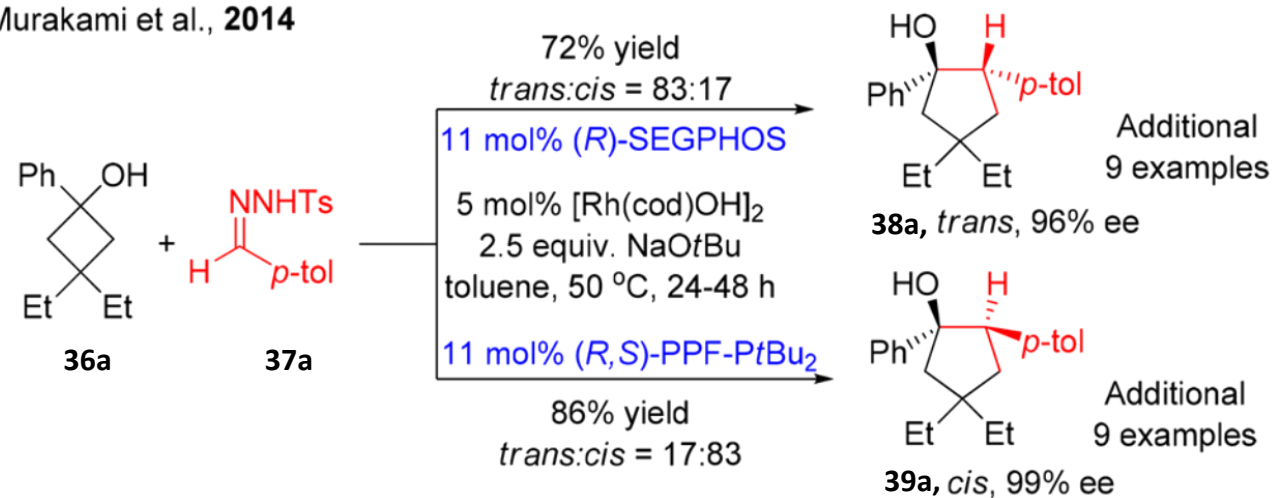
2.2.3 C-C Bond Cleavage



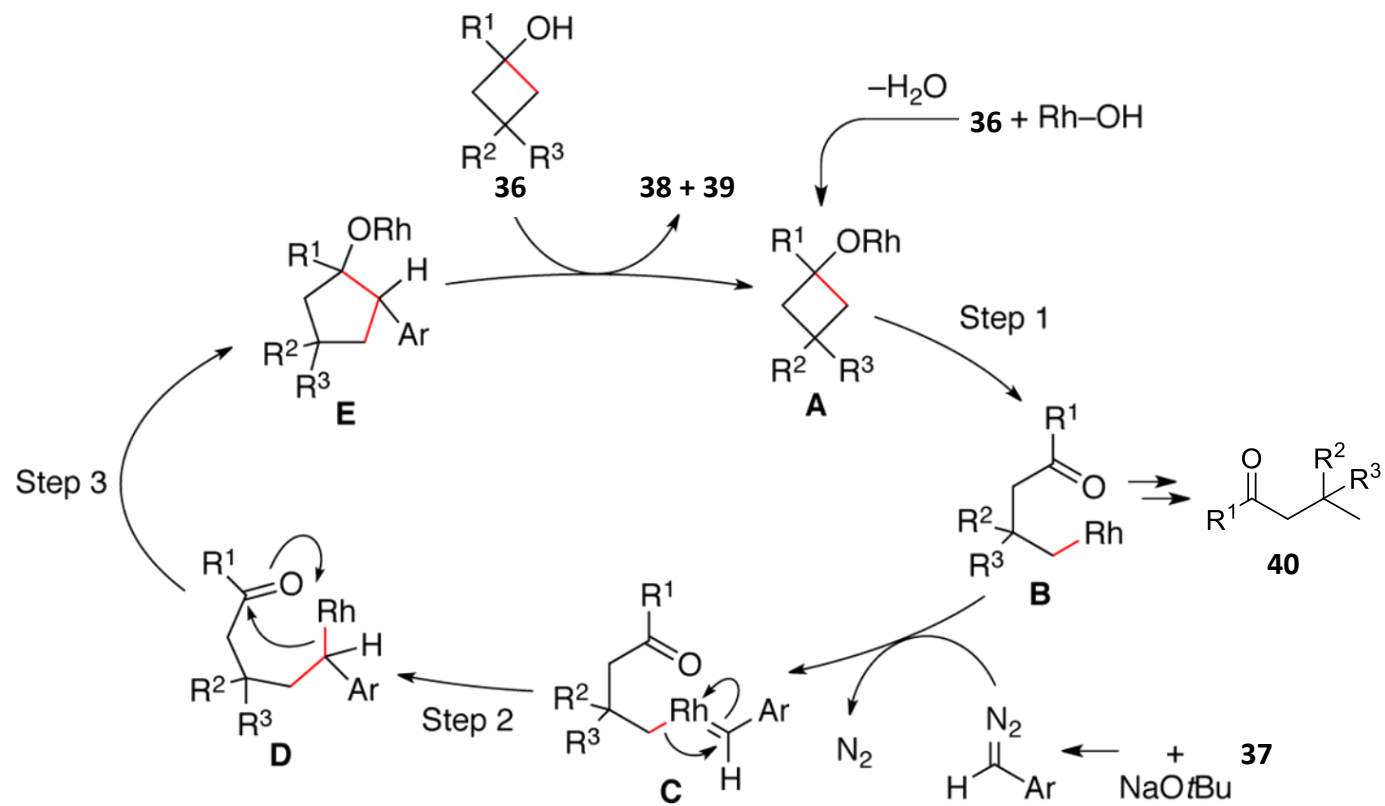
entry	conditions	yields/% ^b	
		34a	35a
1	toluene, 100 °C	86	0
2	NaOH aq, dioxane, rt	87	0
3	$h\nu$, benzene, rt	30 ^c	0
4	5 mol % of Rh(acac)(CH ₂ CH ₂) ₂ 10 mol % of P(<i>t</i> -Bu) ₃ , toluene, 100 °C	14	74
5	2.5 mol % of [Rh(OH)(cod)] ₂ , toluene, 100 °C	0	89
