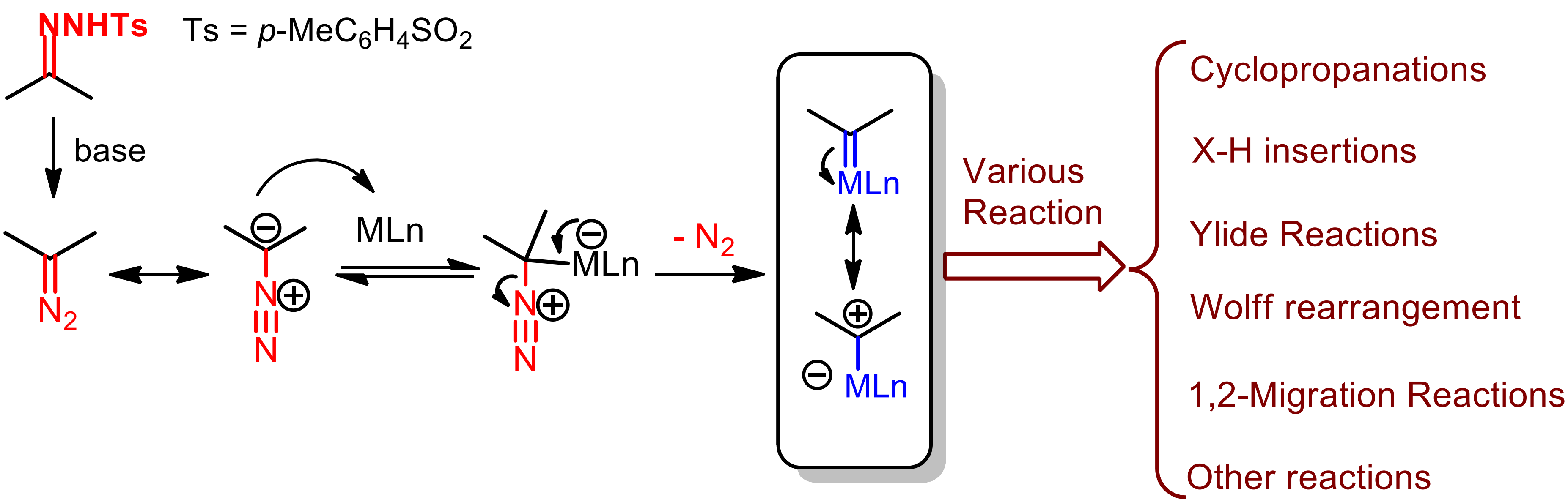
Cross-Coupling Reactions Involving Metal Carbene Migratory Insertion

(Report of PhD Work in Prof. Jianbo Wang's group)

Reporter： Ying Xia
Supervisor: Prof. Guangbin Dong

11/11/2015

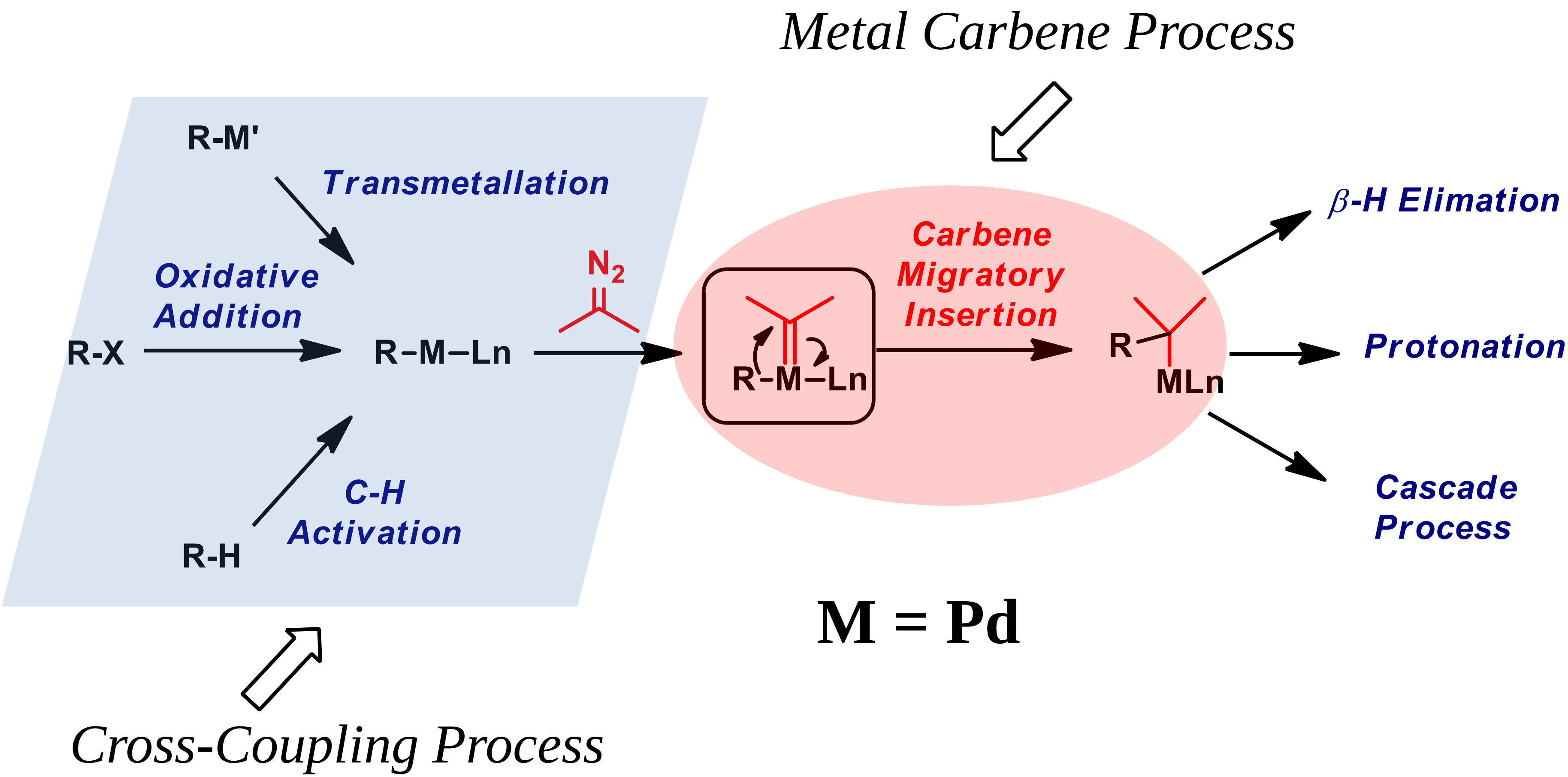
Generation of Metal Carbene and Their Classic Reactions



For reviews, see:

(a) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.
(b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
(c) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015.

When Metal Carbene Process Meets Cross-Coupling Process



For reviews, see:

(a) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486.

(b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560.

(c) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236.

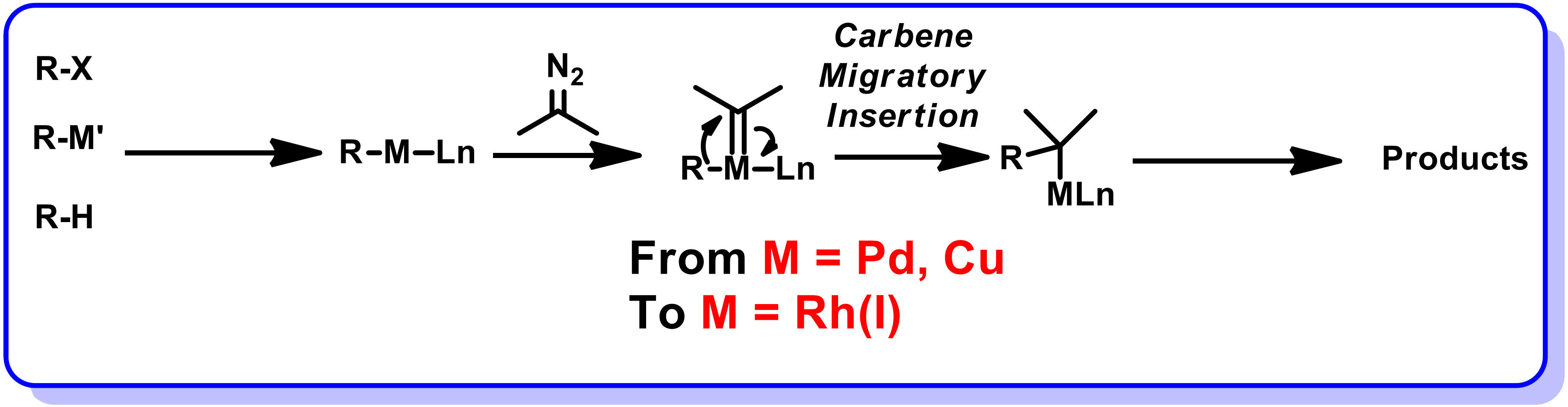
Content

1. Carbene Reactions Involving Diazo Compounds or *N*-Tosylhydrazones
2. Carbene Cross-Coupling Reactions Involving Non-Diazo Compounds
3. Intramolecular Metal Carbene Dimerization and Beyond

Content

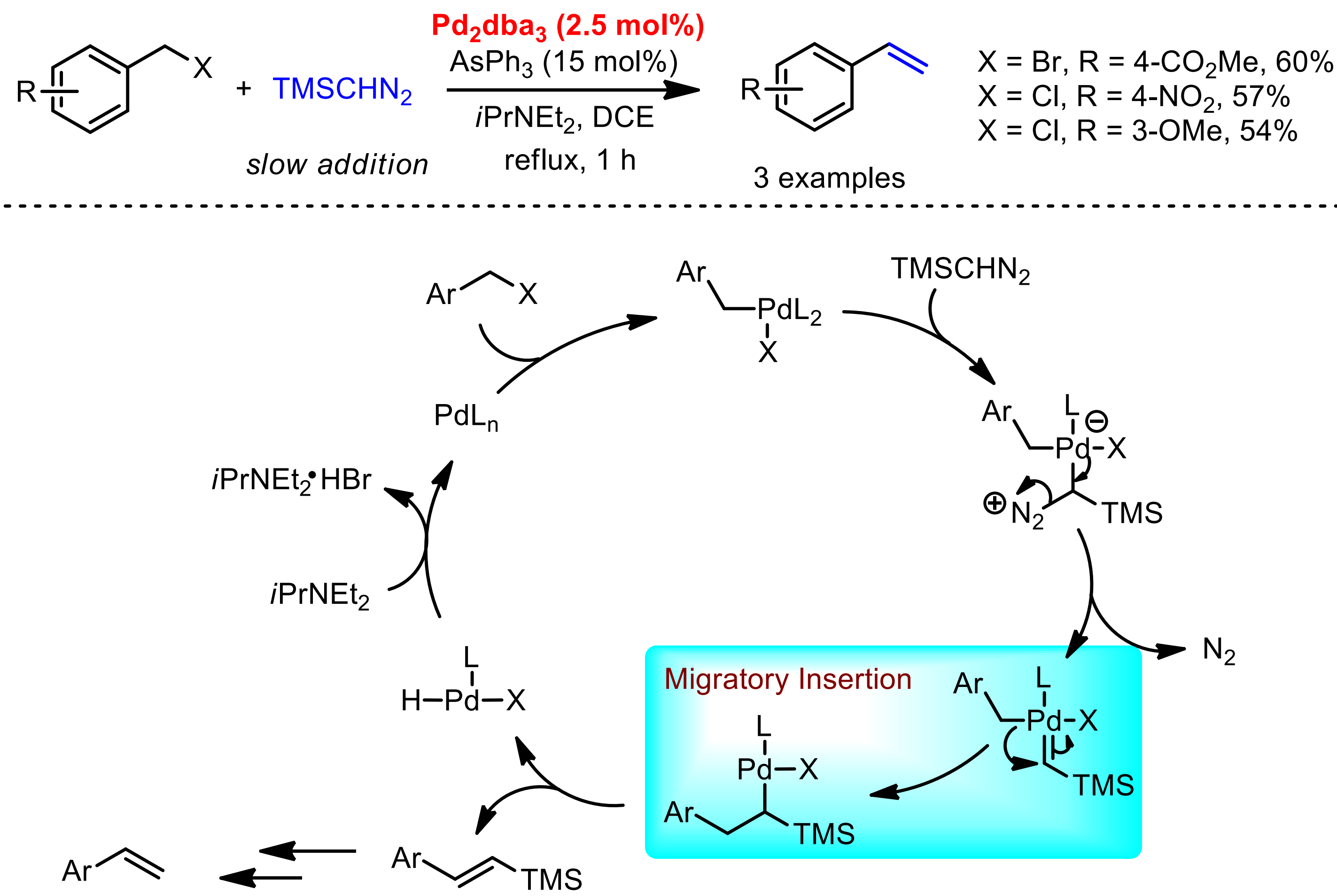
1. Carbene Cross-Coupling Reactions Involving Diazo Compounds or *N*-Tosylhydrazones

From Pd, Cu Catalysis to Rh(I) Catalysis



Brief Introduction of Carbene Coupling Reactions

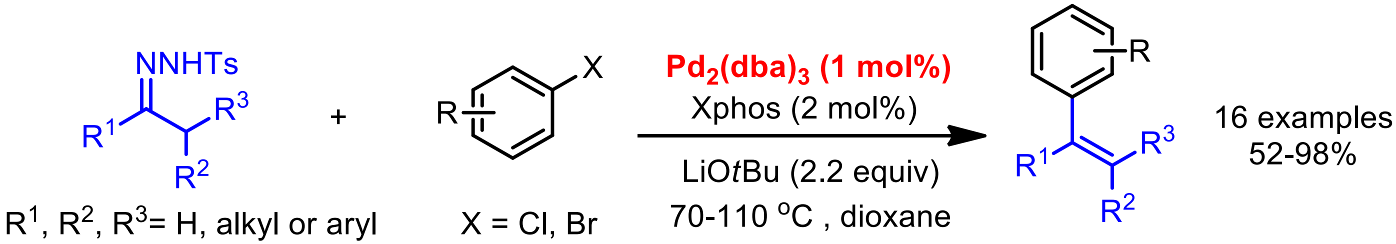
The First Catalytic Carbene Coupling Reaction:



Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219.

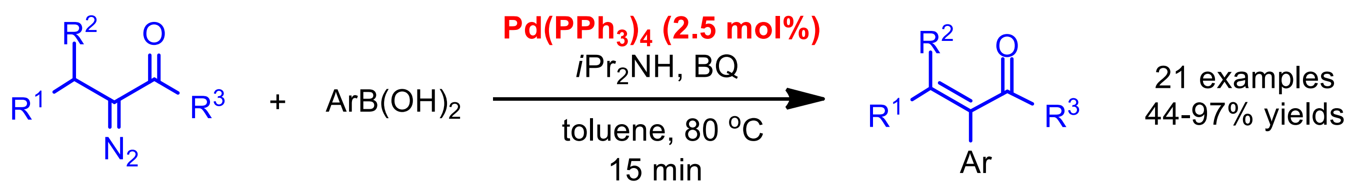
The Development of Pd, Cu Catalysis

N-Tosylhydrazones (Good Precursors for Non-Stabilized Diazo Compounds)



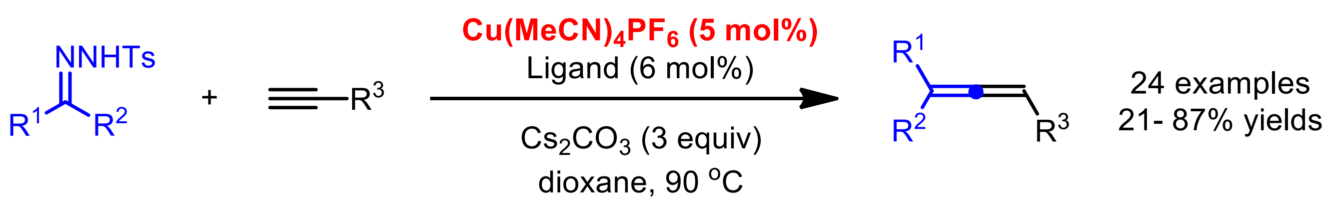
Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 5587.

Oxidative Carbene Cross-Coupling



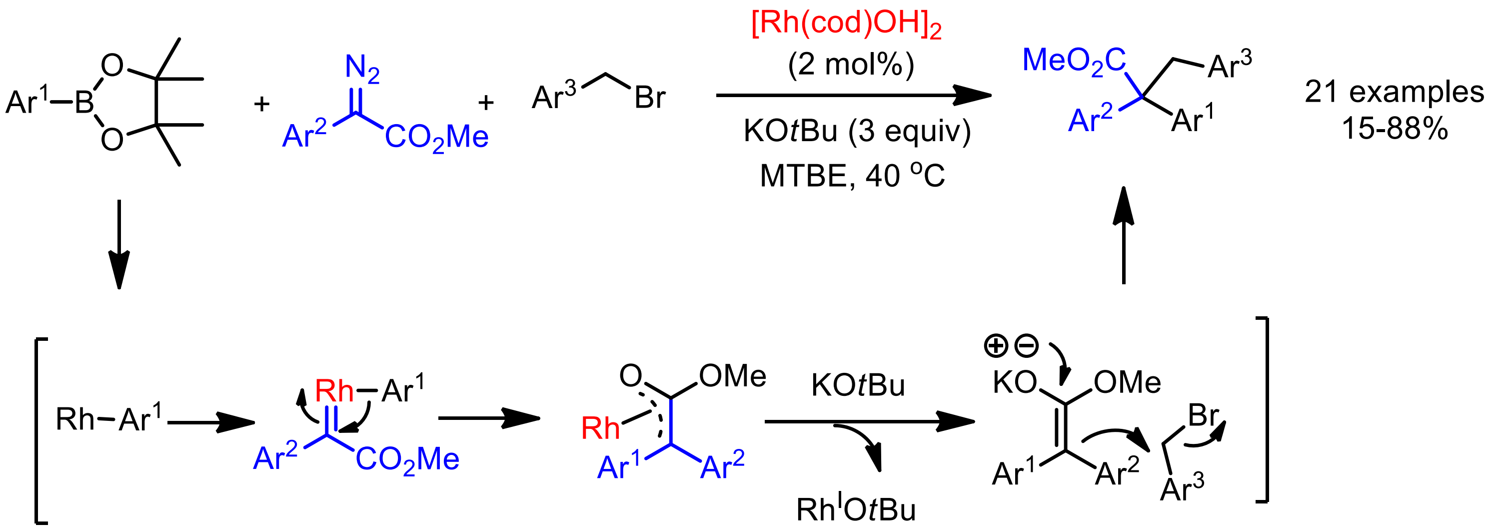
Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566.

Cu(I)-Catalyzed Oxidative Carbene Cross-Coupling

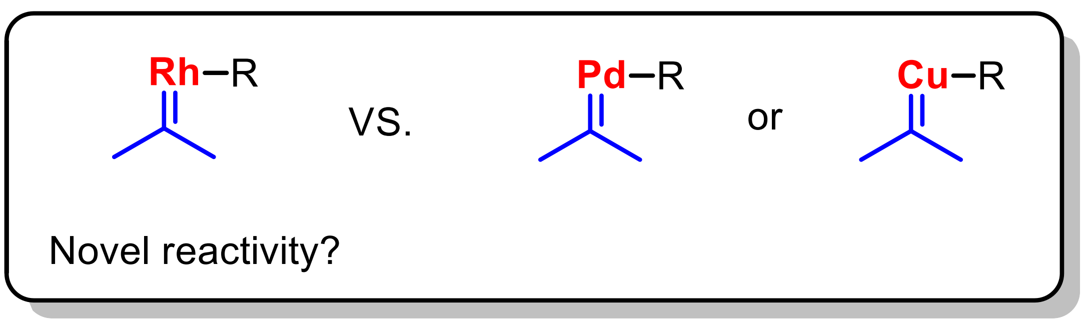


Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1114.

Rh(I)-Catalyzed Carbene Cross-Coupling

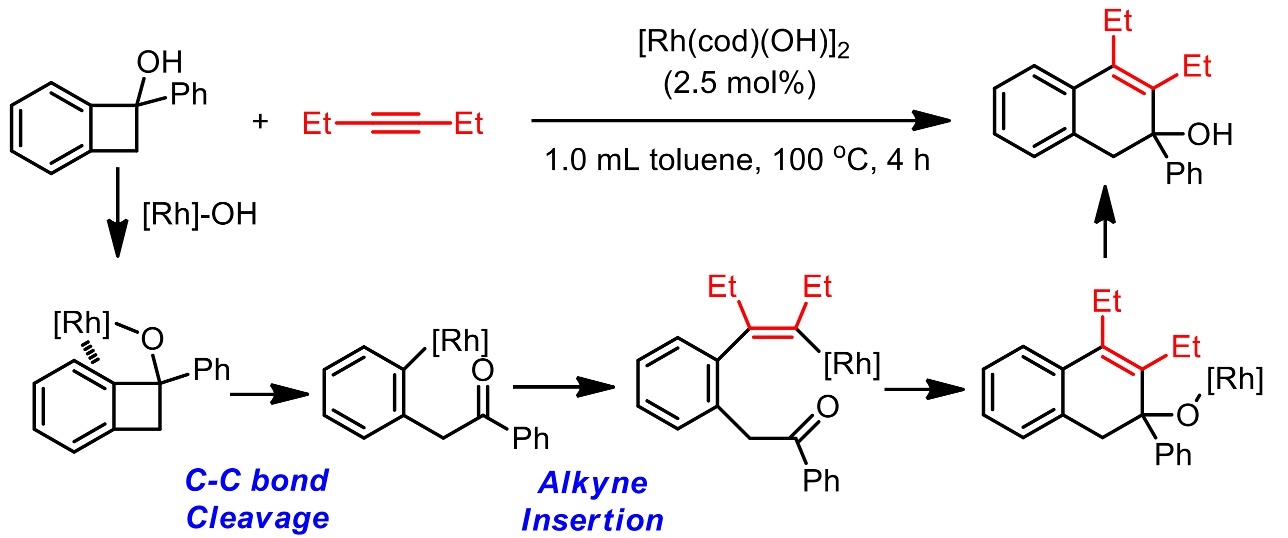


Tsoi, Y.-K.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *13*, 5370.



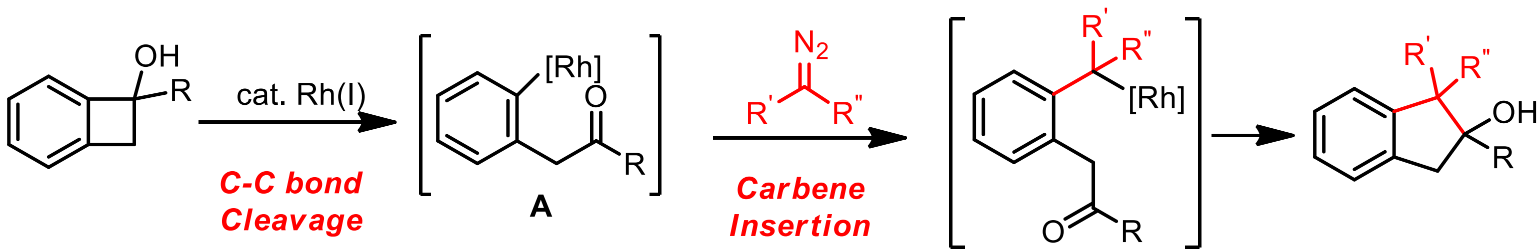
Merging with C-C Activation of Benzocyclobutenols

Prof. Murakami gave a report in Perking University on October 22nd, 2013.

