Aïssa Research Group

UNIVERSITY OF LIVERPOOL

Transition-metal catalysed C-C activation

Strategies and Applications

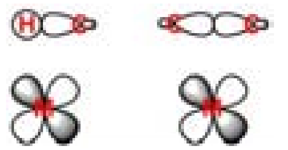
SCI – Review Meeting
2nd of December 2011

Introduction
Overview of strategies
C–C bond activation in acyclic systems
- promoted by chelation
- promoted by formation of metal alkoxides
- activation of C–CN bonds

C–C bond activation relying on strain energy of small rings
- alkylidenecyclopropanes
  - proximal *vs* distal cleavage
  - polymerisation
  - diversion of intramolecular hydroacylation from unproductive pathways
  - chemoselectivity of intramolecular hydroacylation via C–C bond activation
- vinylcyclopropanes
  - early studies
  - [5+2] cycloadditions
- cyclobutanols
- oxime esters
- alkylidenecyclobutanes
- alkylideneazetidines

Why is transition-metal-catalysed activation of C–C bond difficult?

Kinetic barrier
- stereoelectronic
- steric (ligands!)
- statistic



Milstein, *Angew. Chem. Int. Ed.* **1999**, *38*, 878

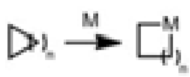
Possible interactions of a metal with a CH_3 group

Perutz, *Chem. Rev.* **1996**, *96*, 3125
Crabtree, *Chem. Rev.* **1985**, *85*, 245

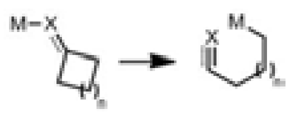
Thermodynamic barrier
- BDE M–C/C–C
- easier to overcome

Strategies used in C–C bond activation

C–C bond activation relying on the strain energy of small ring compounds



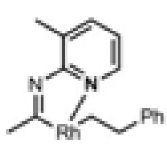
oxidative addition
n = 1, 2



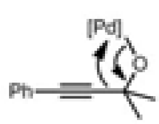
β–carbon elimination
X = C, N, O
n = 0, 1

C–C bond activation in acyclic systems

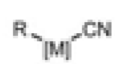
chelation



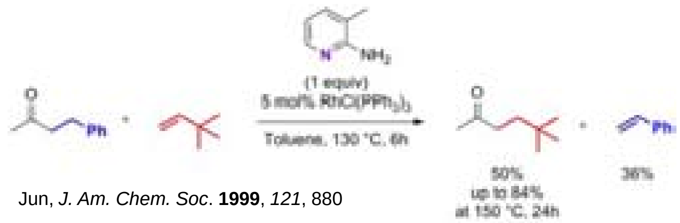
metal alkoxides



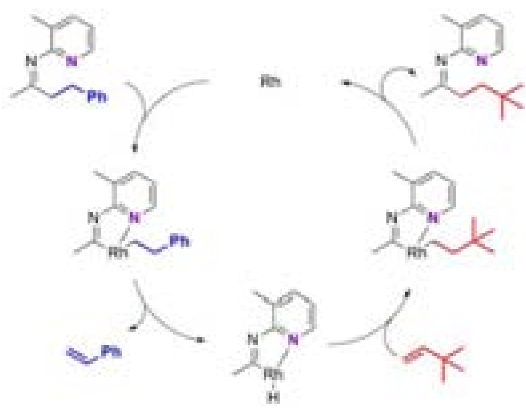
C–CN bonds



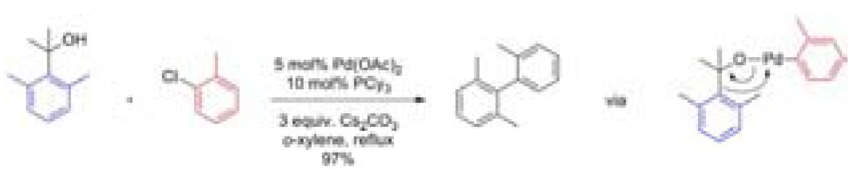
C–C bond activation in acyclic systems: chelation



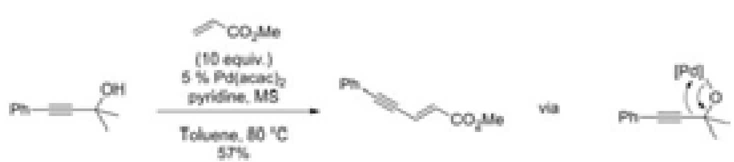
Jun, *J. Am. Chem. Soc*. **1999**, *121*, 880



C–C bond activation in acyclic systems: metal-alkoxides

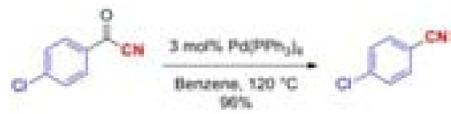


Miura, *J. Am. Chem. Soc*. **2001**, *123*, 10407
Miura, *J. Org. Chem.* **2003**, *68*, 5236