6	2.5 mol % of [Rh(OH)(cod)] ₂ , dioxane, 100 °C	20	74
7	2.5 mol % of [Rh(OH)(cod)] ₂ , 12 mol % of IPr, toluene, 100 °C	80	0

Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502.

Murakami et al., 2014



Murakami, M.; Ishida, N. *J. Am. Chem. Soc.* **2016**, *138*, 13759.

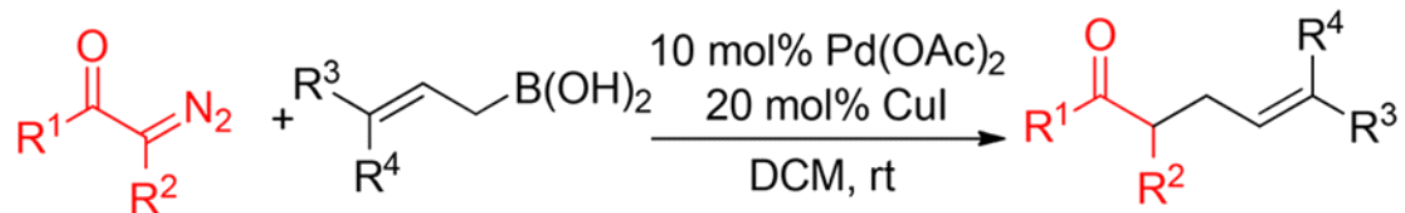


Murakami, M.; Ishida, N. *J. Am. Chem. Soc.* **2016**, *138*, 13759.