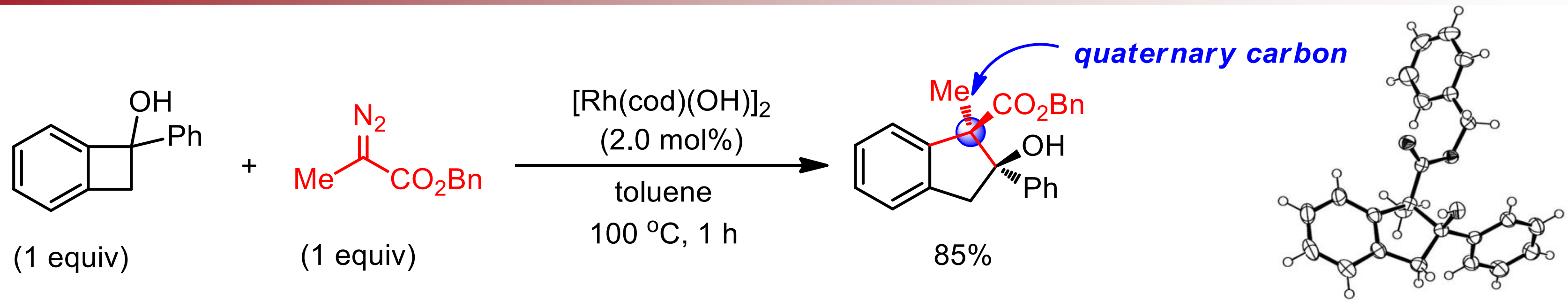


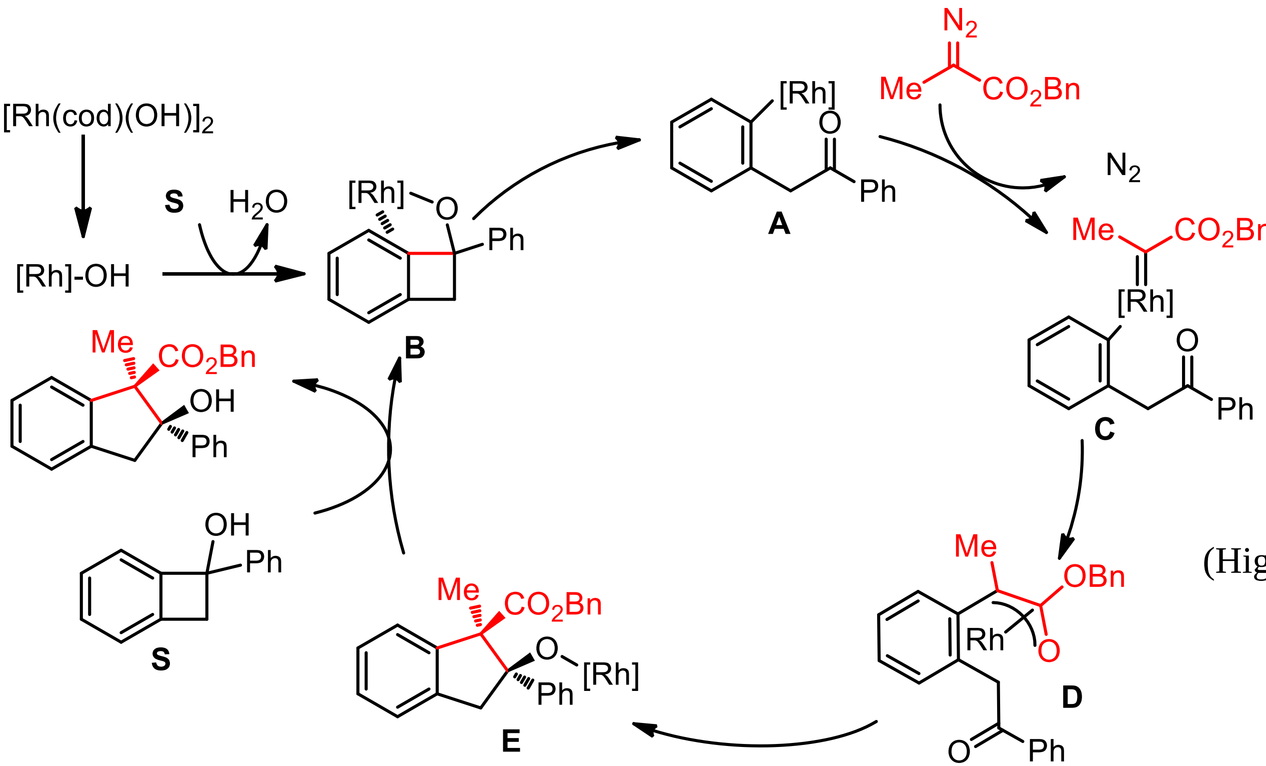
Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc*. **2012**, *134*, 17502.

Our Design:



Merging with C-C Activation of Benzocyclobutenols



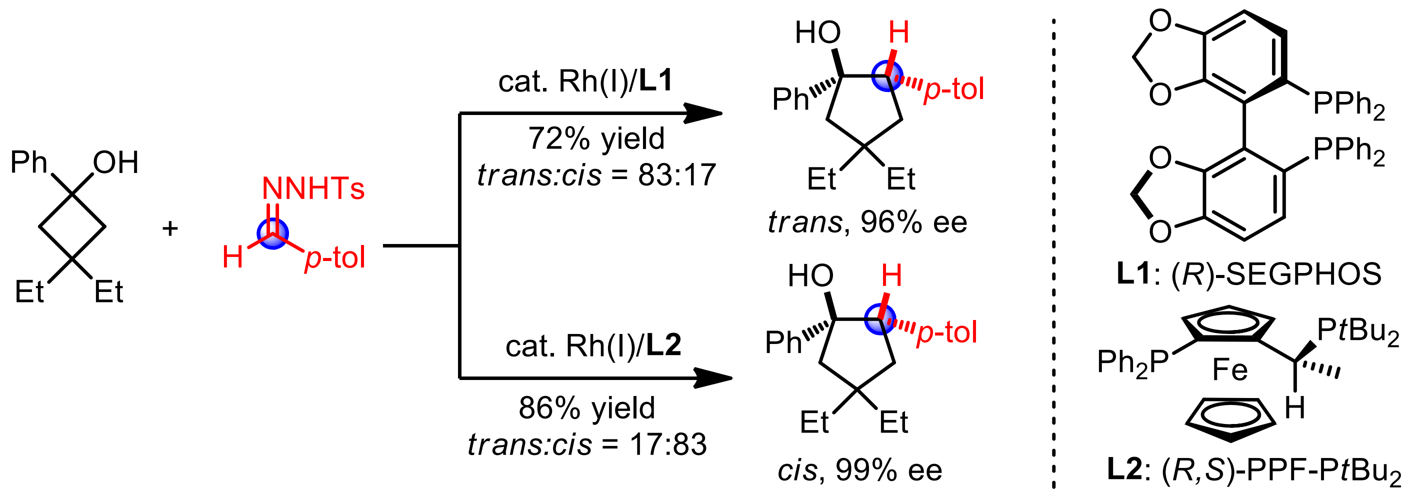


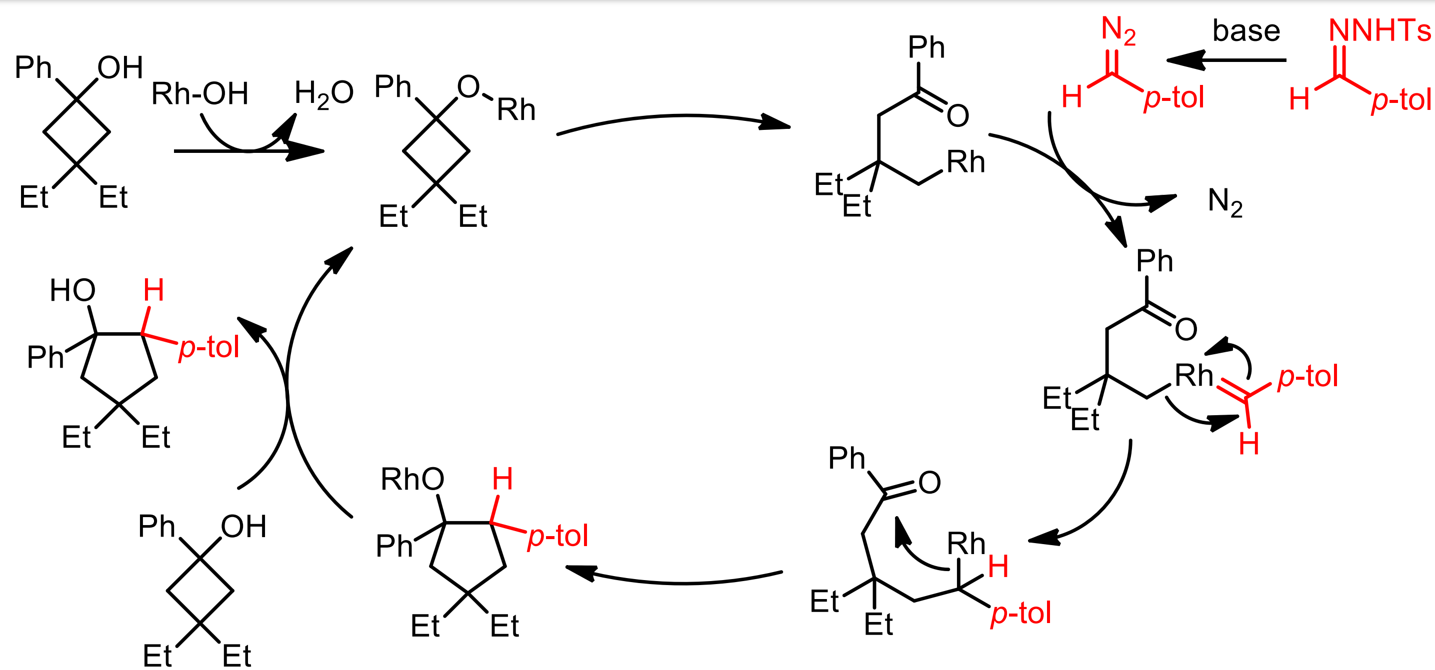
- The first carbene insertion to C-C bond
- N_2 is the only byproduct

(Highlighted by *Synfacts*, **2014**, *10*, 0508)

Xia, Y.; Liu, Z.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2014**, *136*, 3013.
For DFT calculation, see: Wang, Y.; Wang, Y.; Zhang, W.; Zhu, Y.; Wei, D.; Tang, M.; *Org. Biomol. Chem.* **2015**, *13*, 6587-6597.

Murakami's Asymmetric Carbene C-C Bond Insertion

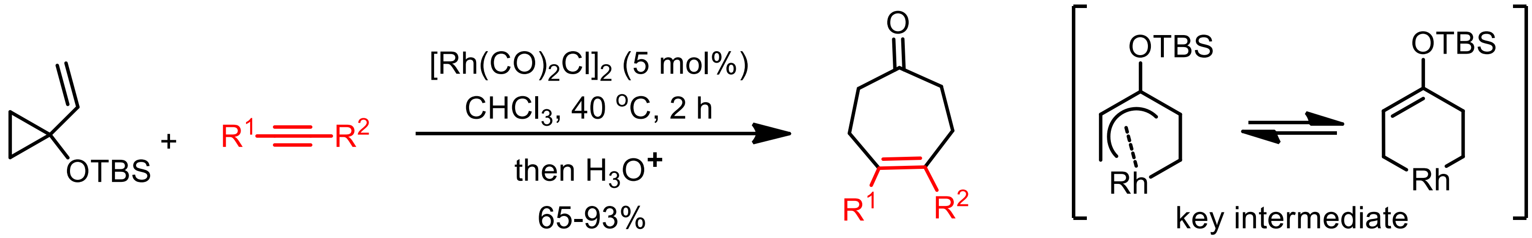




Yada, A.; Fujita, S.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 7217.

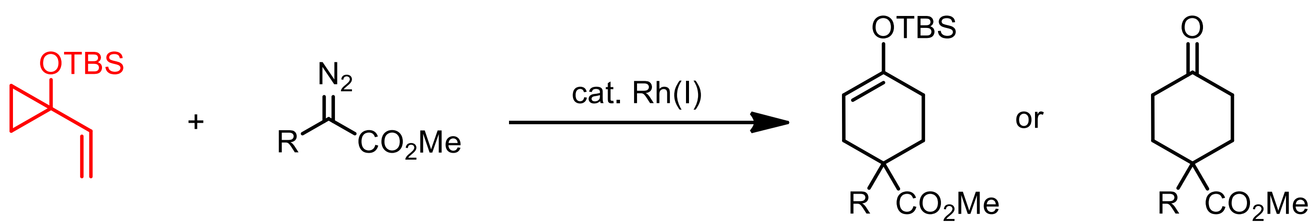
Merging with C-C Activation of VCP

[5+2] Cycloaddition of VCP

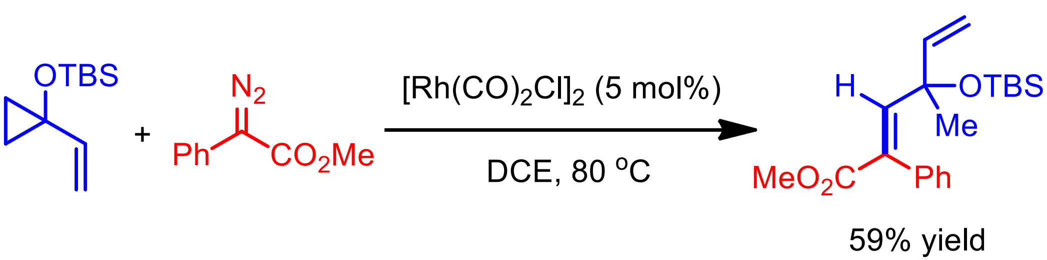


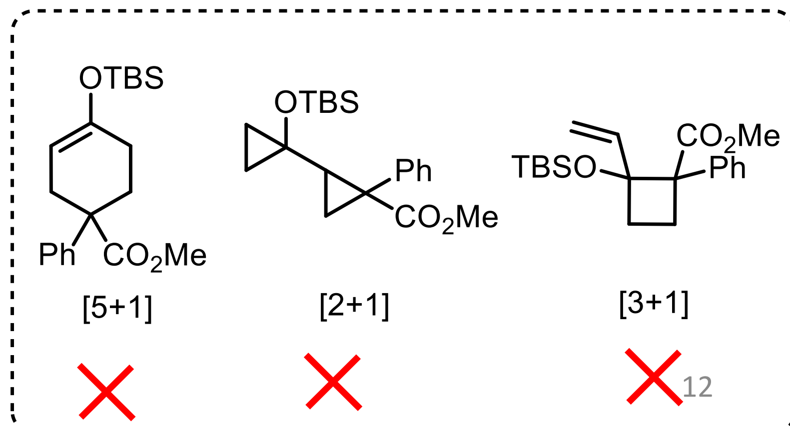
Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976-10977.

Our Design: [5+1] cycloaddition



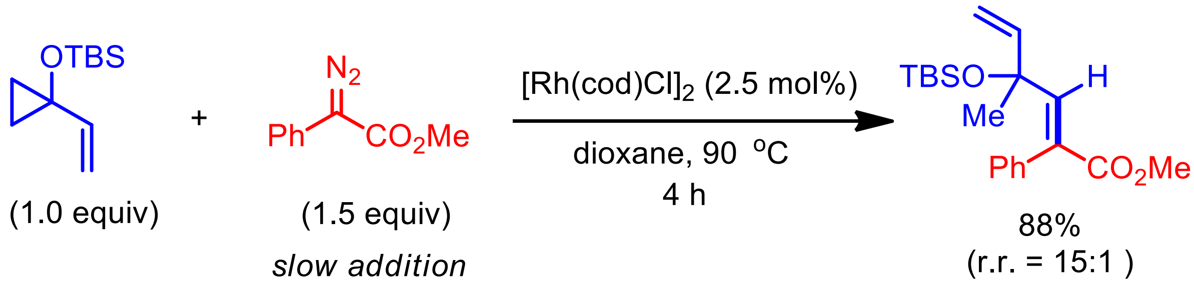
Initial Result:



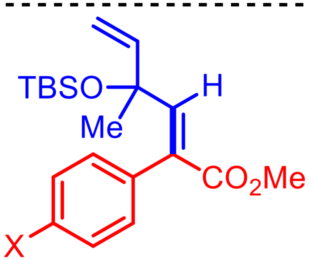


Merging with C-C Activation of VCP

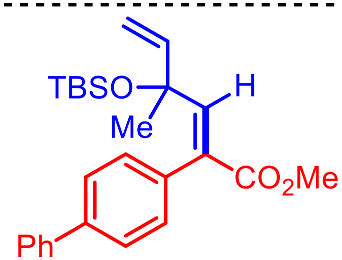
Optimized Condition (By Sheng Feng)



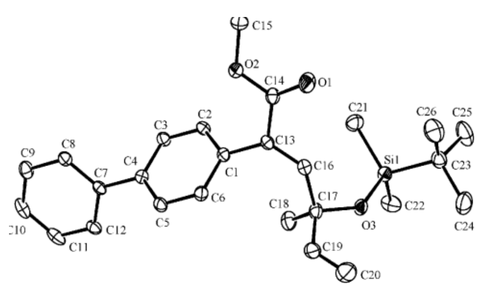
Selected Examples: (By Sheng Feng)

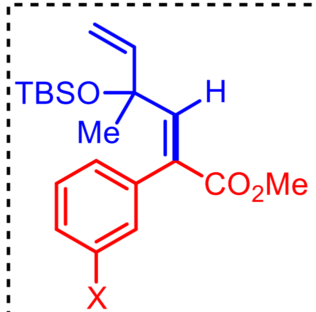


X = H, 88%
X = F, 51%
X = Cl, 84%
X = Br, 68%
X = CF_3, 98%
X = CO_2Me, 58%
X= Me, 79%

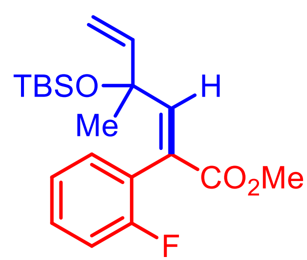


82%

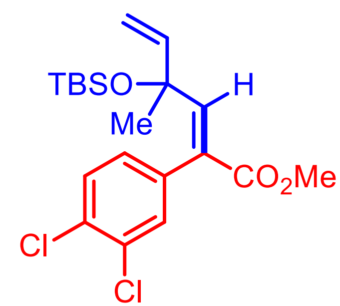




X = OMe, 84%
X = Me, 82%
X = Cl, 79%
X = CF_3, 82%



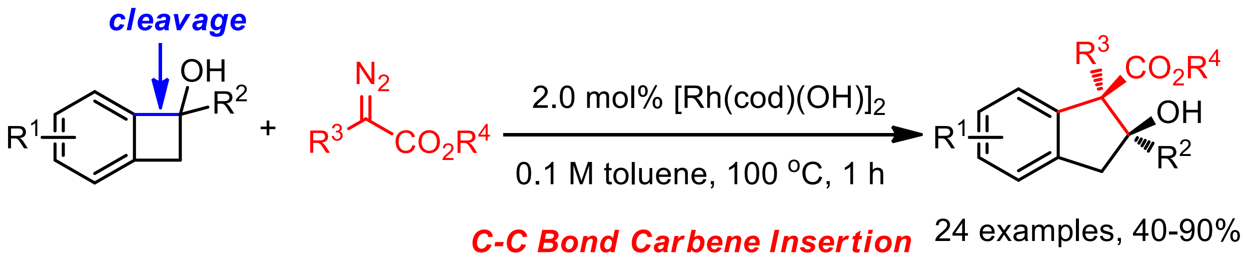
68%



84%

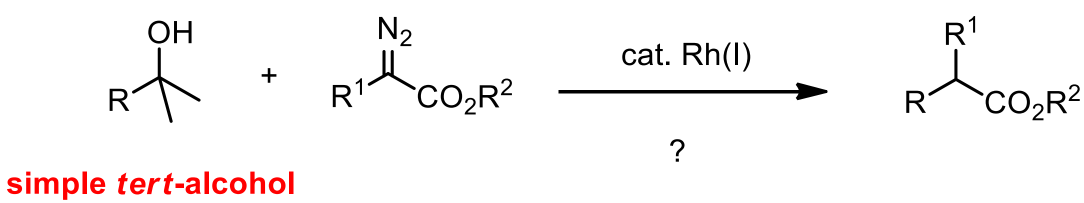
Feng, S.; **Xia, Y.**; Mo, F.; Zhang, Y.; Wang, J. *Unpublished result*.

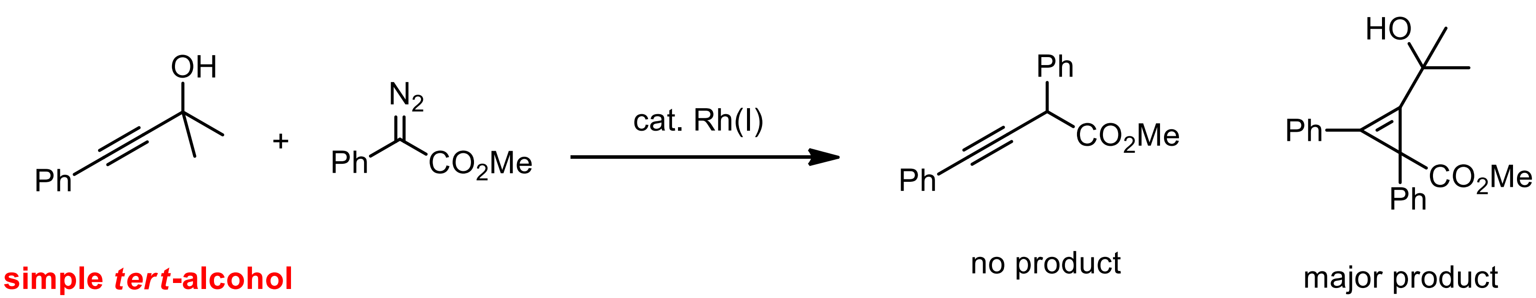
C-C Activation of Simple *tert*-Alcohol

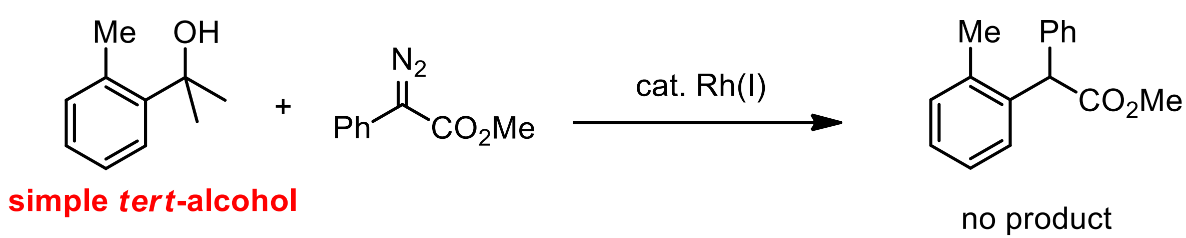


Regioselective & Diastereoselective

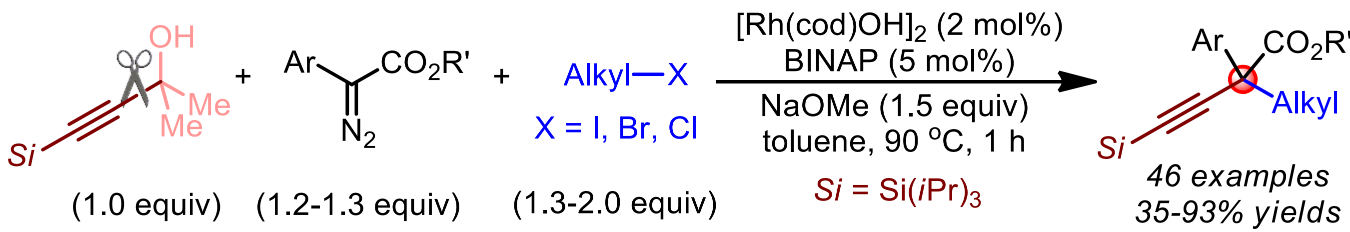
Xia, Y; Liu, Z.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2014**, *136*, 3013.

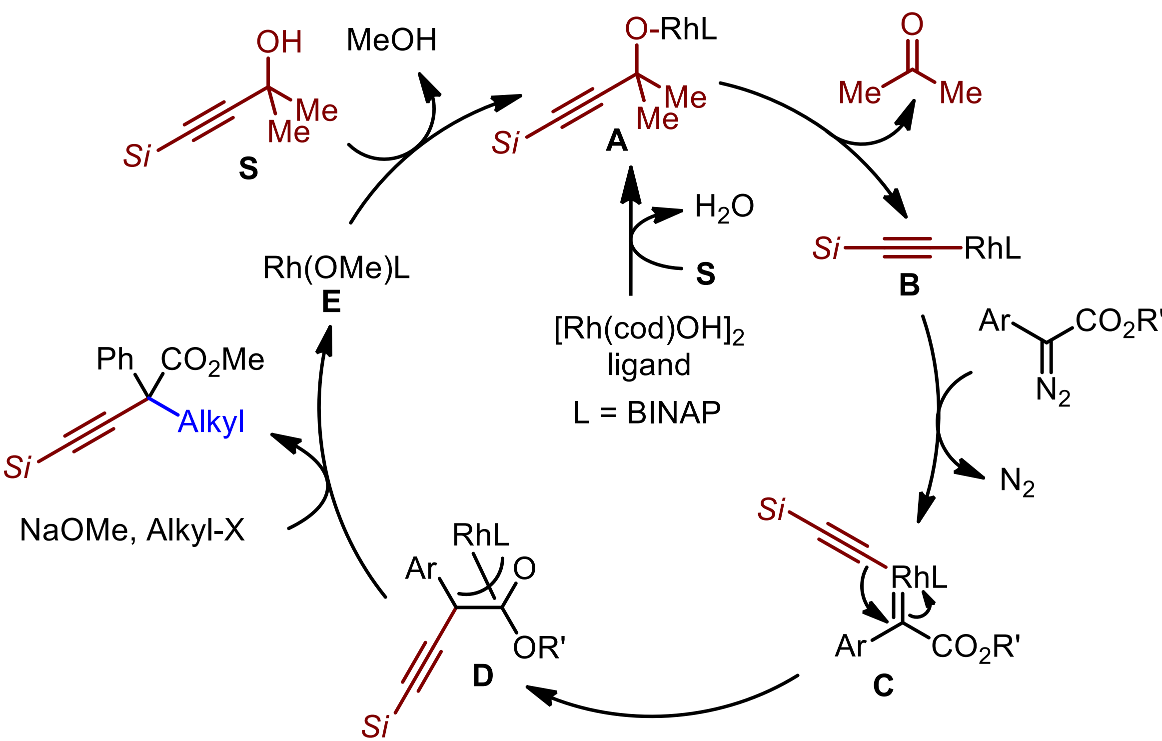


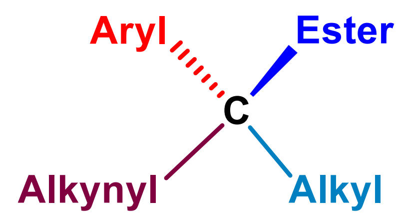




Three-Component Reaction with Propargyl Alcohols and Alkyl Halides



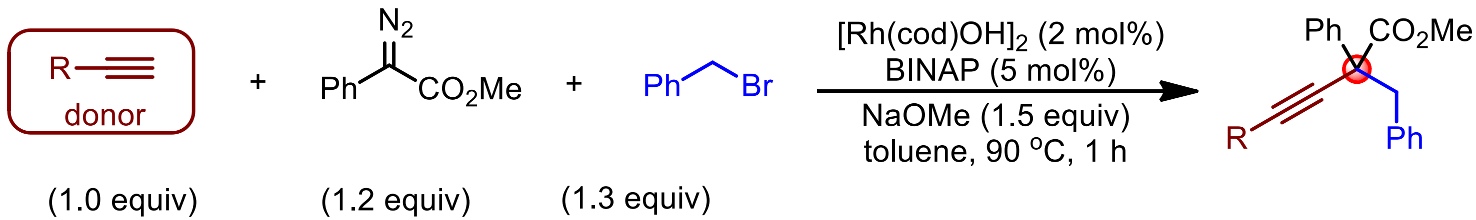




- Two C-C Bonds Formation
- Four Different Carbon Substituents on Quaternary Carbon