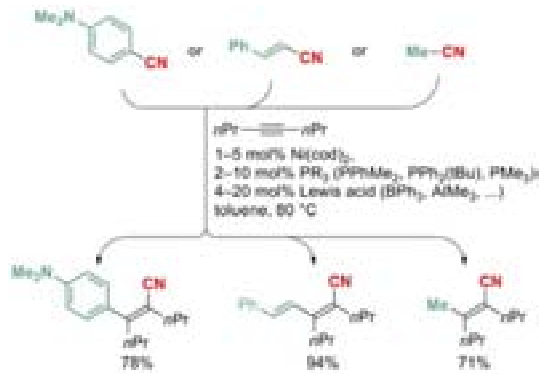


Uemura, *Org. Lett.* **2003**, *5*, 2997

C–C bond activation in acyclic systems: C–CN



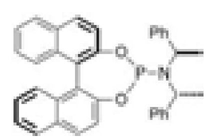
Murahashi, *J. Am. Chem. Soc*. **1986**, *51*, 898

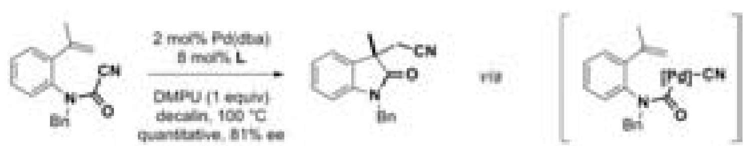


Nakao and Hiyama, *J. Am. Chem. Soc*. **2007**, *129*, 2428

C–C bond activation in acyclic systems: C–CN

L =





Takemoto, *Org. Lett.* **2008**, *10*, 3303

Posiphen ®

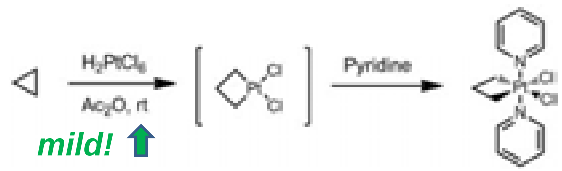
Clinical development – Alzheimer drug
Inhibits β-amyloid plaque formation
QR Pharma

Oxidative addition into small ring compounds

HOMO(cyclopropane)-LUMO(M) HOMO(M)-LUMO(cyclopropane)

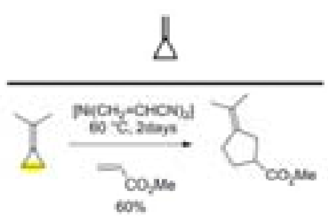
Fe	Co	Ni
Ru	Rh	Pd
	Ir	Pt

Chem. Rev. **1994**, *94*, 2241

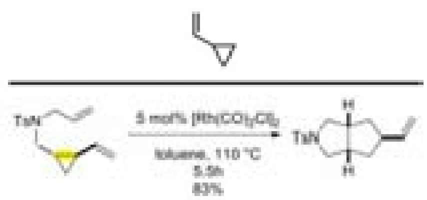


Tipper, *J. Chem. Soc*. **1955**, 2045
Chatt, *Proc. Chem. Soc*. **1960**, 179

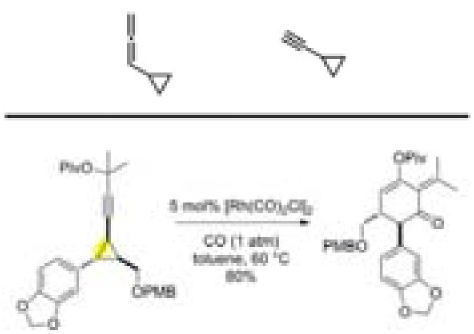
C–C activation involving small ring compounds



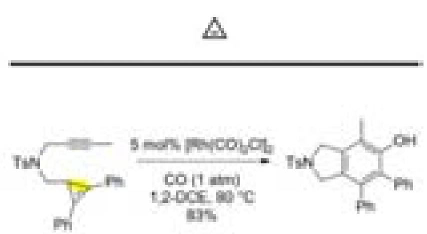
Noyori, *J. Am.Chem. Soc*. **1970**, *92*, 5780



Yu, *J. Am.Chem. Soc*. **2008**, *130*, 7178



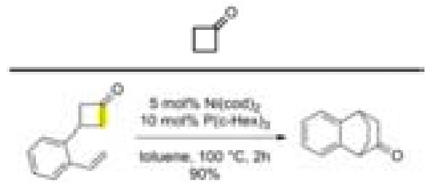
Tang, *Angew. Chem. Int. Ed.* **2011**, *50*, 1346



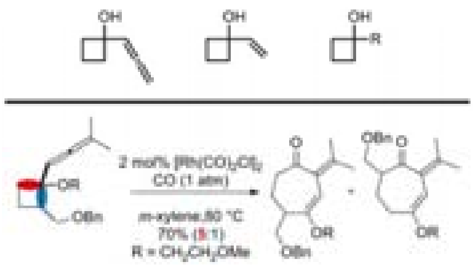
Wang, *Org. Lett.* **2010**, *12*, 3082

C–C activation involving small ring compounds

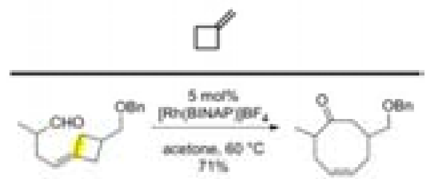
Liebeskind, *J. Am.Chem. Soc*. **1993**, *115*, 4895



Murakami, *Chem. Commun.* **2006**, 4599

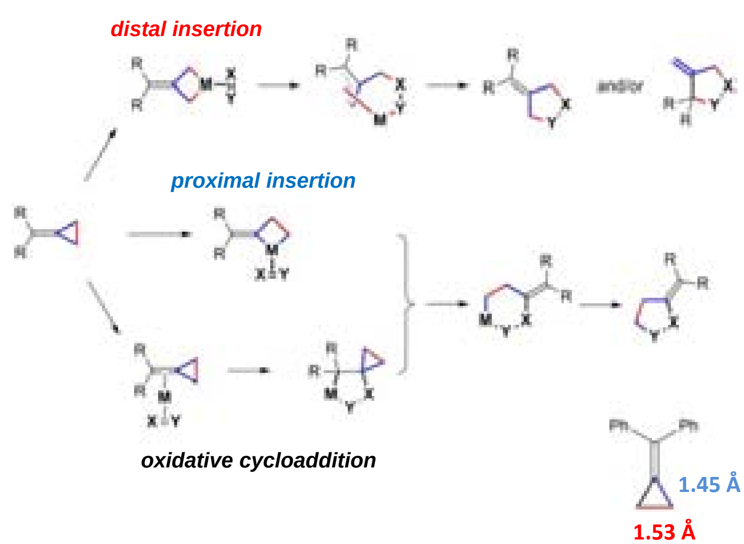


Wender, *Angew. Chem. Int. Ed.* **2006**, *45*, 3957



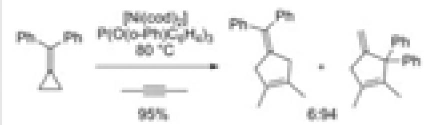
Aïssa, *Angew. Chem. Int. Ed.* **2010**, *49*, 620

Reactivity of alkylidenecyclopropanes

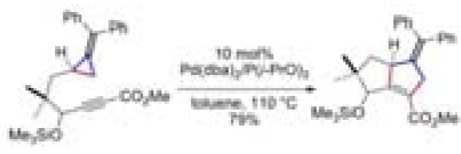


Reactivity of alkylidenecyclopropanes: distal insertion

Noyori, *J. Am.Chem. Soc*. **1970**, *92*, 5780

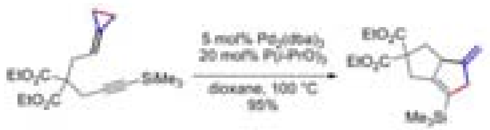


Binger, *Angew. Chem. Int. Ed*. **1985**, *24*, 316

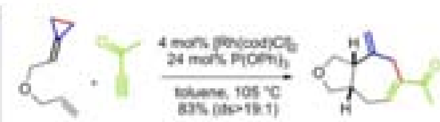


Motherwell, *Chem Commun*. **1988**, 948

Nakamura, *Chem Commun*. **1988**, 1112



Mascarenas, *J. Am. Chem. Soc*. **2003**, *125*, 9282

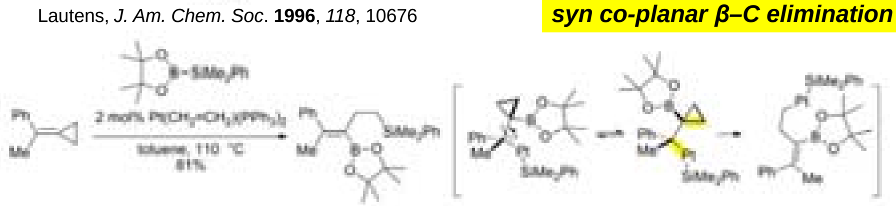


Evans, *J. Am. Chem. Soc*. **2008**, *130*, 12838

Reactivity of alkylidenecyclopropanes: proximal cleavage

Lautens, *J. Am. Chem. Soc*. **1996**, *118*, 10676

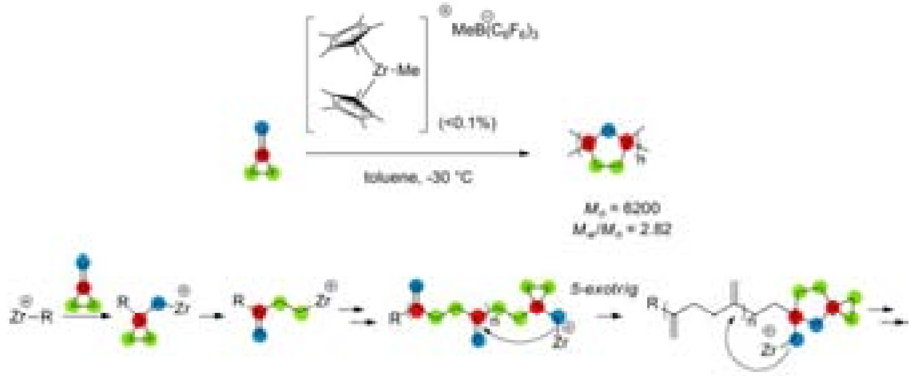
syn co-planar β–C elimination



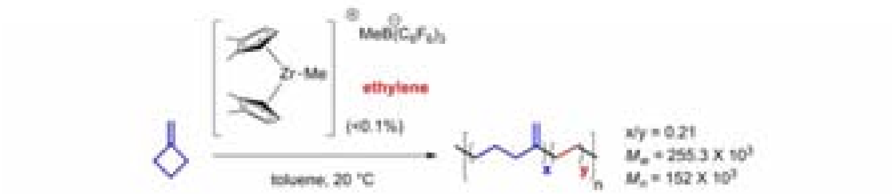
Suginome and Ito, *J. Am. Chem. Soc*. **2000**, *122*, 11015

Saito, *J. Am. Chem. Soc*. **2004**, *126*, 10540

Reactivity of alkylidenecyclopropanes: polymerisation

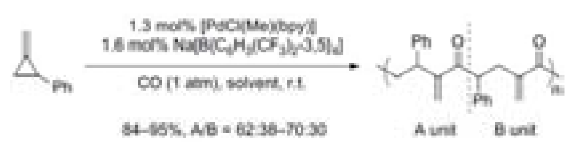


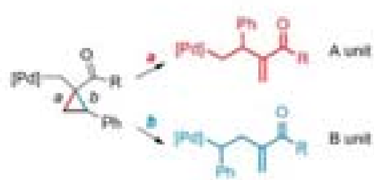
Marks, *J. Am. Chem. Soc*. **1996**, *118*, 1547



Marks, *J. Am. Chem. Soc*. **1993**, *115*, 3392

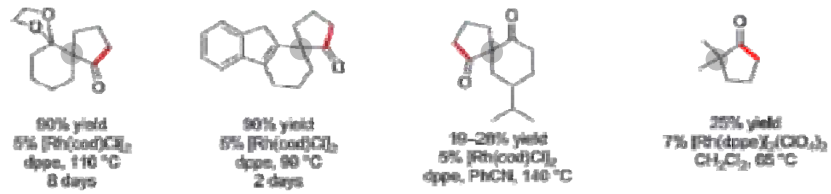
Reactivity of alkylidenecyclopropanes: polymerisation





Osakada, *J. Am. Chem. Soc*. **2002**, *124*, 762
Osakada, *Macromol. Chem. Phys.* **2003**, *204*, 666

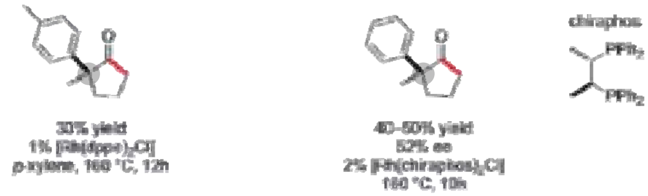
Intramolecular hydroacylation – Quaternary centres



Undheim, K. *et al.*
Tetrahedron **2005**, *61*, 4129
Synthesis **2008**, 962

Eilbracht, P. *et al.*
Tetrahedron Lett. **1998**, 39, 936

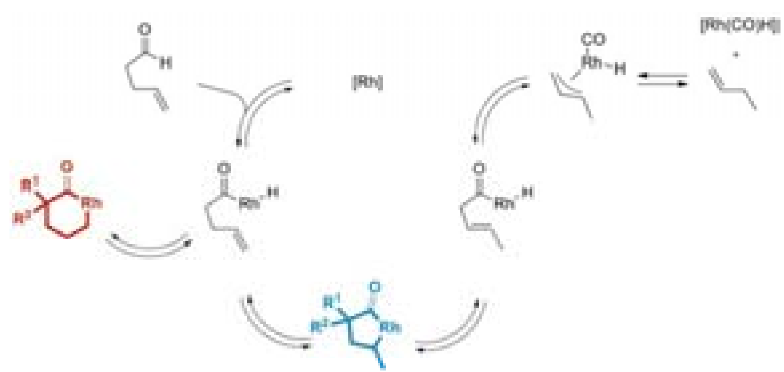
Bosnich, B. *et al.*
Organometallics **1988**, *7*, 936



List, B. *et al.*
J. Am. Chem. Soc **2007**, *129*, 11336

James, B. R. *et al.*
Chem. Commun. **1983**, 1215

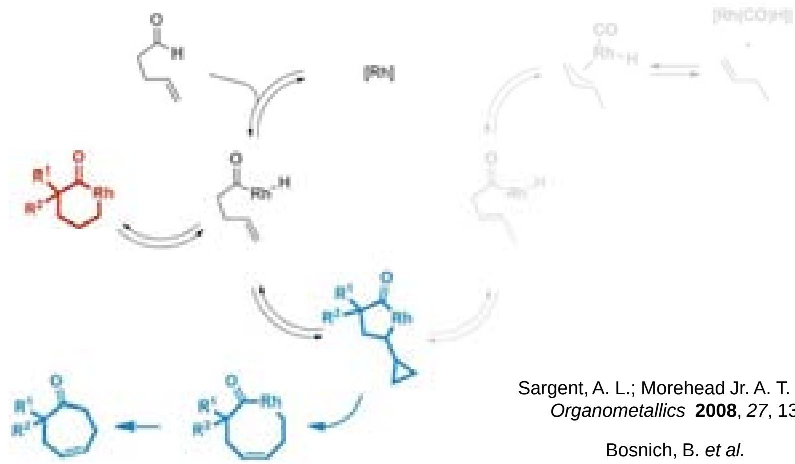
Diversion from unproductive pathway via C–C bond activation



Sargent, A. L.; Morehead Jr. A. T. *et al.*
Organometallics **2008**, *27*, 135

Bosnich, B. *et al.*
Organometallics **1988**, *7*, 936 & 945

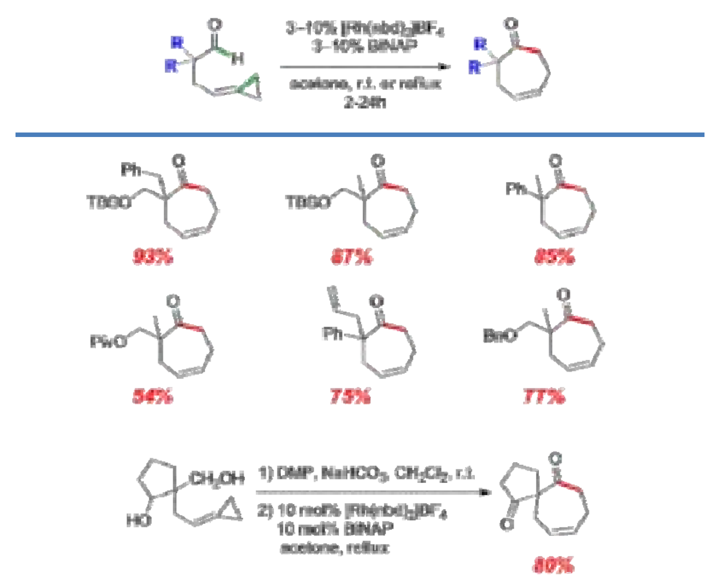
Diversion from unproductive pathway via C–C bond activation



Sargent, A. L.; Morehead Jr. A. T. *et al.* *Organometallics* **2008**, *27*, 135

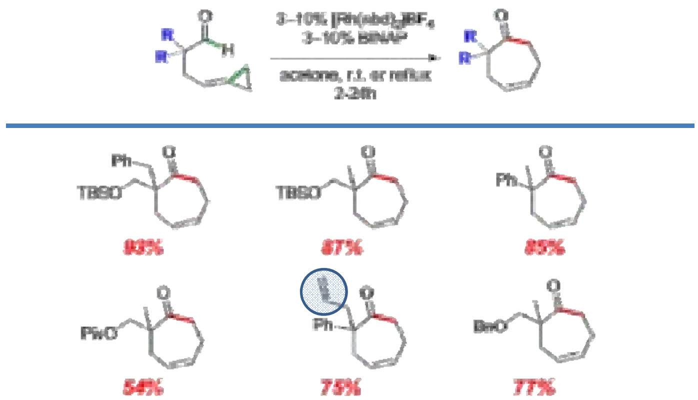
Bosnich, B. *et al.* *Organometallics* **1988**, *7*, 936 & 945

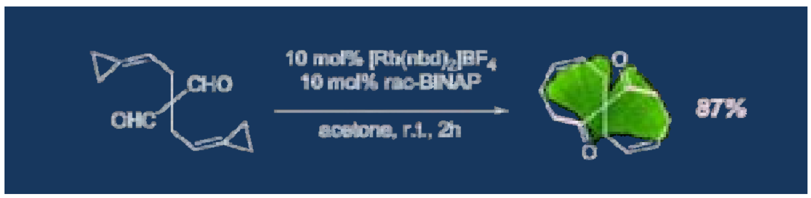
Reactivity of alkylidenecyclopropanes: Intramol. hydroacylation



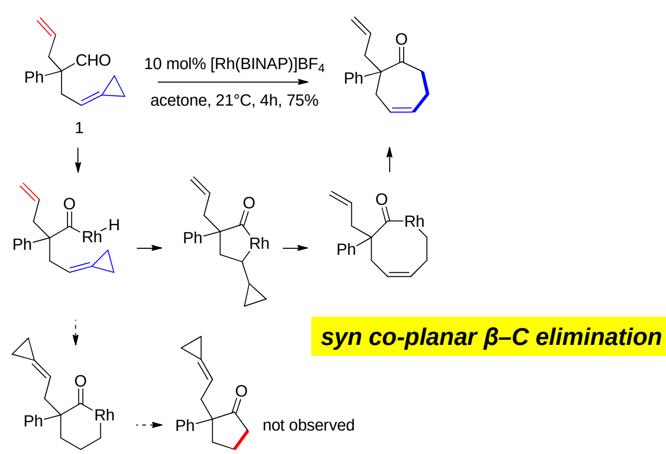
Crépin, D.; Tugny, C.; Murray, J. H.; Aïssa, C. *Chem. Commun.* **2011**, *47*, 10957

Reactivity of alkylidenecyclopropanes: Intramol. hydroacylation



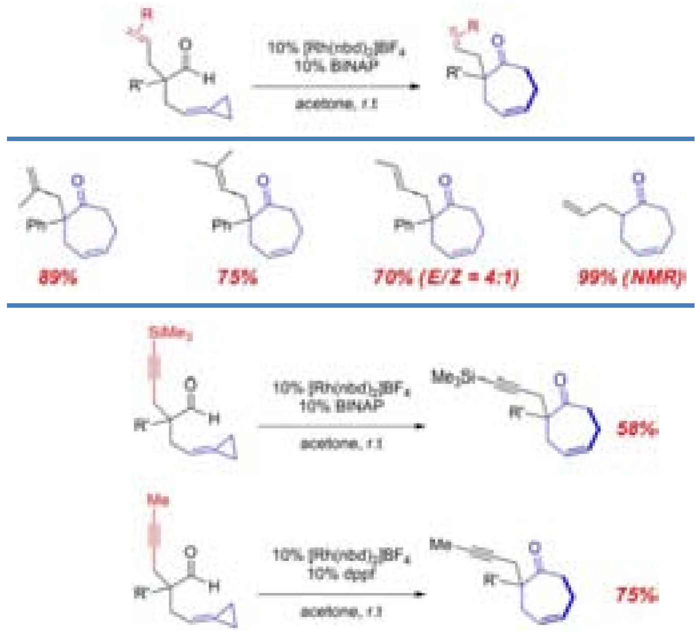


Chemoselectivity via C–C bond activation



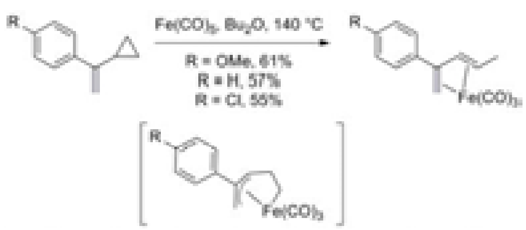
Crépin, D.; Tugny, C.; Murray, J. H.; Aïssa, C. *Chem. Commun.* **2011**, *47*, 10957

Chemoselectivity via C–C bond activation

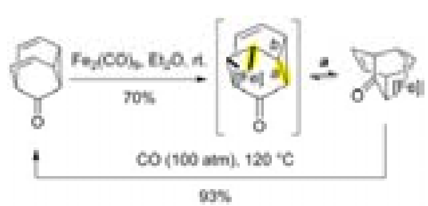


Crépin, D.; Tugny, C.; Murray, J. H.; Aïssa, C. *Chem. Commun.* **2011**, *47*, 10957

Reactivity of vinylcyclopropanes

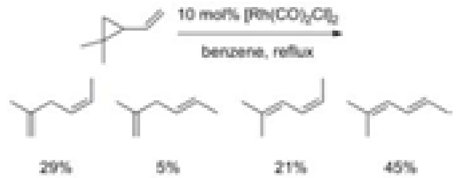


Sarel, *J. Am. Chem. Soc*. **1965**, *87*, 2517

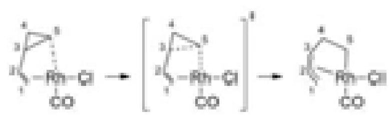


Eisenstadt, *Tetrahedron Lett*. **1972**, 2005
Lewis, *J. Chem. Soc., Dalton Trans.* **1975**, 567

Reactivity of vinylcyclopropanes



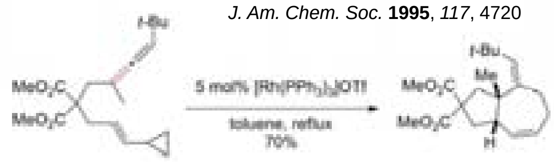
Salomon, *J. Chem. Soc., Chem Commun.* **1976**, 89
Salomon, *J. Am. Chem. Soc*. **1977**, *99*, 1043



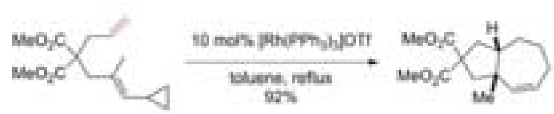
Wender and Houk, *J. Am. Chem. Soc*. **2004**, *126*, 9154

Vinylcyclopropanes: [5+2]-cycloadditions

J. Am. Chem. Soc. **1995**, *117*, 4720

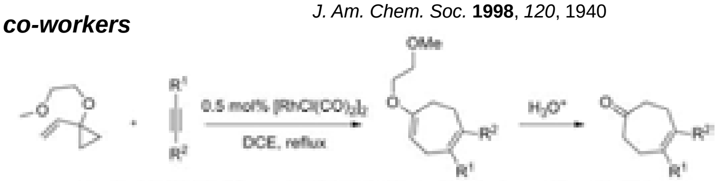


J. Am. Chem. Soc. **1999**, *121*, 5348



Wender and co-workers

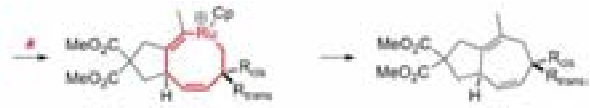
J. Am. Chem. Soc. **1998**, *120*, 1940



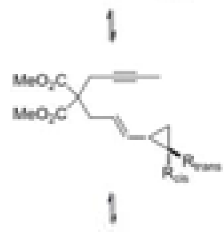
R^1, R^2 = CO_2Et, CH_2OMe, $NHSO_2$(p-Tol), H, alcohols, olefins, yields = 75–96%

J. Am. Chem. Soc. **1998**, *120*, 10976

Vinylcyclopropanes: [5+2]-cycloadditions



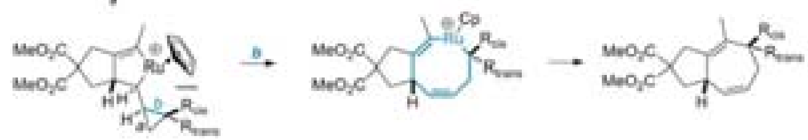
favoured by minimisation of steric congestion



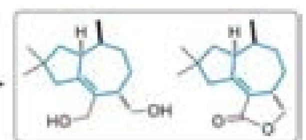
Trost (Ru)
J. Am. Chem. Soc. **2000**, *122*, 2379
Org. Lett. **2000**, *2*, 2523
Angew. Chem. Int. Ed. **2001**, *40*, 1313
Chem. Eur. J. **2005**, *11*, 2577

Wender (Rh)
J. Am. Chem. Soc. **1999**, *121*, 10442
Org. Lett. **1999**, *1*, 2089

favoured by R = electron-withdrawing groups



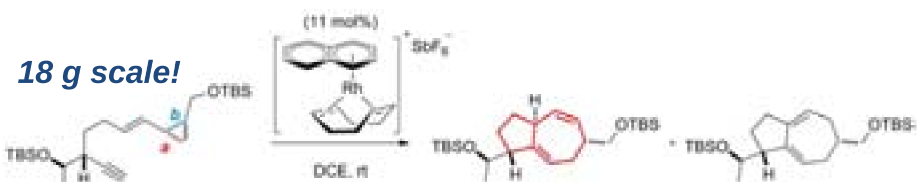
Vinylcyclopropanes: [5+2]-cycloadditions



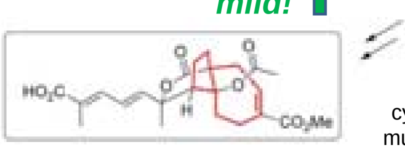
Tremulenediol A
Tremulenolide A

Martin, *Org. Lett.* **2005**, *7*, 4535

18 g scale!

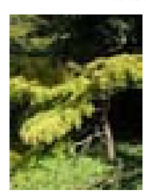


mild!



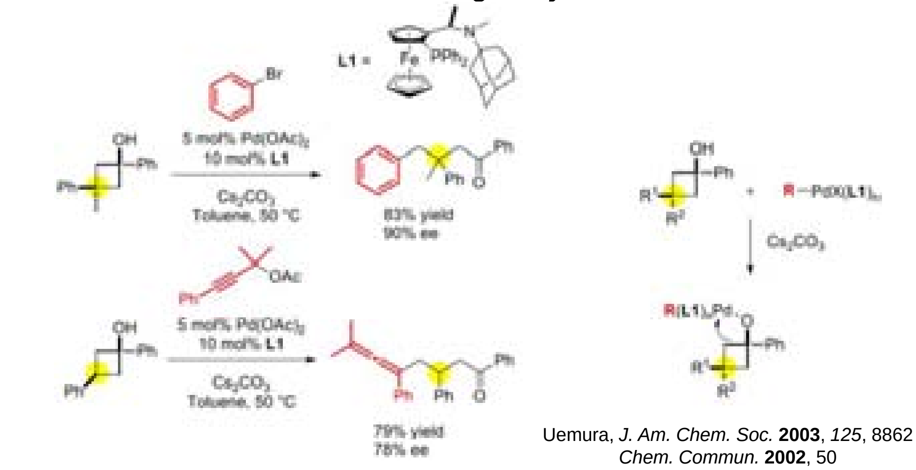
Pseudolaric acid B

cytotoxic against
multidrug resistant
cancer cell lines



Trost, *J. Am. Chem. Soc.* **2007,** *129*, 14556; ibid, **2008**, *130*, 16424

C–C activation in 4-membered rings - cyclobutanols



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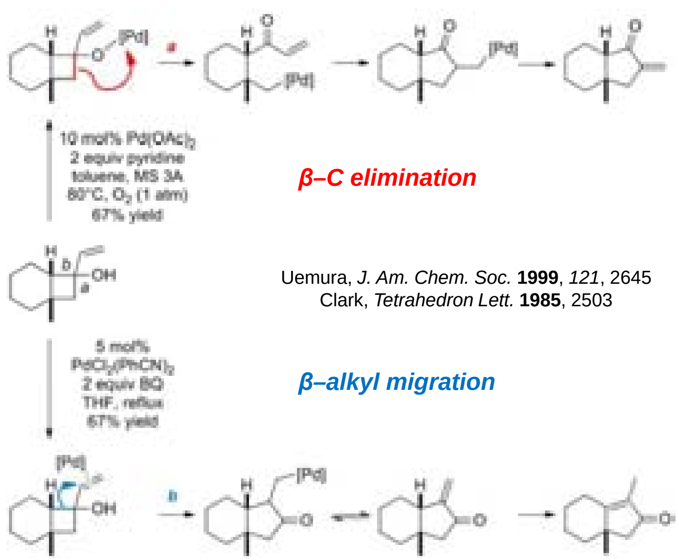
C–C activation in 4-membered rings - cyclobutanols



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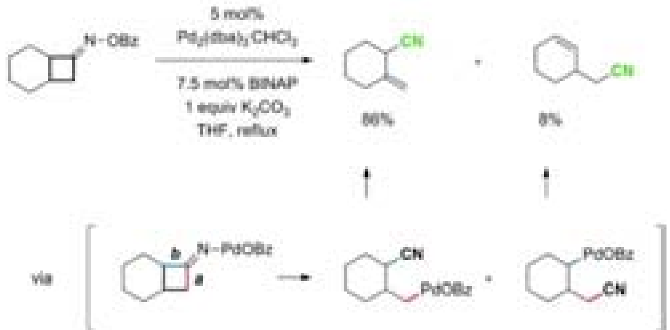
C–C activation in 4-membered rings – nitriles without cyanide



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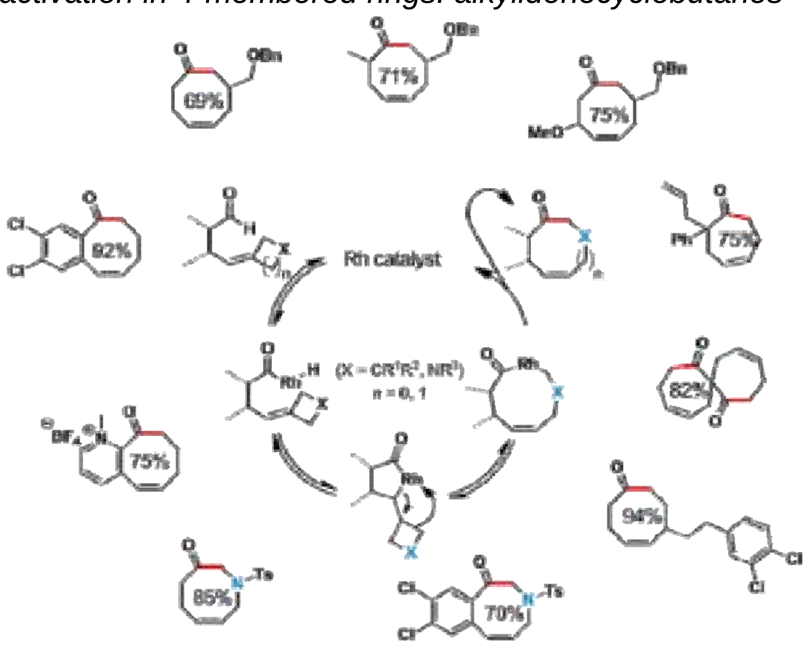
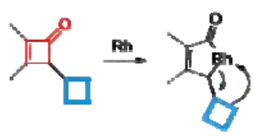
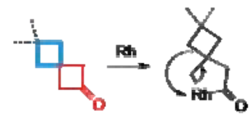
C–C activation in 4-membered rings: alkylidenecyclobutanes



Crépin, D.; Dawick, J.; Aïssa, C. *Angew. Chem. Int. Ed*. **2010**, *49,* 620

C–C activation in 4-membered rings: alkylidenecyclobutanes





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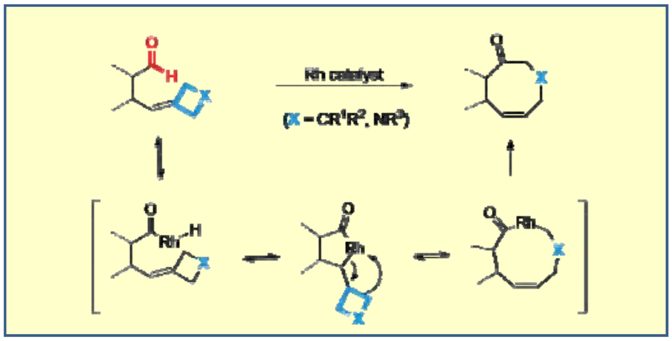

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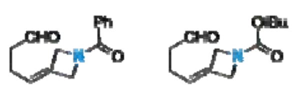
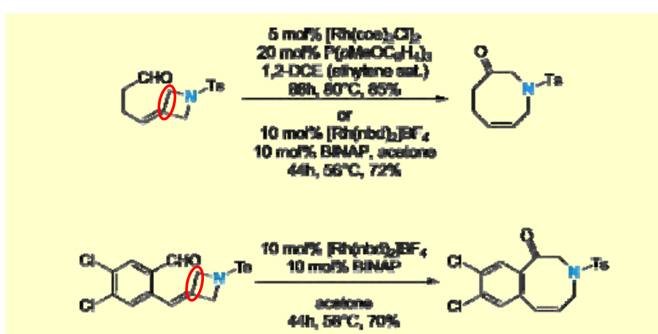
C–C activation in 4-membered rings: alkylideneazetidines





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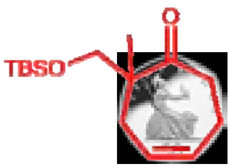

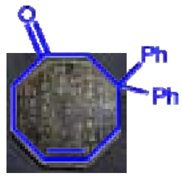

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