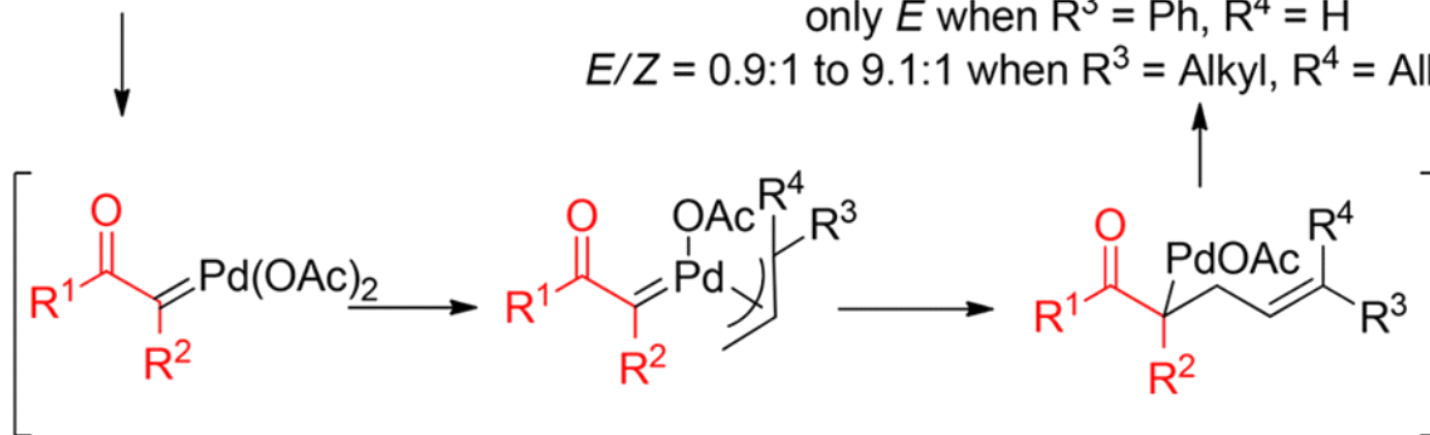
3. Outlook

1. Combination of the classic cross-coupling and a carbene process.
 - a) A variety of cascade processes
 - b) Multicomponent reactions
2. Development of novel asymmetric cross coupling reactions.
3. Direct experimental evidence for mechanism
4. Safe and easily available carbene precursors

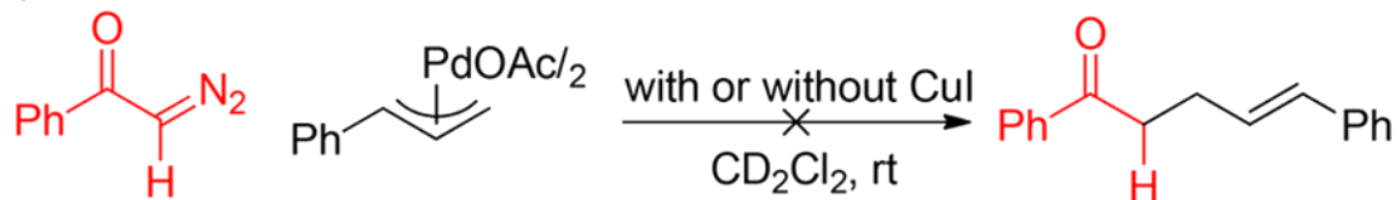
Thank you for your attention.

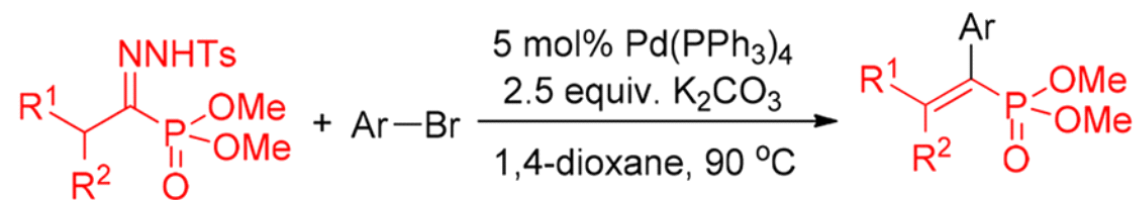


16 examples, 43-71% yields
 only *E* when $\text{R}^3 = \text{Ph}$, $\text{R}^4 = \text{H}$
 $E/Z = 0.9:1$ to $9.1:1$ when $\text{R}^3 = \text{Alkyl}$, $\text{R}^4 = \text{Alkyl or H}$