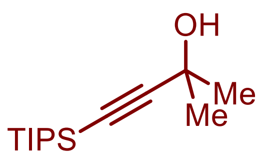
Xia, Y.; Feng, S.; Liu, Z.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 7891-7894. (Hot Paper)

The Effect of Propargyl Alcohols



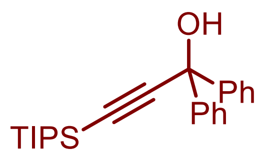
1a

25%



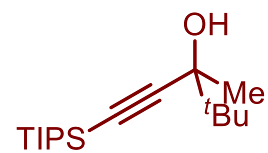
1b

79%



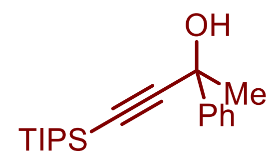
1c

82%



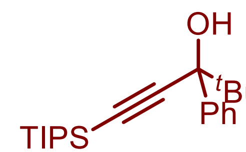
1d

41%



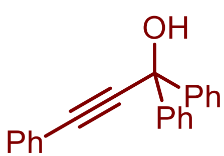
1e

80%



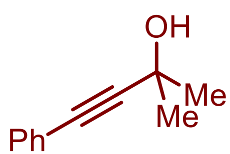
1f

55%



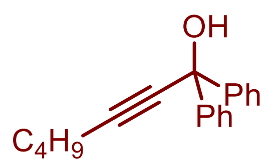
1g

0%



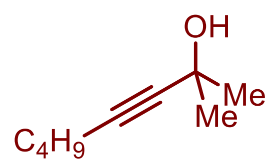
1h

0%



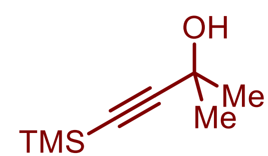
1i

0%



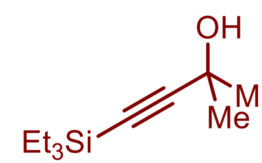
1j

0%



1k

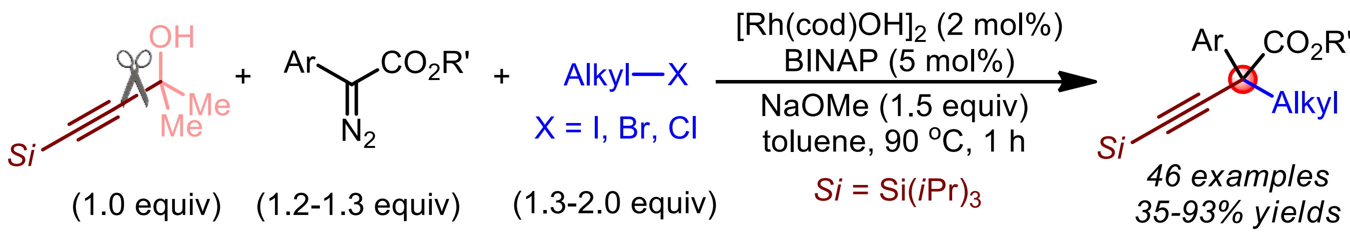
0%



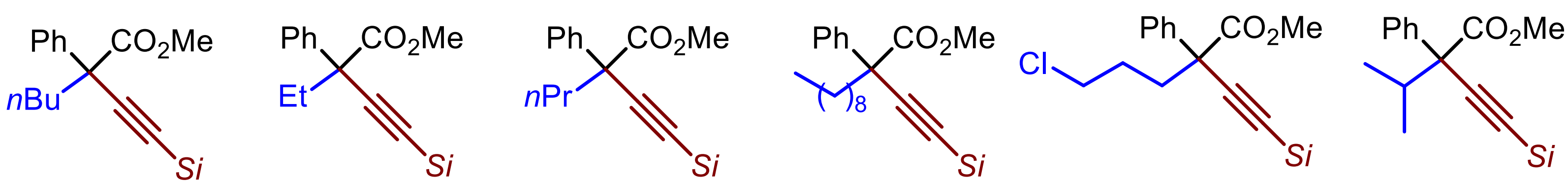
1l

35%

Selected Examples

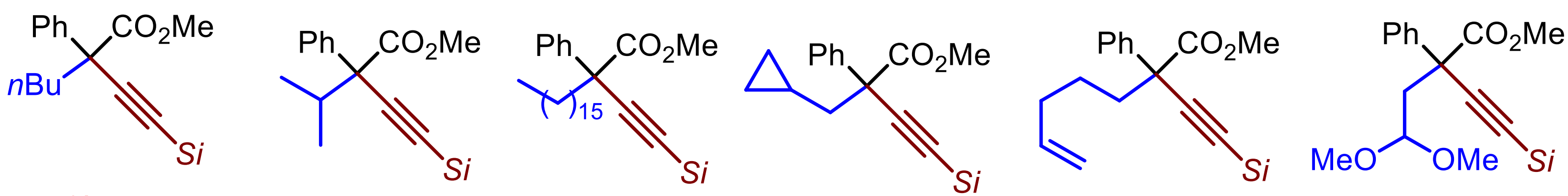


X = I:



80% 76% 73% 76% 54% 84%

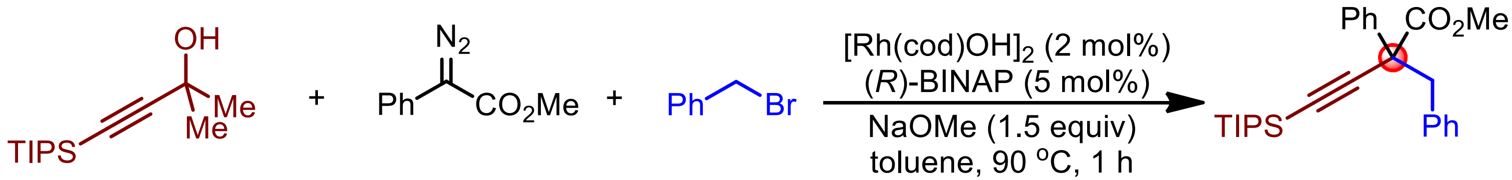
X = Br (20 mol% **TBAI** was added):



92%, 1.77 g (5 mmol scale) 93% 88% 66% 86% 53%

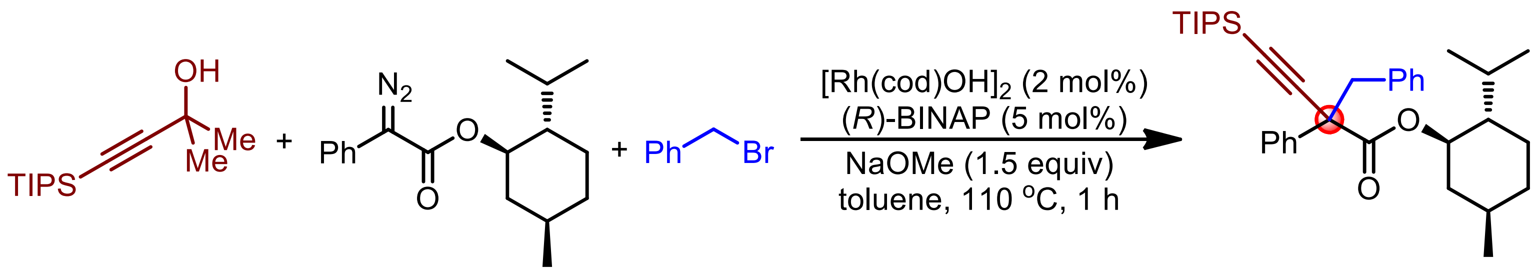
Attempts to Asymmetric Synthesis

Asymmetric Catalysis

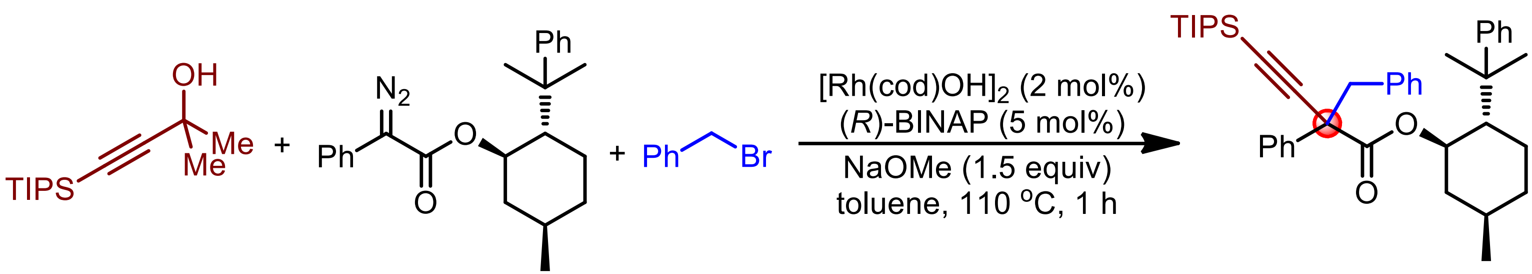


79% yield, < 5% ee

Asymmetric Induction



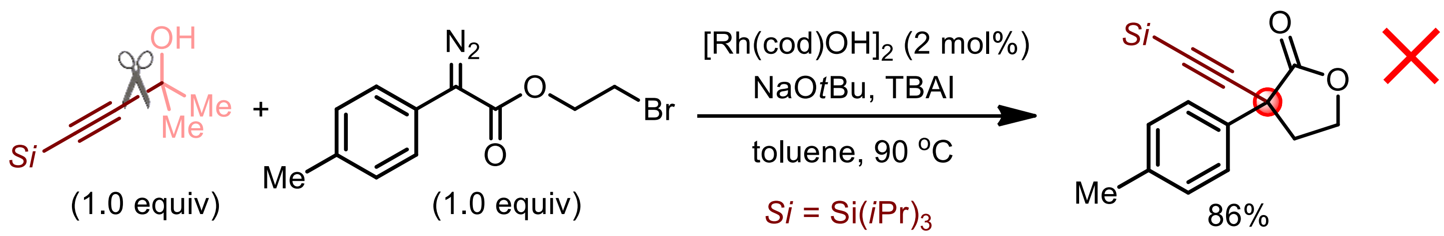
77% yield, dr = 1.2:1

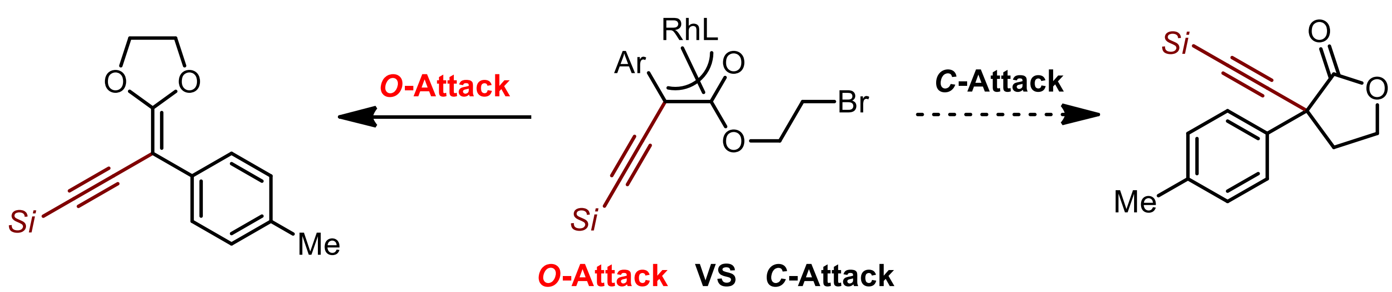


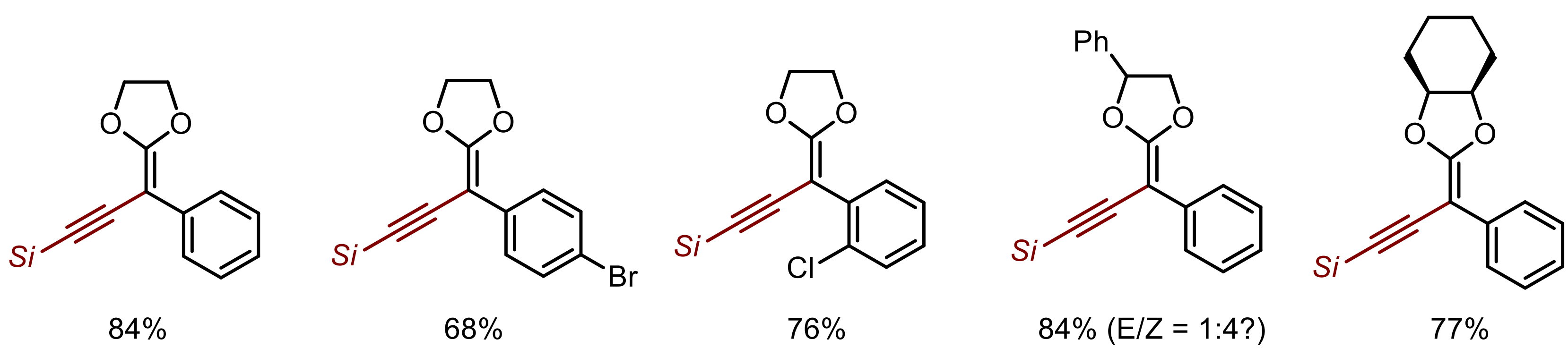
73% yield, dr = 2.6:1

Reaction with Propargyl Alcohols and Internal Alkyl Halides

Design:

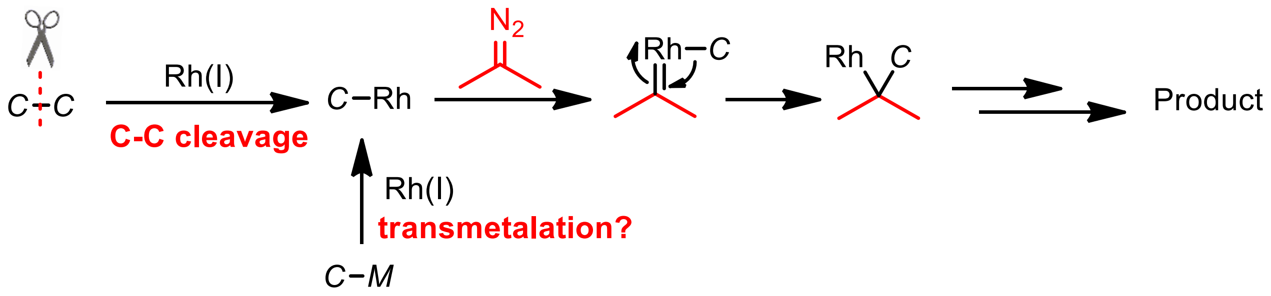




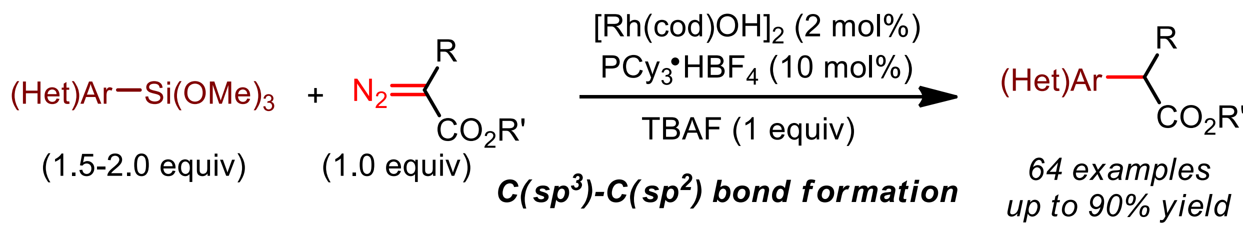


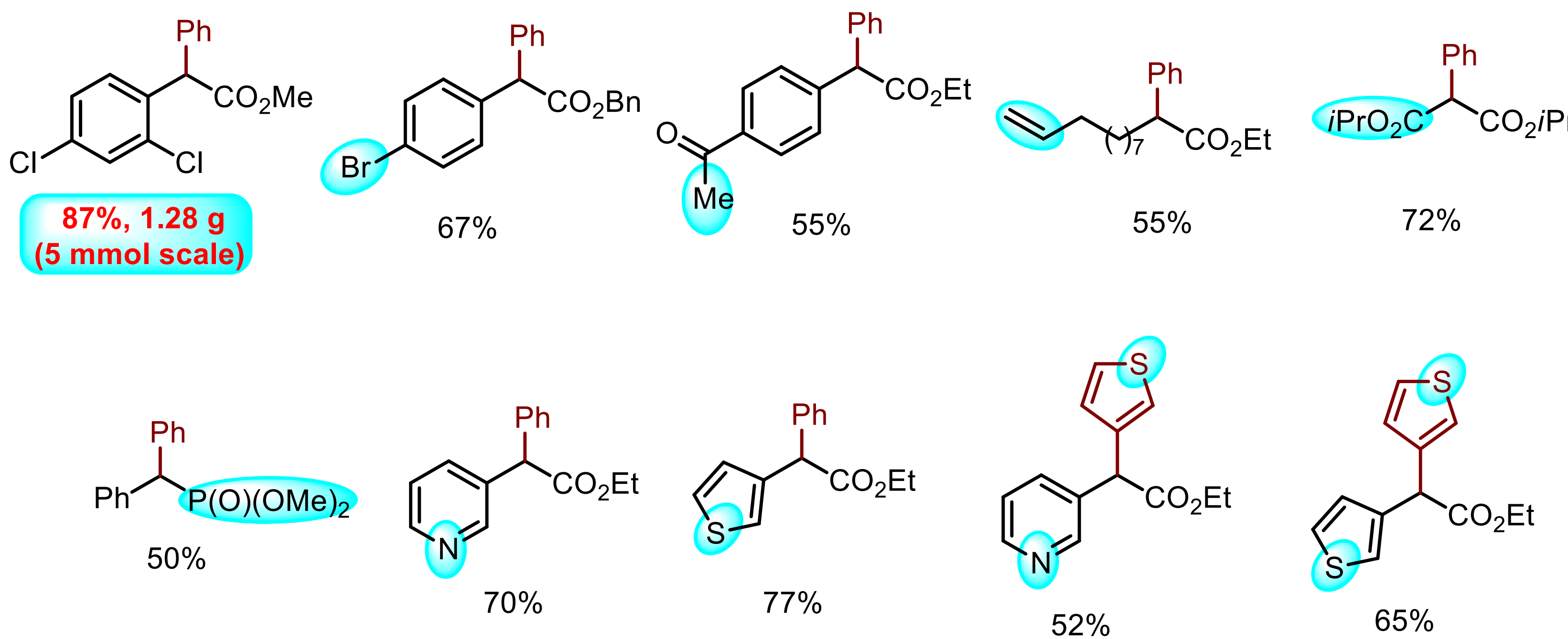
Liu, Z.; **Xia, Y.***; Feng, S.; Zhang, Y.; Wang, J.* *To be submitted.*

Hiyama-Type Coupling with Aryl Silicon Regents



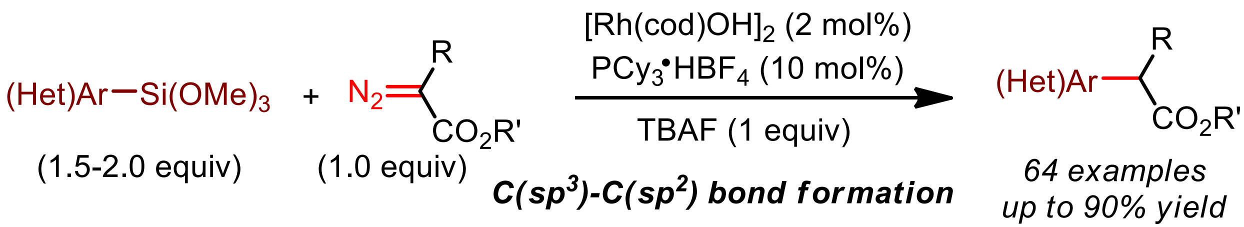
Hiyama-Type Coupling with Aryl Silicon Regents

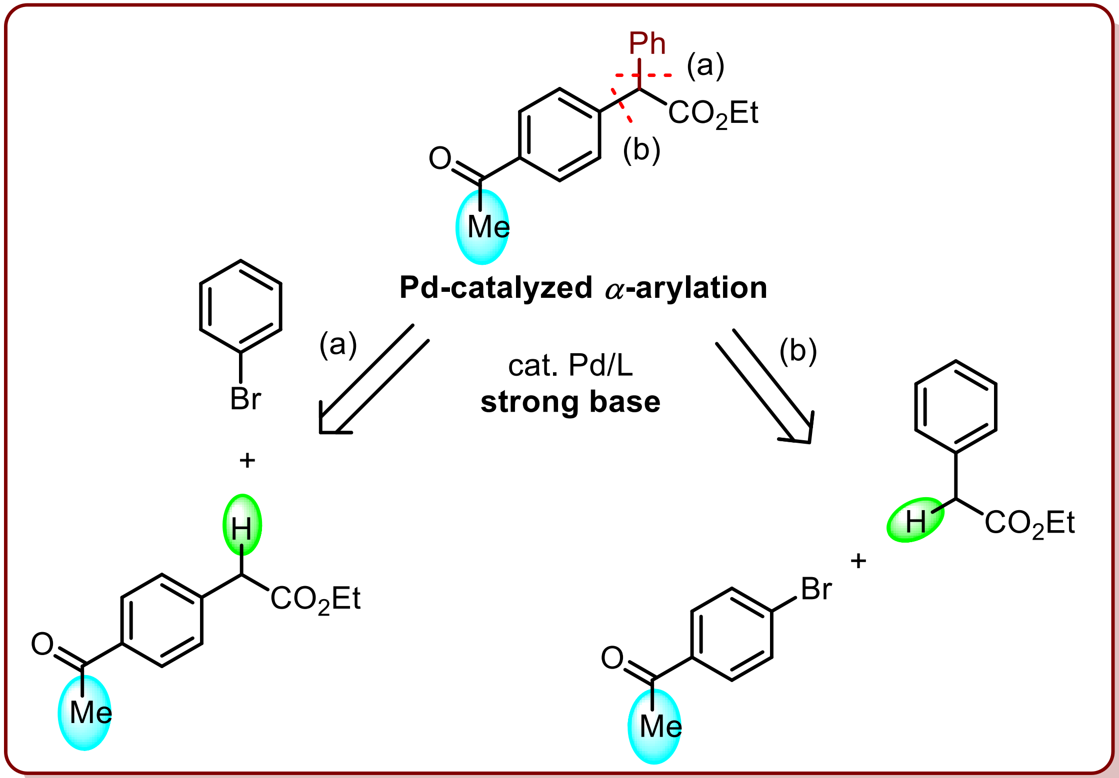




Xia, Y.; Liu, Z.; Feng, S.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2015**, *17*, 956.

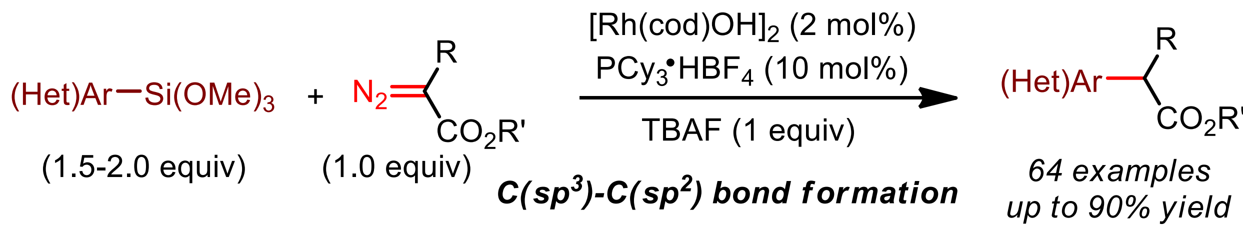
Hiyama-Type Coupling with Aryl Silicon Regents



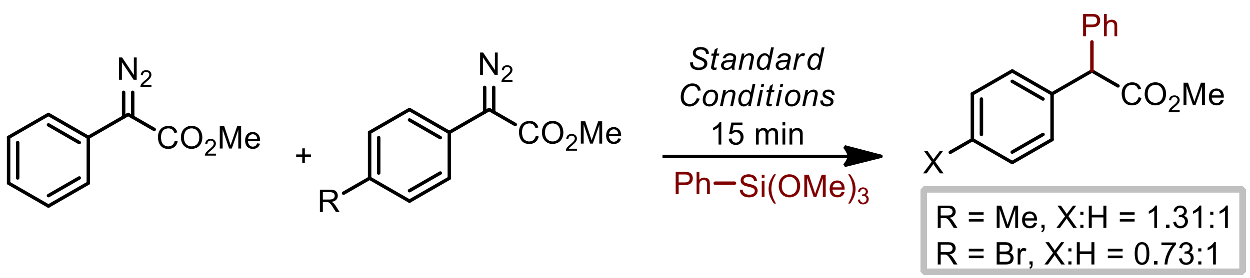


Xia, Y.; Liu, Z.; Feng, S.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2015**, *17*, 956.

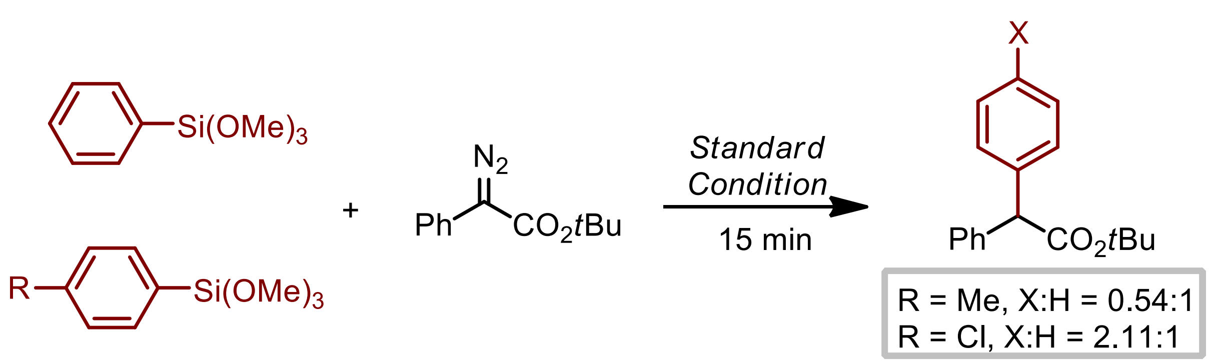
Hiyama-Type Coupling with Aryl Silicon Regents



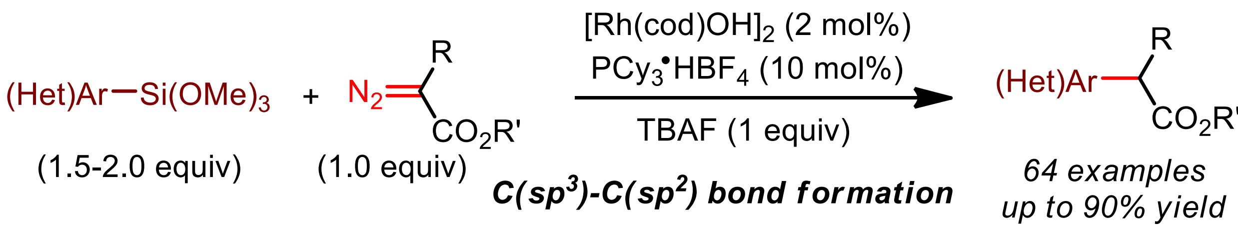
(a) Diazo Competetion： electron-rich diazoester expressed a higher reaction rate

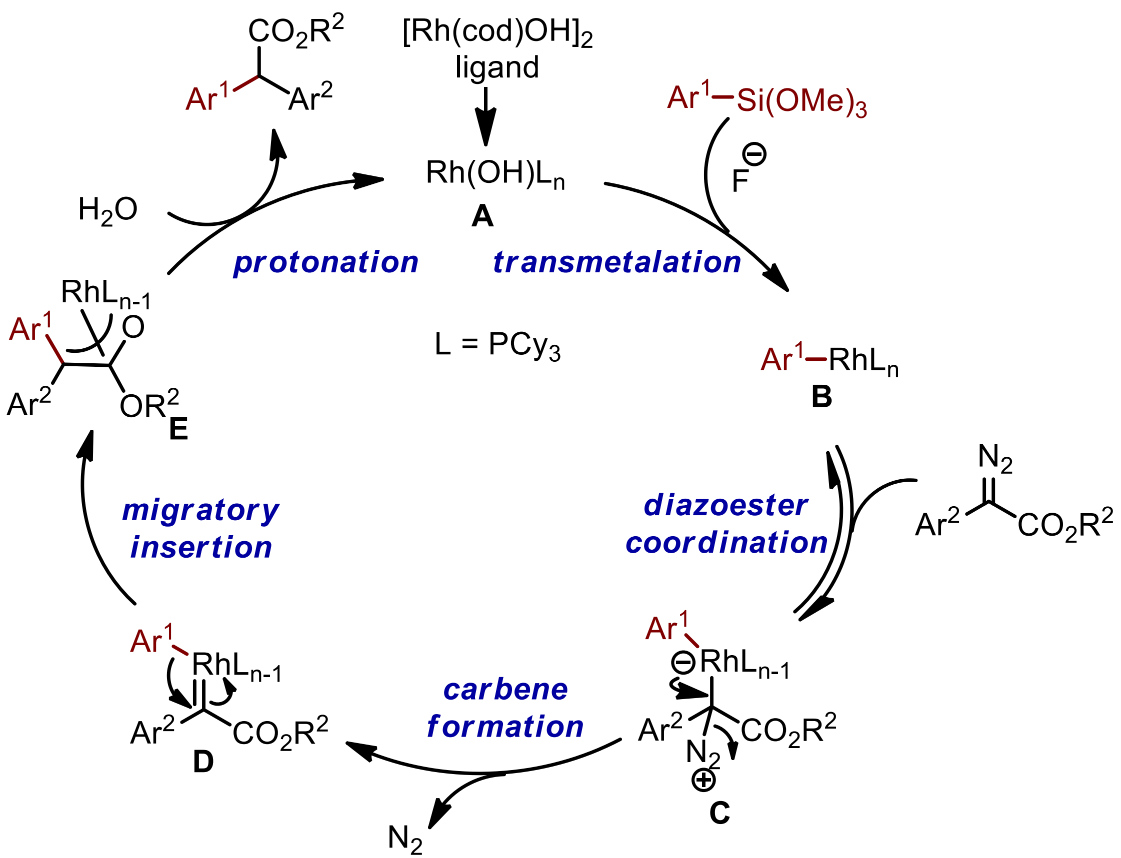


(b) Arylsiloxane Competetion： electron-deficient arylsiloxane expressed a higher reaction rate



Hiyama-Type Coupling with Aryl Silicon Regents

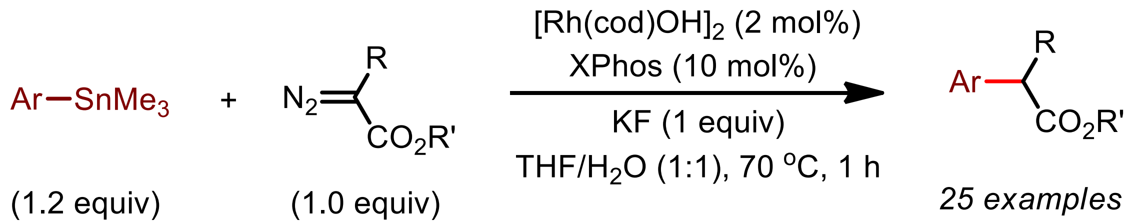




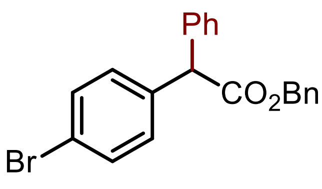
Favored for
Electron-deficient Ar^1
Electron-rich Ar^2

Stille-Type Coupling with Aryl Tin Regents

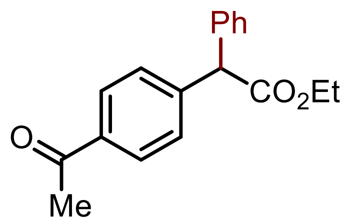
Finished by Zhen Liu



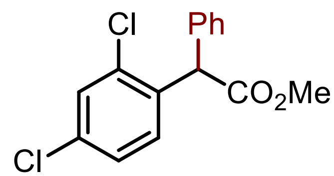
25 examples
up to 99% yield



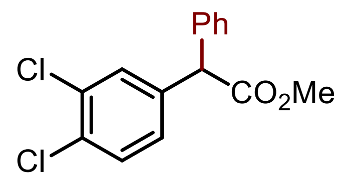
84%
(67% for Hiyama)



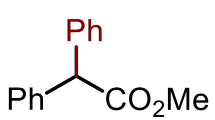
69%
(55% for Hiyama)



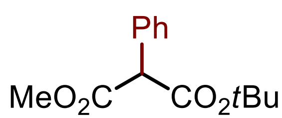
99%
(87% for Hiyama)



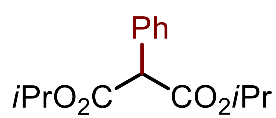
96%
(66% for Hiyama)



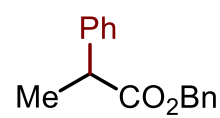
96%
(78% for Hiyama)



80%
(59% for Hiyama)



83%
(72% for Hiyama)

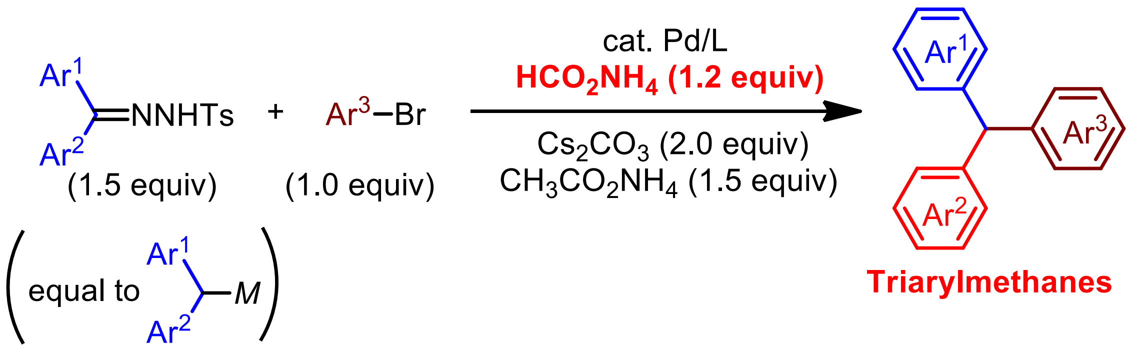


31%
(63% for Hiyama)

Liu, Z.; **Xia, Y.***; Feng, S.; Wang, S.; Qiu, D.; Zhang, Y.; Wang, J.* *Aust. J. Chem.* **2015**, *68*, 1379-1384..

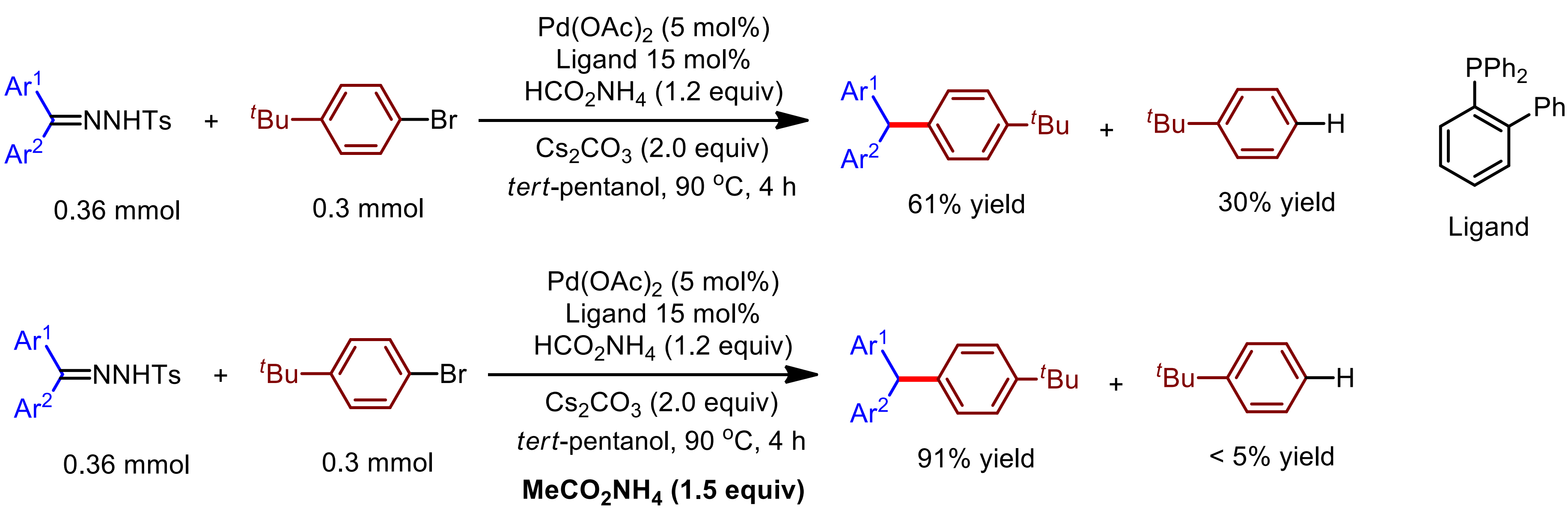
Other TM-Catalyzed Carbene Coupling Reaction-Pd

Reductive Coupling
$C(sp^3)$-$C(sp^2)$ Bond Formation



32 examples
30-95% yields

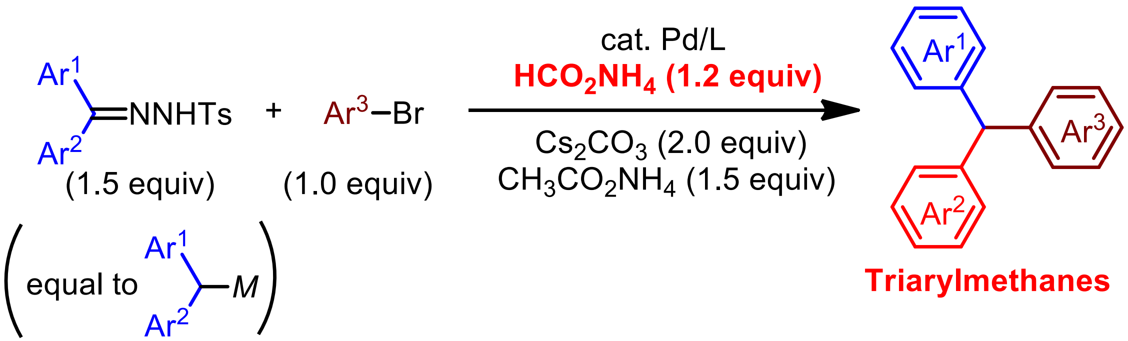
The Effect of $CH_3CO_2NH_4$



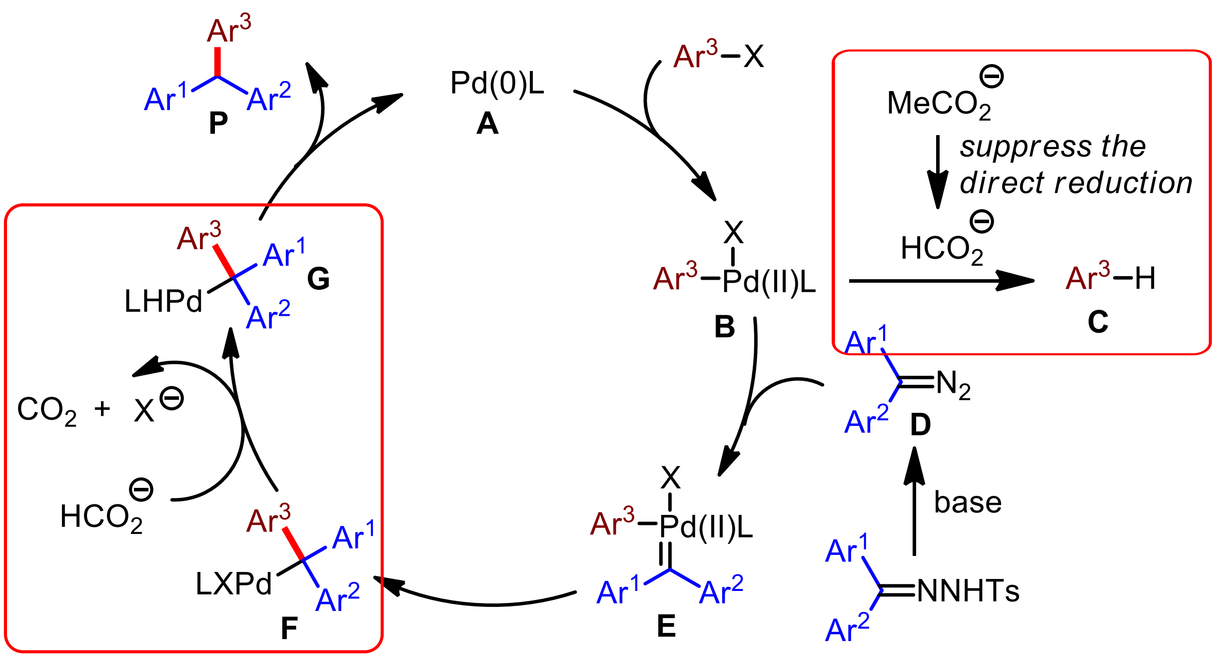
Xia, Y.; Hu, F.; Liu, Z.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 1784.
(Highlighted by *organic-chemistry.org*)

Other TM-Catalyzed Carbene Coupling Reaction-Pd

Reductive Coupling
$C(sp^3)$-$C(sp^2)$ Bond Formation

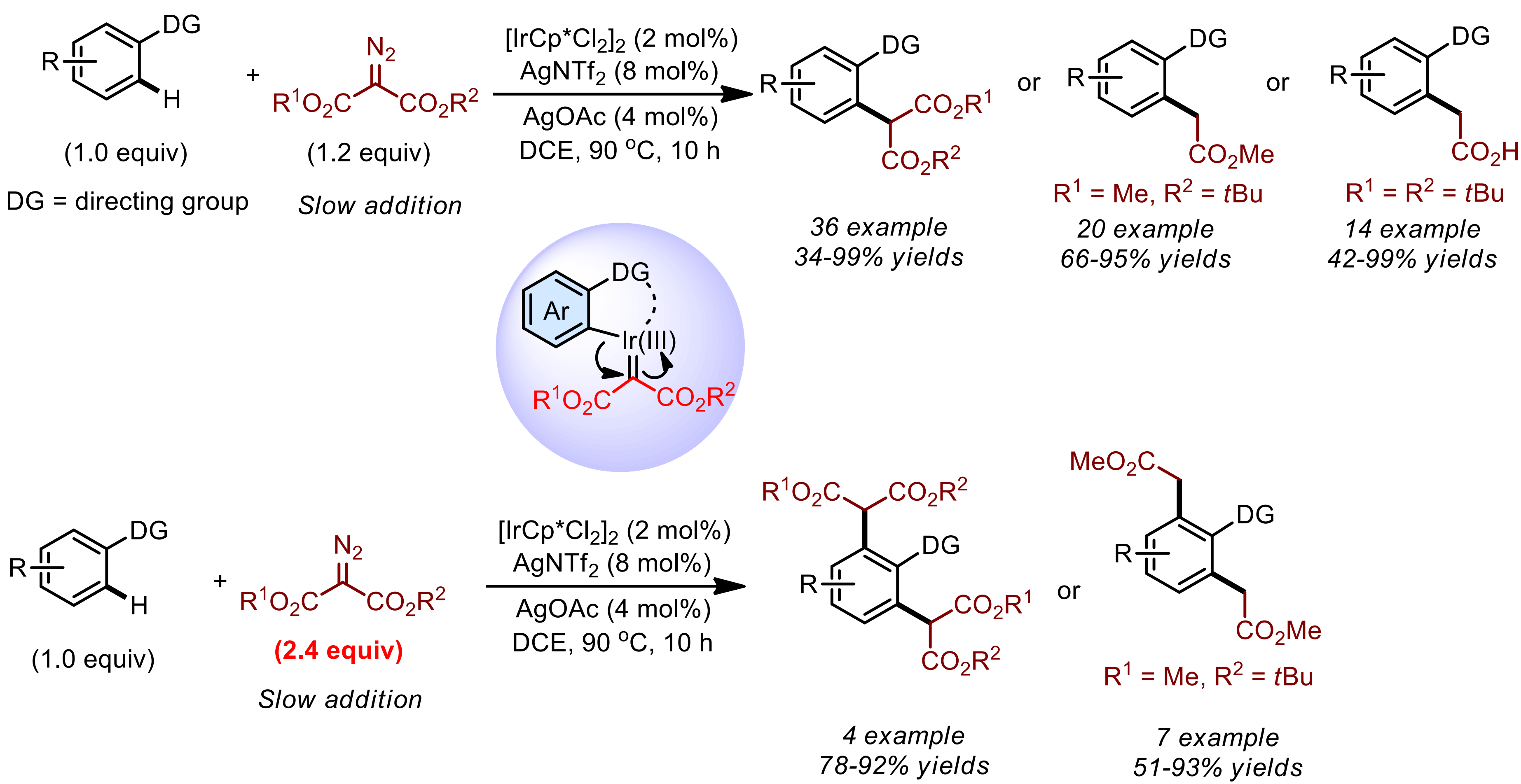


32 examples
30-95% yields



Xia, Y.; Hu, F.; Liu, Z.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 1784.
(Highlighted by *organic-chemistry.org*)

Other TM-Catalyzed Carbene Coupling Reaction-Ir

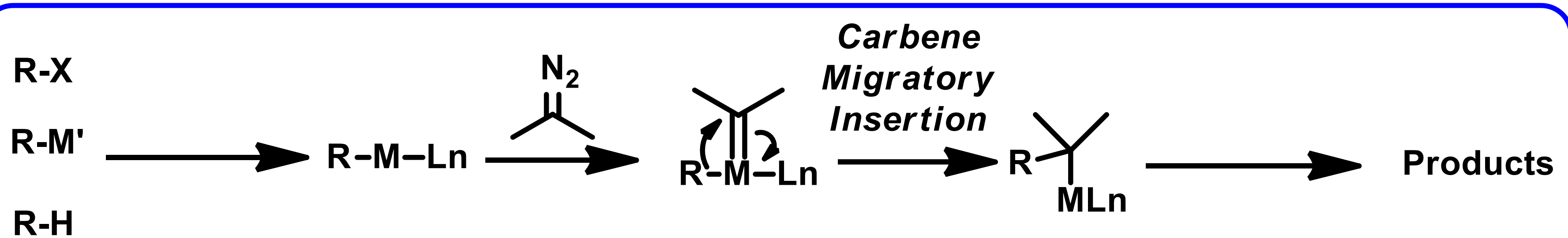


Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223.

Content

1. Carbene Cross-Coupling Reactions Involving Diazo Compounds or *N*-Tosylhydrazones

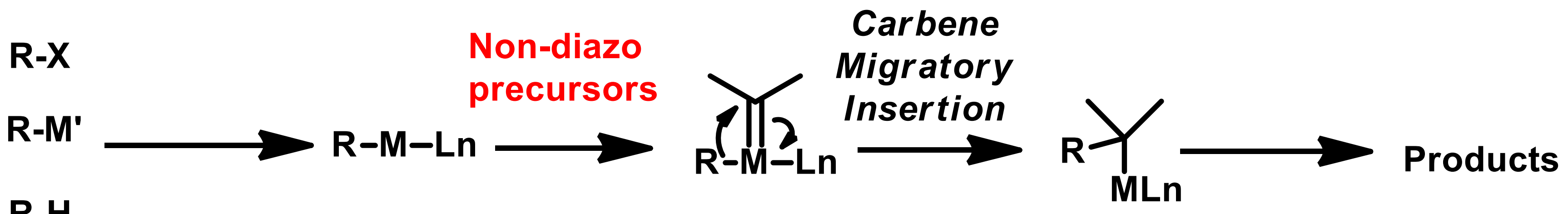
From Pd, Cu Catalysis to Rh(I) Catalysis



From M = Pd, Cu
To M = Rh(I) (C-C activation, transmetalation)

Content

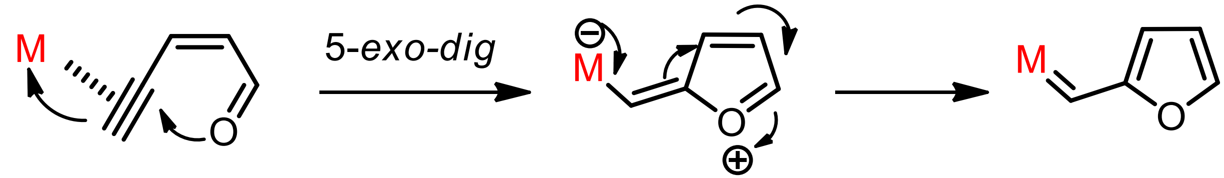
2. Carbene Cross-Coupling Reactions Involving Non-Diazo Compounds

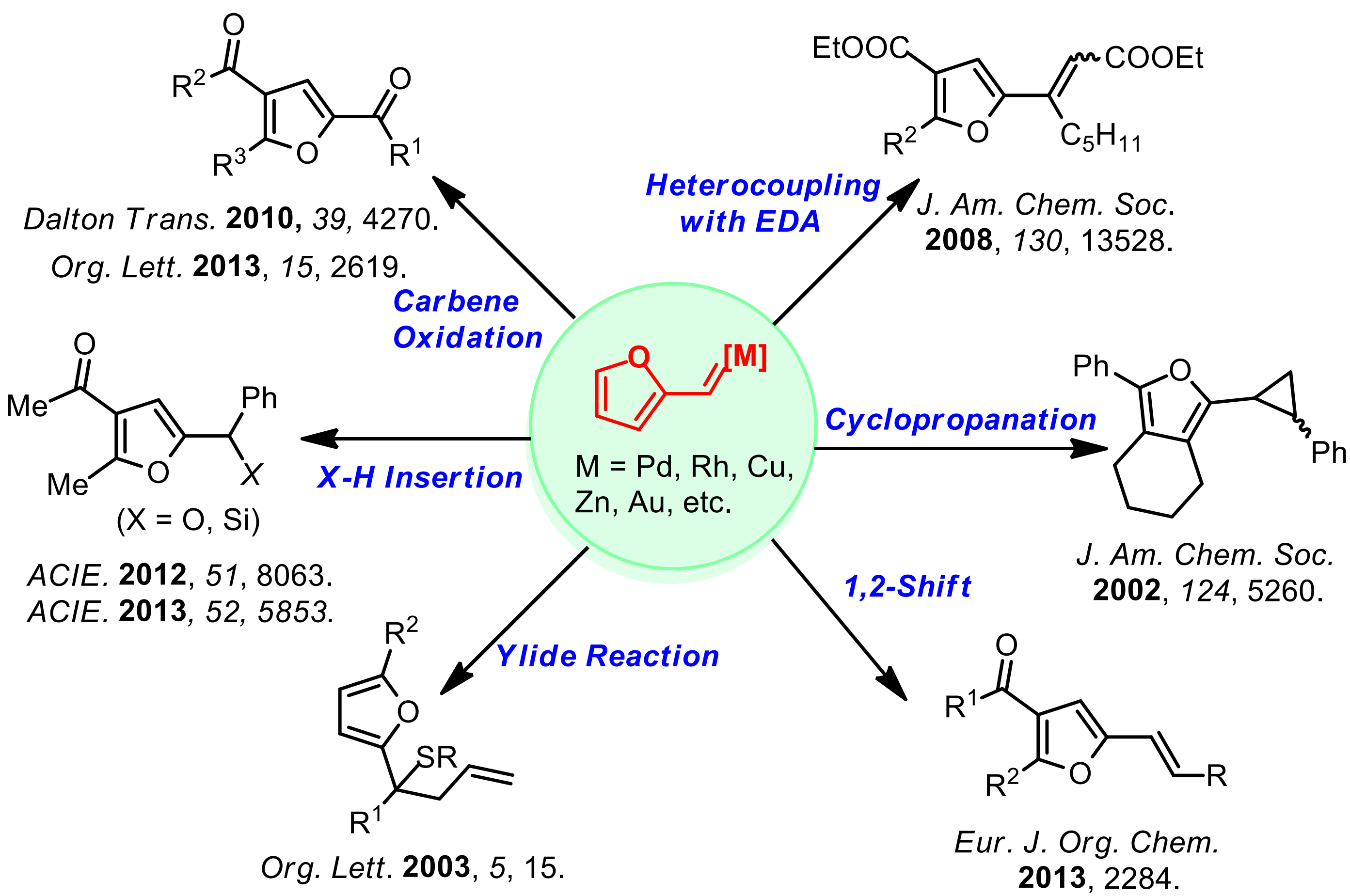


From Diazo compounds
To Non-diazo precursors

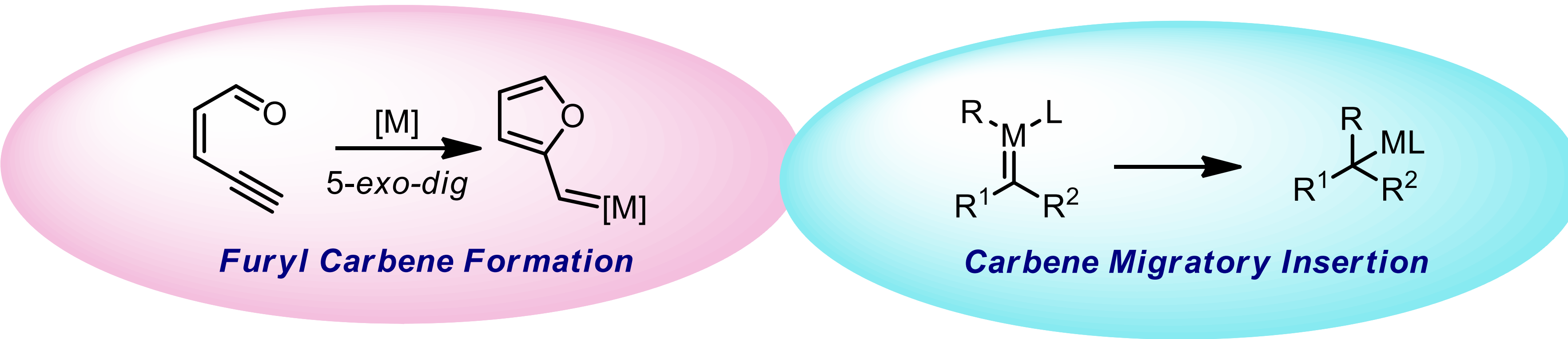
Conjugated Enynone Used as Carbene Precursor

Carbene Generation
（Conjugated Enynone）

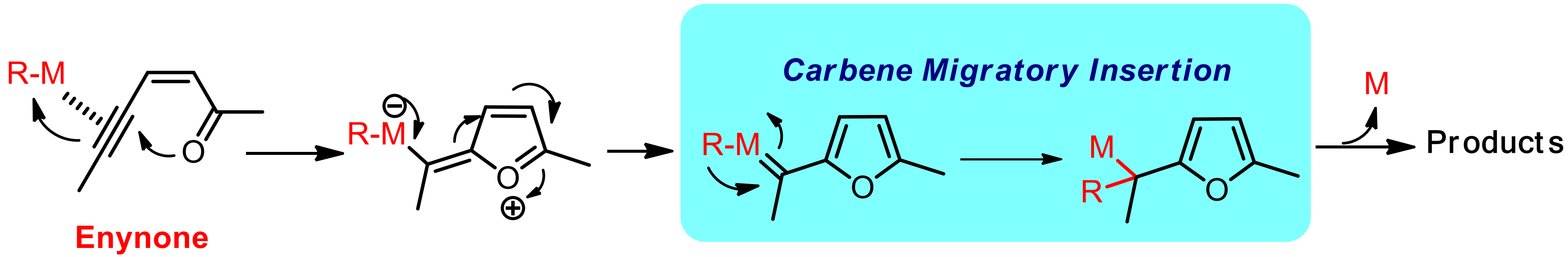




Design of Carbene Coupling Reaction Using Conjugated Enynone

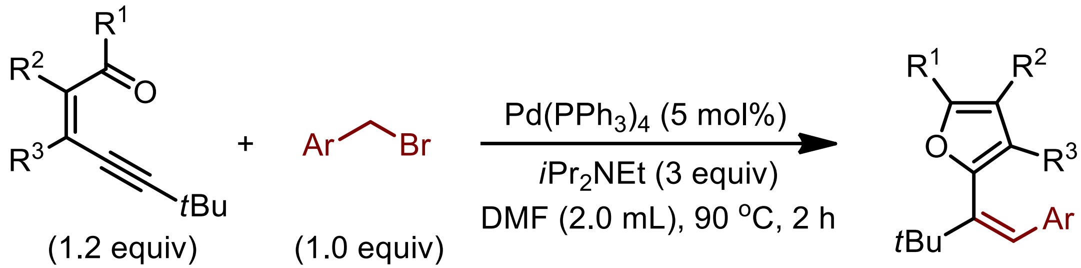


Carbene Coupling Reaction
Using Conjugated Enynone



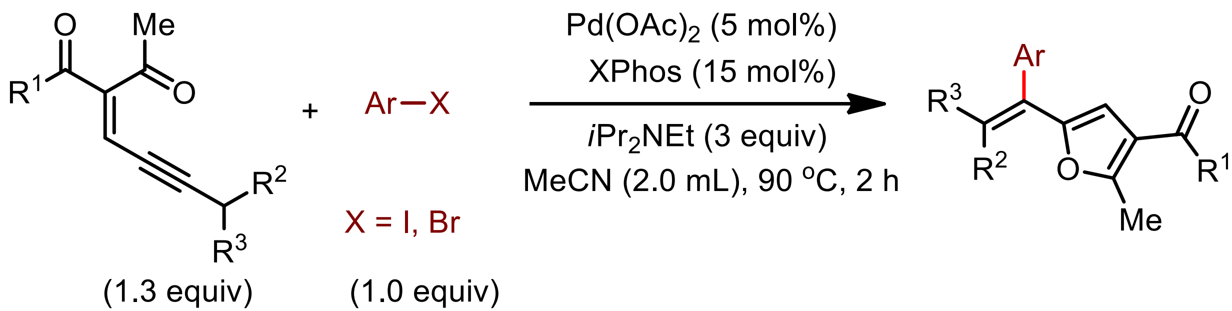
Pd-Catalyzed Coupling Reaction of Enynones with Organo Halides

Benzyl Bromides:



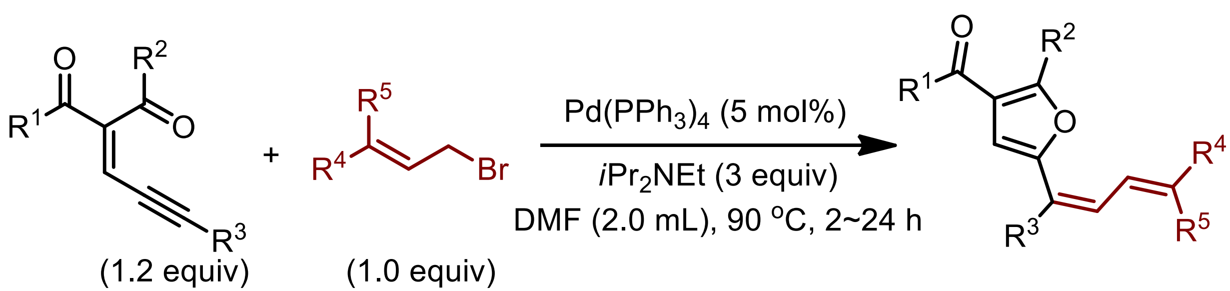
20 examples
35-95% yields

Aryl Halides:



14 examples
52-82% yields

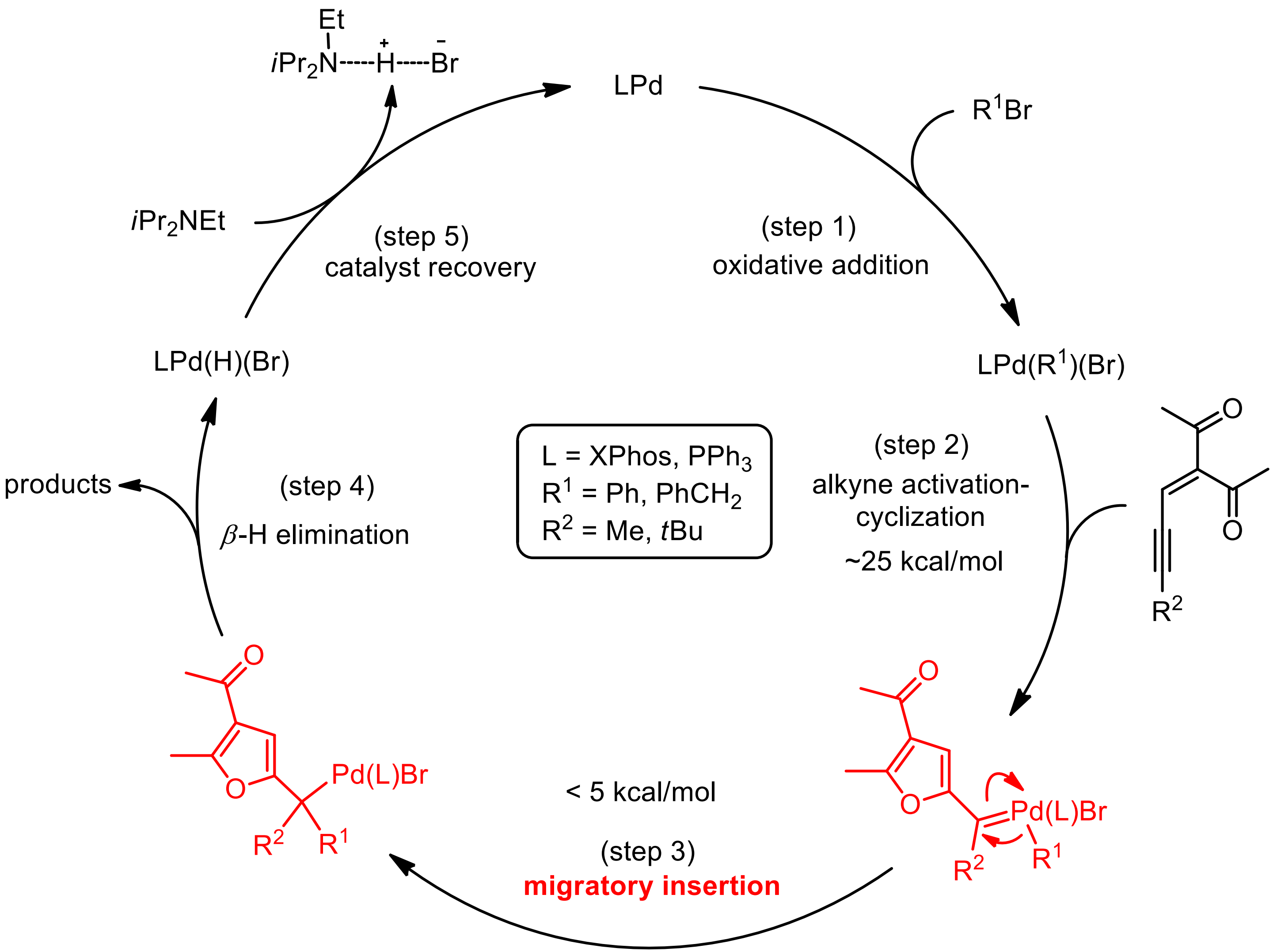
Allylic Halides:



6 examples
35-55% yields

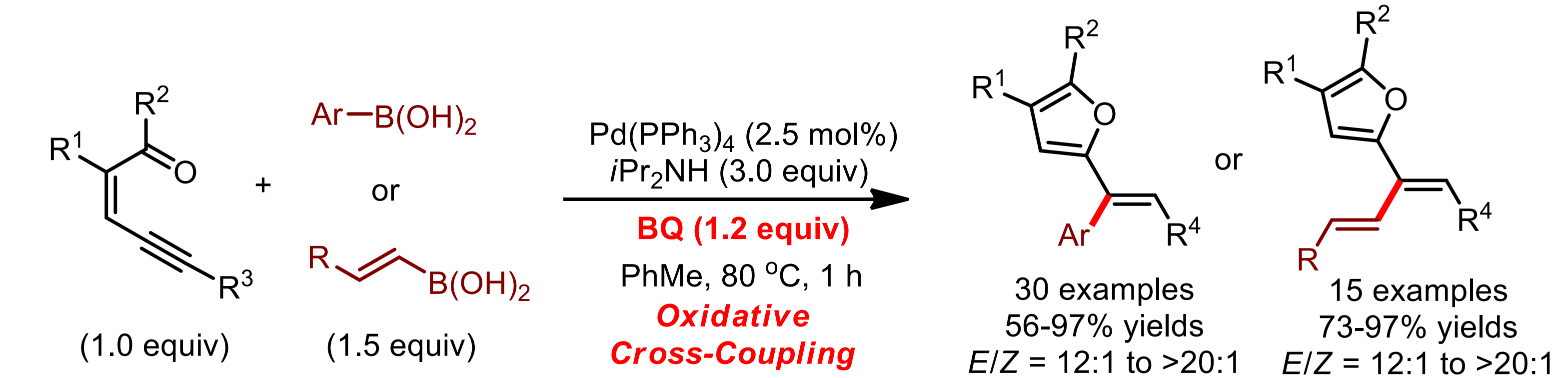
<u>Xia, Y.; Qu, S.; Xiao, Q.;</u> Wang, Z.-X.; Qu, P.; Chen, L.; Liu, Z.; Tian, L.; Huang, Z.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc*. **2013**, *135*, 13502. (Contributed Equally) (Highlighted by *ChemCatChem* **2014**, *6*, 711)

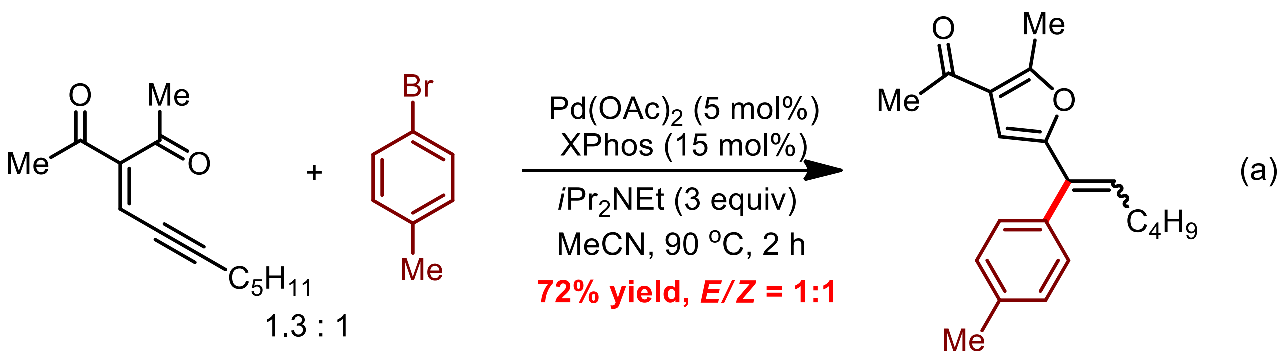
Proposed Mechanism

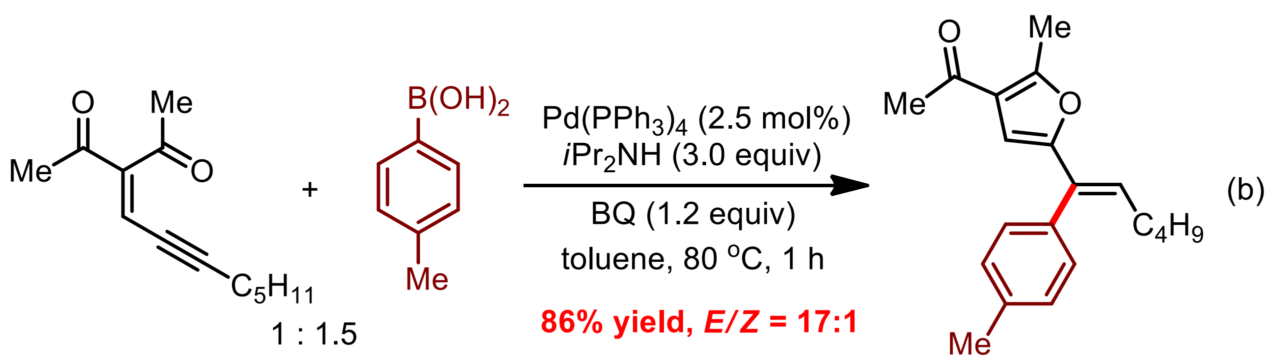


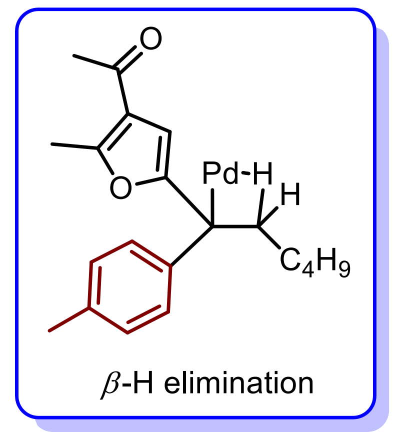
Xia, Y.; Qu, S.; Xiao, Q.; Wang, Z.-X.*; Qu, P.; Chen, L.; Liu, Z.; Tian, L.; Huang, Z.; Zhang, Y.; Wang, J.* *J. Am. Chem. Soc*. **2013**, *135*, 13502. (Contributed Equally) (Highlighted by *ChemCatChem* **2014**, *6*, 711)

Pd-Catalyzed Oxidative Coupling of Enynones with Organoboronic Acid





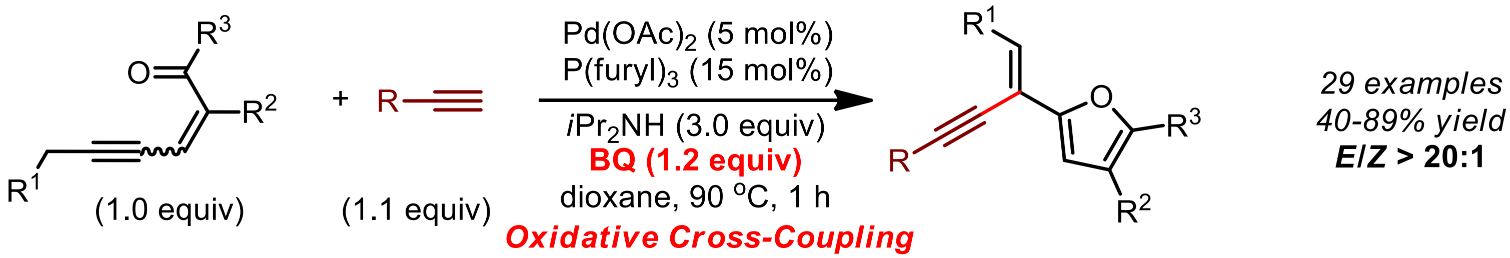


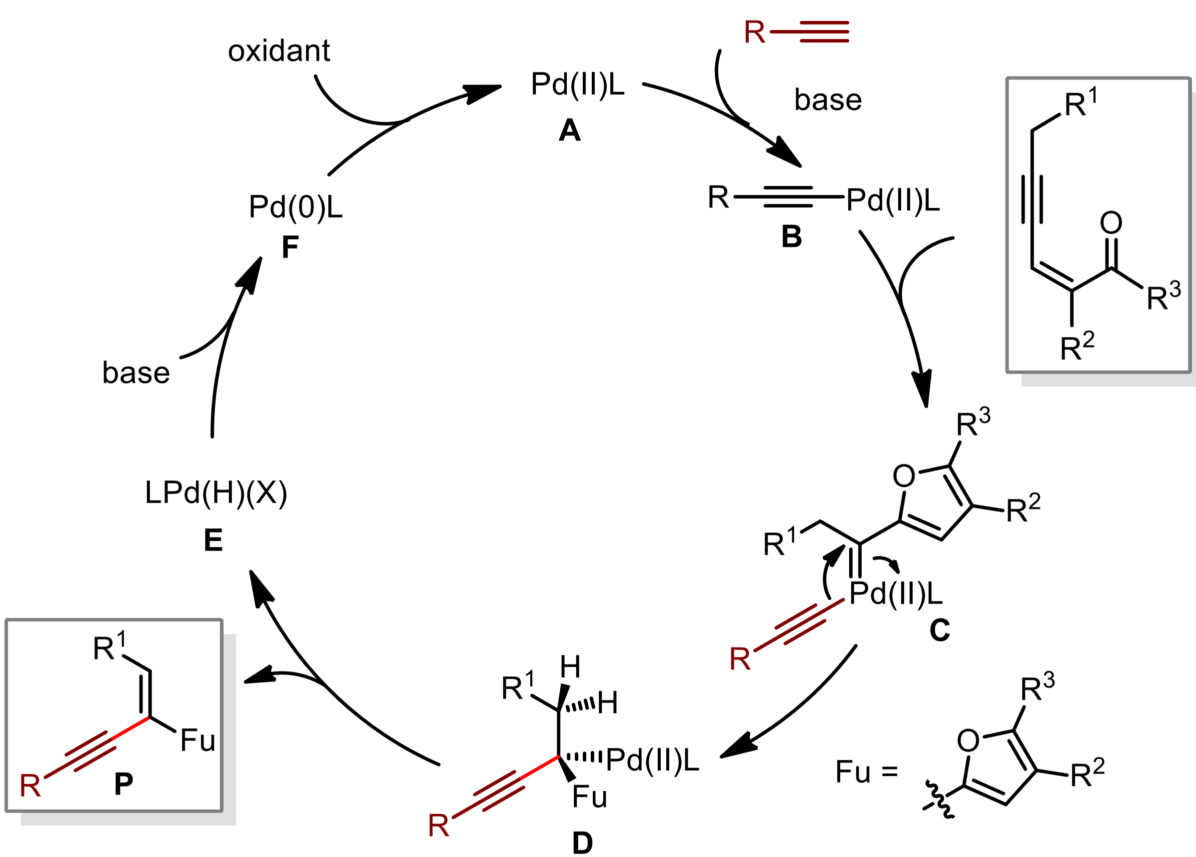


Strange E/Z Selectivity

Xia, Y.; Ge, R.; Chen, L.; Liu, Z.; Xiao, Q.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 7856-7864.

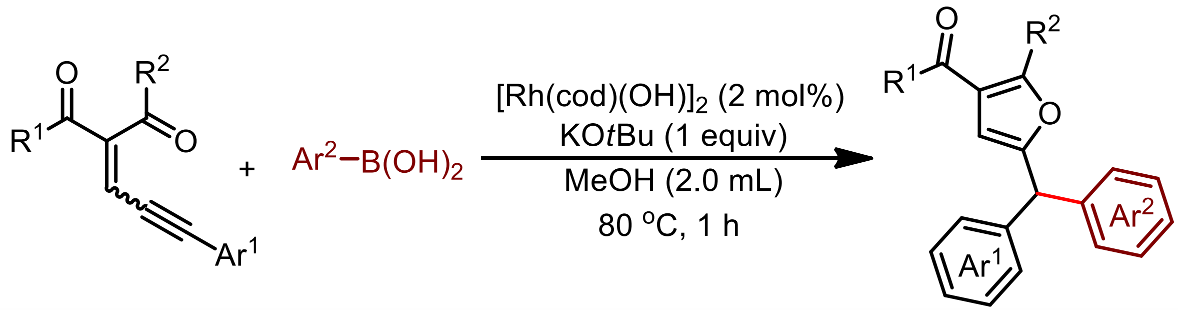
Pd-Catalyzed Oxidative Coupling of Enynones with Terminal Alkynes





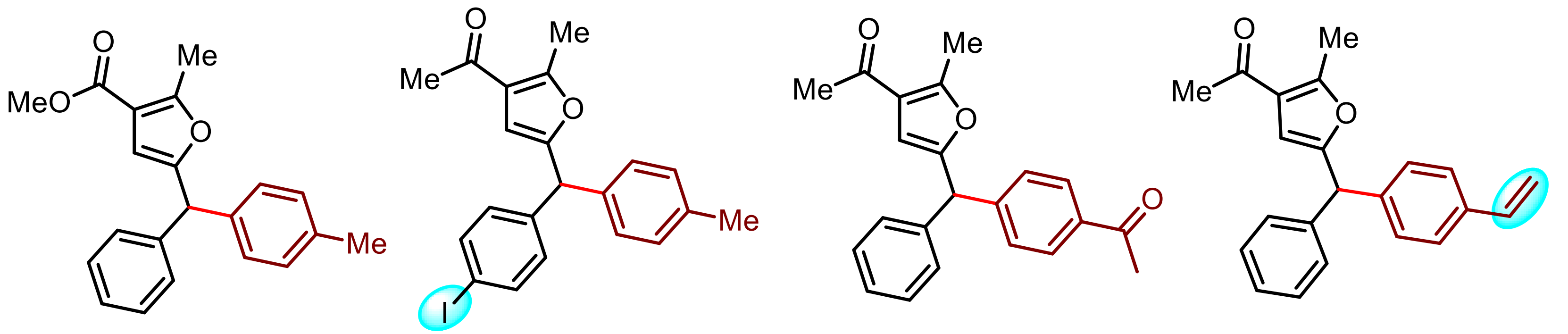
Xia, **Y.**; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 11233-11235.

Rh(I)-Catalyzed Coupling of Enynones with Organoboronic Acids

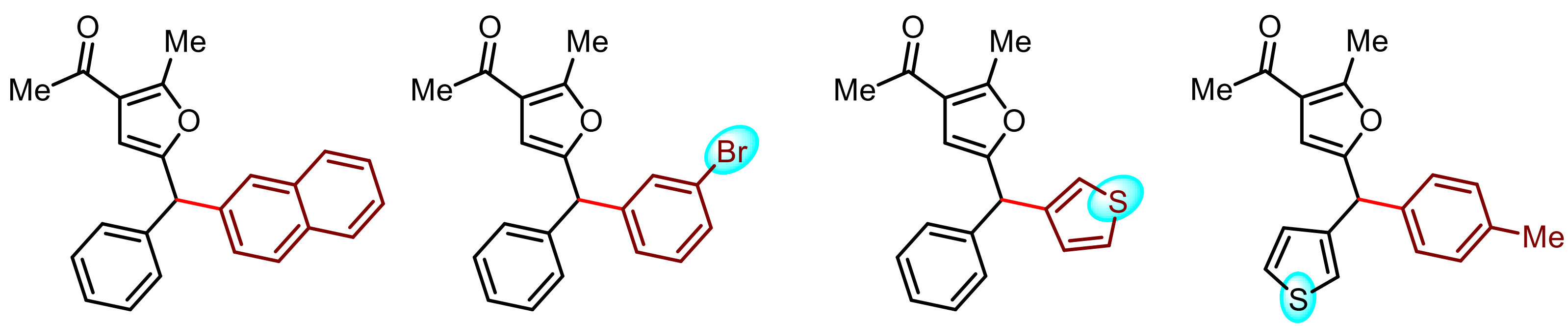


Furyl-Contained Triarylmethanes

30 examples
34-75% yields



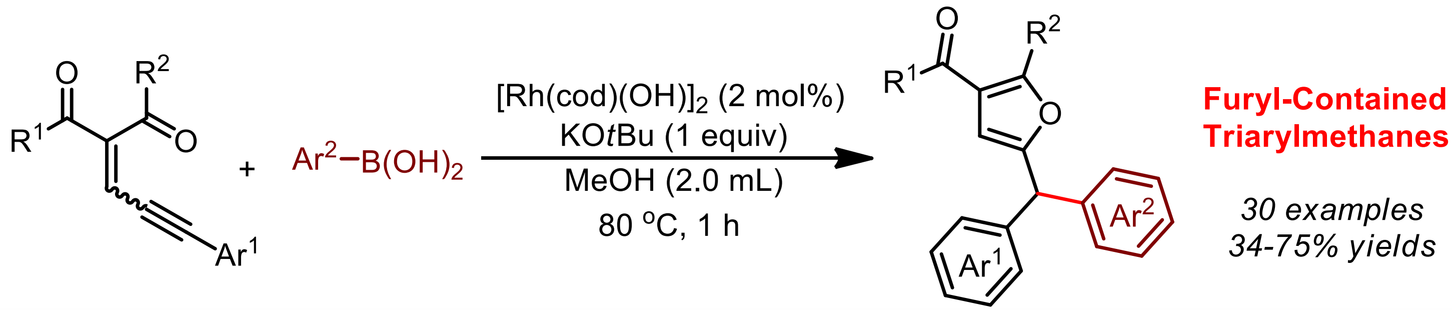
75% 65% 56% 62%

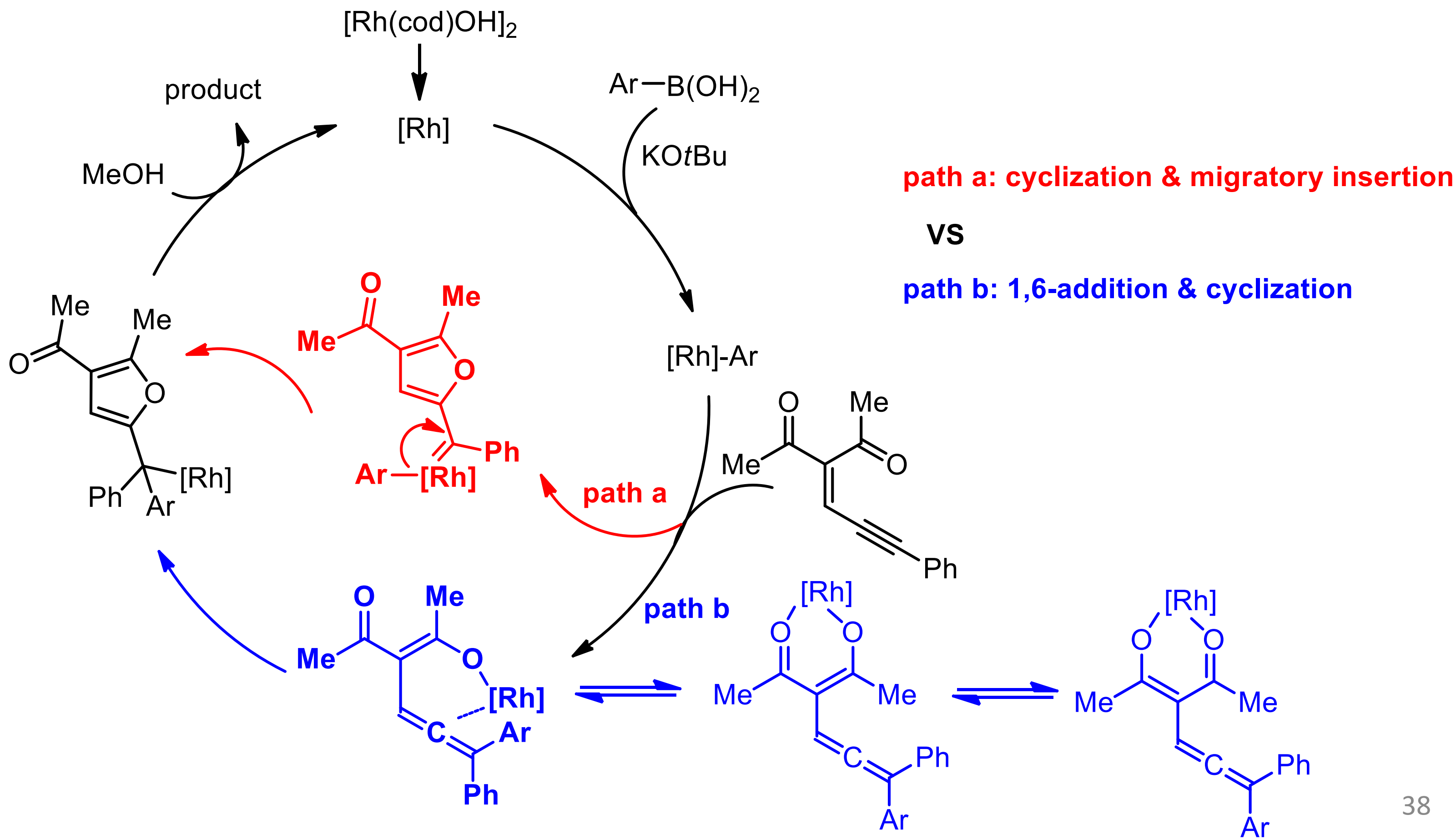


71% 60% 48% 40%

Xia, Y.; Chen, L.; Qu, P.; Ji, G.; Xiao, Q.; Zhang, Y.; Wang, J. *To be submitted.*

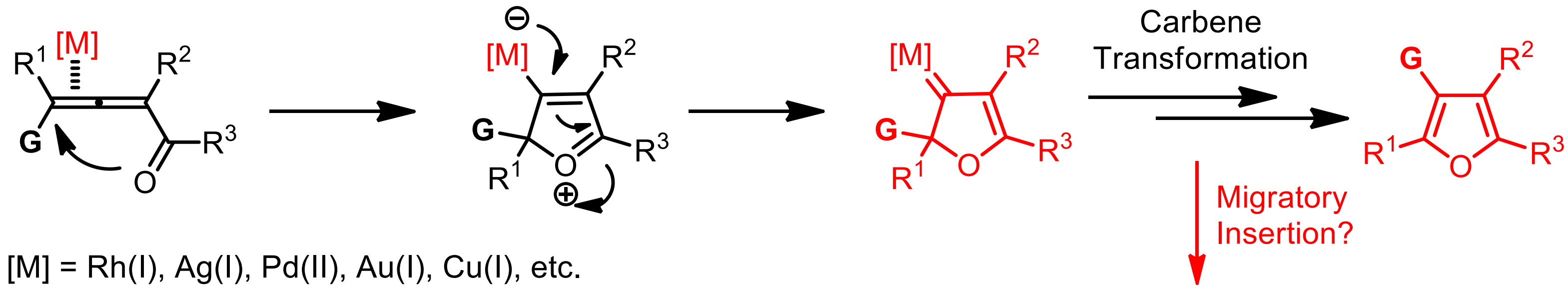
Proposed Mechanism





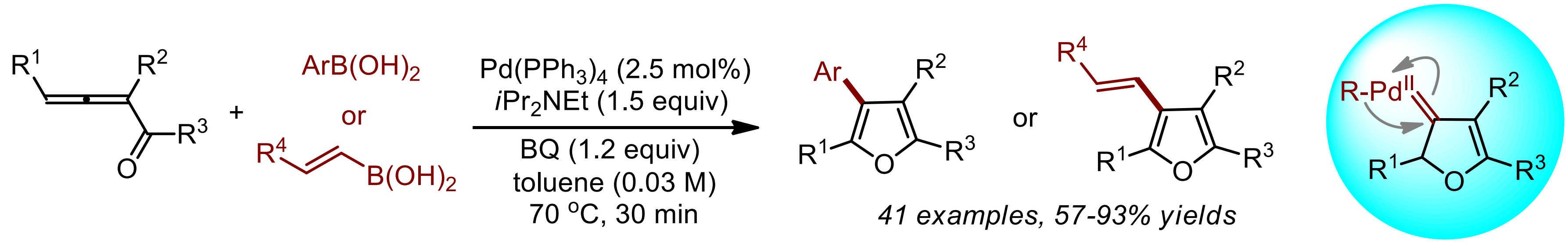
Carbene Coupling Reaction Involving Conjugated Allenyl Ketones

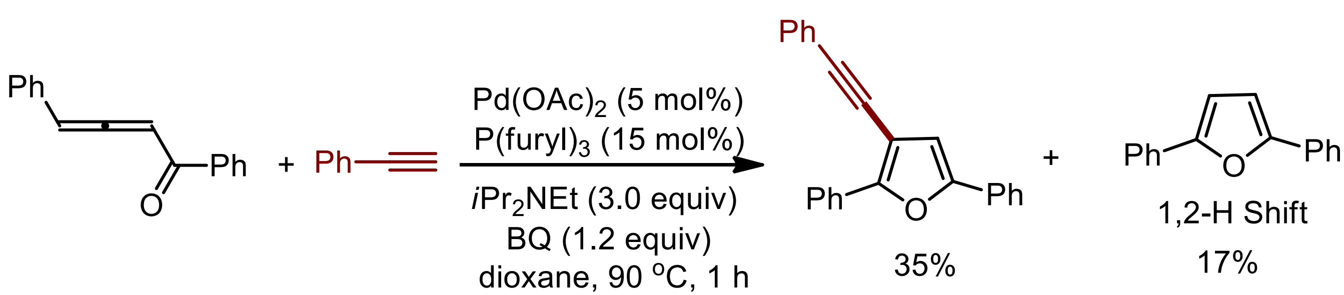
Carbene Generation from Allenyl Ketone



For review, see: Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084.

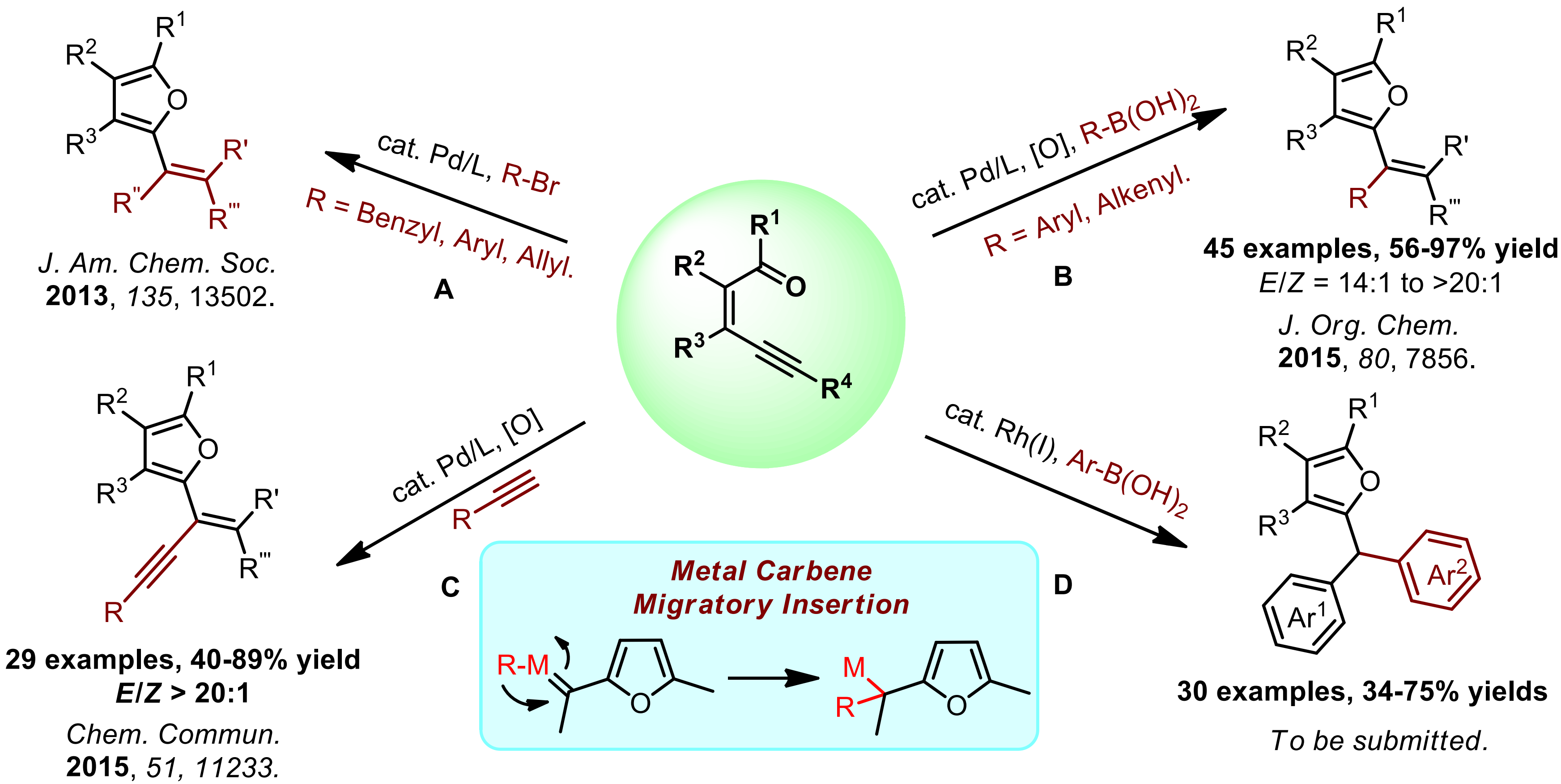
Allenyl Ketone Involved Carbene Coupling Reaction

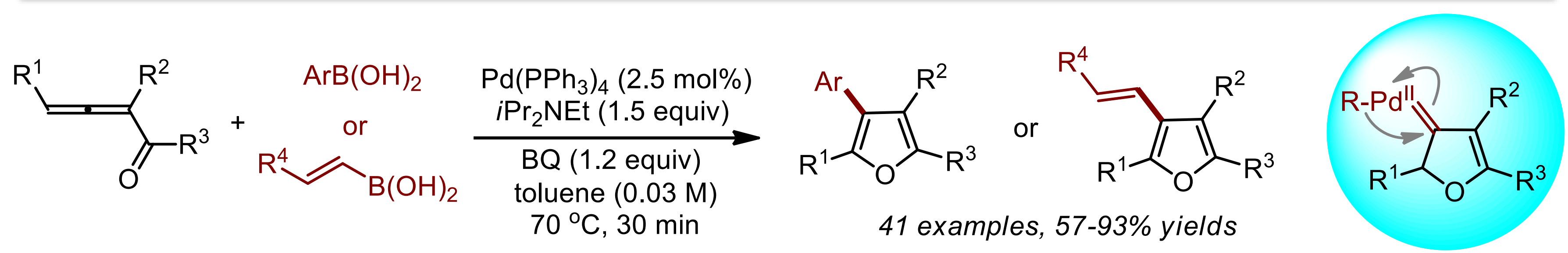




Xia, Y.; Xia, Y; Ge, R.; Liu, Z.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed*. **2014**, *53*, 3917.

Summary of Carbene Coupling Reaction Using Non-Diazo Precursors



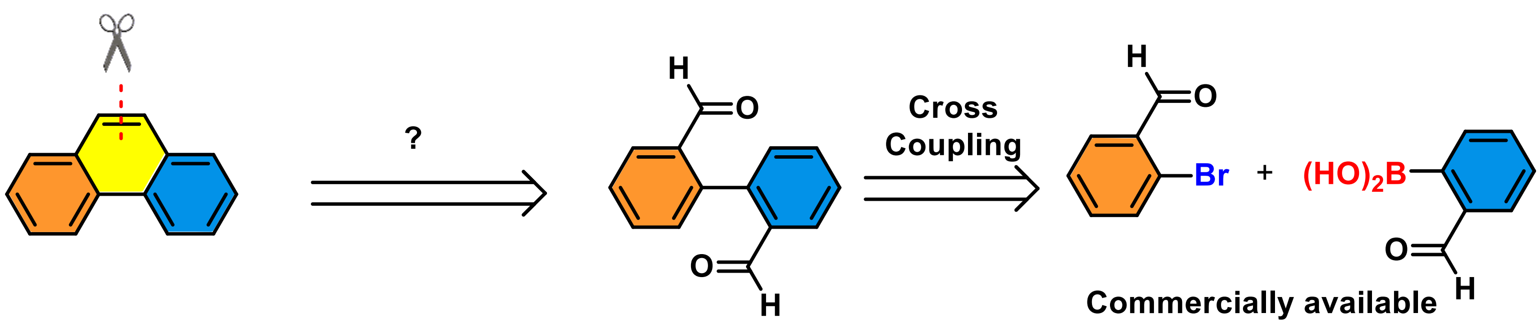


Xia, Y.; Xia, Y; Ge, R.; Liu, Z.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3917.

Content

3. Intramolecular Metal Carbene Dimerization and Beyond

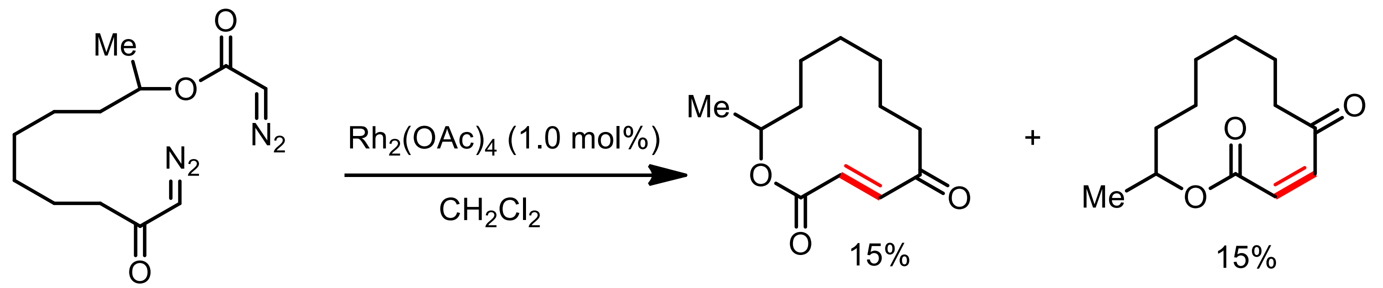
Construction Of Polycyclic Aromatic Compounds (PACs)



Brief Introduction of Carbene Dimerization

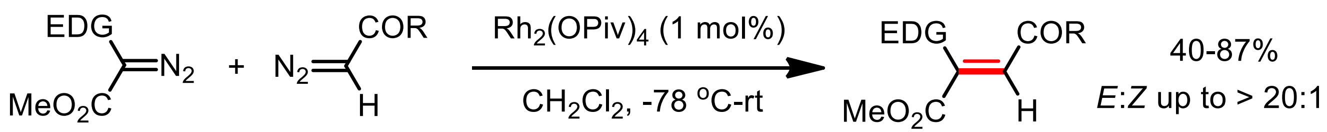
Widely Exist in Carbene Involved Reactions (Controllability, Selectivity)

Intramolecular



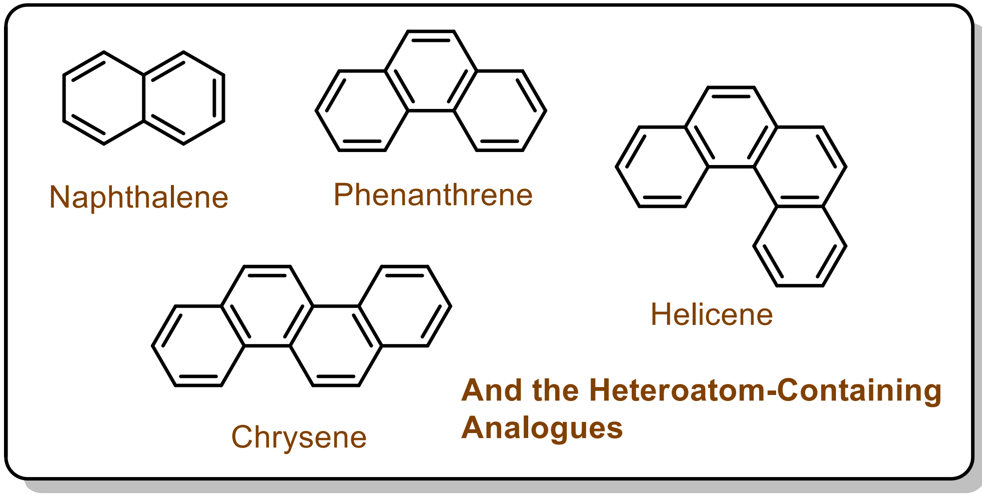
Doyle, M. P.; Hu, W.; Phillips, I. M. *Org. Lett.* **2000**, *2*, 1777

Intermolecular



Hansen, J. H.; Parr, B. T.; Pelphrey, P.; Jin, Q.; Autschbach, J.; Davies, H. M. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 2544.

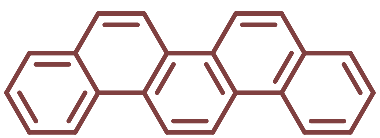
Application of Polycyclic Aromatic Compounds (PACs)



Wide Applicatiion in

- Chemical Feedstock
- Material Science
- Pharmaceutical Industry
- Total Synthesis
- 。。。

Polycyclic Aromatic Hydrocarbons; Harvey, R. G., Eds.; Wiley-VCH: New York, N. Y., 1997.

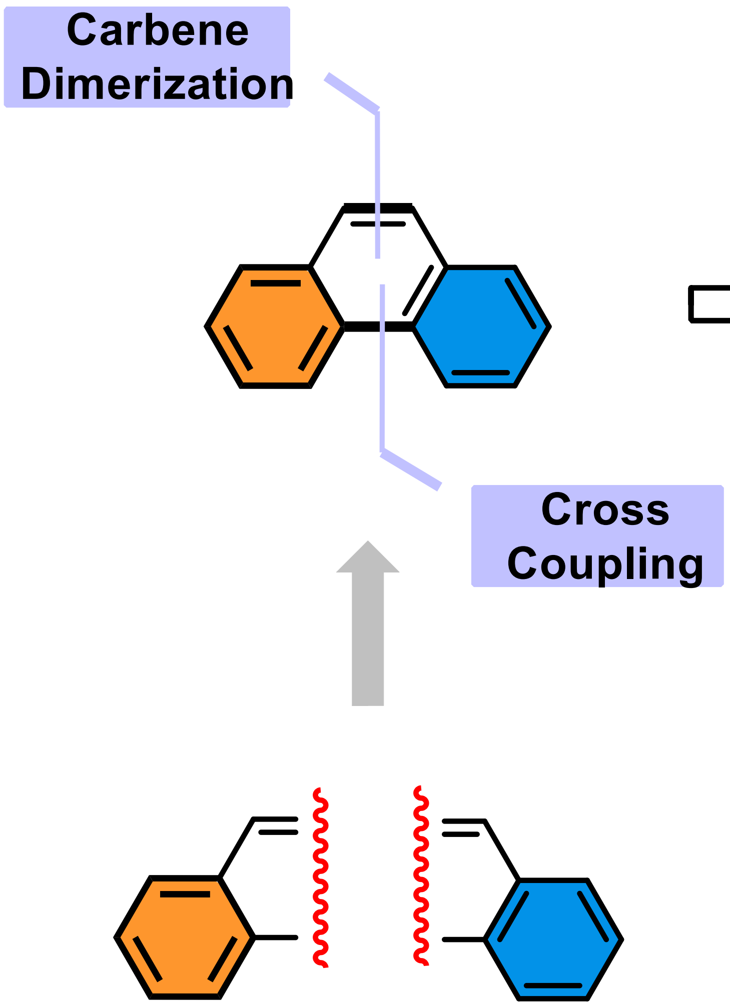


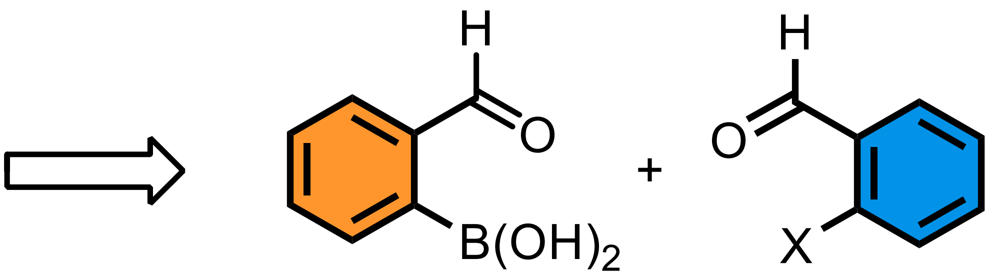
picene

Alkali-metal-doped picene can show superconductivity (T_c = 18 K), and this is the first example of organic superconducting material.

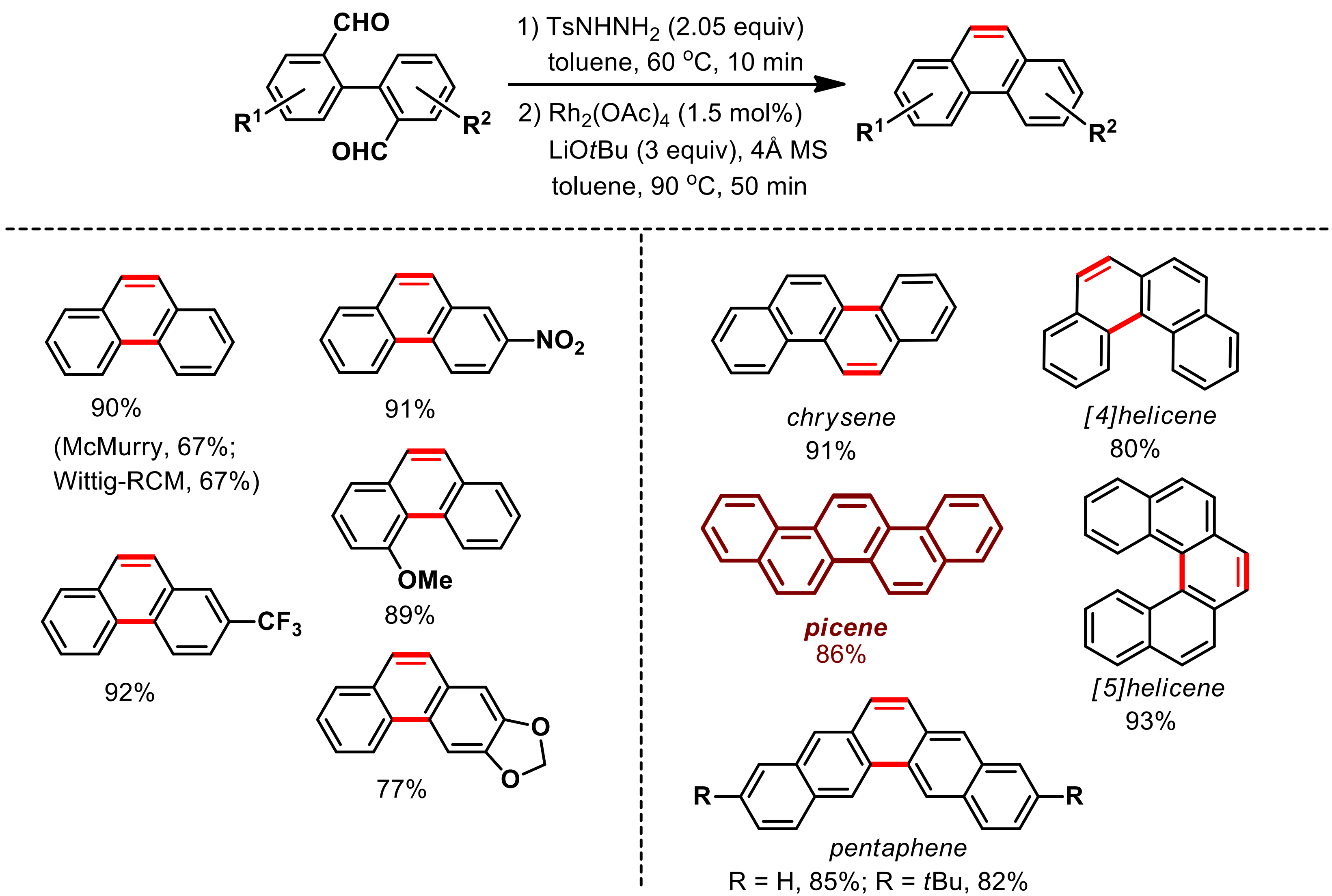
Mitsuhashi, R.; Suzuki, Y.; Yamanari, Y.; Mitamura, H.; Kambe, T.; Ikeda, N.; Okamoto, H.; Fujiwara, A.; Yamaji, M.; Kawasaki, N.; Maniwa, Y.; Kubozono, Y. *Nature* **2010**, *464*, 76.

Design for Construction Of PACs





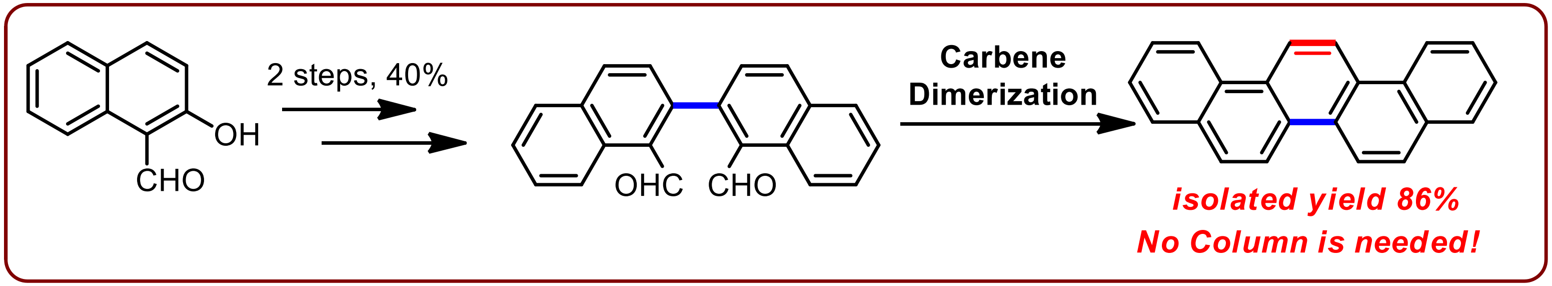
Construction of PACs via Carbene Dimerization



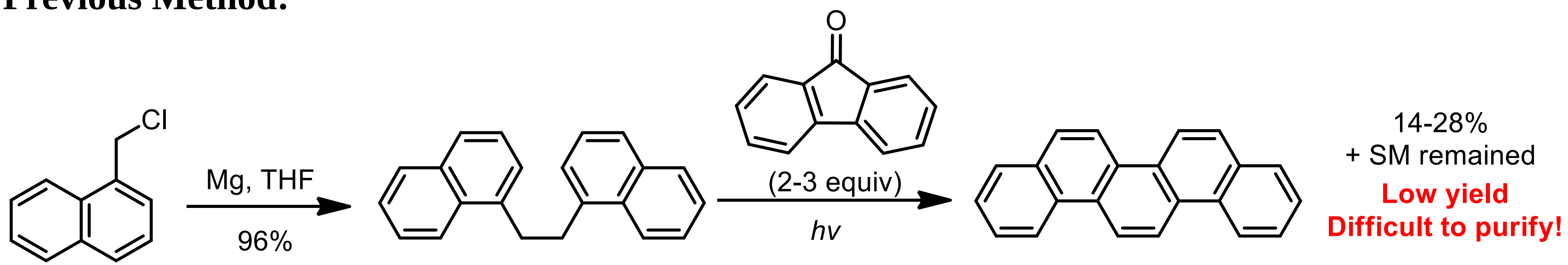
Xia, Y.; Liu, Z.; Xiao, Q.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5714.
(Highlighted by *ACS Noteworthy Chemistry*)

Applications of Carbene Dimerization Methodology

Our Method:



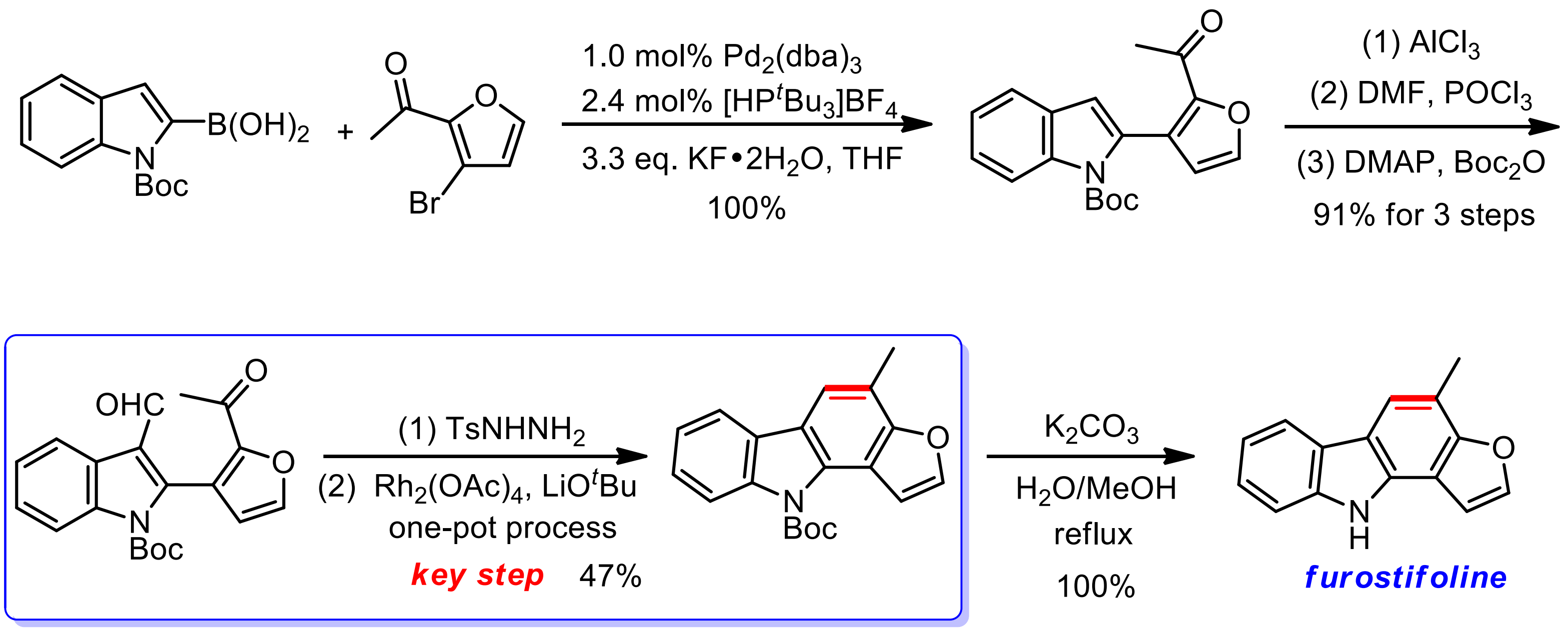
Previous Method:



Okamoto, H. et al, *Org. Lett.* **2011**, *13*, 2758.

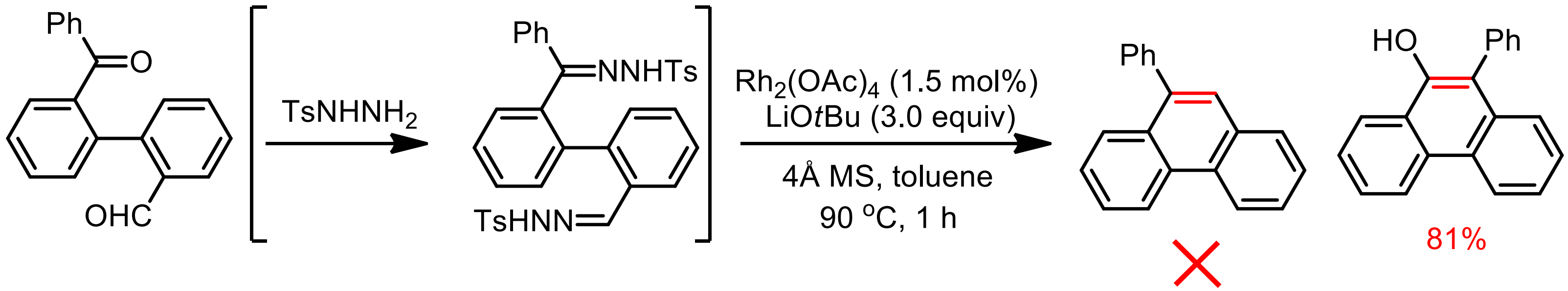
Applications of Carbene Dimerization Methodology

A concise synthesis of furostifoline

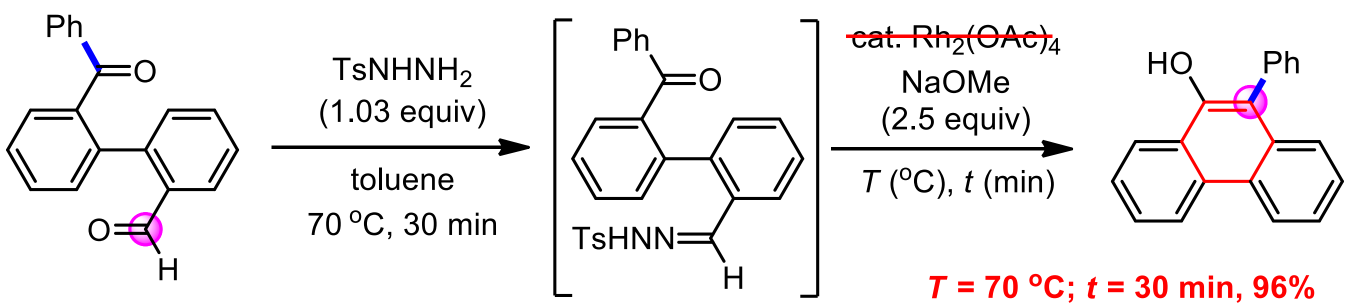


6 steps, overall yield 42.7%

Unexpected Result



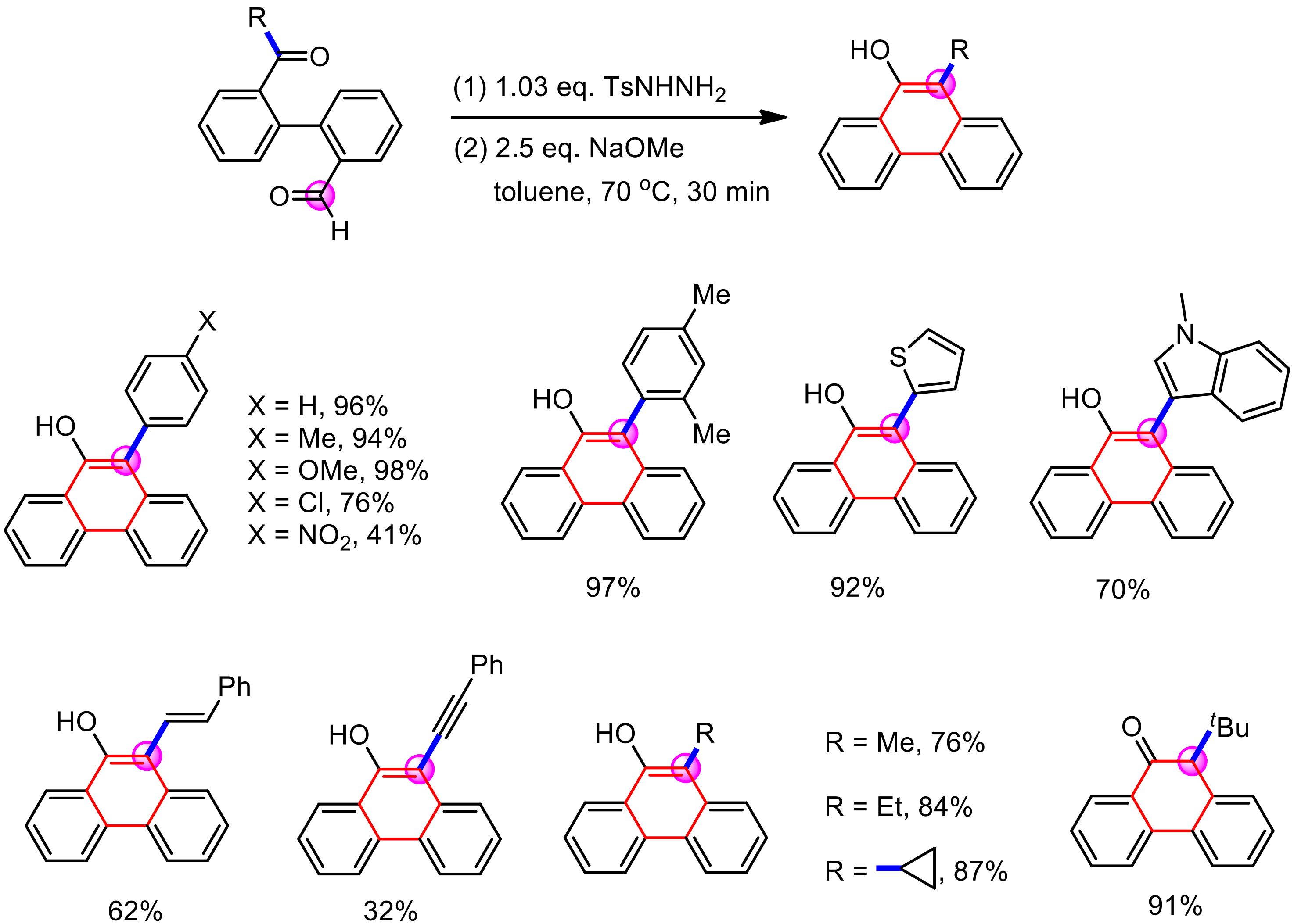
Optimized Conditions：



***T* = 70 °C; *t* = 30 min, 96%**

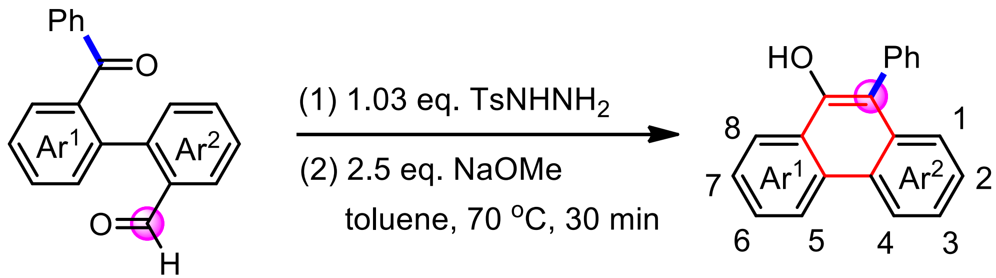
T = 25 °C; *t* = 180 min, 62%

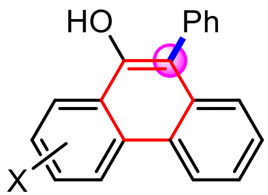
Substrate Scope: *Migratory Group Investigation*



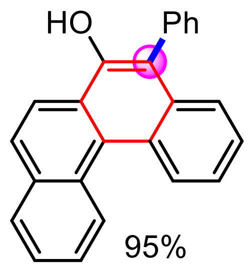
Xia, Y.; Qu, P.; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 2543.
(Highlighted *by Synfacts* **2013**, *9*, 0492.)

Substrate Scope: ***Substituted Phenanthrenes***

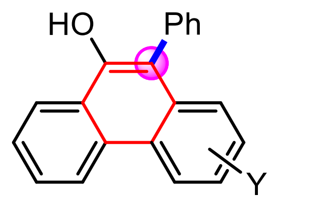




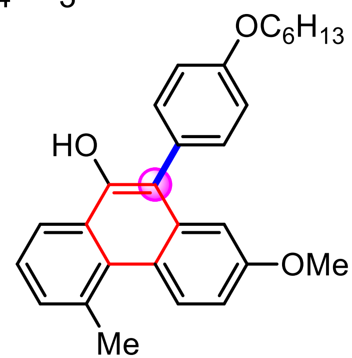
X = 7-CF_3, 87%
X = 6-Cl, 80%



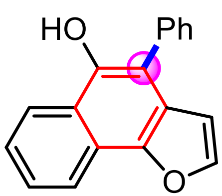
95%



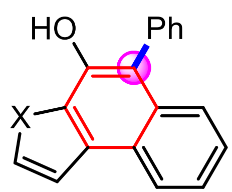
Y = 2-OMe, 97%
Y = 2,3-OCH_2O-, 95%
Y = 3-F, 87%
Y = 2-NO_2, 75%



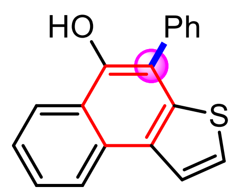
93%



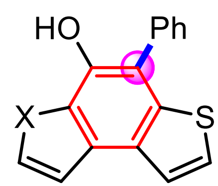
87%



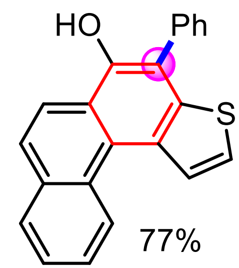
X = O, 90%
X = S, 98%



93%

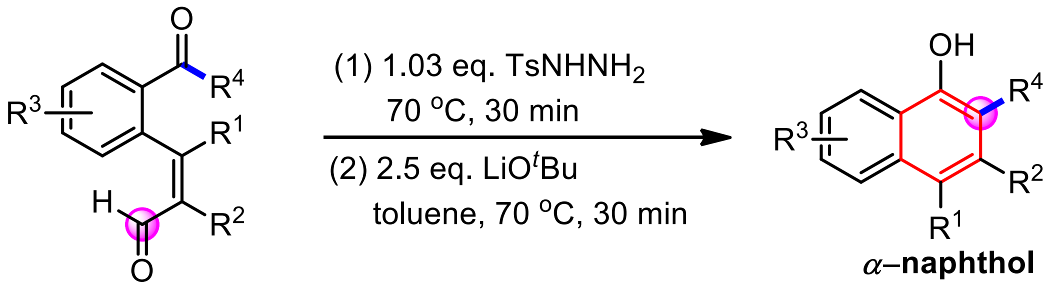


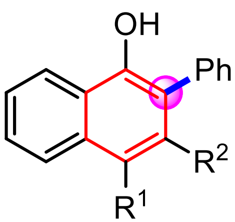
X = S, 99%
X = O, 40%



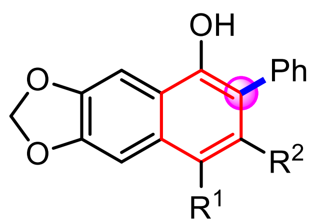
77%

Substrate Scope: *α-Naphthol*

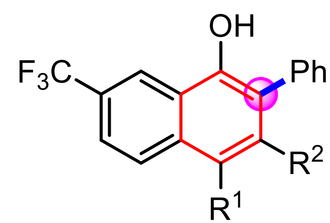




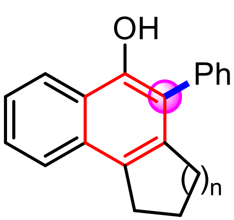
R^1 = Ph, R^2 = Me, 87%
R^1 = Me, R^2 = Ph, 80%



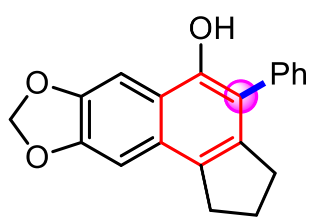
R^1 = Ph, R^2 = Me, 76%
R^1 = Me, R^2 = Ph, 74%



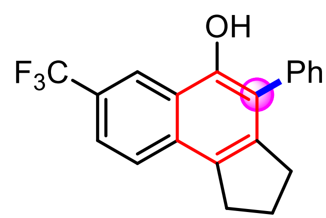
R^1 = Ph, R^2 = Me, 78%
R^1 = Me, R^2 = Ph, 64%



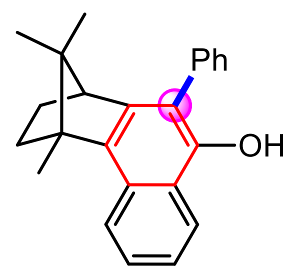
n = 1, 93%
n = 2, 99%
n = 3, 86%
n = 4, 85%



77%

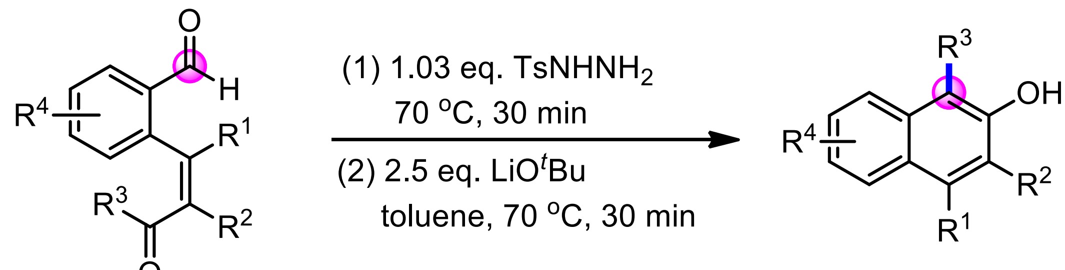


79%

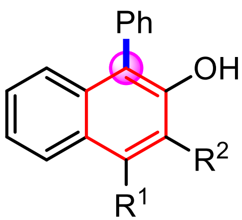


89%

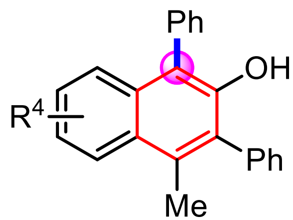
Substrate Scope: ***β-Naphthol***



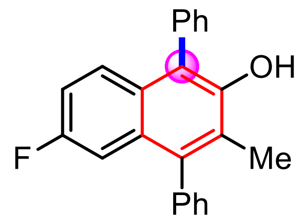
***β*–naphthol**



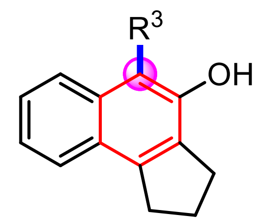
R^1 = Ph, R^2 = Me, 92%
R^1 = Me, R^2 = Ph, 75%



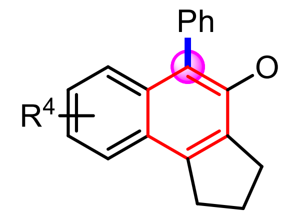
R^4 = 6-Me, 74%
R^4 = 7-OMe, 68%



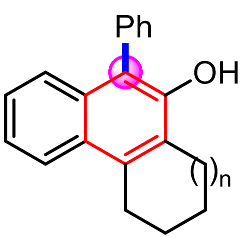
96%



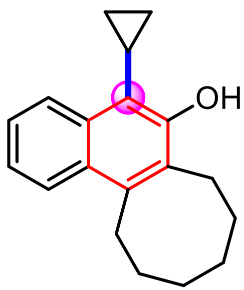
R^3 = Ph, 89%
R^3 = Et, 74%



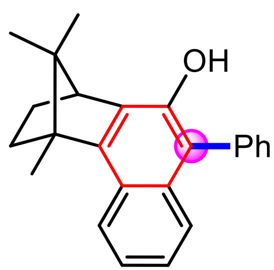
R^4 = 6-Me, 72%
R^4 = 7-OMe, 81%



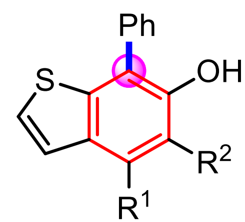
n = 1, 85%
n = 2, 88%



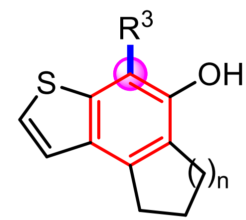
82%



85%

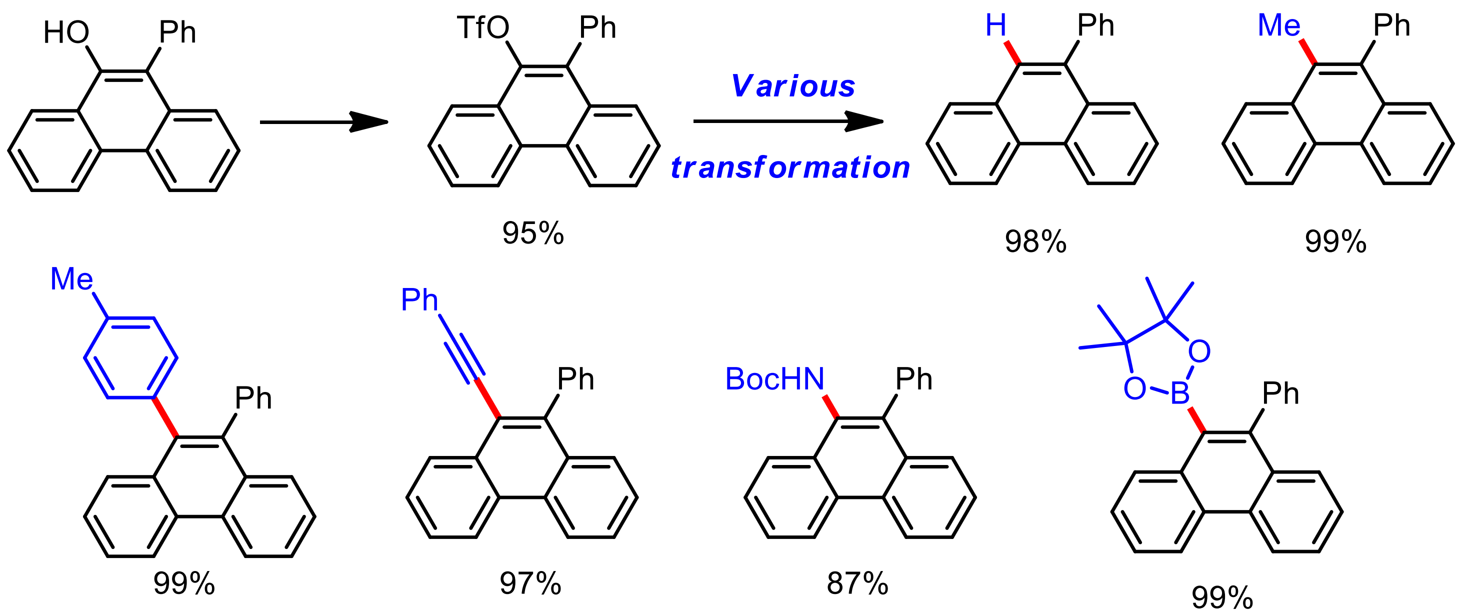


R^1 = Me, R^2 = Ph, 86%
R^1 = Ph, R^2 = Me, 72%



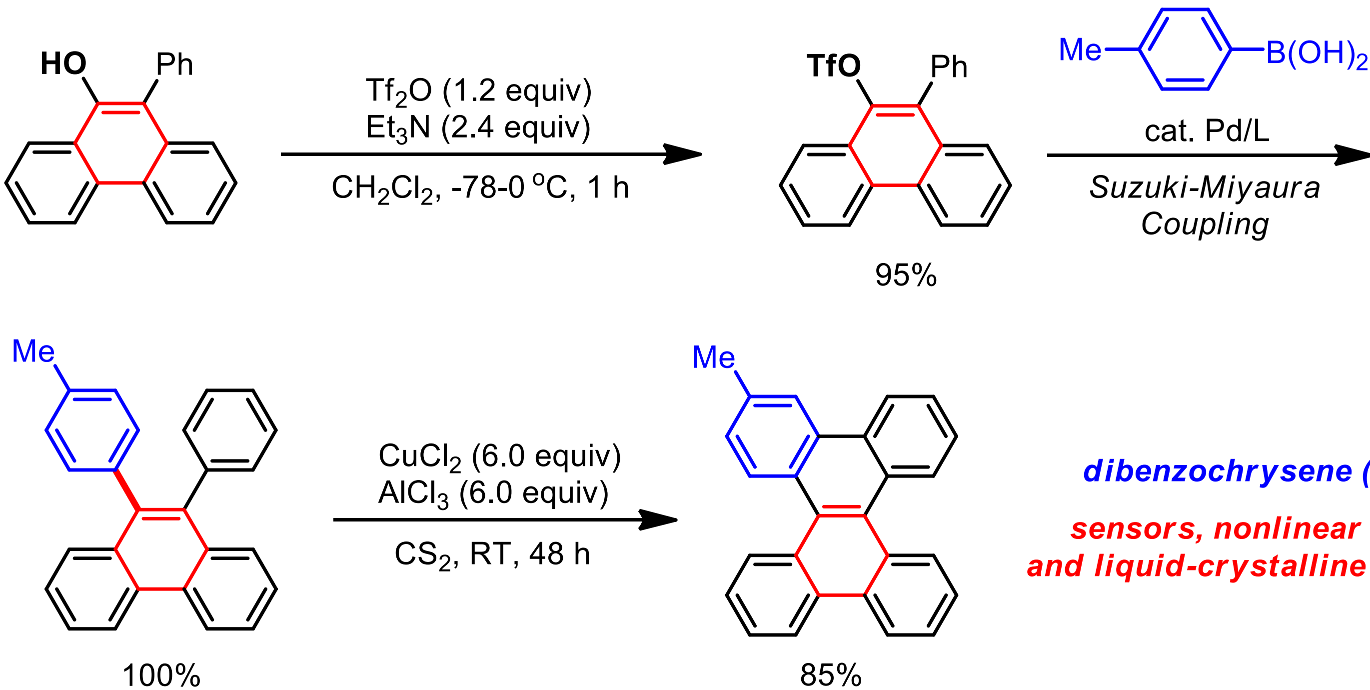
R^3 = Et, n = 1, 53%
R^3 = Ph, n = 3, 68%

Application: *Further Transformation*



Xia, Y.; Qu, P.; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 2543.
(Highlighted *by Synfacts* **2013**, *9*, 0492.)

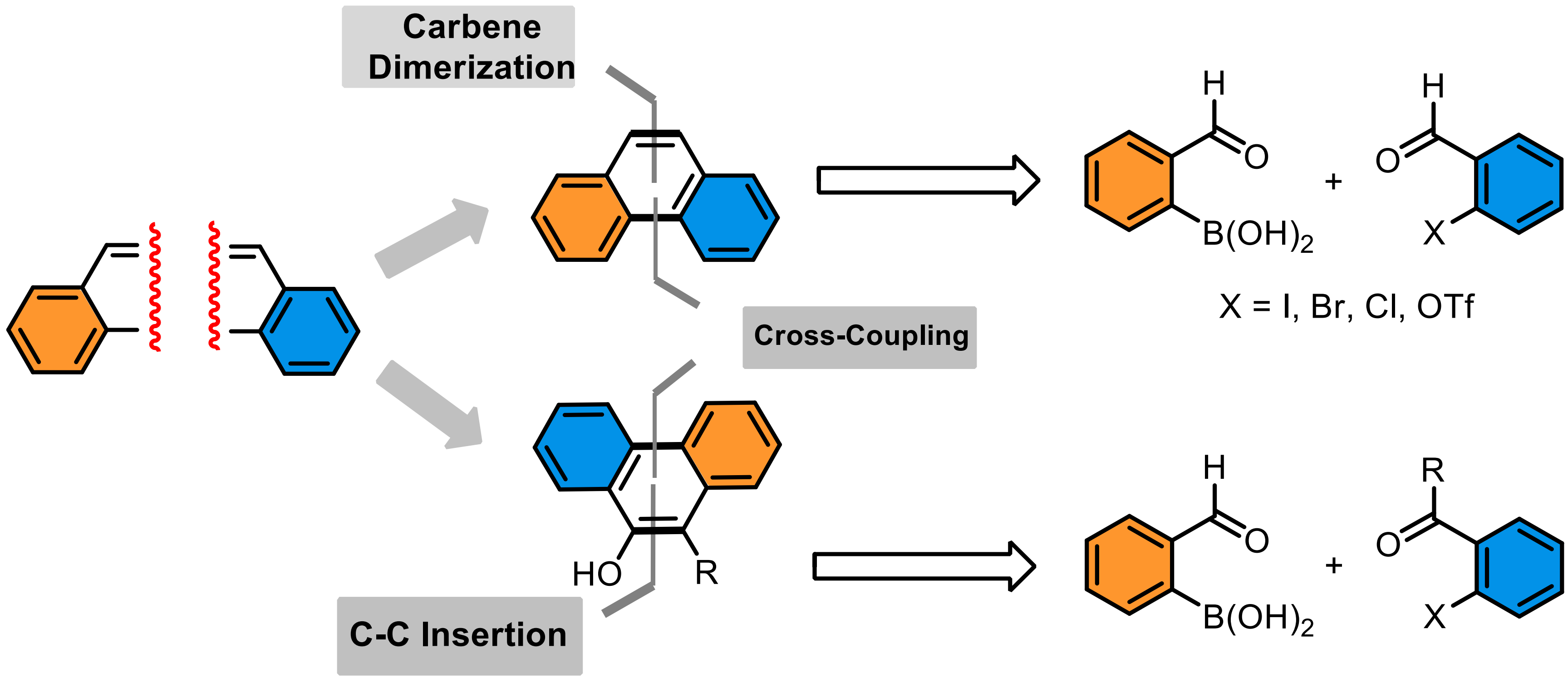
Application: ***Synthesis of DBC Derivatives***

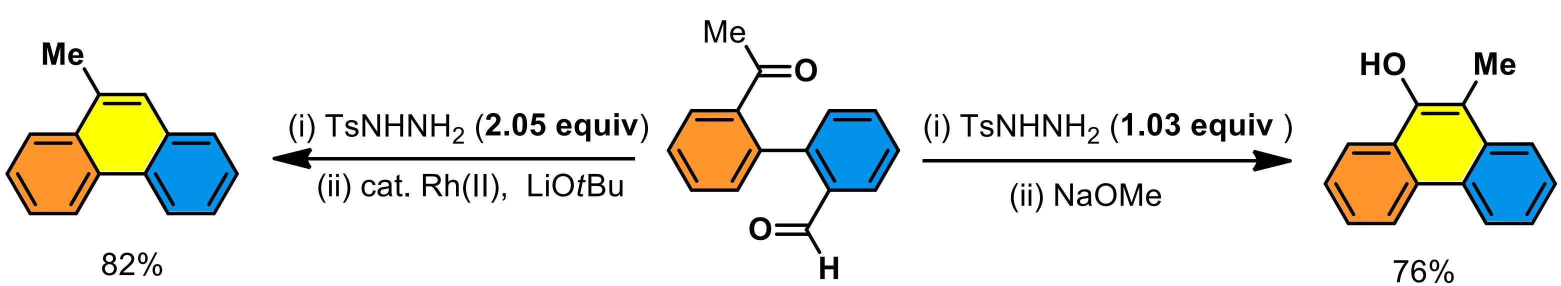


dibenzochrysene (DBC)

sensors, nonlinear optical and liquid-crystalline materials

Summary of Carbene Dimerization





Angew. Chem. Int. Ed. **2012**, *51*, 5714.

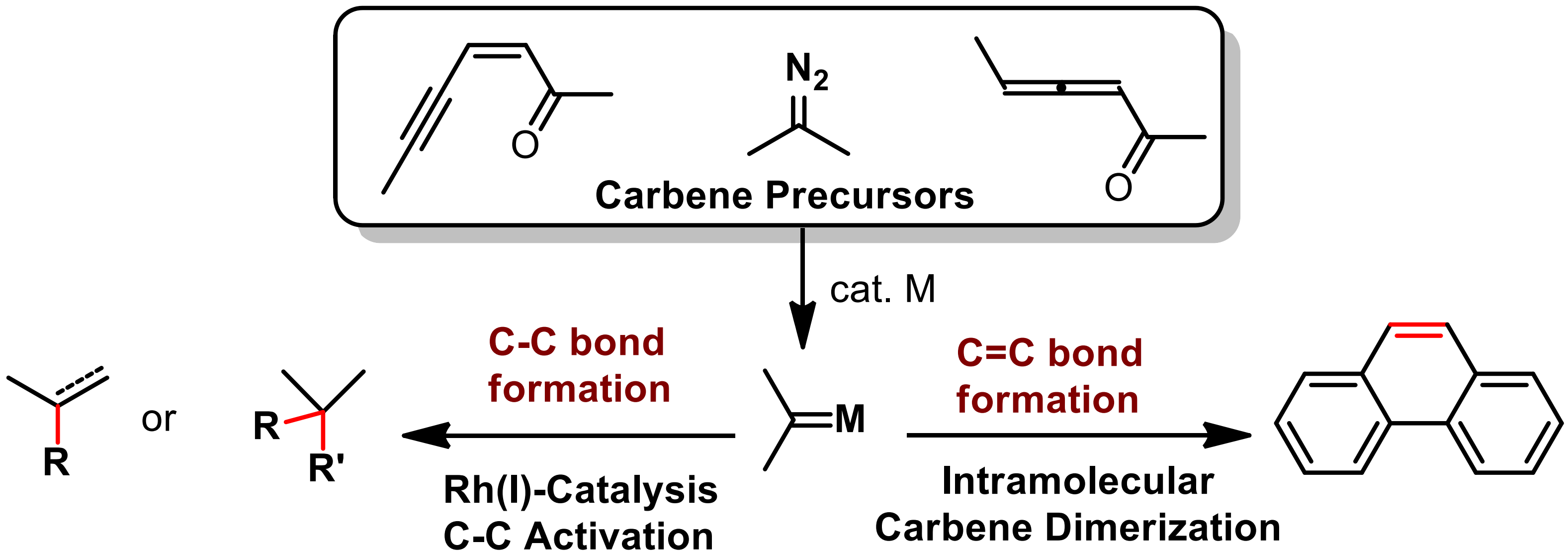
(Highlighted by ACS Noteworthy Chemistry)

Angew. Chem. Int. Ed. **2013**, *52*, 2543.

(Highlighted by Synfacts)

Conclusion and Outlook

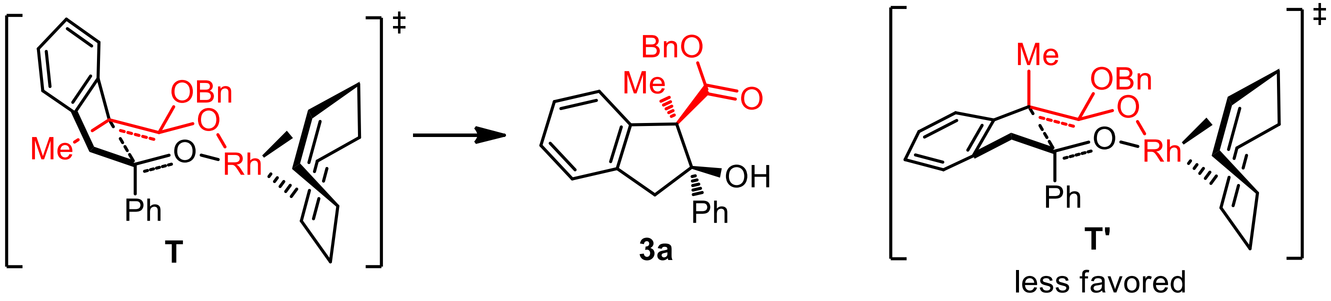
- Intermolecular Couplings of Metal Carbene—**C-C Bond Formation**
- Intramolecular Couplings of Metal Carbene—**C=C Bond Formation**



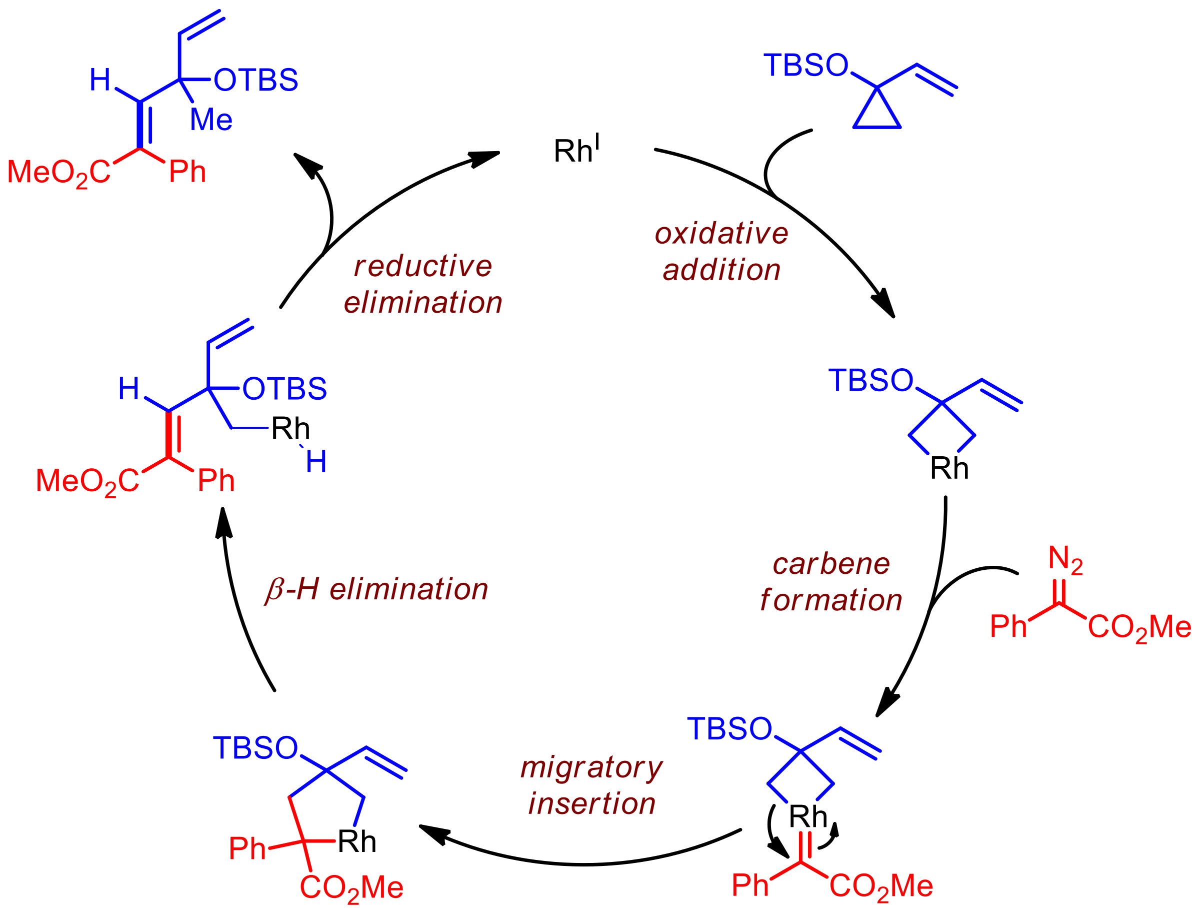
New Transition Metal	New Coupling Partners	Asymmetric Carbene Coupling	Mechanistic Study

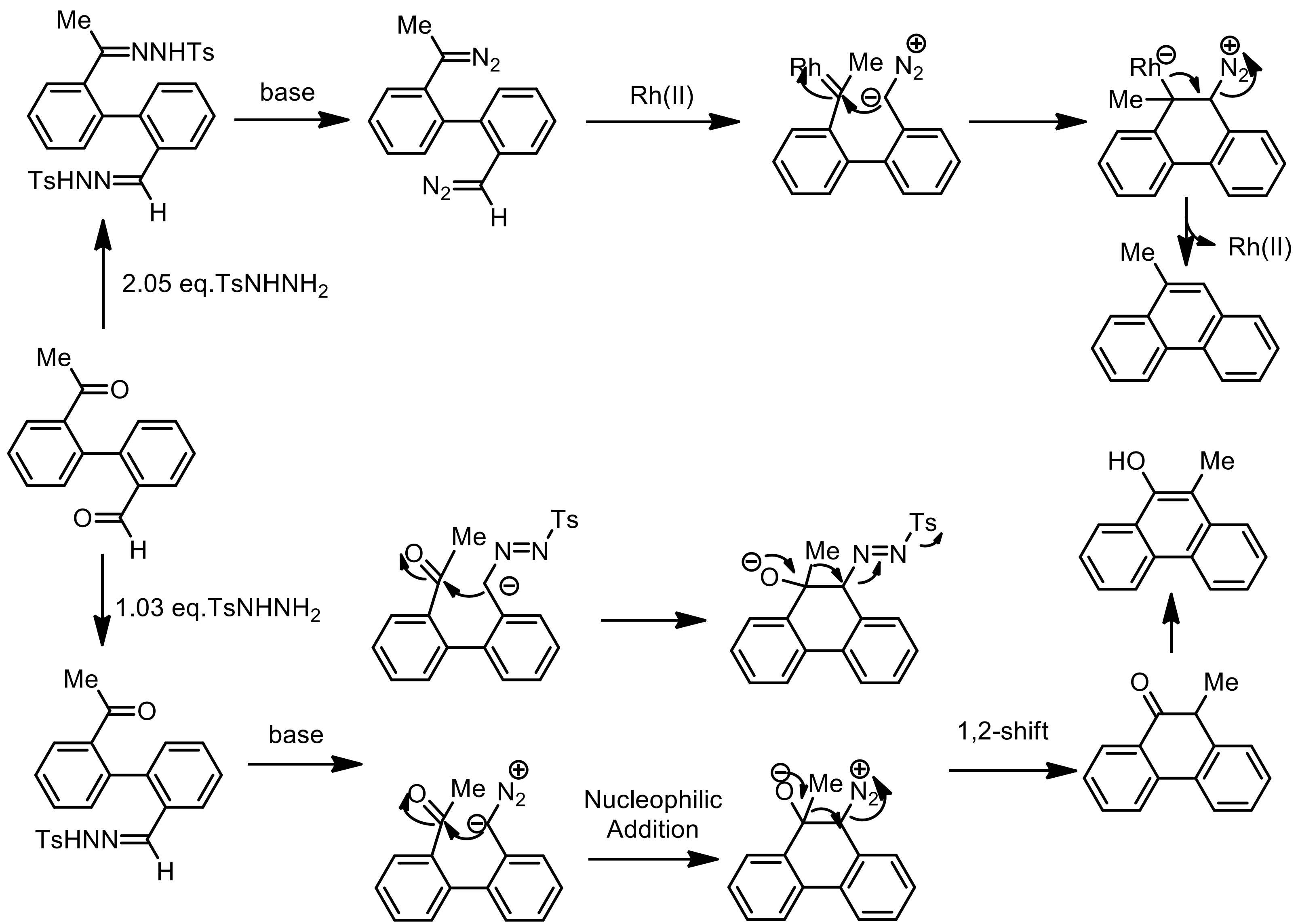
Thank you for your attention!

Rationalization of diastereoselectivity：



Proposed Mechanism:





base
Rh(II)
2.05 eq.TsNHNH2
1.03 eq.TsNHNH2
base
Nucleophilic Addition
1,2-shift
Rh(II)