Non-Metathesis Ruthenium-Catalyzed Reactions for Organic Synthesis

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MacMillan Group Meeting
May 23, 2002

I. Properties of Ruthenium

II. Reductions

III. Oxidations

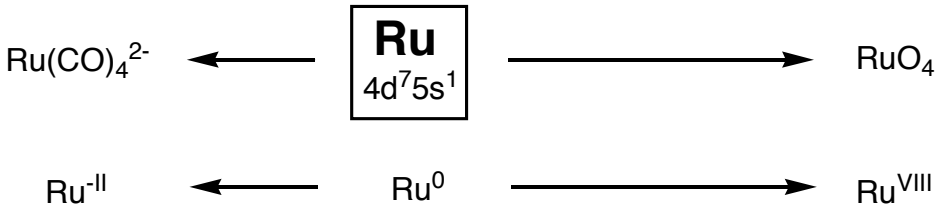
IV. Isomerizations

V. C-C bond forming reactions

Murahashi, Chem. Rev., 1998, 2599.
Trost, Toste, Chem. Rev., 2001, 2067.

Properties of Ruthenium

- Ruthenium has the widest range of accessible oxidation states of any element in the periodic table



- Ruthenium complexes of each oxidation state can assume several coordination geometries

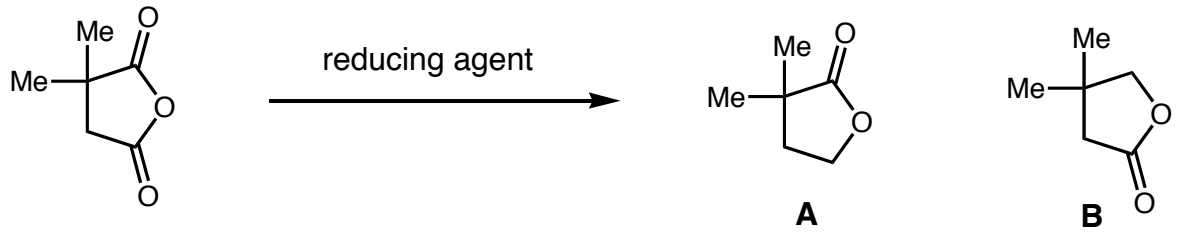
Oxidation state	Coordination number	Geometry	Examples
Ru^{0}	5	trigonal bipy.	$Ru(CO)_5$
Ru^{II}	5	trigonal bipy.	$RuHCl(PPh_3)_3$
	6	octahedral	$RuCl_2CO(PR_3)_3$
Ru^{III}	6	octahedral	$[Ru(NH_3)_5Cl]^{2+}$
Ru^{VI}	4	tetrahedral	RuO_4^{2-}
Ru^{VII}	4	tetrahedral	RuO_4^{-}
Ru^{VIII}	4	tetrahedral	RuO_4

Cotton, 5th Ed.

- Ru complexes are generally characterized as having high electron transfer ability, high Lewis acidity, low redox potentials, and the ability to stabilize reactive species such as oxometals, metallacycles, and metal carbene complexes.

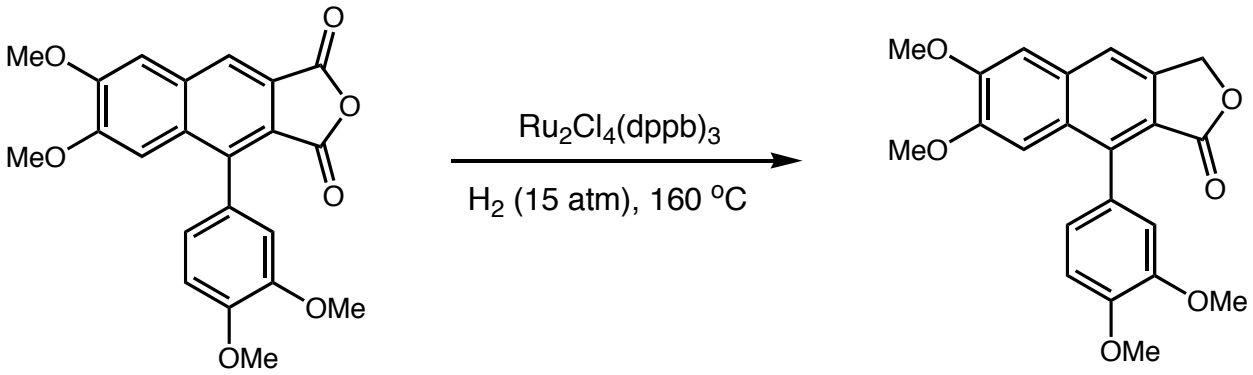
- The wide range of oxidation states, coordination geometries, and tunable properties result in the ability of Ru complexes to catalyze a remarkable range of chemical transformations

Regioselective Reduction of Unsymmetrical Cyclic Anhydrides



reducing agent	yield %	**A : B**
$LiAlH_4$	70	1 : 19
2 mol% $RuCl_2(PPh_3)_3$ H_2	72	9 : 1

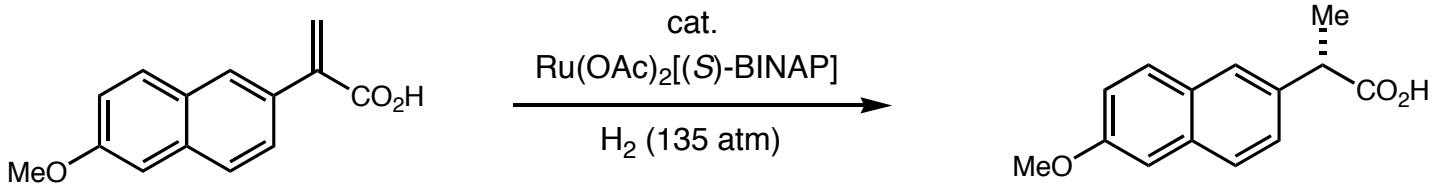
Morand and Kayser, J.C.S., Chem. Comm., 1976, 314.



88%

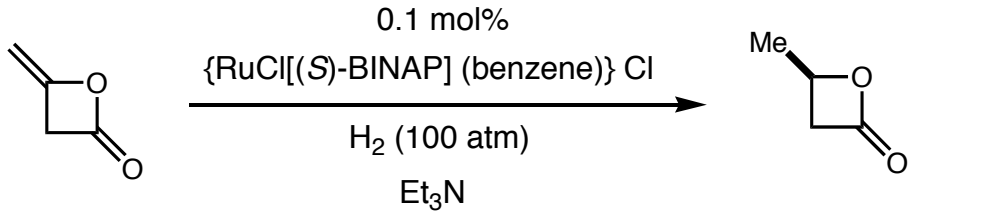
Ikariya, Tetrahedron Lett., 1986, 365.

Asymmetric Hydrogenation of Prochiral Olefins



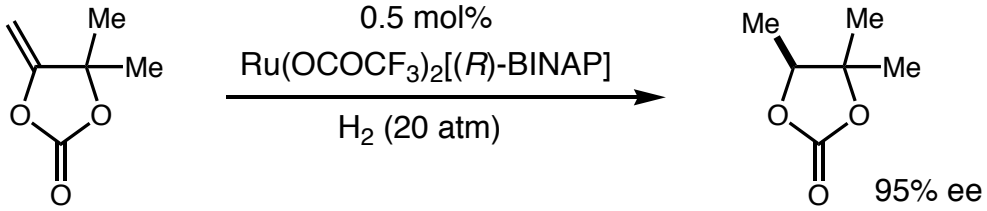
Noyori, J. Org. Chem., 1987, 3176.

(S)-naproxen
97% ee



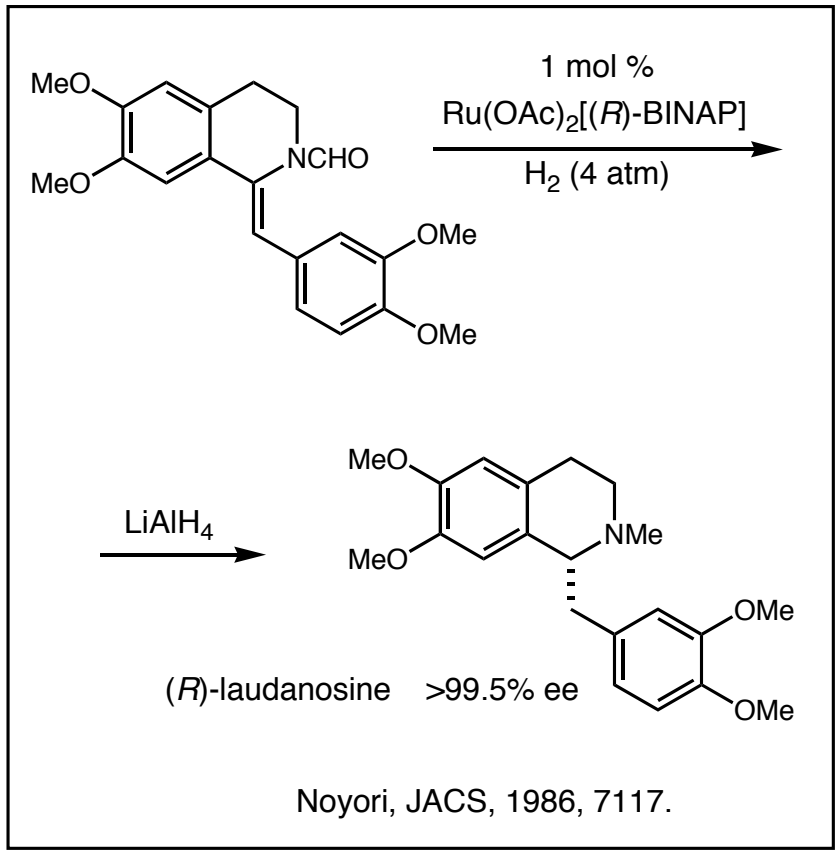
92% ee

Takaya, J. C. S., Chem. Comm., 1992, 1725.



95% ee

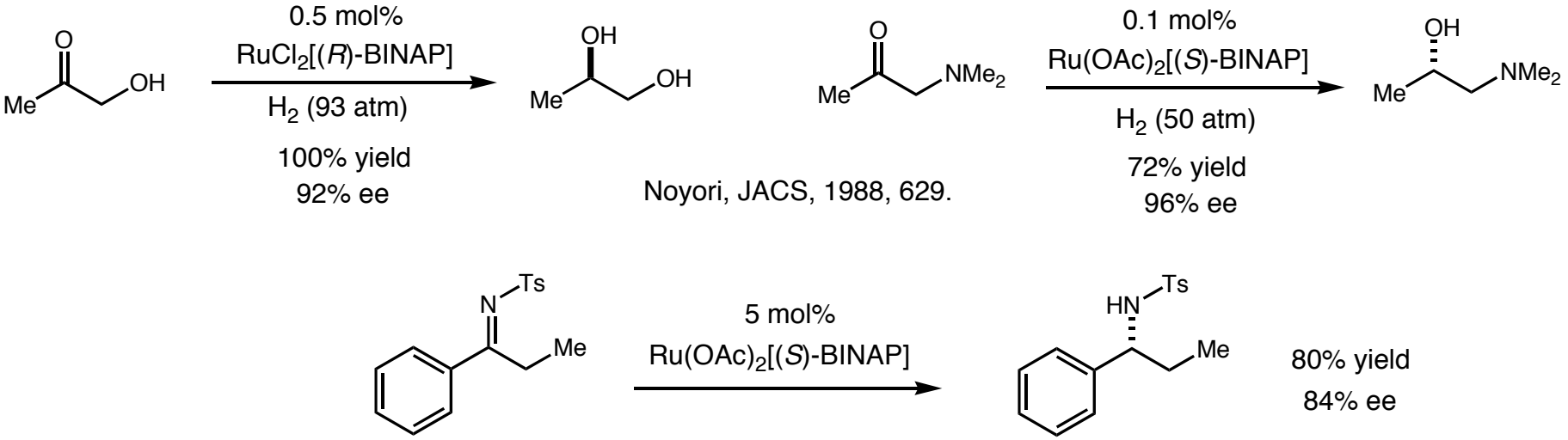
Bruneau and Dixneuf, J. Org. Chem., 1996, 8453.



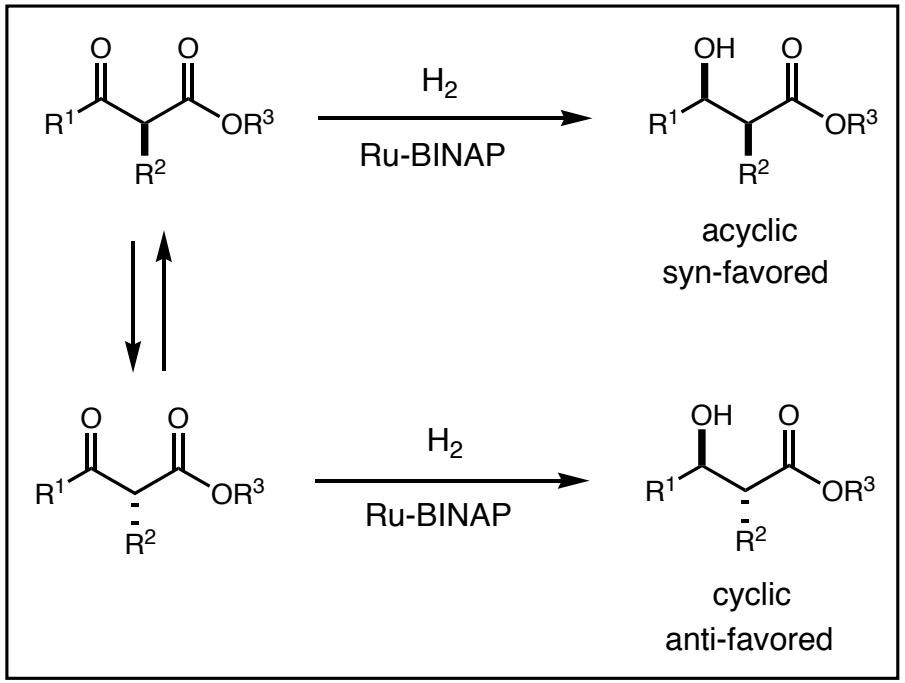
(*R*)-laudanosine >99.5% ee

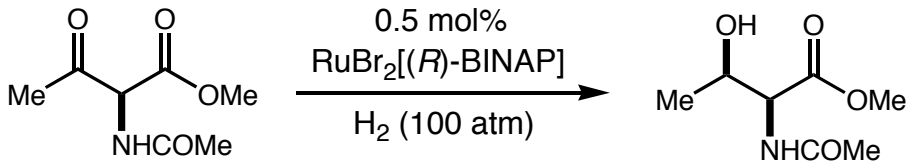
Noyori, JACS, 1986, 7117.

Enantioselective Reduction of Ketones

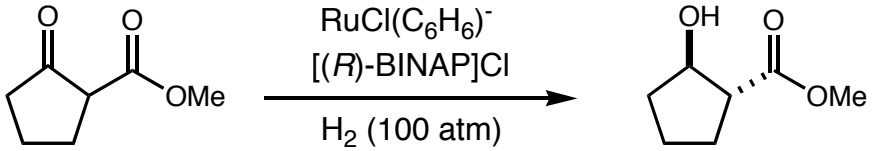


Dynamic Kinetic Resolution of β-Keto Esters





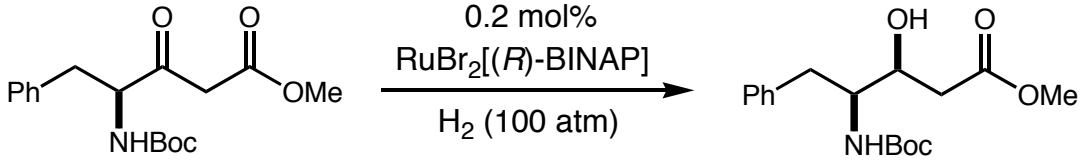
99 : 1 *syn : anti*
98% ee



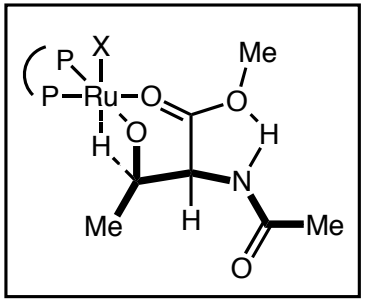
Noyori, JACS, 1989, 9134.

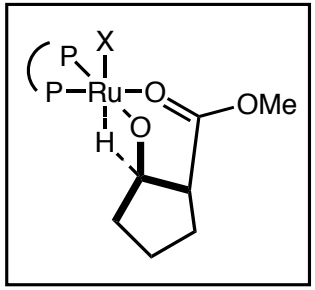
1 : 99 *syn : anti*
93% ee

■ If equilibration is faster than hydrogenation, high ee's can be obtained



> 99 : 1 *syn : anti*
99% ee



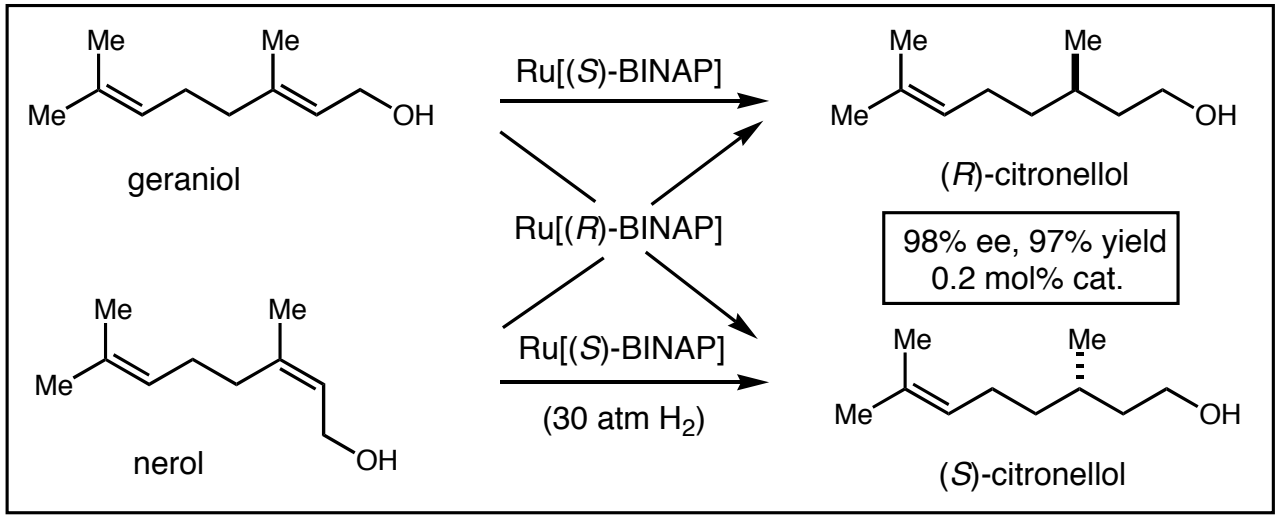


■ 4-Substituted β–keto-esters can be used as well

Noyori, Tetrahedron Lett., 1988, 6327.

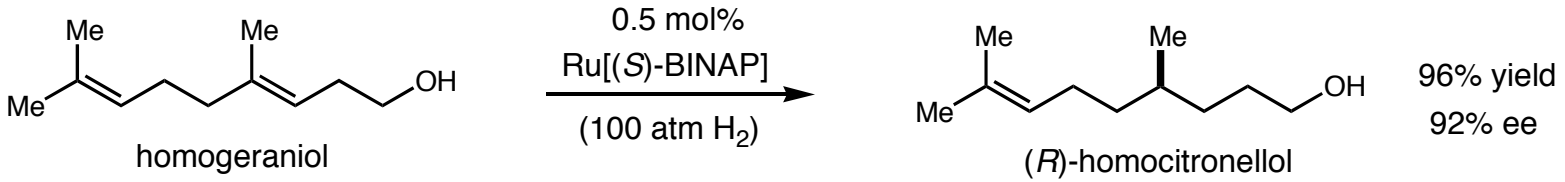
Directed Hydrogenation of Allylic and Homoallylic Alcohols

- Olefins allylic to alcohols can be selectively and asymmetrically hydrogenated

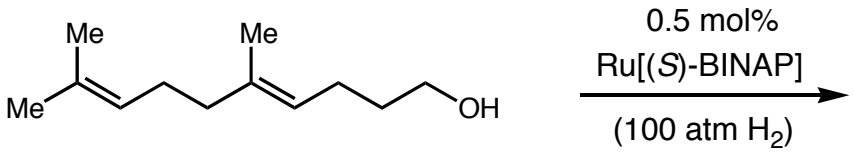


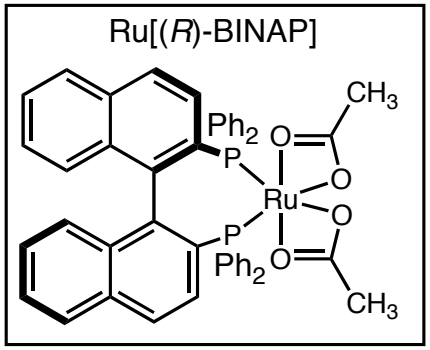
Noyori, JACS, 1987, 1596.

- Homoallylic alcohols similarly under slightly more forcing conditions

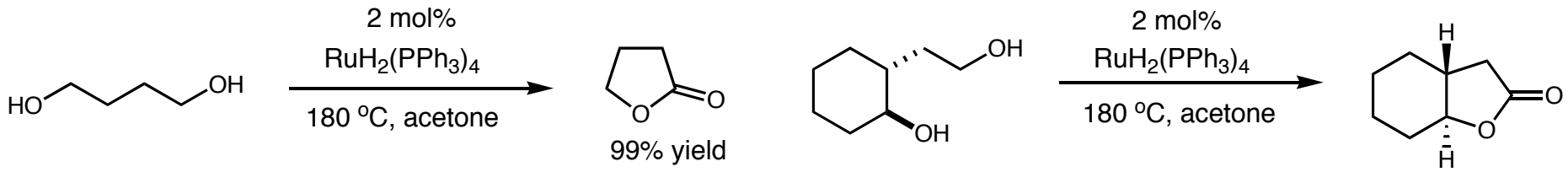


- Homo homoallylic alcohols and higher analogs are inert

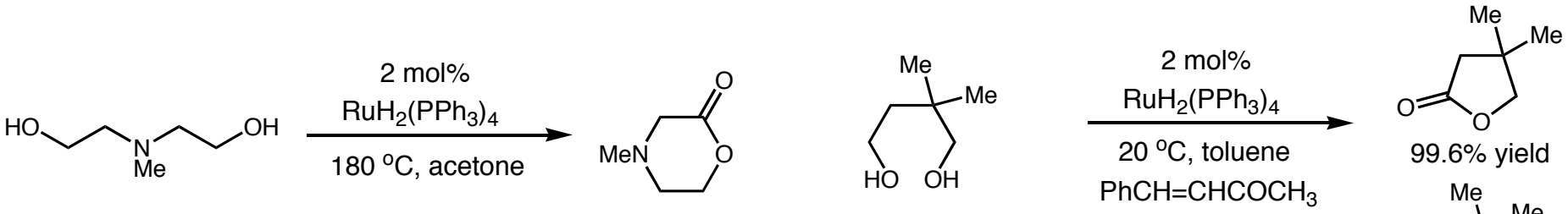




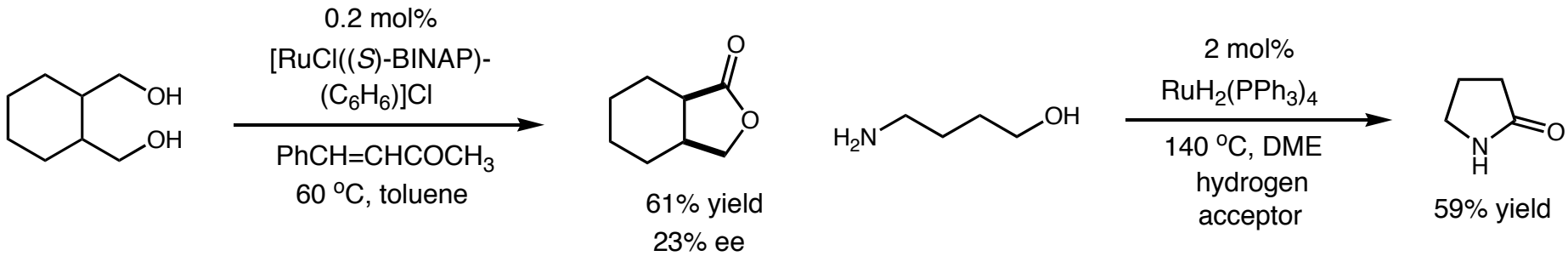
Oxidation of Diols to Lactones



Murahashi, JOC, 1987, 4319.