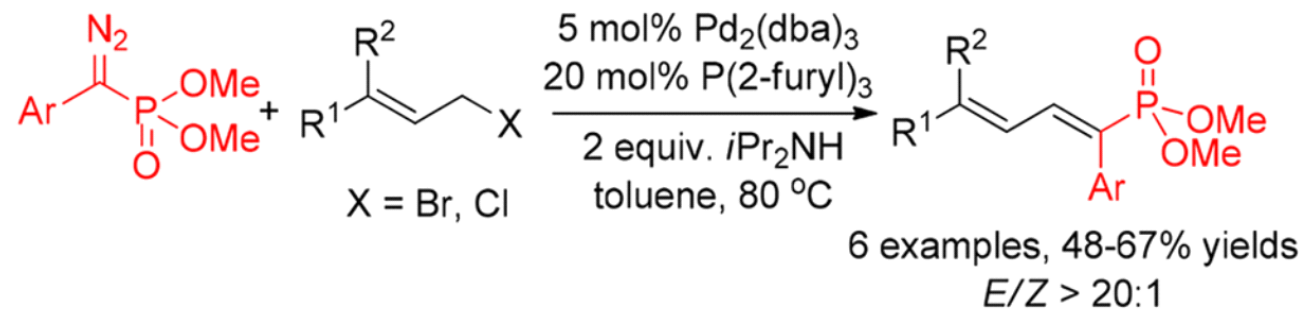
Stoichiometric
 experiment:



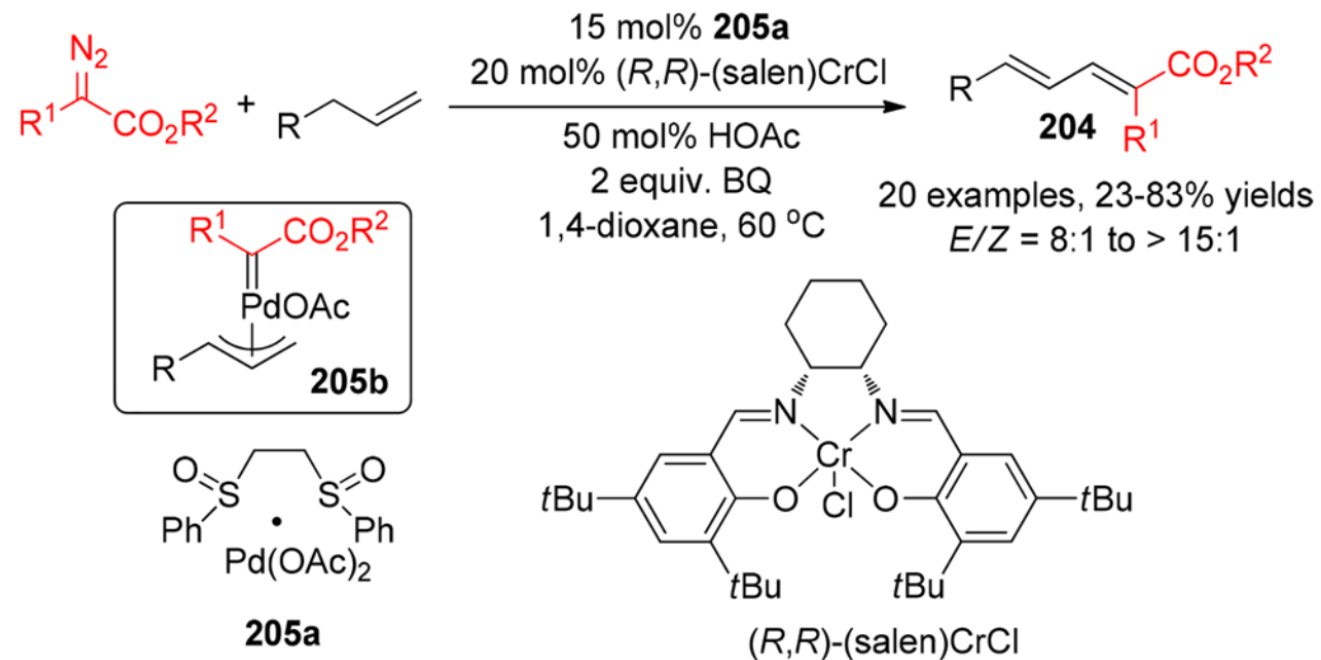


12 examples, 50-89% yields

c) Wang et al., 2015



Gong et al., 2014



Stoichiometric Experiment:

