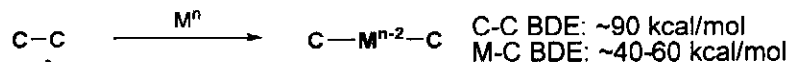


## Introduction: General Mechanism



Thermodynamic and Kinetic Issues:

C-H vs. C-C

- 1) Easier approach (sterically) of metal to C-H bond vs. C-C bond
- 2) Statistically more C-H bonds than C-C bonds
- 3) Higher Activation barrier of C-C bonds vs. C-H bonds

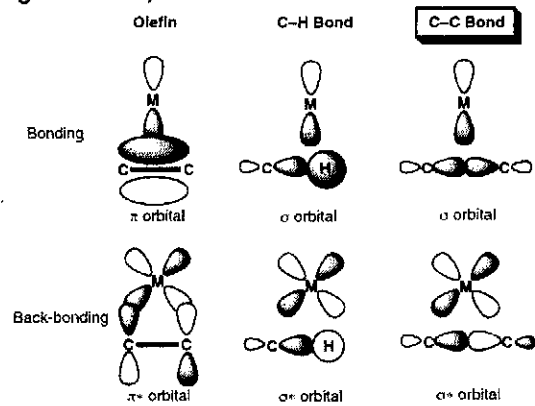
Thermodynamic considerations:

C-H bond activation more thermodynamically favorable than C-C b/c M-H bonds generally much more stable than M-C bonds (15-25 kcal/mol), though C-C bond cleavage is not thermodynamically forbidden.

Kinetic considerations:

Because the microscopic reverse of C-C bond activation is reductive elimination which is kinetically more favorable, the kinetic barrier for oxidative addition is much higher than for C-H activation

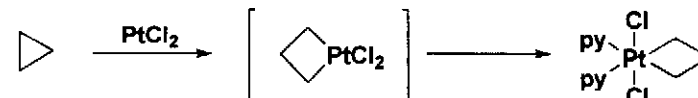
Oxidative addition depends of the nature of the C-X bond. For C-C bond activation, two alkyl groups must rotate to optimal trajectory for oxidation to happen. Basically, C-H is easier to insert b/c of rotational sterics (see figure below).



## Initial Approaches to C-C Oxidative Addition:

Ring Strain Relief:

First Report: C. F. H. Tipper, J. Chem. Soc. 1955, 2045.



Later confirmed by NMR and IR by Chatt:

D. M. Adams, J. Chatt, R. Guy, and N. Sheppard, J. Chem. Soc., 738 (1961)

Later confirmed crystallographically

M. Keeton, R. Mason, and D. R. Russell, J. Organomet. Chem., 33, 259 (1971).

Walsh Orbitals can show interactions for oxidative addition:

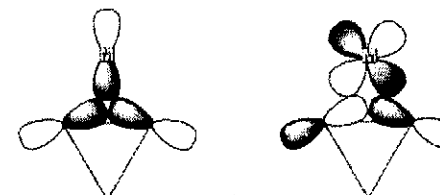
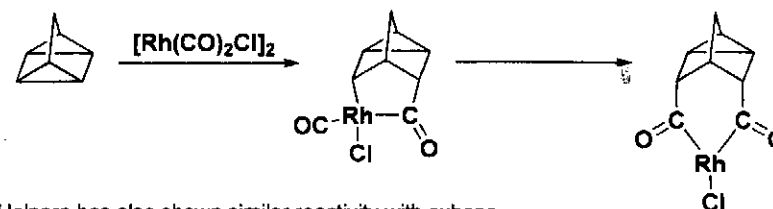


Figure 2. Cyclopropane-metal orbital interactions. Left:  $\sigma$  bond formed by the interaction of metal  $p_z$  and cyclopropane  $\sigma$  orbitals. Right:  $\pi$  bond formed by the interaction of metal  $d_{xy}$  and cyclopropane  $\sigma^*$  orbitals.

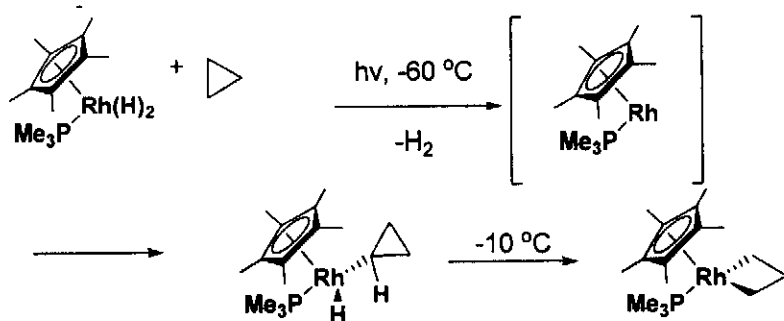
Other early examples:

L. Cassar, J. Halpern, J. Chem. Soc. Chem. Commun. 1970, 1082.

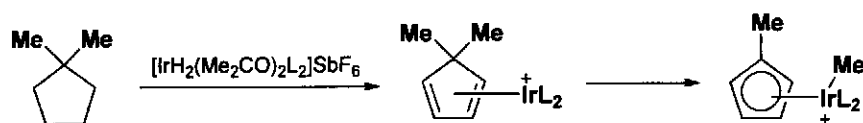
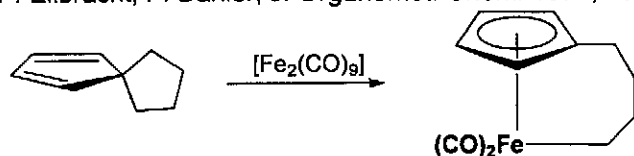
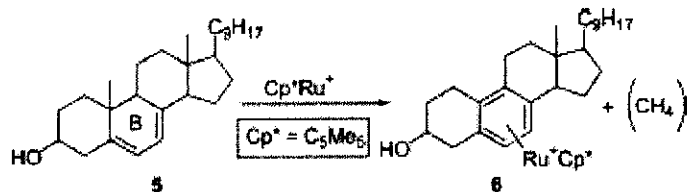


Halpern has also shown similar reactivity with cubane

Other early examples (Ring strain con't):

R. A. Periana and R. G. Bergman, *J. Am. Chem. Soc.*, 1984, 106, 7272.

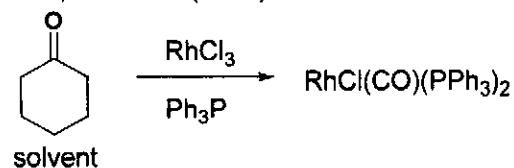
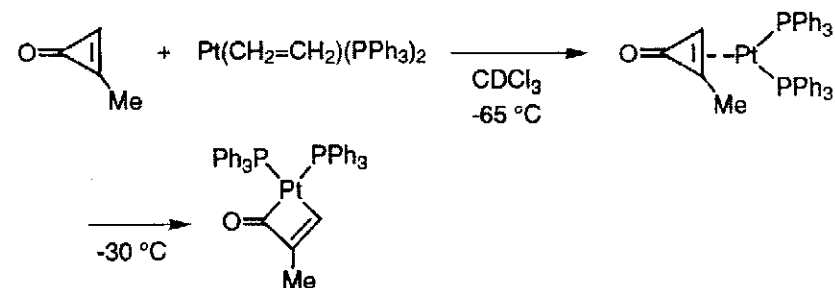
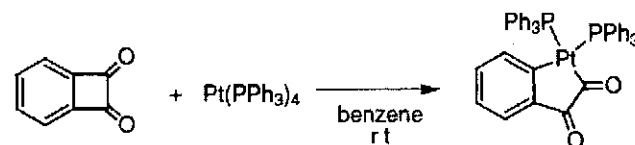
C-C Activation due to aromatization:

R. H. Crabtree, R. P. Dion, *J. Chem. Soc. Chem. Commun.* 1984, 1260P. Eilbracht, P. Dahler, *J. Organomet. Chem.* 1977, 135,M. A. Halcrow, F. Urbanos and B. Chaudret, *Organometallics*, 1993, 12, 955

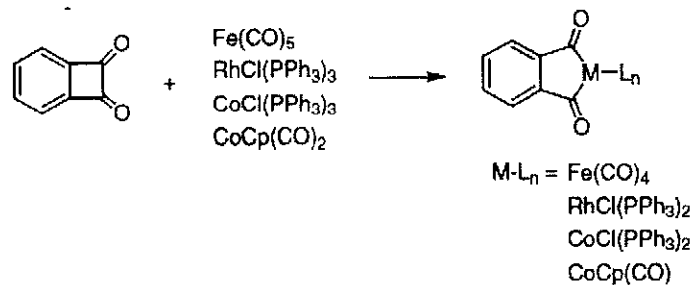
C-C bond activations utilizing carbonyl moiety and strain:

Employing the reactivity (and stability) of metal-carbonyl bonds

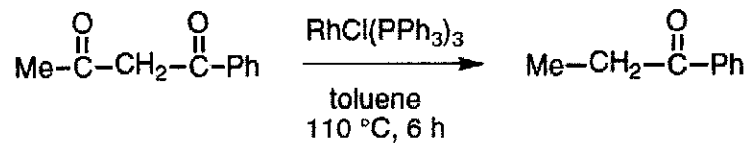
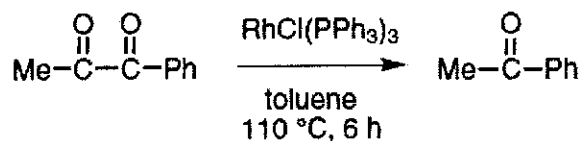
First example of utilizing carbonyl group

Rusina A, Vicek AA (1965) *Nature* 206:295a) Wong W, Singer SJ, Pitts WD, Watkins SF, Baddley (1972) *J Chem Soc Chem Commun*: 672, b) Visser JP, Ramakers-Blom JE (1972) *J Organomet Chem* 44:C63Evans JA, Everitt GF, Kemmitt RDW, Russell DR (1973) *J Chem Soc Chem Commun*:158

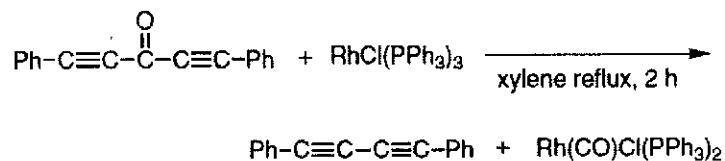
Liebeskind LS, Baysdon SL, South MS (1980) *J Organomet Chem* 202:C73  
 Liebeskind LS, Baysdon SL, South MS, Iyer S, Leeds JP  
 (1985) *Tetrahedron* 41:5839



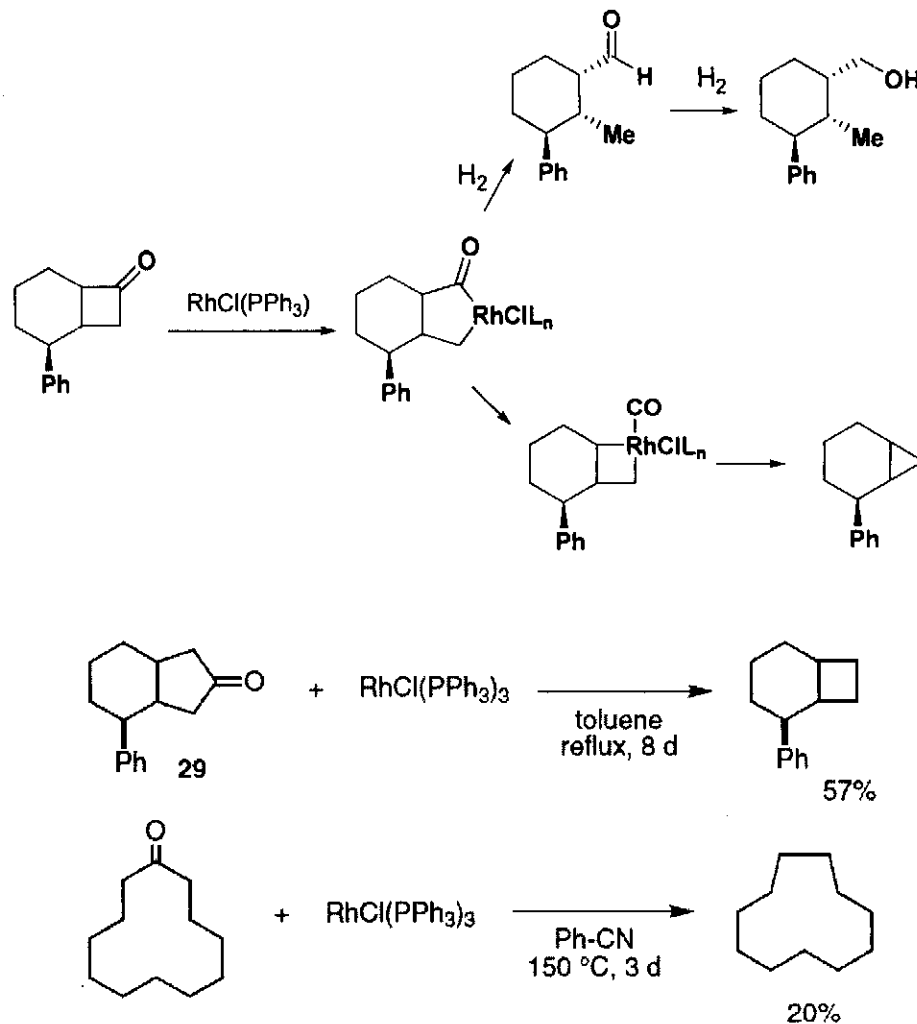
Using reactivity of metal decarbonylation:  
 Kaneda K, Azuma H, Wayaku M, Teranishi S (1974) *Chem Lett*:215



Müller E, Segnitz (1973) *Liebigs Ann Chem*:1583

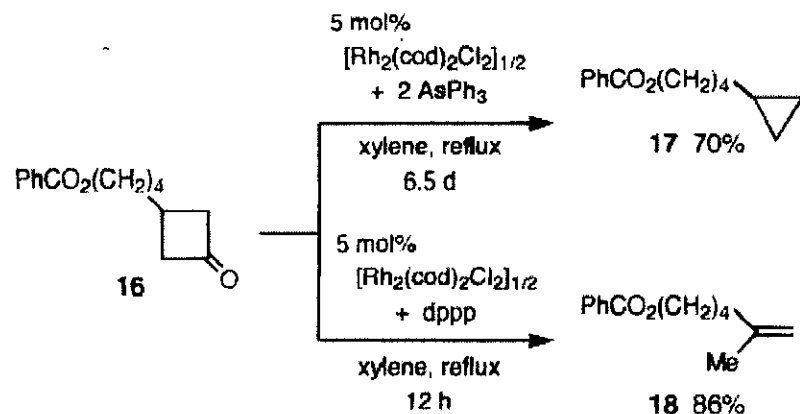
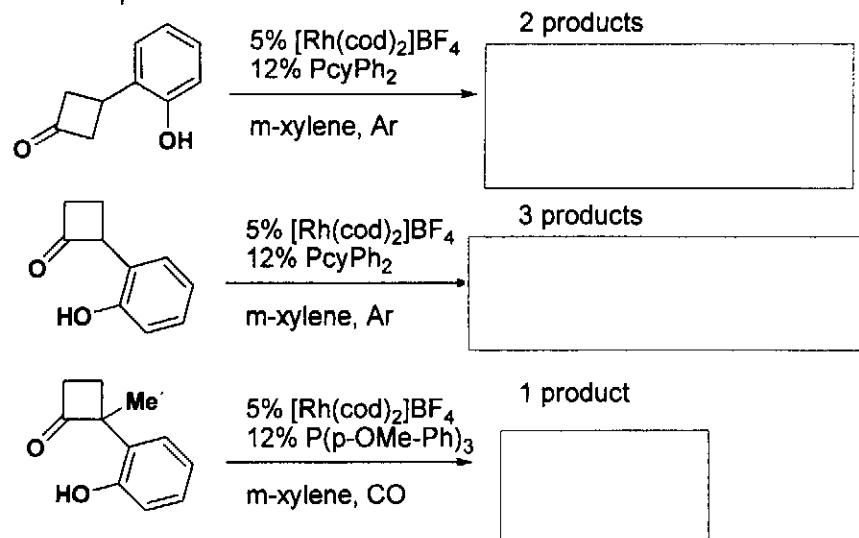


Cyclic ketones can be shortened by decarbonylation:  
 Murakami M, Amii H, Ito Y (1994) *Nature* 370:540



C-C bond activations utilizing carbonyl moiety (con't):

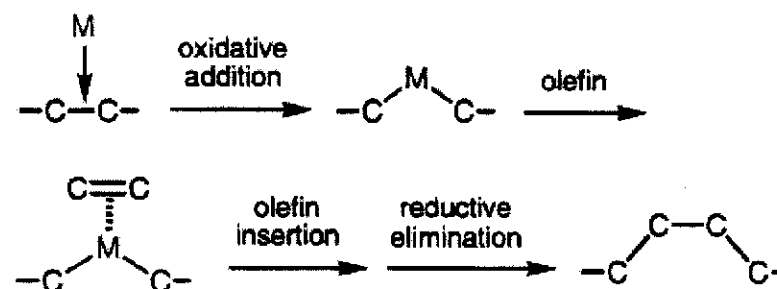
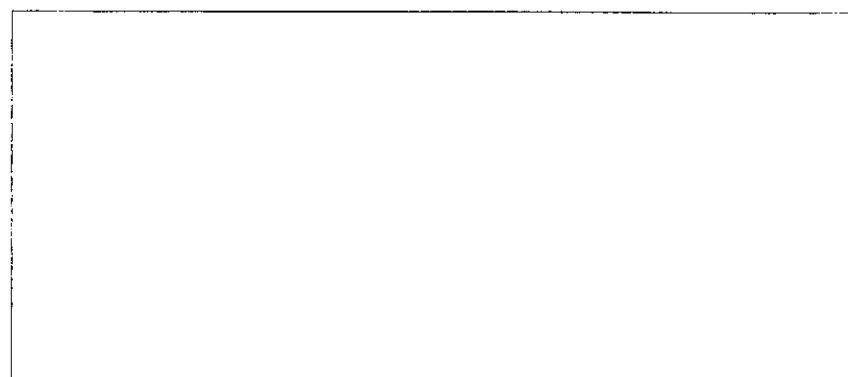
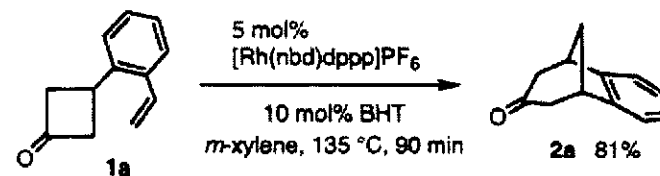
Murakami M, Amii H, Shigeto K, Ito Y (1996) J Am Chem Soc 118:8285

Murakami and Ito ACIEE, 2000, 39, 2484.  
Provide products and mechanisms

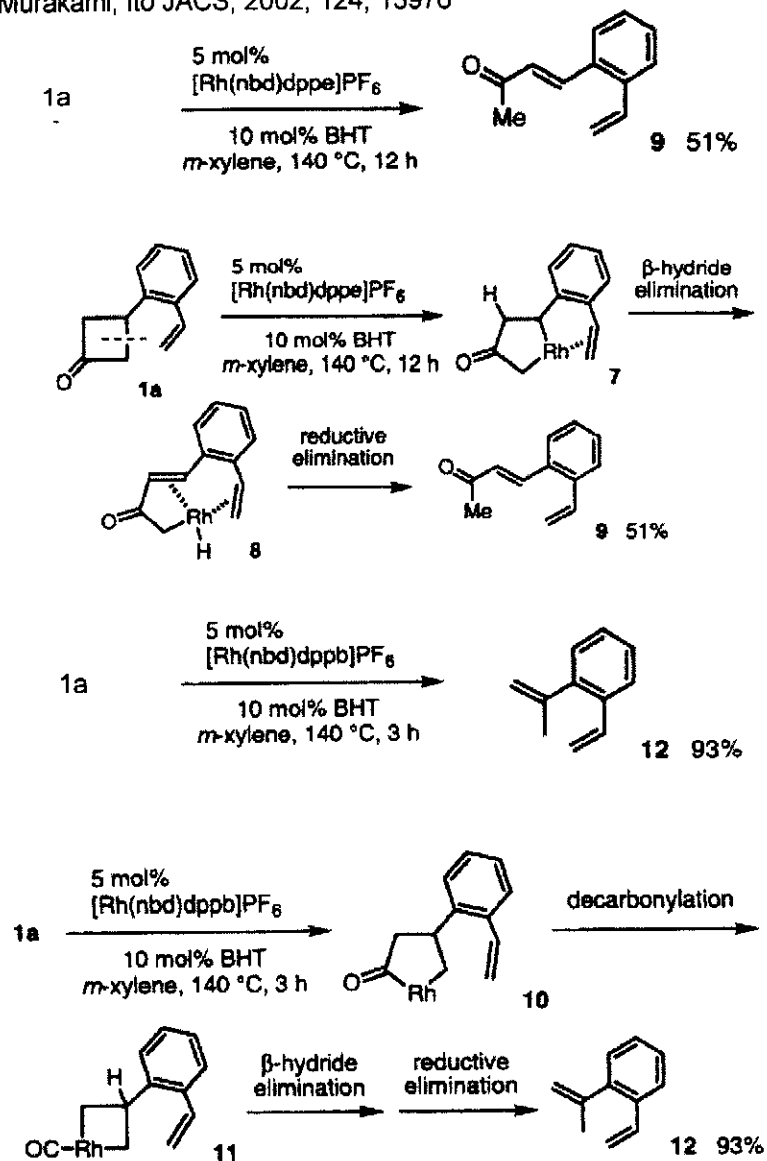
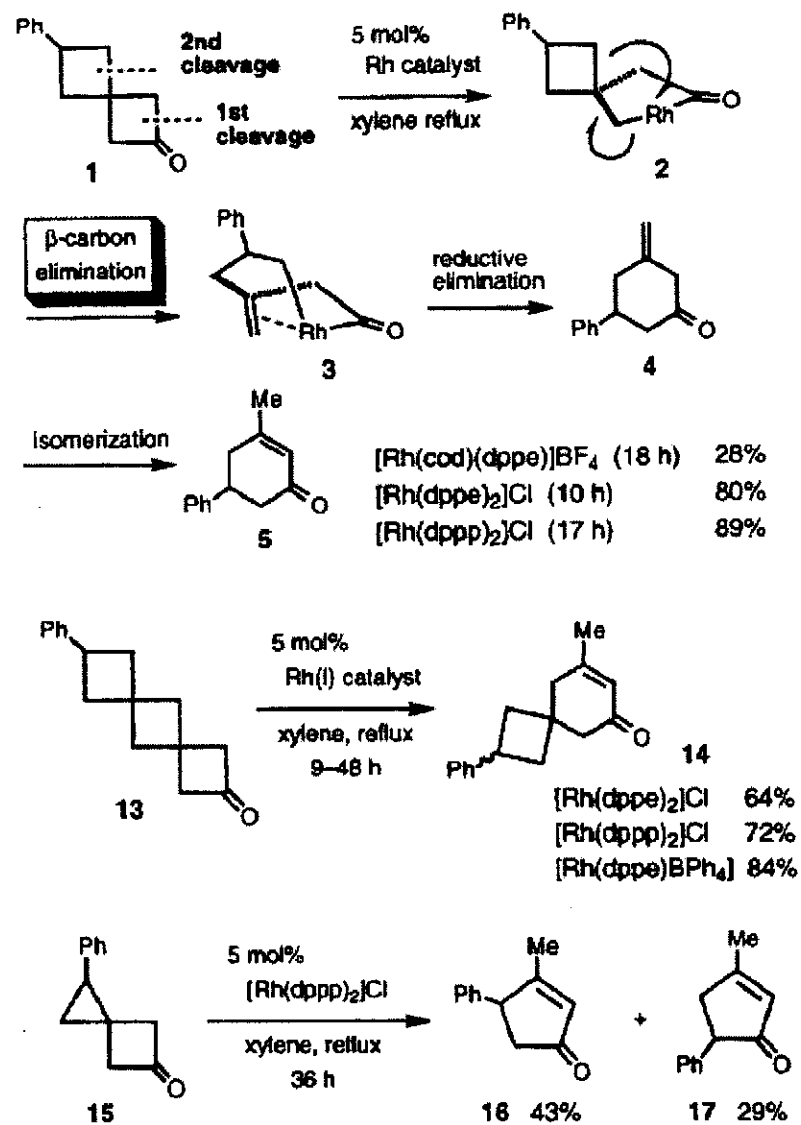
Murakami, Ito JACS, 2002, 124, 13976

Two plausible mechanisms for 1st rxn:

how can you determine which one is likely?

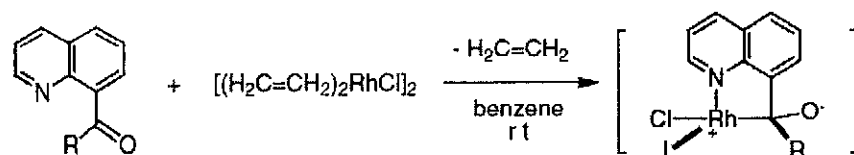


Murakami, Ito JACS, 2002, 124, 13976

Other rxns involving carbonyl cleavage (tandem cleavage):  
Murakami, Ito JACS, 1997, 119, 9307

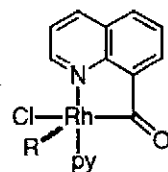
C-C activation due to chelation:

a) J. W. Suggs, C.-H. Jun, J. Am. Chem. Soc. 1984, 106, 3054; b) J. W. Suggs, C.-H. Jun, J. Chem. Soc. Chem. Commun. 1985, 92; c) J. W. Suggs, C.-H. Jun, J. Am. Chem. Soc. 1986, 108, 4679.

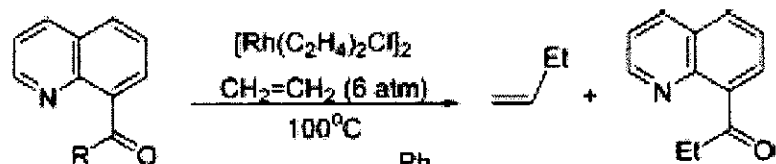
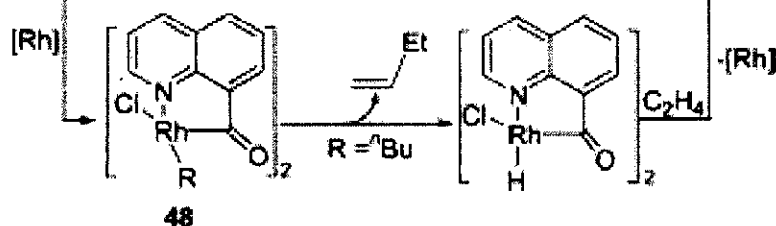
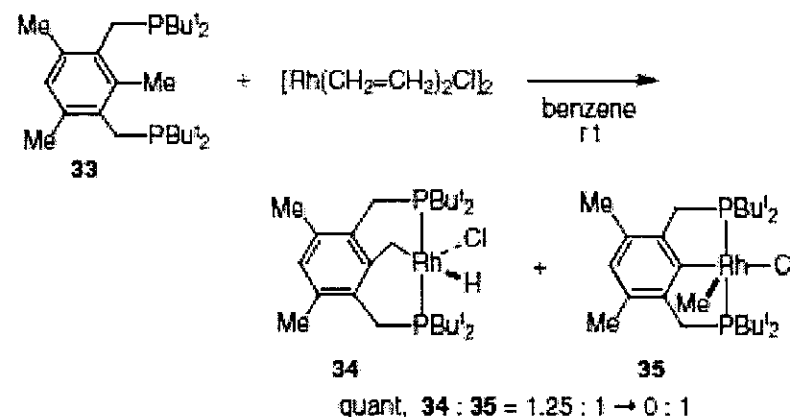
19 R = CH<sub>2</sub>Ph20 R = CD<sub>2</sub>Ph21 R = <sup>n</sup>CH(OMe)Ph

22 R = Et

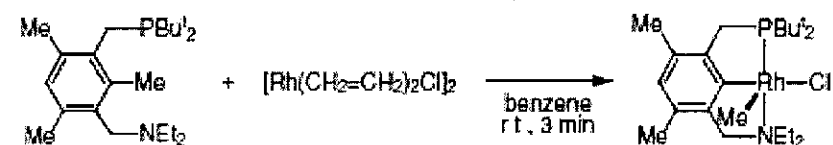
pyridine

23 R = CH<sub>2</sub>Ph24 R = CD<sub>2</sub>Ph25 R = <sup>n</sup>CH(OMe)Ph

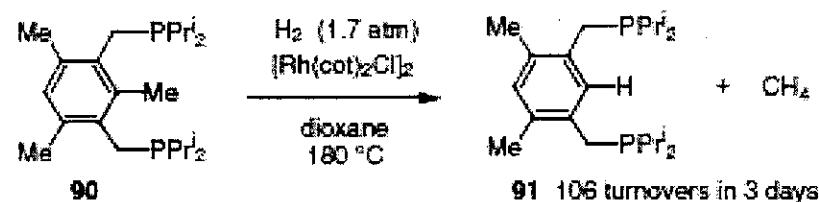
26 R = Et

47 (R = Me, CH<sub>2</sub>Ph, <sup>n</sup>CH(OMe)Ph)S.-Y. Liou, M. Gozin, D. Milstein, J. Am. Chem. Soc. 1995, 117, 9774.  
Must go through C-H activation first:

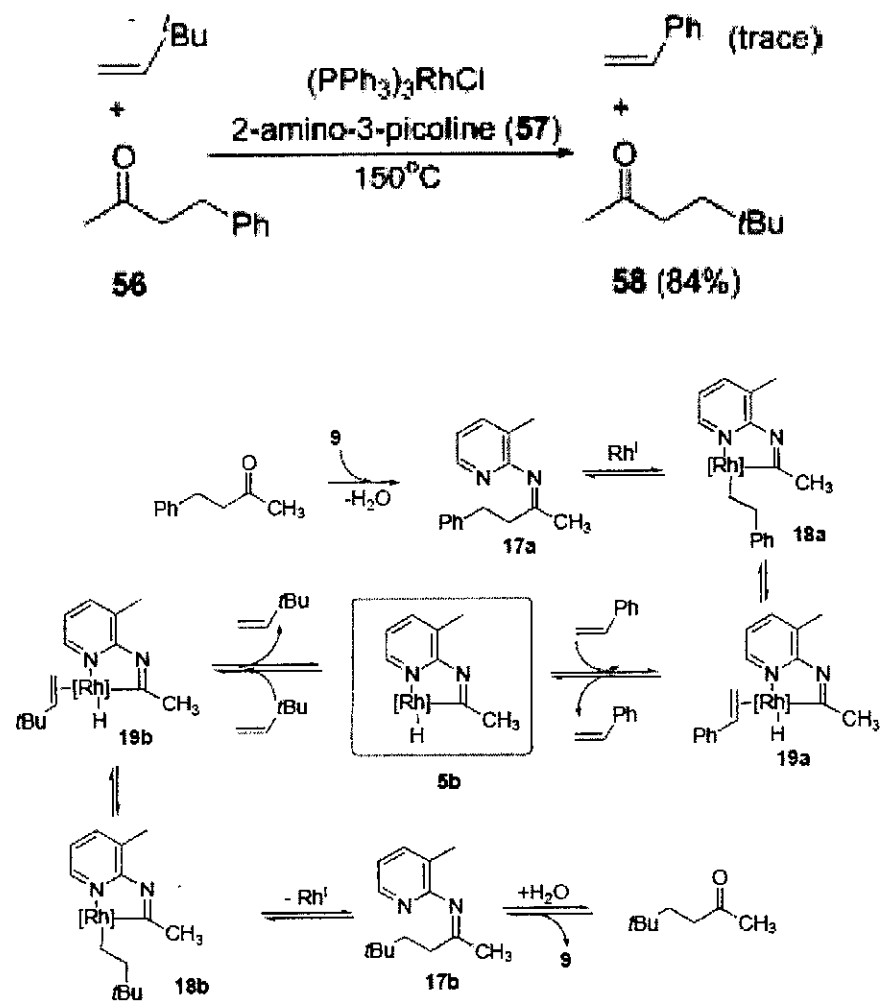
Can not detect C-H activation in this example:



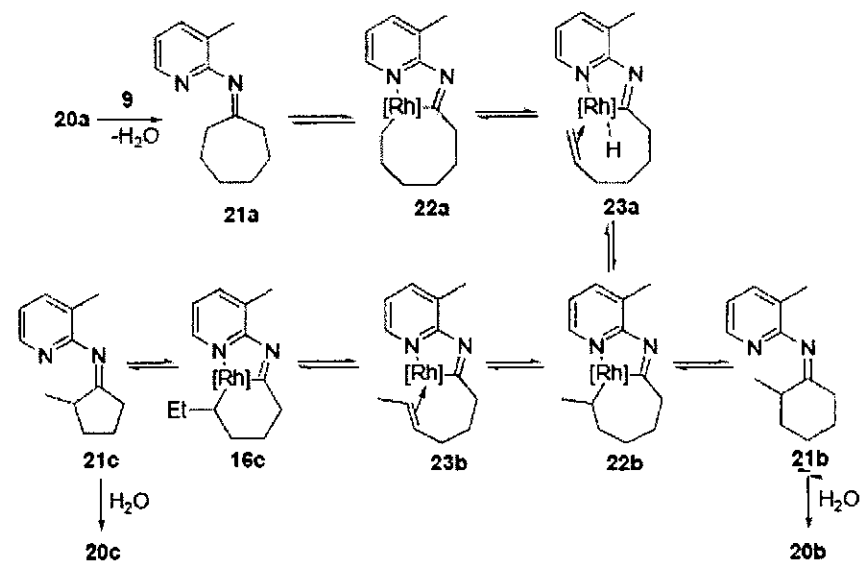
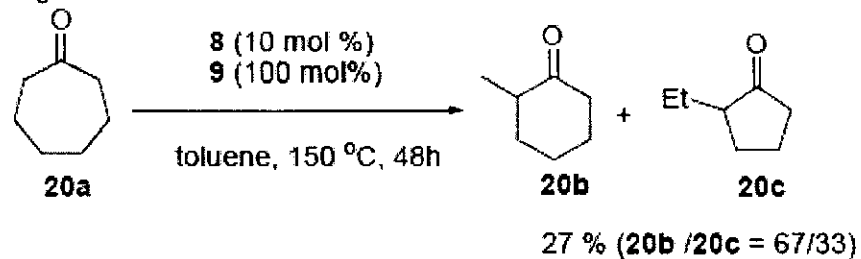
Thermodynamically favorable due to formation of 5-membered ring metallocycle.



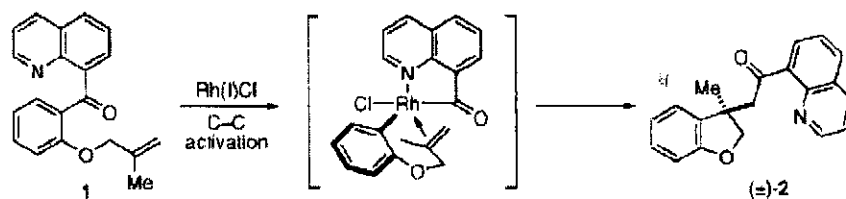
Chul-Ho Jun's work using chelation: Chem Eur J, 2002, 8, 2422  
In situ imine formation to direct cleavage



Ring contraction:

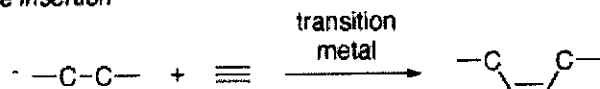


Ring formation: Douglas, J. Am. Chem. Soc., 2009, 131 (2), pp 412–413

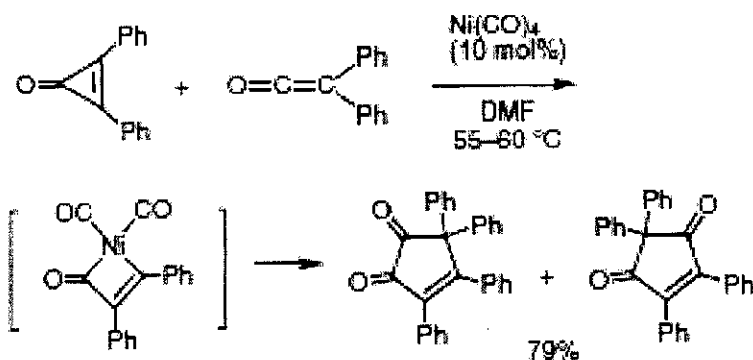


Now alkyne insertion and entry into Ni catalysis:

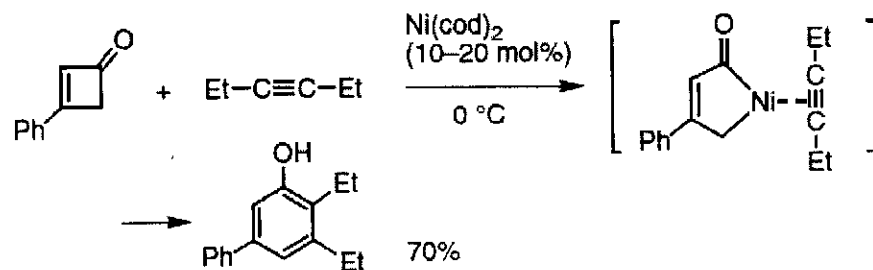
*alkyne insertion*



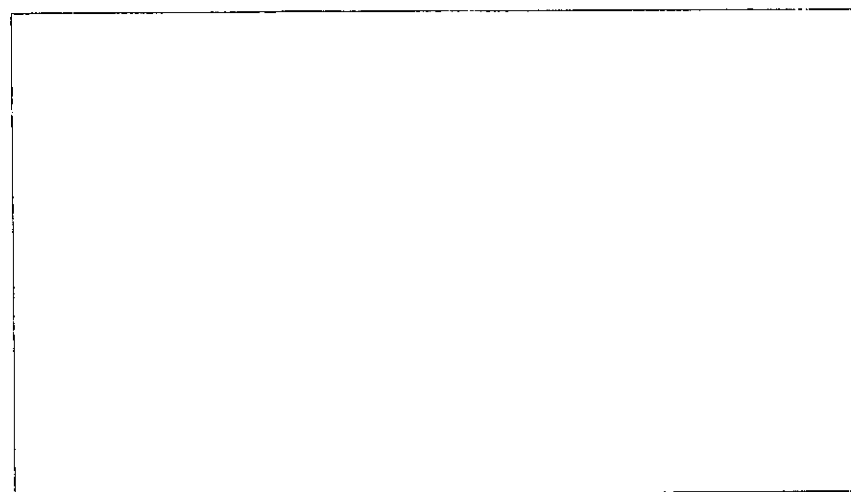
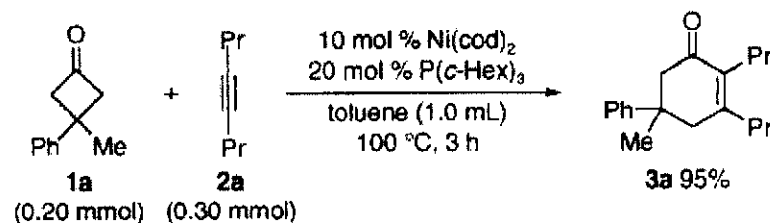
Baba A, Ohshiro Y, Agawa T (1976) J Organomet Chem 110:121



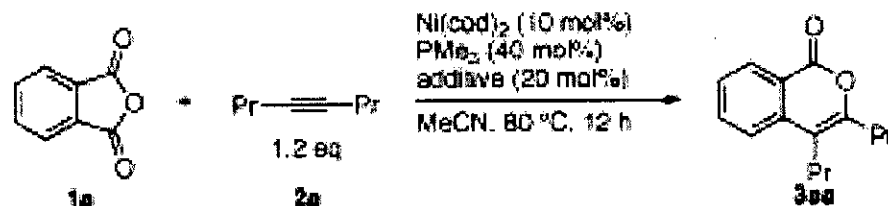
Huffman MA, Liebeskind LS (1991) J Am Chem Soc 113:2771



Not direct cleavage but B-carbon elimination:  
Murakami, M. et. al. JACS, 2005, 127, 6932

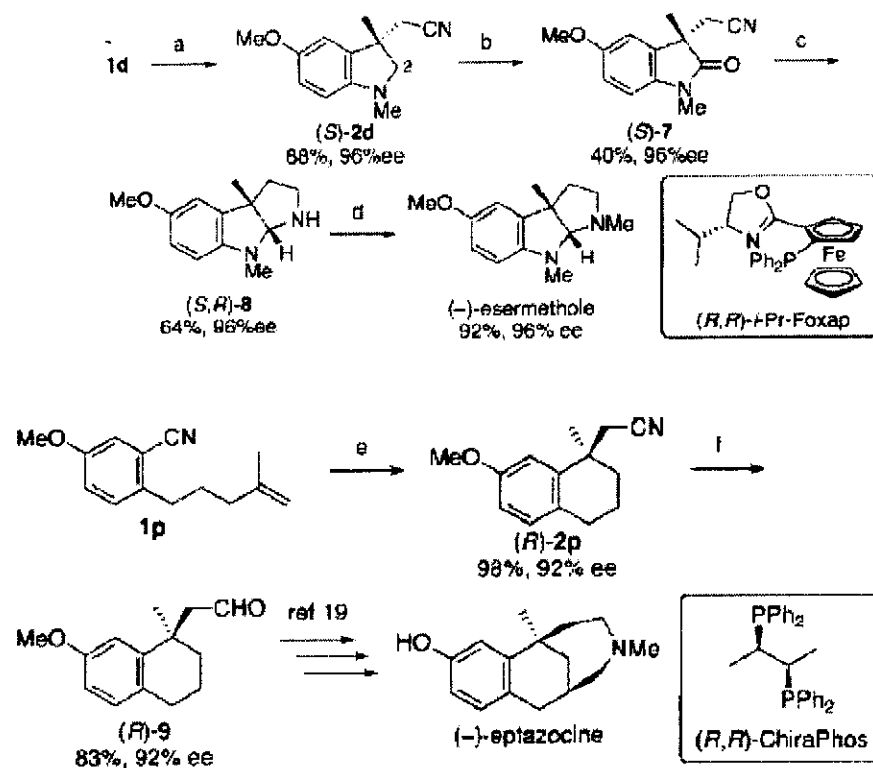


Matsubara, JACS, 2008, 130, 17226.



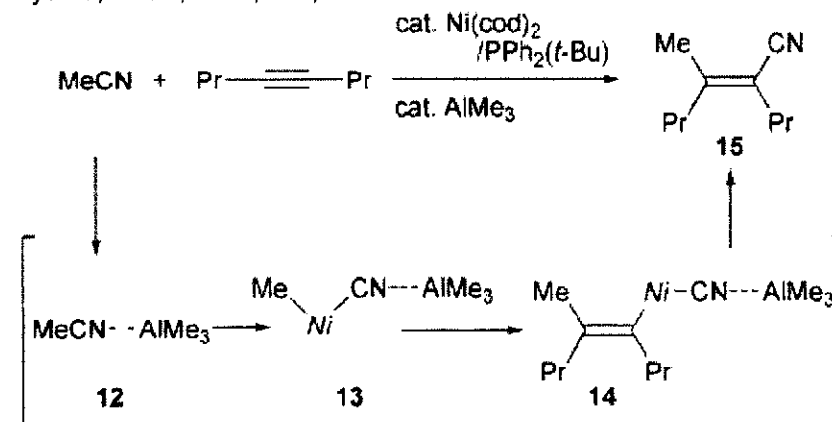


Application to total synthesis: Hiyama, JACS, 2008, 130, 12874

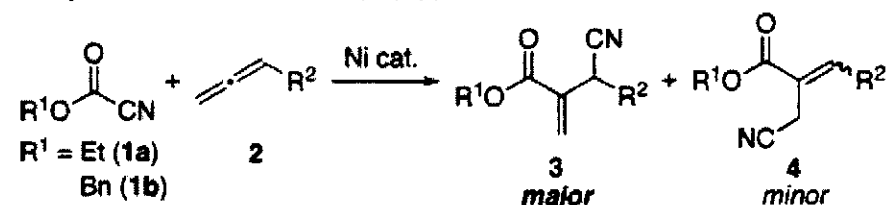


<sup>a</sup> Reagents and Conditions: (a)  $\text{Ni}(\text{cod})_2$  (10 mol %),  $(R,R)\text{-}i\text{-Pr-Foxap}$  (20 mol %),  $\text{AlMe}_2\text{Cl}$  (40 mol %), DME, 100 °C, 10 h; (b)  $\text{PhIO}$  (6.0 equiv),  $\text{CH}_2\text{Cl}_2$ , room temp, 2.5 h; (c)  $\text{LiAlH}_4$  (4.0 equiv), THF, room temp, 1 h, then reflux, 0.5 h; (d)  $\text{HCHO}$  aq (5.0 equiv),  $\text{NaBH}(\text{OAc})_3$  (5.0 equiv), MeOH, 0 °C to room temp, 1.5 h; (e) neat,  $\text{Ni}(\text{cod})_2$  (5 mol %),  $(R,R)\text{-ChiraPhos}$  (6 mol %),  $\text{AlMe}_2\text{Cl}$  (20 mol %), 120 °C, 1 h; (f)  $\text{DIBAL-H}$  (2.0 equiv), toluene, -78 °C, 2 h, then 1 M HCl (aq), THF, 0 °C to room temp, 2 h.

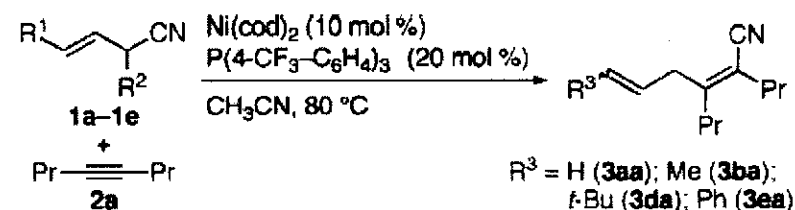
Hiyama, JACS, 2007, 129, 2428



Hiyama, JACS, 2006, 128 (23), pp 7420



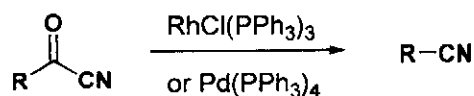
Hiyama, JACS, 2006, 128 (22), pp 7116



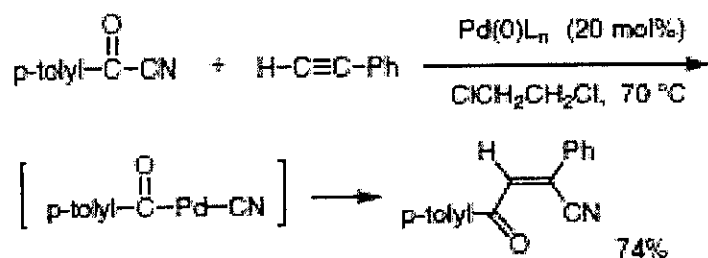
## C-CN Bond Activation

Blum J, Oppenheimer E, Bergmann ED (1967) J Am Chem Soc 89:2338

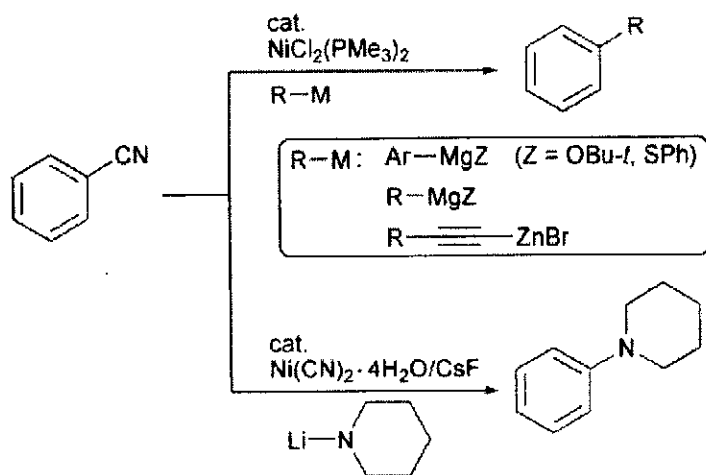
Murahashi SI, Naota T, Nakajima N (1986) J Org Chem 51:898



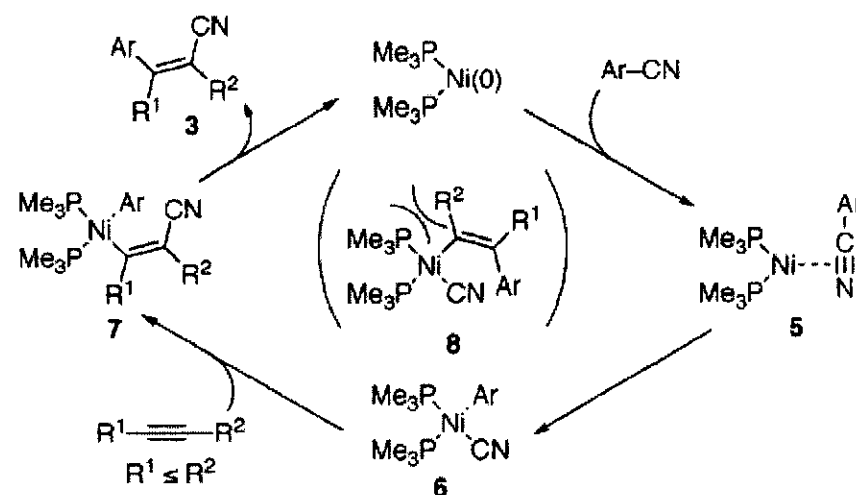
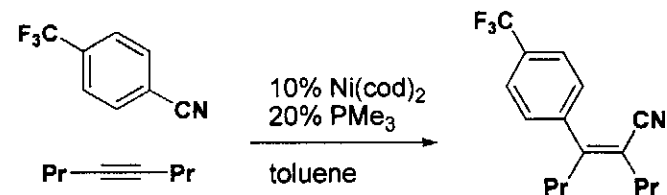
Nozaki K, Sato N, Takaya H (1996) Bull Chem Soc Jpn 69:1629



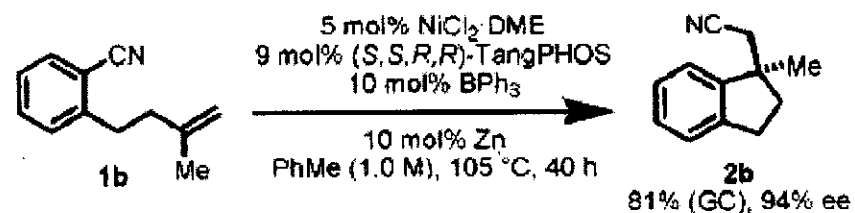
J. A. Miller, Tetrahedron Lett., 2001, 42, 6991; J. A. Miller and J. W. Dankwardt, Tetrahedron Lett., 2003, 44, 1907

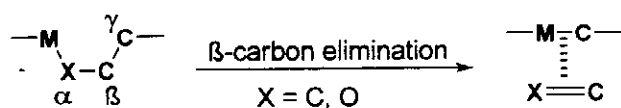
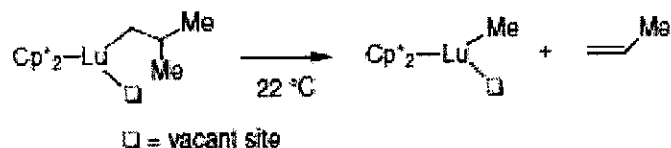


Hiyama, JACS, 2004, 126, 13904

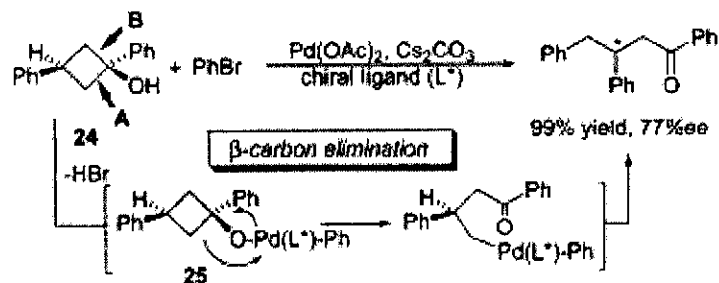


Simultaneously published: Jacobsen, JACS, 2008, 130, 12594

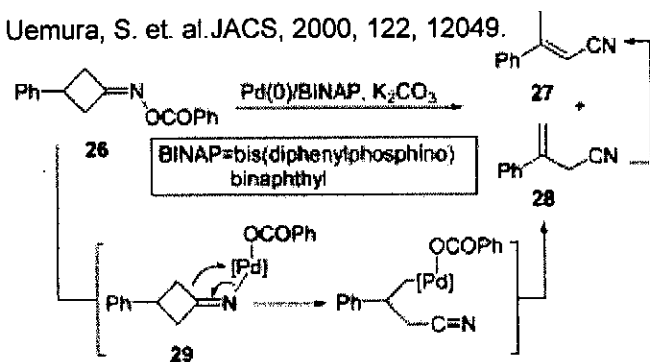


C-C bond cleavage rxns via  $\beta$ -alkyl eliminationEarly example of  $\beta$ -carbon elimination from du Pont  
Watson PL, Roe DC (1982) J Am Chem Soc 104:6471

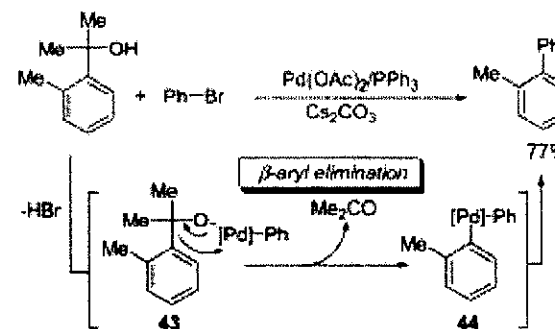
S. Matsumura, Y. Maeda, T. Nishimura and S. Uemura, J. Am. Chem. Soc., 2003, 125, 8862



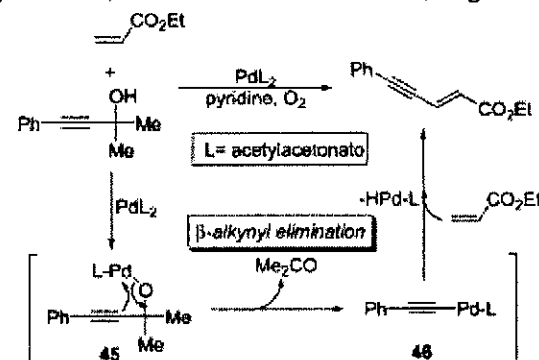
Uemura, S. et al. JACS, 2000, 122, 12049.



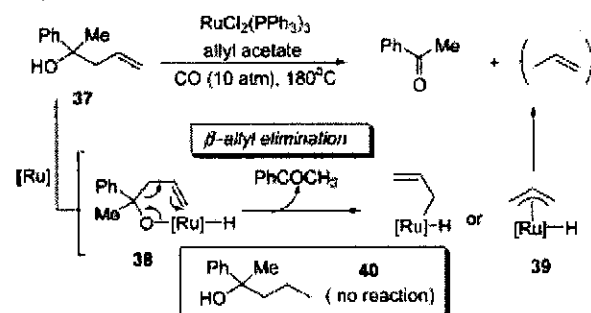
Y. Terao, H. Wakui, T. Satoh, M. Miura and M. Nomura, J. Am. Chem. Soc., 2001, 123, 10407.



T. Nishimura, H. Araki, Y. Maeda and S. Uemura, Org. Lett., 2003, 5, 2997.

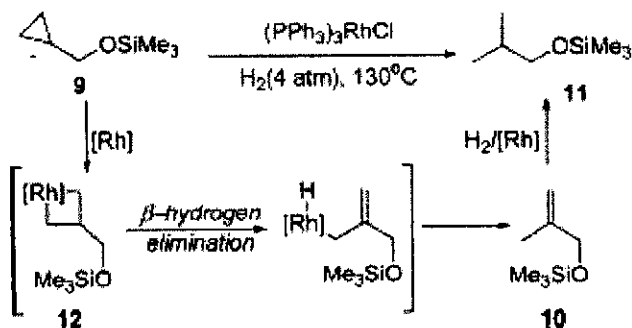
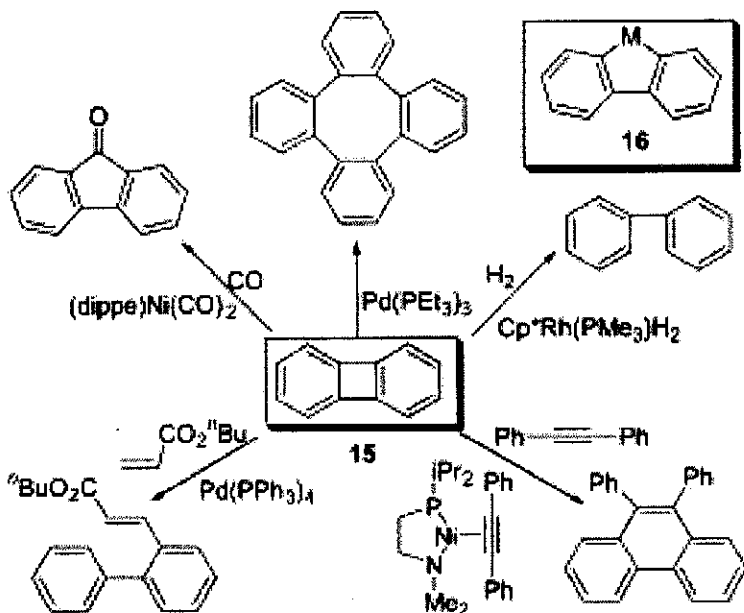


T. Kondo, K. Kodoi, E. Nishinaga, T. Okada, Y. Morisaki, Y. Watanabe and T.-a. Mitsudo, J. Am. Chem. Soc., 1998, 120, 5587.

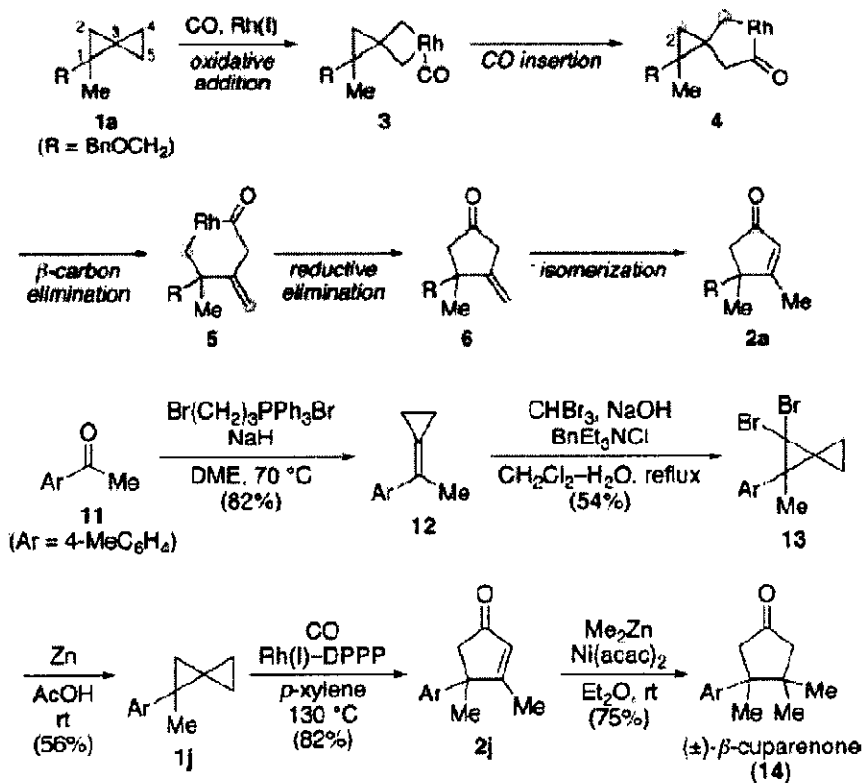


## Miscellaneous rxns:

Chirik, P. J., et. al. JACS, 2003, 125, 886

C. Perthuisot, B. L. Edelbach, D. L. Zubris, N. Simhai,  
C. N. Iverson, C. Müller, T. Satoh and W. D. Jones, J. Mol.  
Catal. A: Chem., 2002, 189, 157

Murakami, M. et. al. JACS 2007, 129, 12596.



## Selected reviews:

- Murakami, M., Ito, Y. Topics in Organometallic Chemistry 1999, 97-129
- Jun, C.-H. Chem. Soc. Rev., 2004, 33, 610-618.
- Milstein, D., Rybtchinski B. ACIEE 1999, 38, 870-883.
- Crabtree, Chem. Rev. 1985, 85, 245-269.