Saburi and Yoshikawa, JOC, 1986, 2034

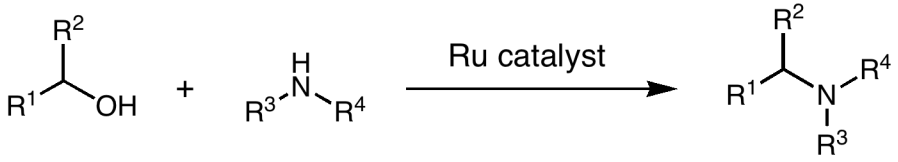


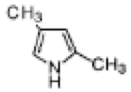
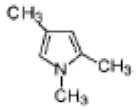
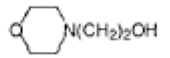
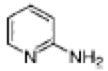
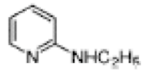
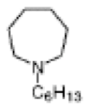
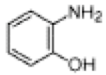
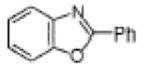
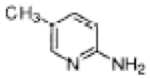
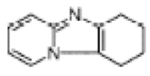
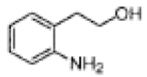
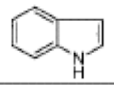
Nozaki, JOMC, 1994, 473, 253.

Murahashi, SynLett, 1991, 693.

■ Reactions can be performed intermolecularly to form esters and amides

One Pot Reductive Amination of Amines and Alcohols



entry	catalyst	amine	alcohol	product	yield, %	ref.
1	$RuH_2(PPh_3)_4$	$C_8H_{17}NH_2$	$C_7H_{15}OH$	$C_7H_{15}NHC_8H_{17}$	92	120
2	$RuCl_2(PPh_3)_3$	$PhNH_2$	C_3H_7OH	$PhN(C_3H_7)_2$	88	121b
3	$RuCl_3{\cdot}nH_2O$-$P(OBu)_3$	$PhNH_2$	CH_3OH	$PhN(CH_3)_2$	80	123a
4	$RuCl_3{\cdot}nH_2O$-$P(OBu)_3$		CH_3OH		99	123b
5	$RuCl_3{\cdot}nH_2O$-PPh_3		$HO(CH_2)_6OH$		84	123c
6	Ru(cod)(cot)		C_2H_5OH		85	124
7	$RuH_2(PPh_3)_4$	$H_2N(CH_2)_4OH$			79	120
8	$RuH_2(PPh_3)_4$	$C_6H_{13}NH_2$	$HO(CH_2)_5OH$		87	120
9	$RuCl_2(PPh_3)_3$	$PhNH_2$	$HO(CH_2)_5OH$		89	125a
10	$RuCl_2(PPh_3)_3$		$PhCH_2OH$		80	126
11	$RuCl_2(PPh_3)_3$				74	127
12	$RuCl_2(PPh_3)_3$				100	128

Murahashi, Tetrahedron Lett., 1982, 229.

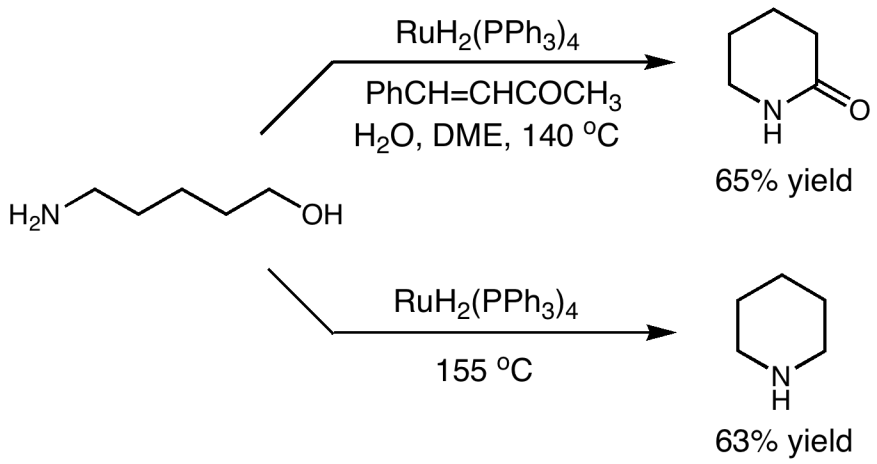
mechanism:

$R^1R^2OH + (Ru) \rightleftharpoons (R^1R^2C{=}O)(Ru)(H_2)$

$(R^1R^2C{=}O)(Ru)(H_2) + R^3R^4NH \rightleftharpoons (R^1R^2C{=}N^+R^3R^4)(Ru)(H)^- + H_2O$

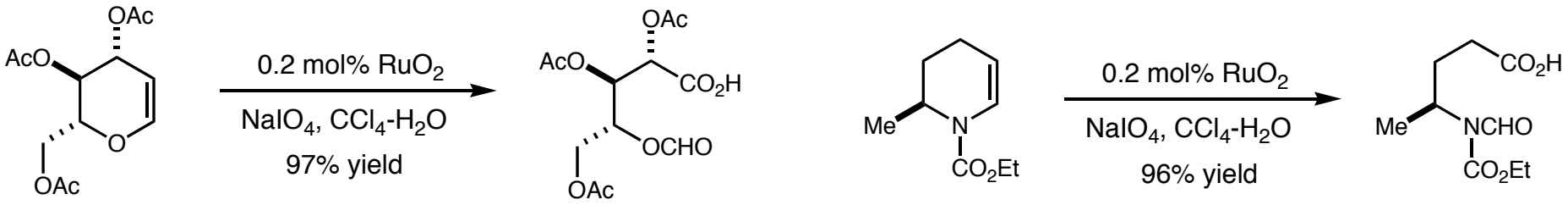
$(R^1R^2C{=}NR^3R^4)(Ru)(H)^- \rightleftharpoons R^1R^2CNR^3R^4 + (Ru)$

- Lactams obtained by use of hydrogen acceptor; amines with none



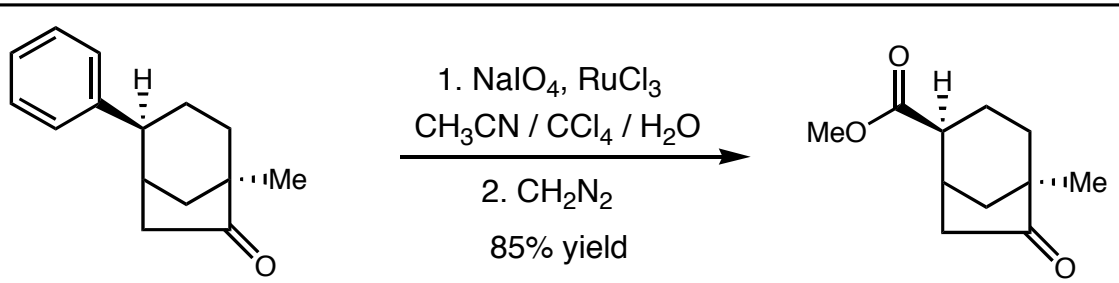
Murahashi, SynLett., 1991, 693.

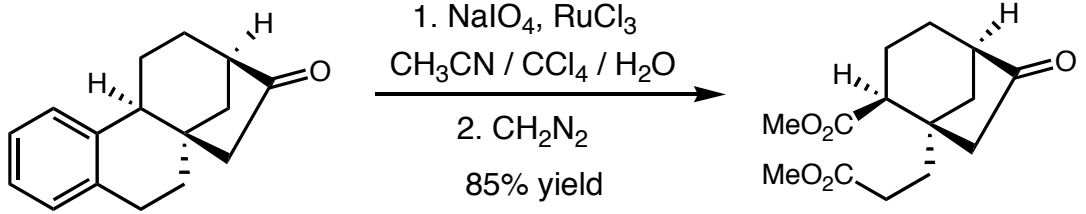
Oxidative Cleavage of Olefins



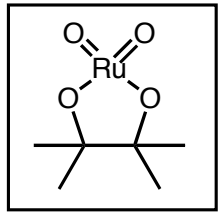
Torii, JOC, 1985, 4980.

■ Oxidative cleavage of aromatic rings





Ghatak, Synthesis, 1983, 746.



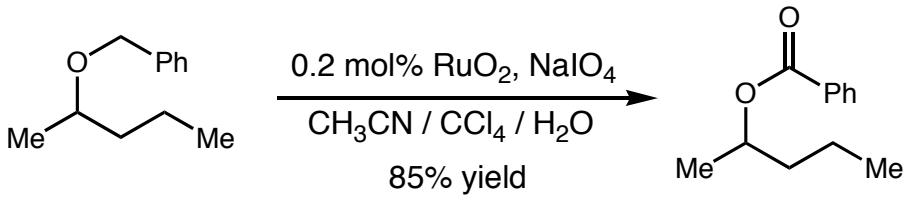
reactions proceed through
a cyclic ruthenium (VI) diester

■ In reactions where carboxylic acids are generated, the addition of CH_3CN has a dramatic effect on rate and efficiency due to the disruption of insoluble Ru-carboxylate species

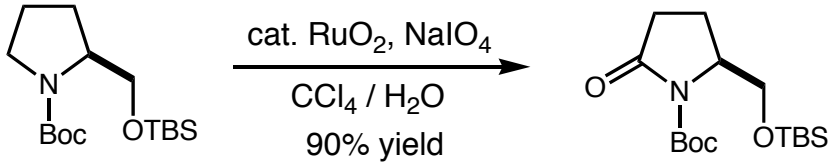
Sharpless, JOC, 1981, 3936.

Oxidation of Ethers, Amines, and Alkanes

- Oxidation of α-methylenes of ethers and amines



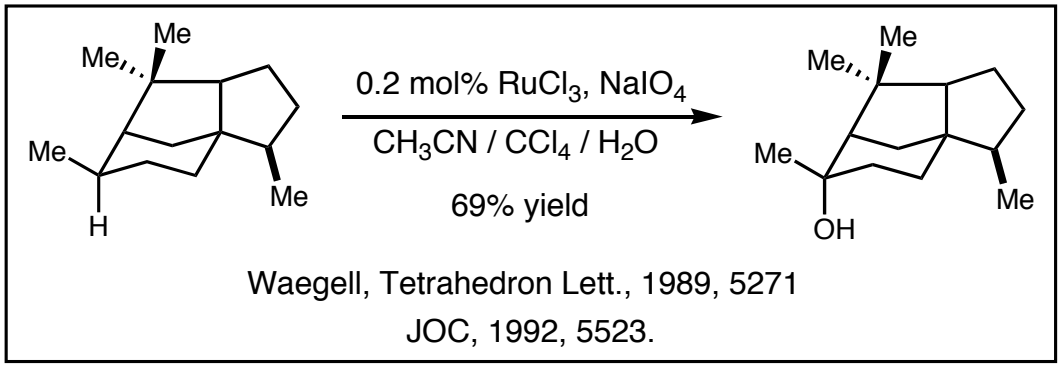
Schuda, Tetrahedron Lett., 1983, 3829.



Tanaka, Chem. Pharm. Bull., 1986, 3879.

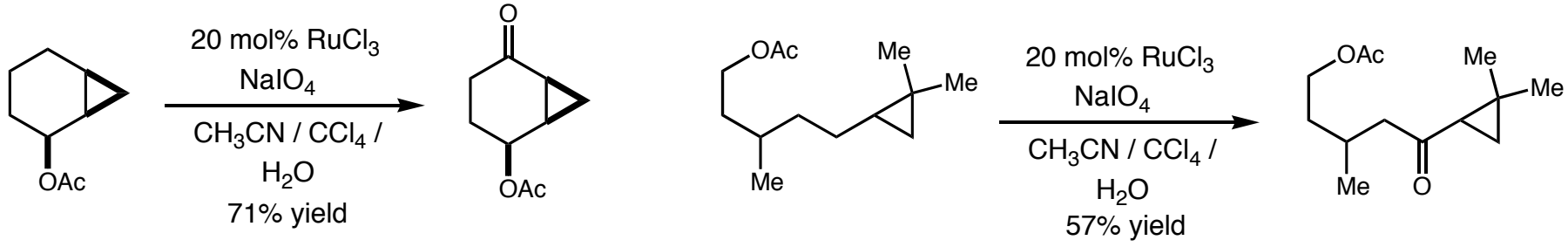
- Amides can be oxidized in a similar manner to imides

- Oxidation of unactivated alkanes



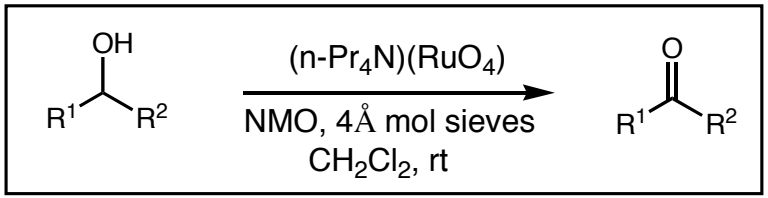
Waegell, Tetrahedron Lett., 1989, 5271

JOC, 1992, 5523.



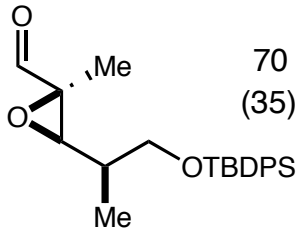
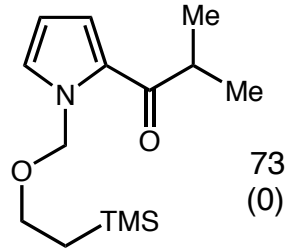
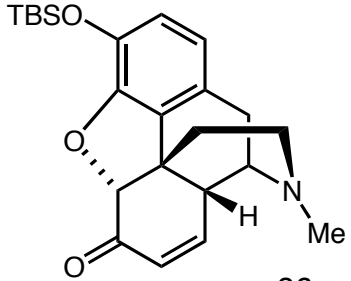
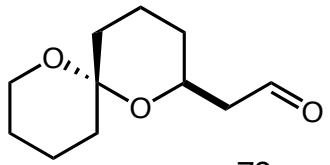
Yamada, Chem. Lett., 1985, 1385.

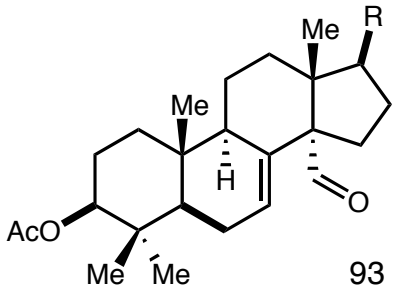
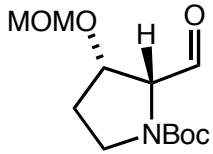
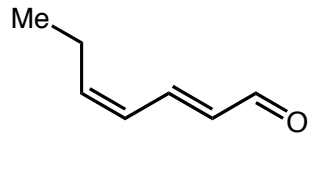
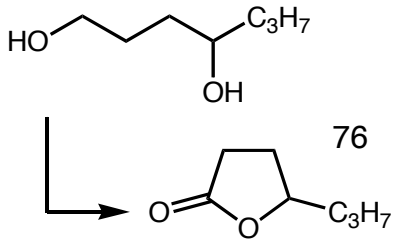
Tetrapropylammonium Perruthenate (TPAP) Oxidations



- RuO_4 (Ru^{VIII}, d^0) is a powerful, nonselective oxidant.
- Perruthenate ion, $[RuO_4]^-$ (Ru^{VII}, d^1) is a milder oxidant though it will still cleave some C=C bonds. Disproportionates in aqueous solution below pH = 8.
- Salts of the anion with large, organic cations are soluble in organic solvents and are much milder and selective oxidants. The tetrapropylammonium salt is the easiest to prepare.
- Water retards catalyst turnover so mol sieves are required
- Although $[RuO_4]^-$ is an overall $3e^-$ oxidant, studies suggest the oxidation process is of the $2e^-$ type.

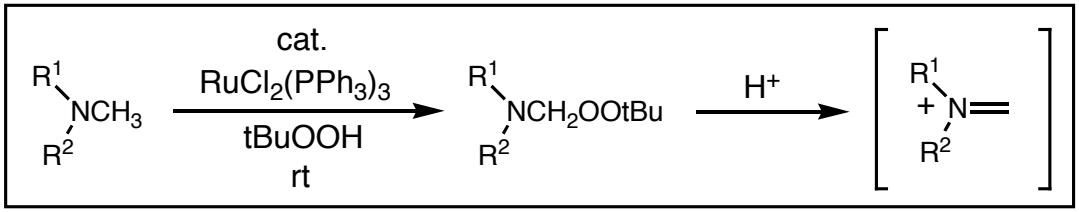
Ru(VII) + $2e^-$	→	Ru(V)
2Ru(V)	→	Ru(VI) + Ru(IV)
Ru(VI) + $2e^-$	→	Ru(IV)

Product	Yield % (Swern)
	70 (35)
	73 (0)
	86
	78

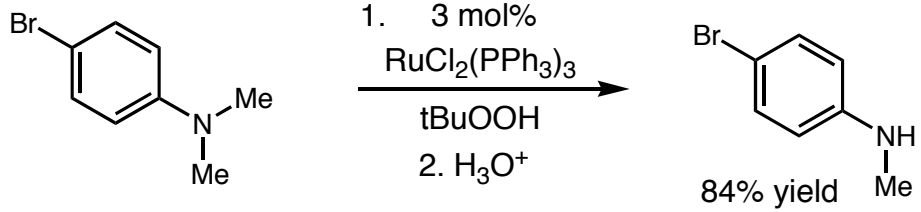
Product	Yield %
	93
	92
	73
	76

Review: Ley, Synthesis, 1994, 639 and ref. therein.

Oxidation of 3 ^{o} Amines to Iminium Ions

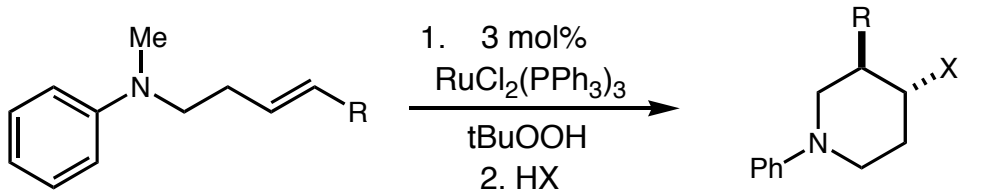


■ Demethylation of anilines



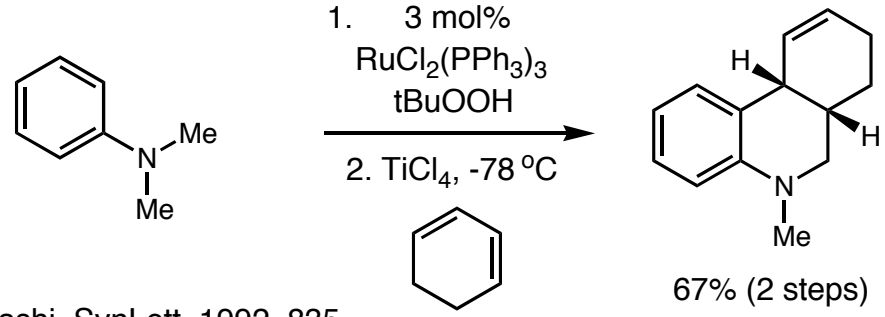
Murahashi, JACS, 1988, 8256.

■ Iminium ion intermediate can be trapped



R = H, X = OH
R = C_3H_7, X = Cl

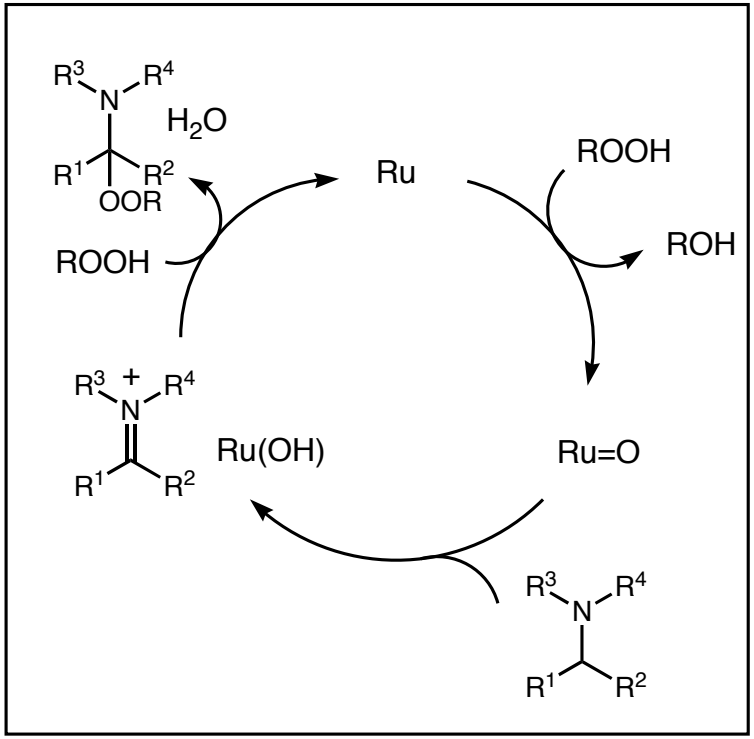
Murahashi, JACS, 1988, 8256.

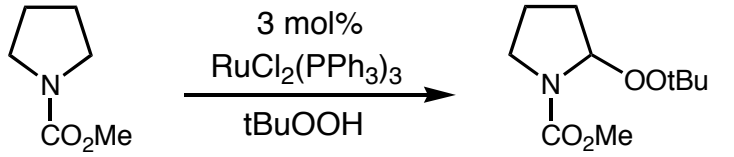


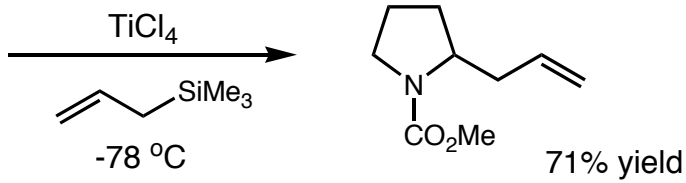
67% (2 steps)

Murahashi, SynLett, 1992, 835.

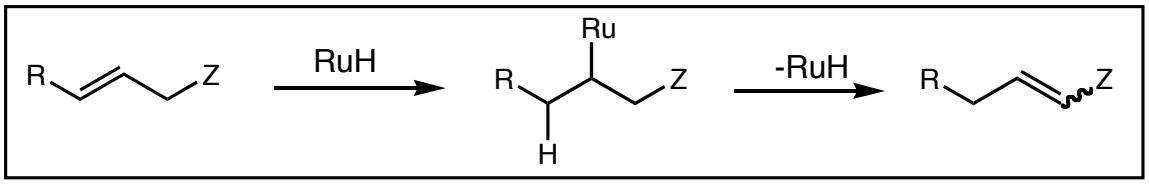
Mechanism:

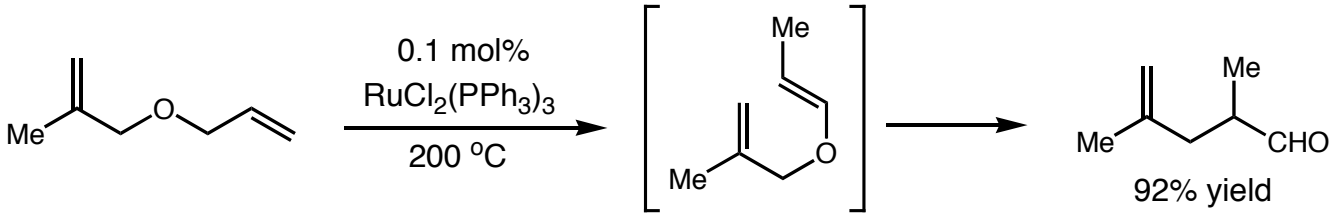






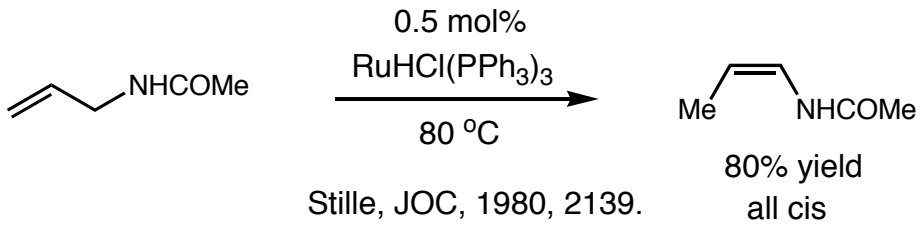
Isomerization of Allylic Alcohols, Amines, and Ethers





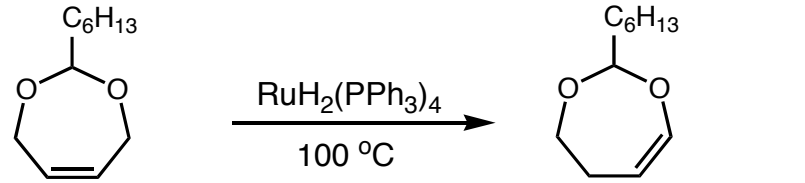
92% yield

Salomon, JOC, 1977, 3360.

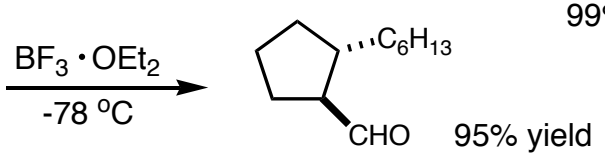


80% yield
all cis

Stille, JOC, 1980, 2139.

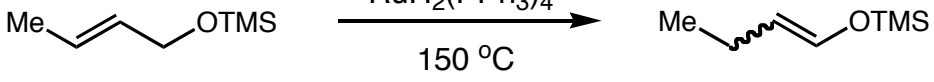


99% yield



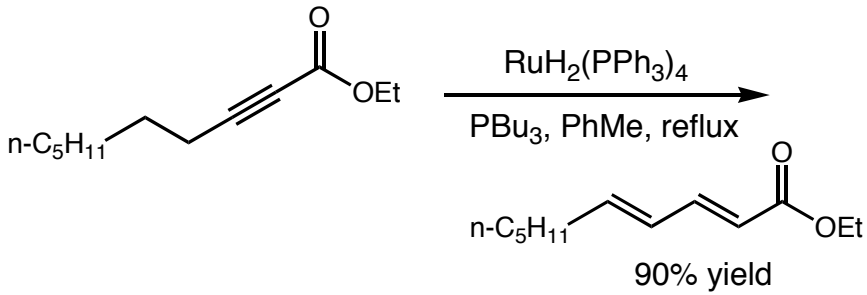
95% yield

Suzuki, Tetrahedron Lett., 1980, 4927.



100% yield
(E / Z = 45 / 55)

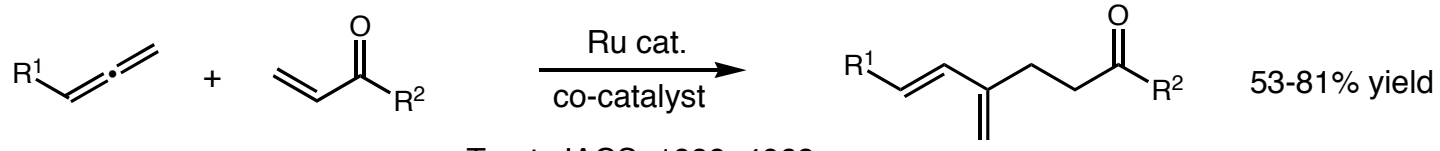
Suzuki, Tetrahedron Lett., 1979, 1415.



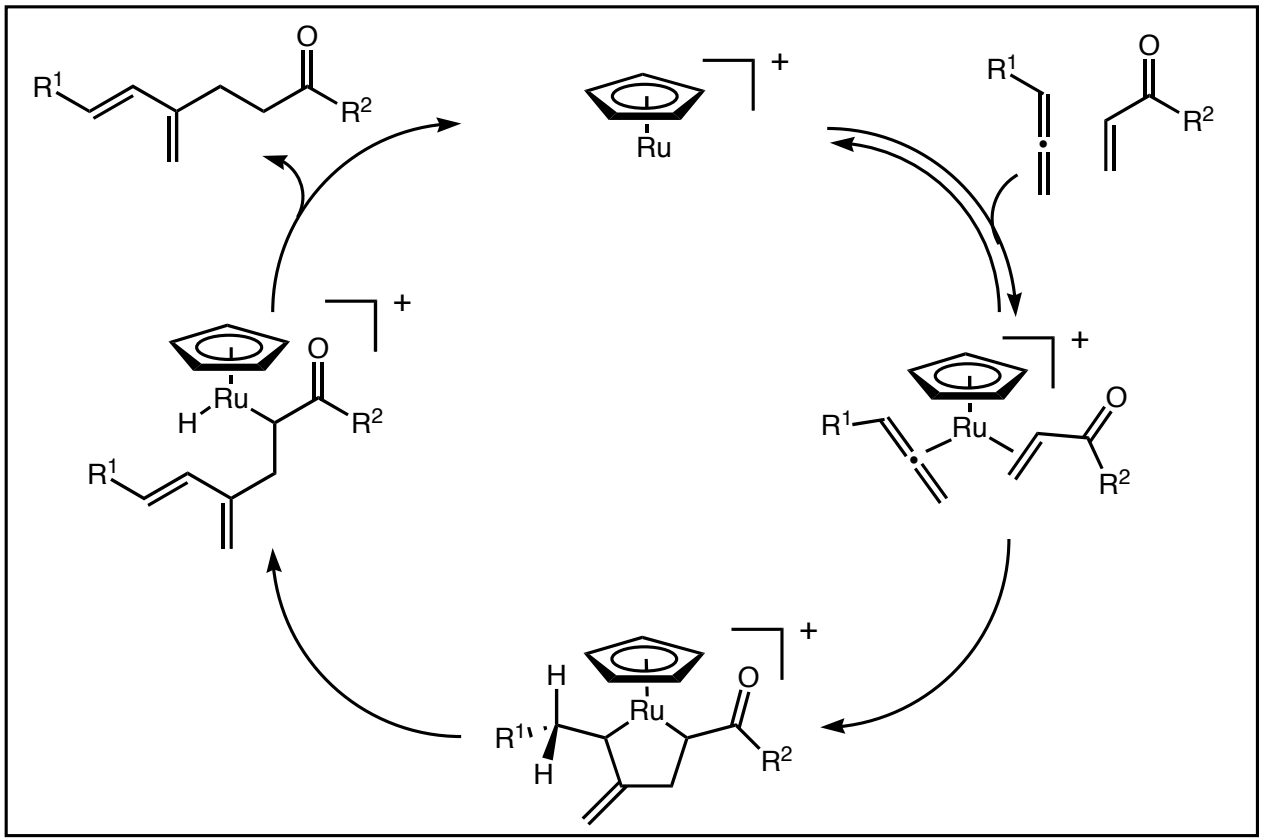
90% yield

Ma, Tetrahedron Lett., 1989, 843.

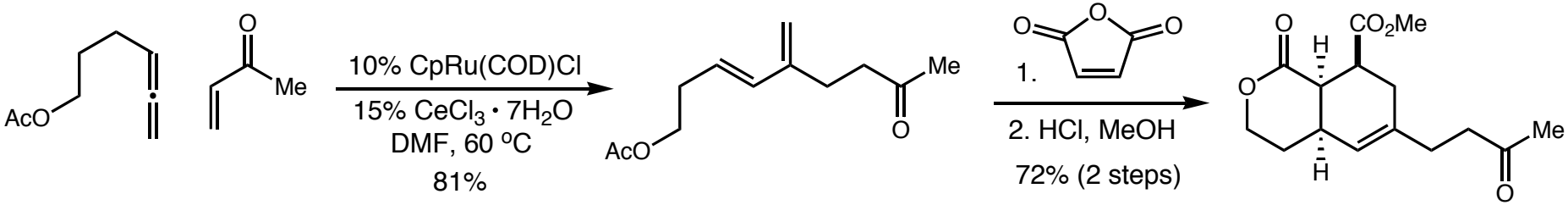
Coupling of Allenes and Vinyl Ketones to Form Dienes



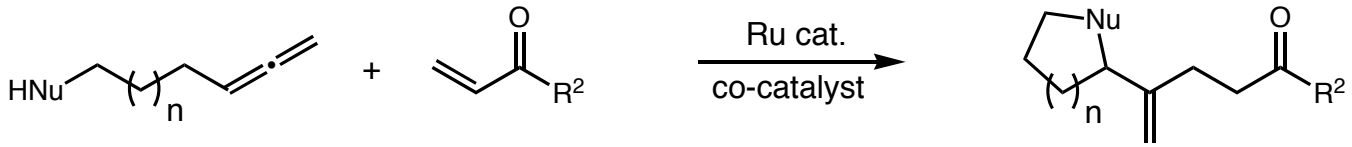
Trost, JACS, 1999, 4068.



■ Role of cocatalyst unknown, possibly activates enone.

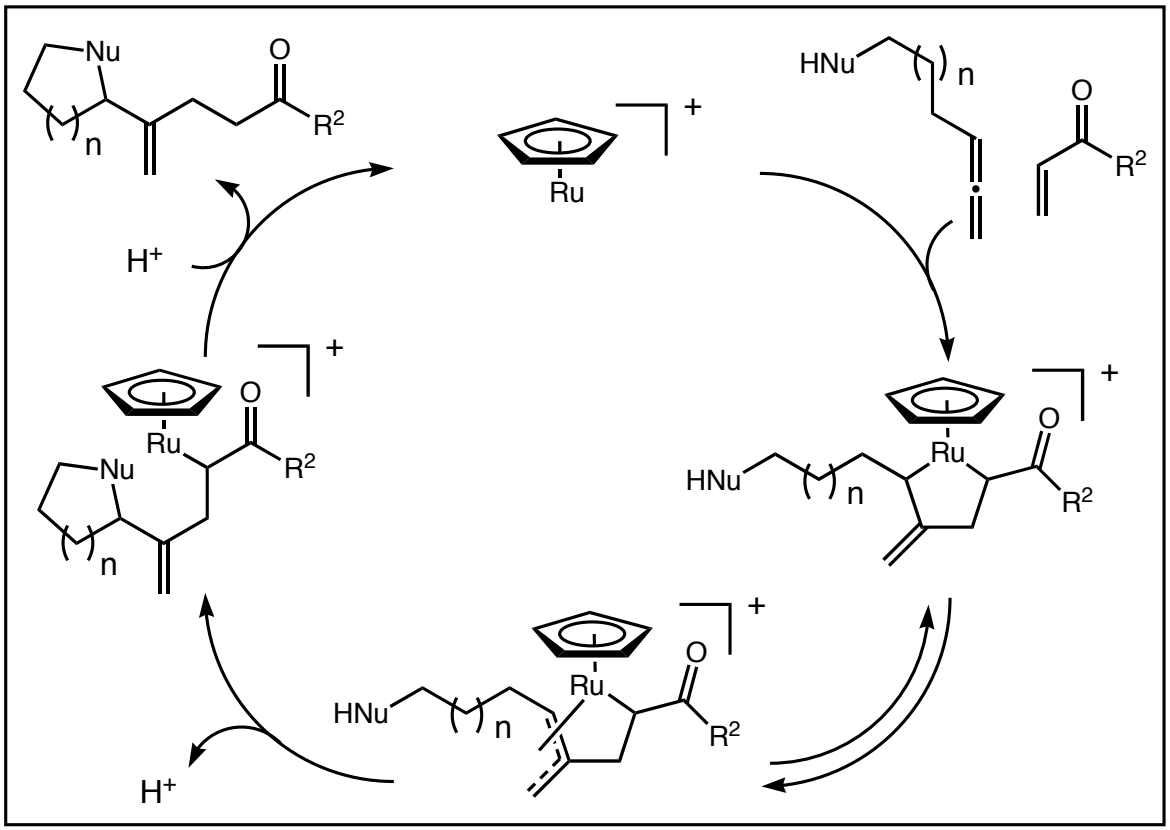


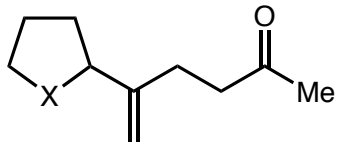
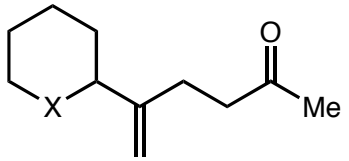
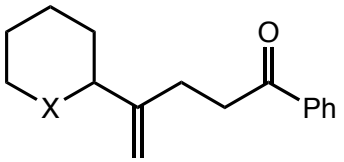
Coupling of Allenes and Vinyl Ketones: Formation of Cyclic Ethers and Amines

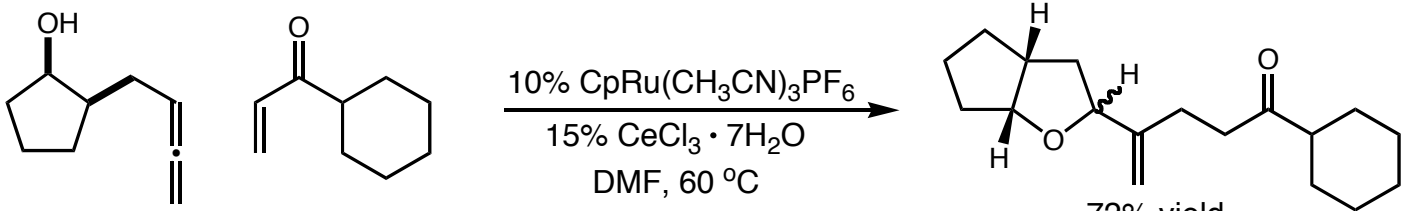


62-90% yields
Nu = OH or NHR
n = 1, 2

Trost, JACS, 1999, 10842 and 2000, 12007.

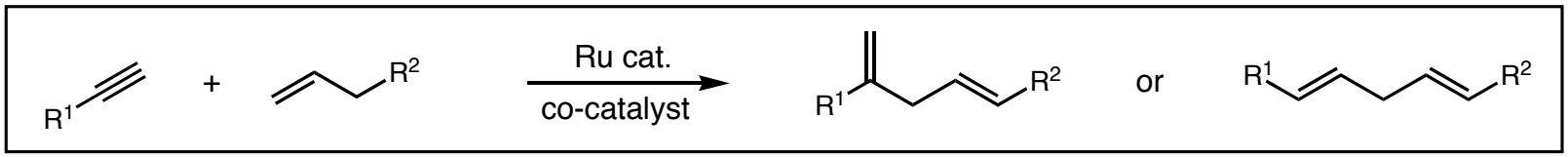


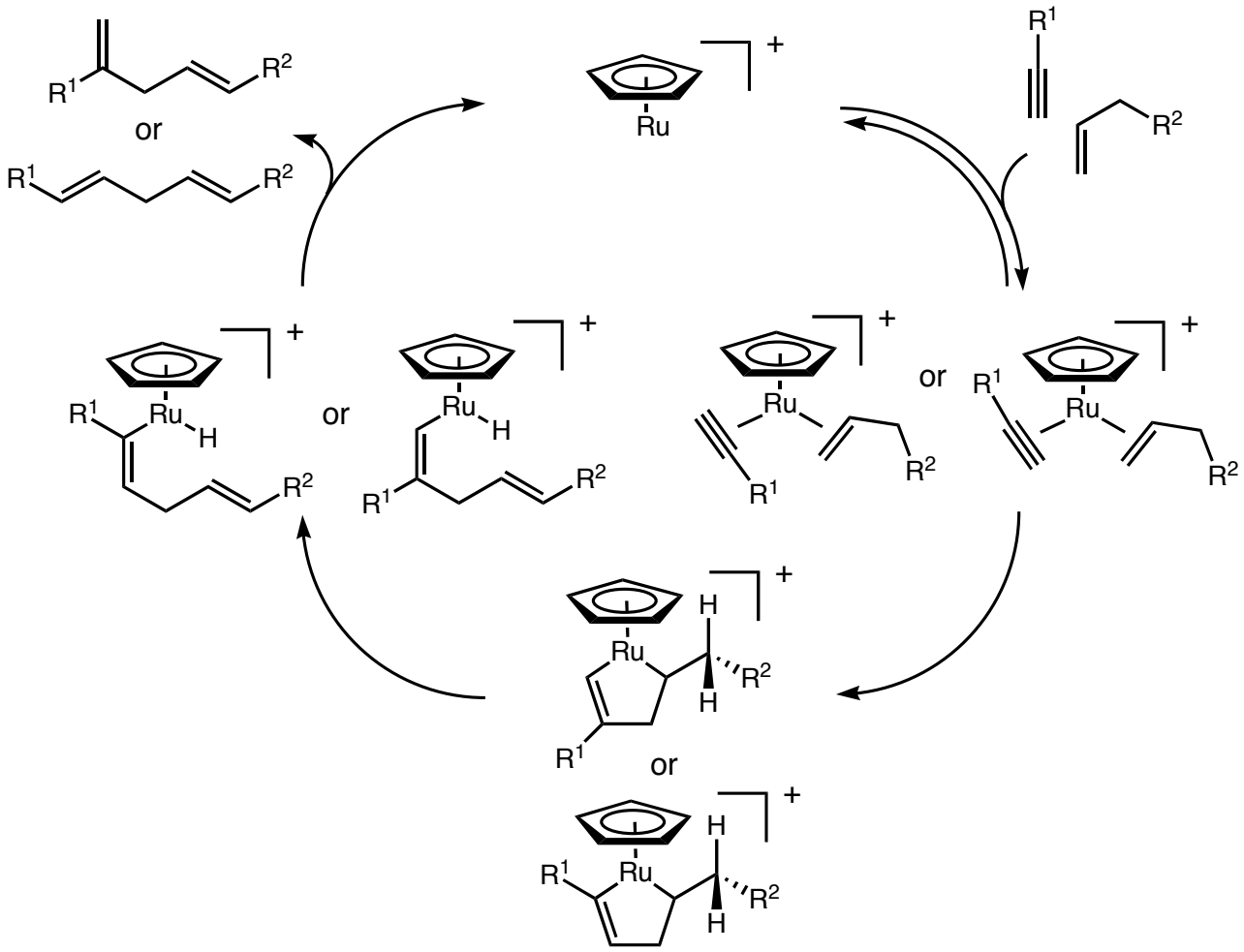
Product	Yield
	X = O 82% X = NBn 73%
	X = O 74% X = NBn 67%
	X = O 70% X = NBn 62%

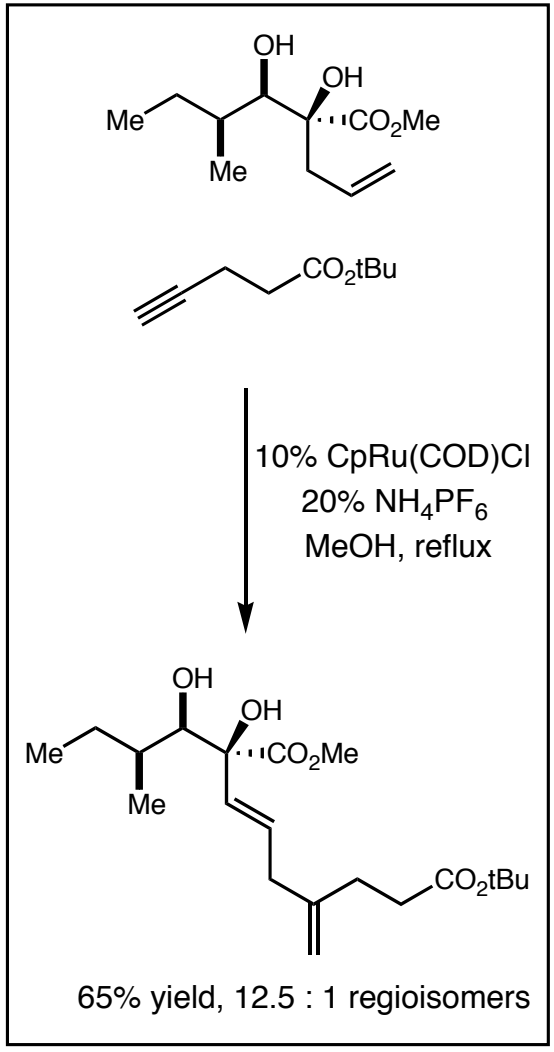


72% yield

Coupling of Alkenes and Alkynes: Ruthenium Catalyzed Alder-Ene Reaction



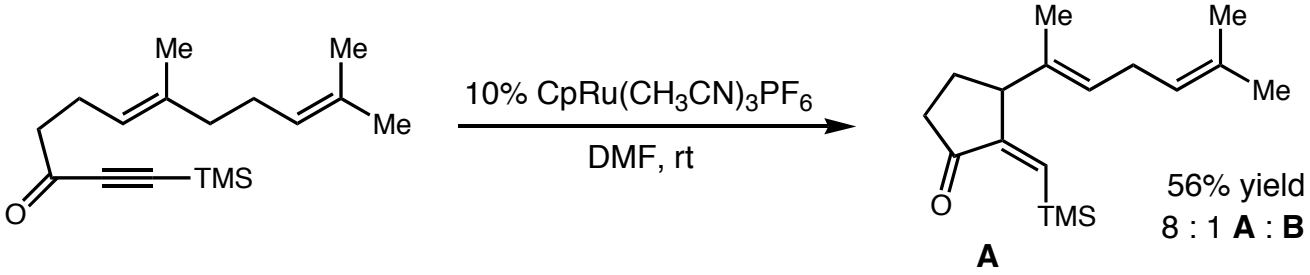


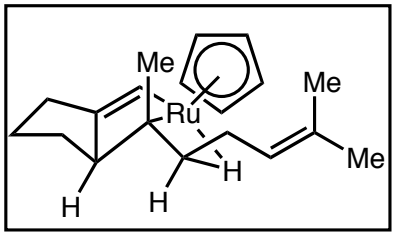


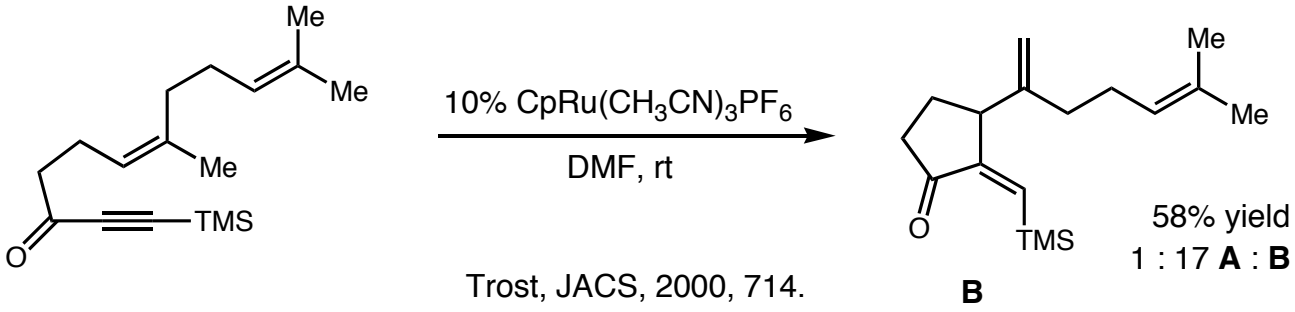
Trost, JACS, 1993, 4361 and 1995, 615.

Intramolecular Coupling of Alkenes and Alkynes

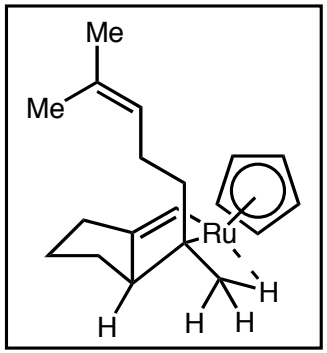
■ Olefin geometry of substrate can dictate product distribution



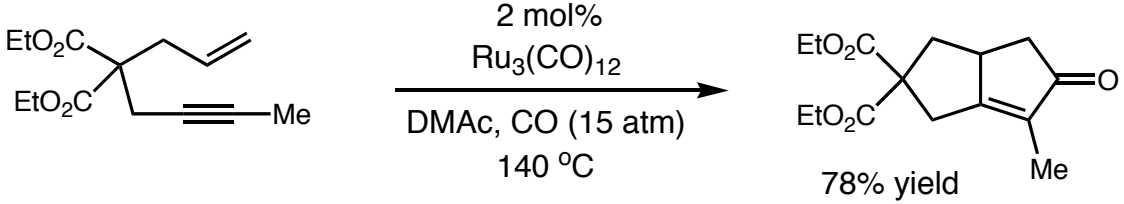




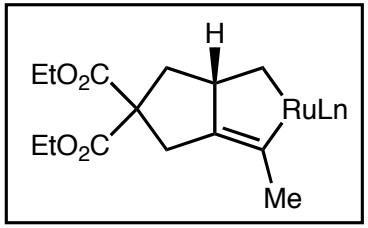
Trost, JACS, 2000, 714.



■ Ruthenium-catalyzed intramolecular Pauson-Khand reaction

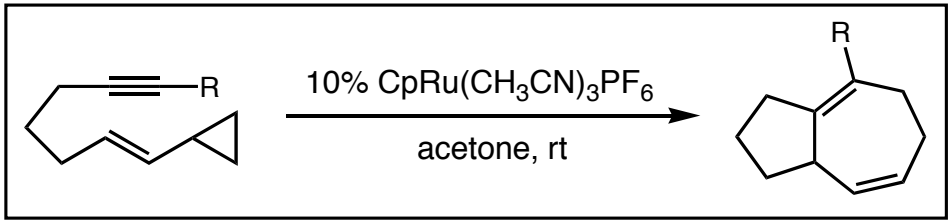


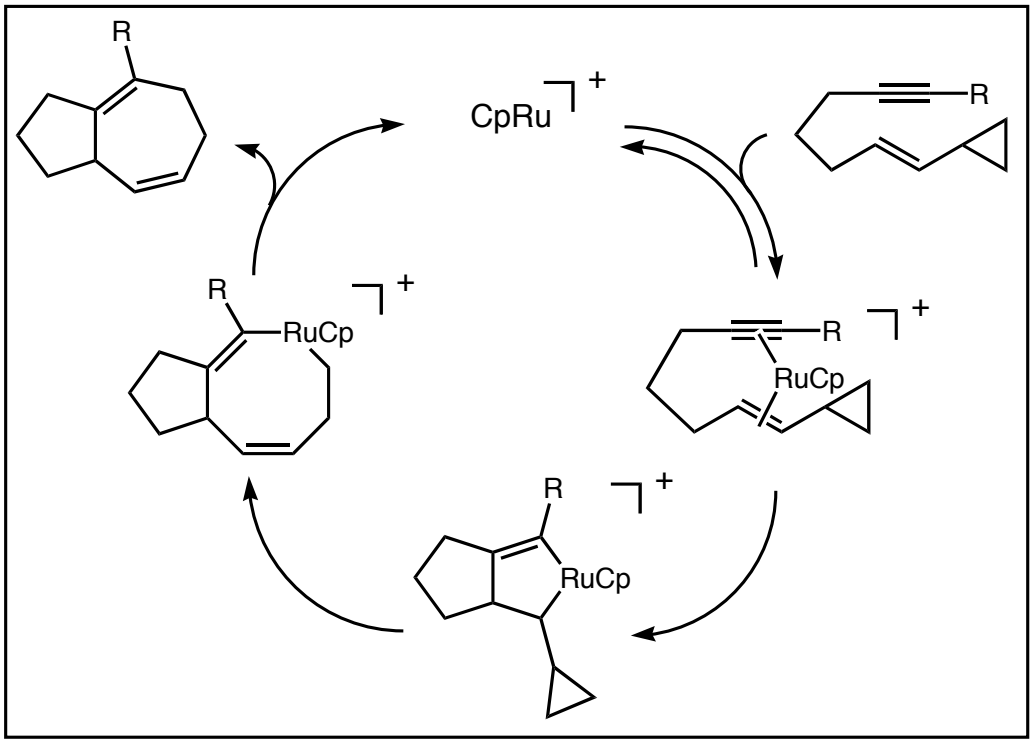
Mitsudo, JACS, 1997, 6187.



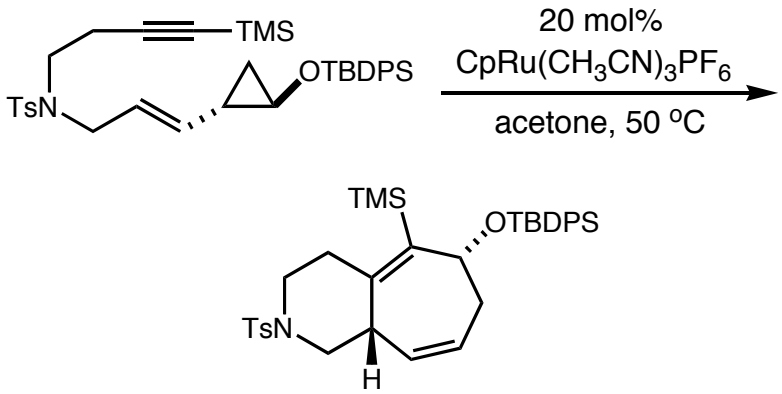
substrate must be unable to undergo β-hydride elimination

Intramolecular [5 + 2] Cycloadditions

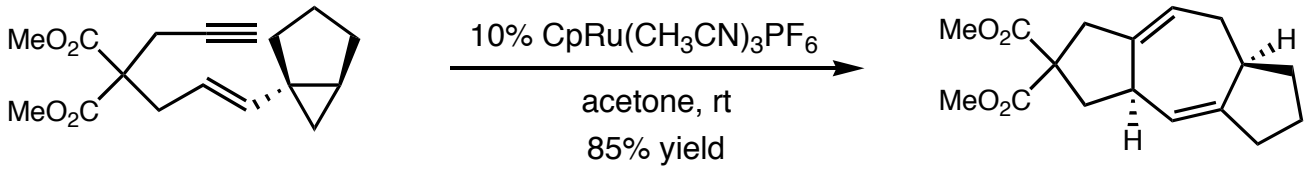




- Wender has reported the same reaction using rhodium. However, Ru is ~10 times cheaper than Rh.

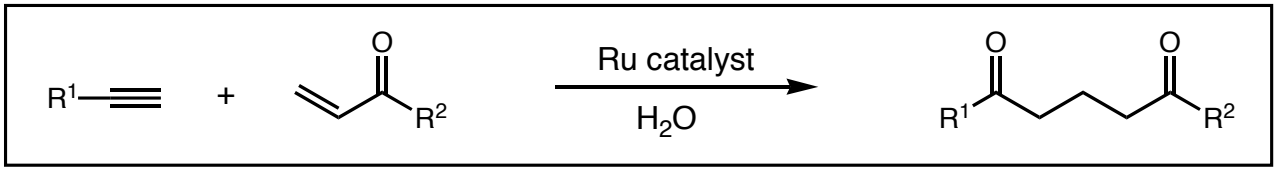


87% yield

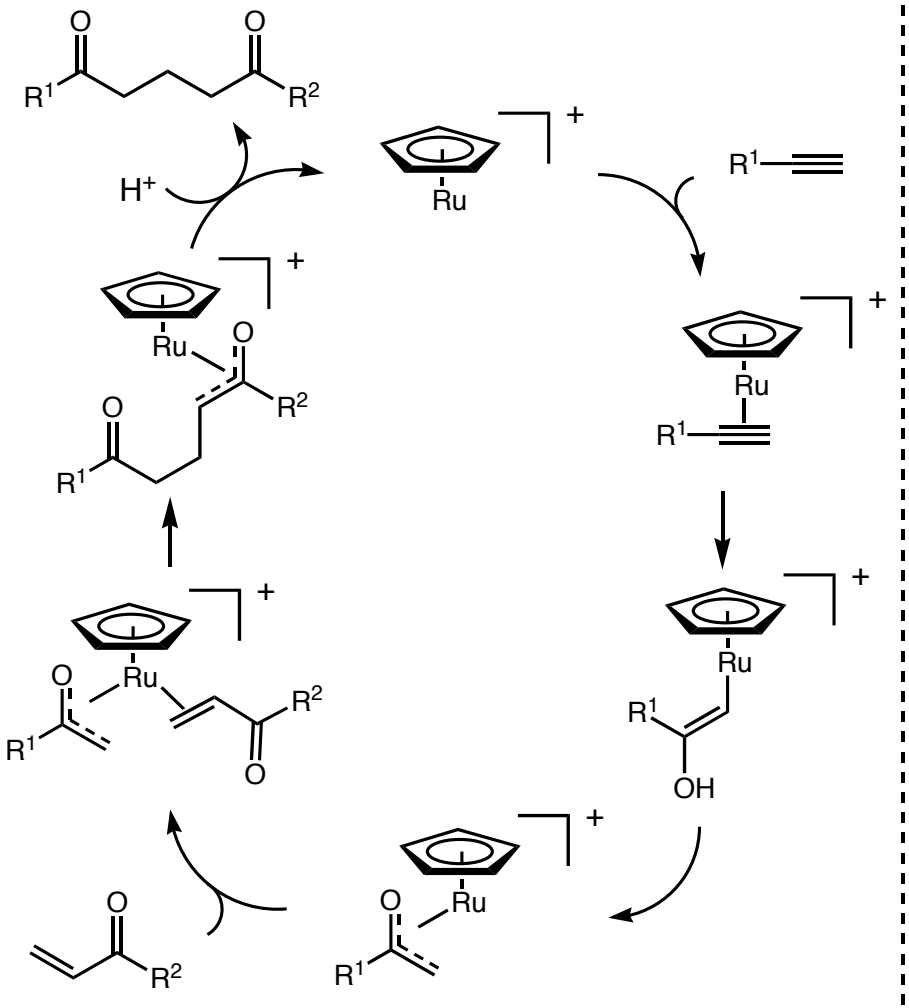


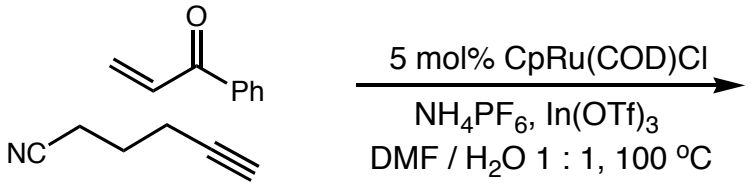
Trost, JACS, 2000, 2379.

Addition of Water to Alkynes: Formation of 1,5-Diketones

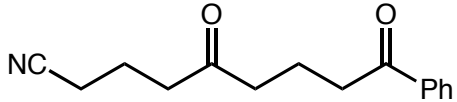


Mechanism:



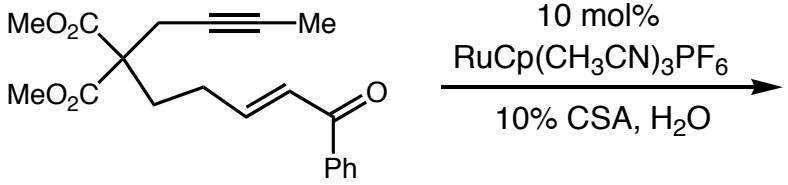


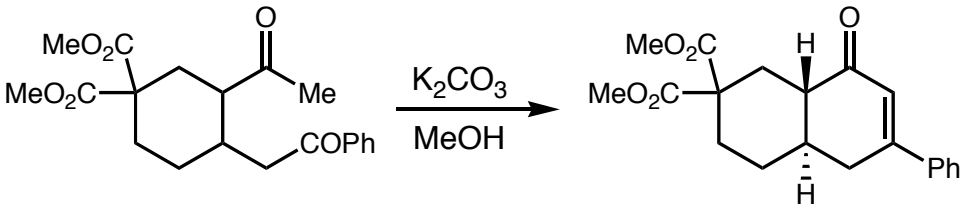
Trost, JACS, 1997, 836.



93% yield

■ Intramolecular variant is also known



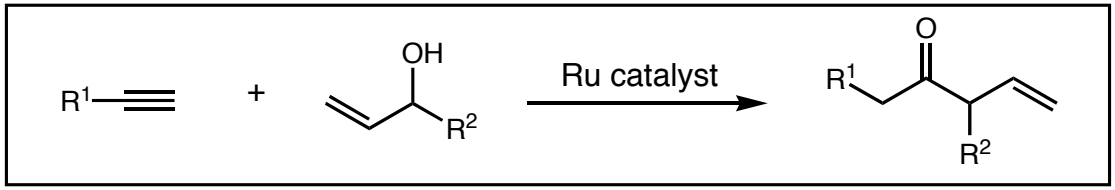


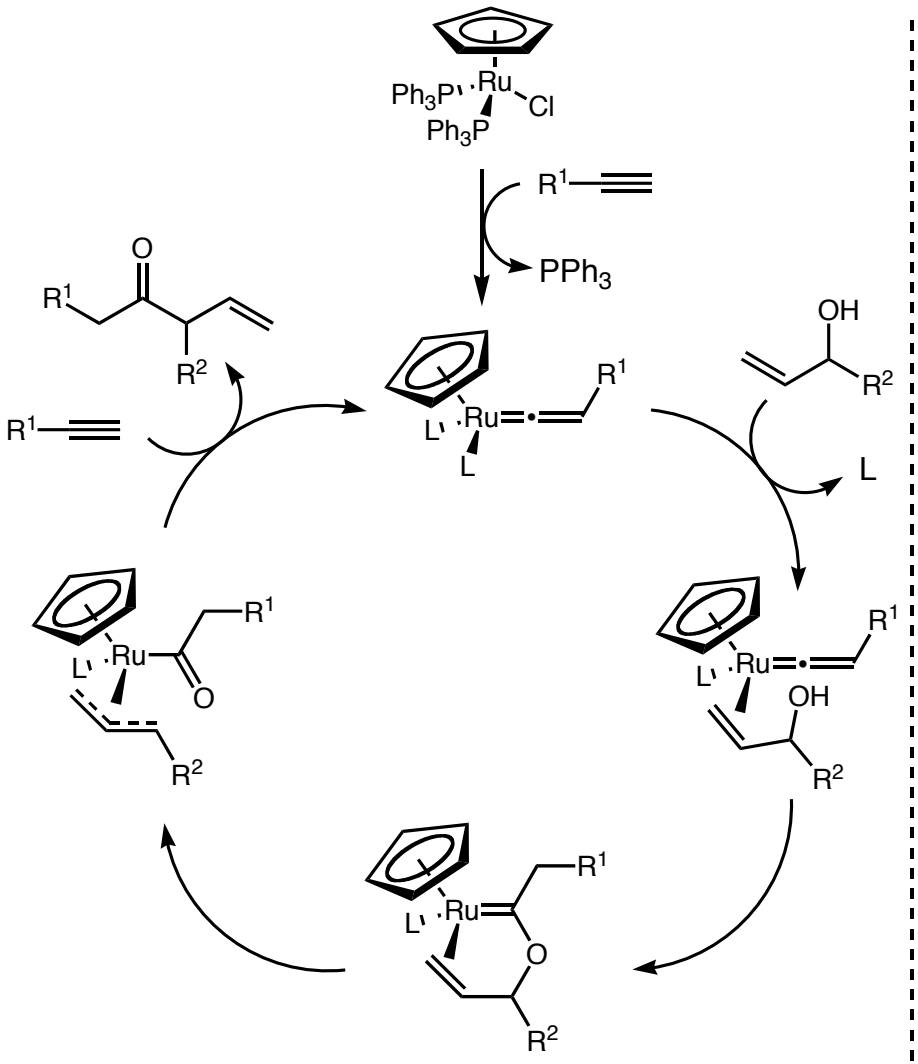
75% yield
2 : 1 dr

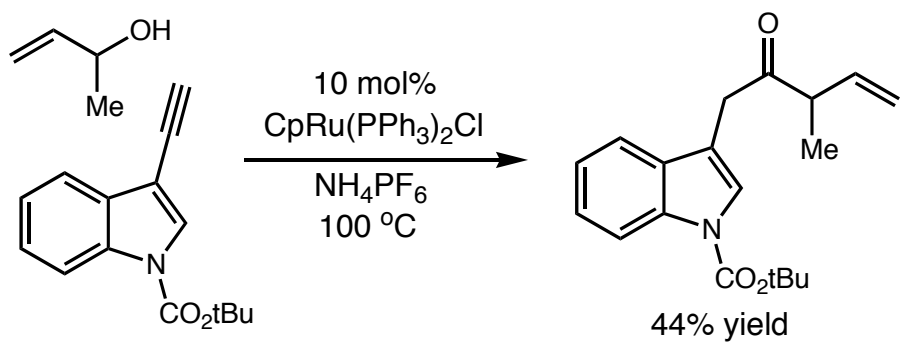
69% yield
one diastereomer

Trost, JACS, 2000, 5877.

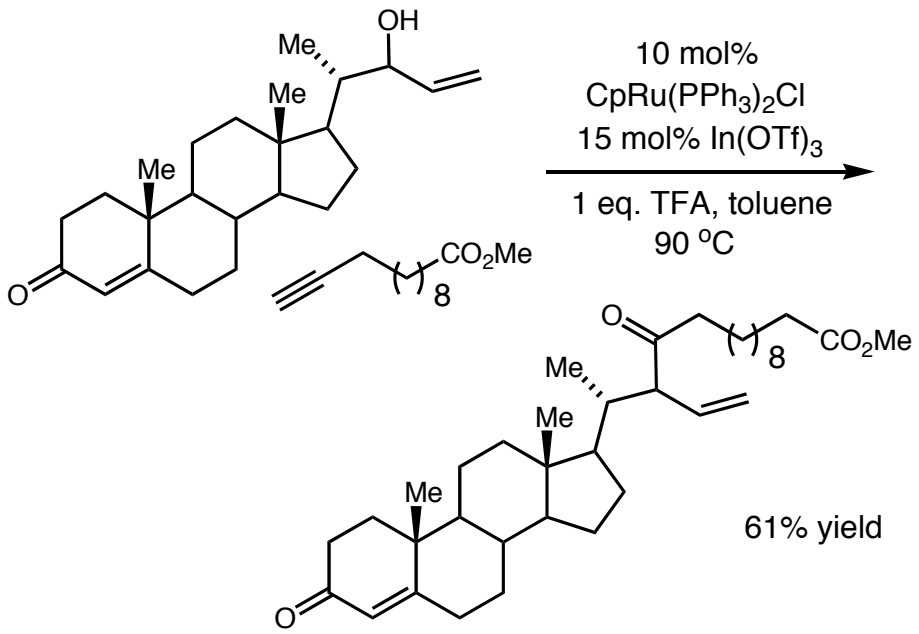
Reconstitutive Addition of Alkynes and Allylic Alcohols





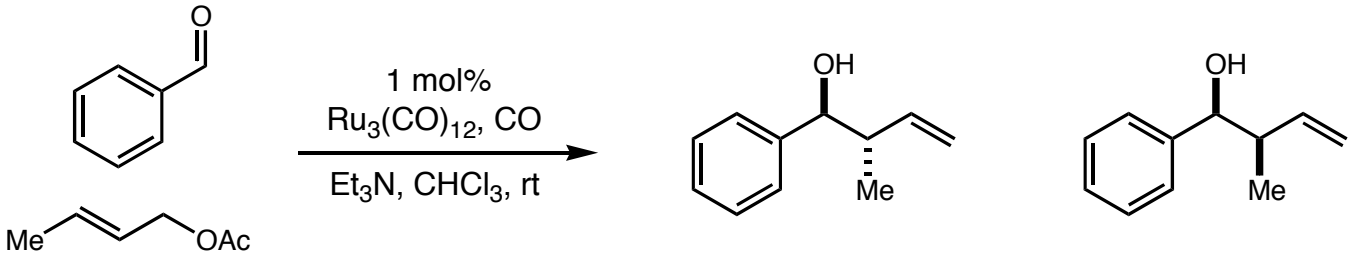


Trost, JACS, 1990, 7809.



Electrophilic Addition to π-Allyl Ruthenium Complexes

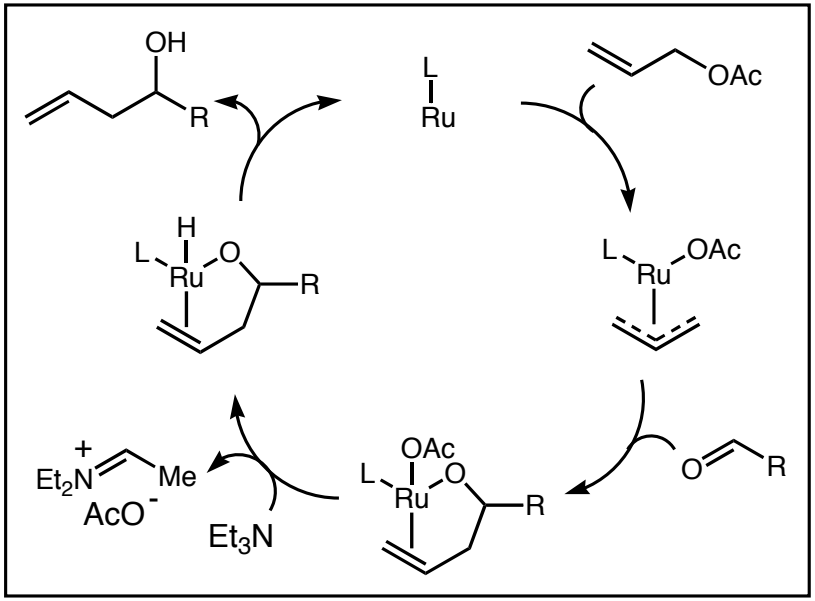
- π-allyl Ru complexes can exhibit nucleophilic as well as electrophilic behavior
- This property is due to the fact that ruthenium can access a wide range of oxidation states



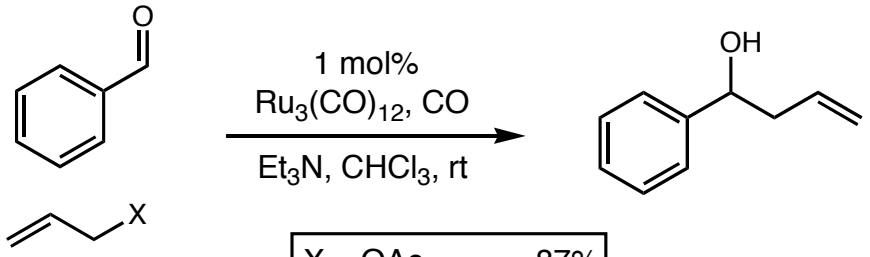
55 : 45

64% yield

Watanabe, Organometallics, 1995, 1945.



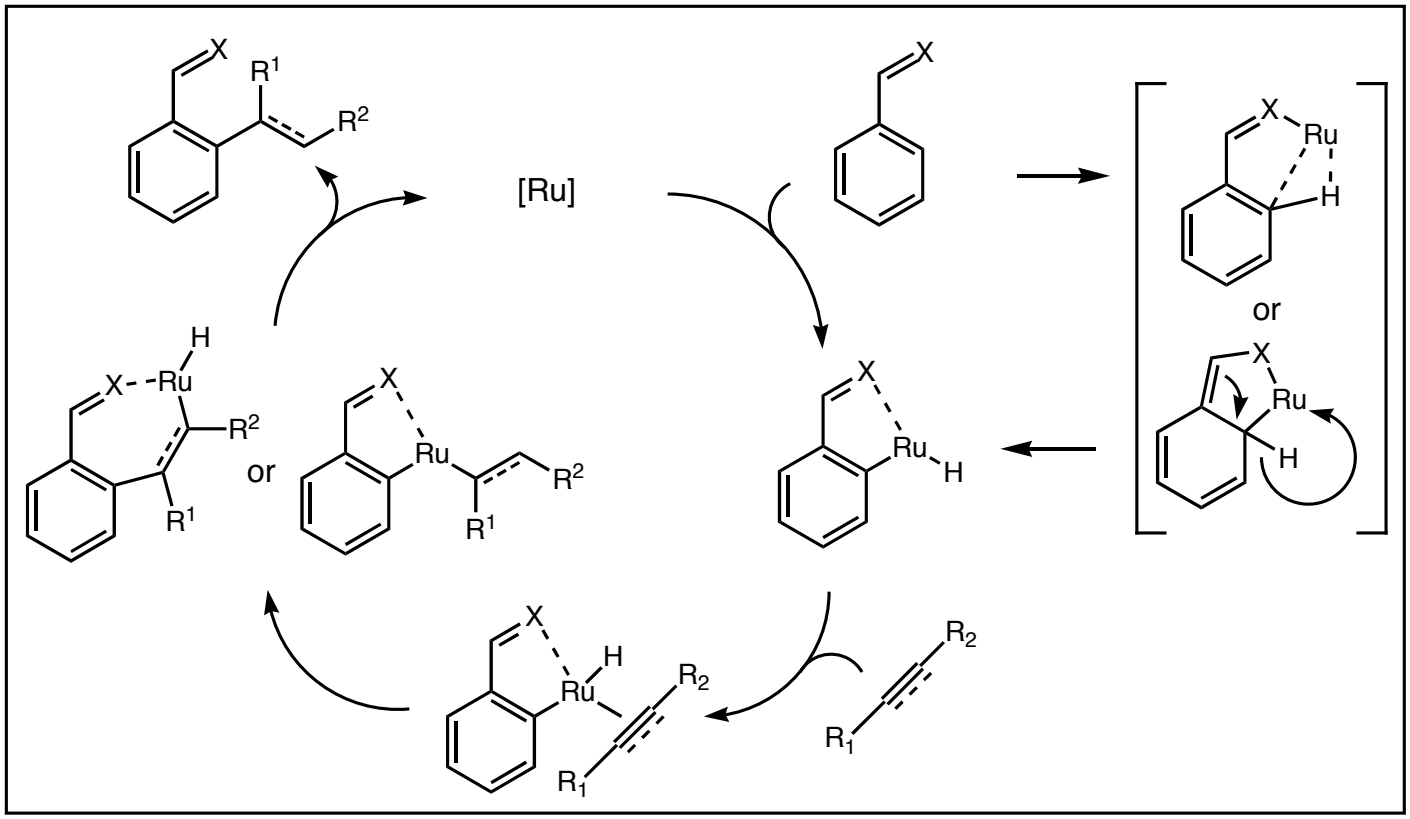
- CO is essential to catalytic activity--no rxn under Argon
- Tertiary amine base crucial, dimethylaniline, pyridine, K_2CO_3 were ineffective (see mechanism)
- Generally, only acetate as allylic group gives good yields



X = OAc	87%
X = Br	38%
X = OCO_2Me	39%
X =OH	0%

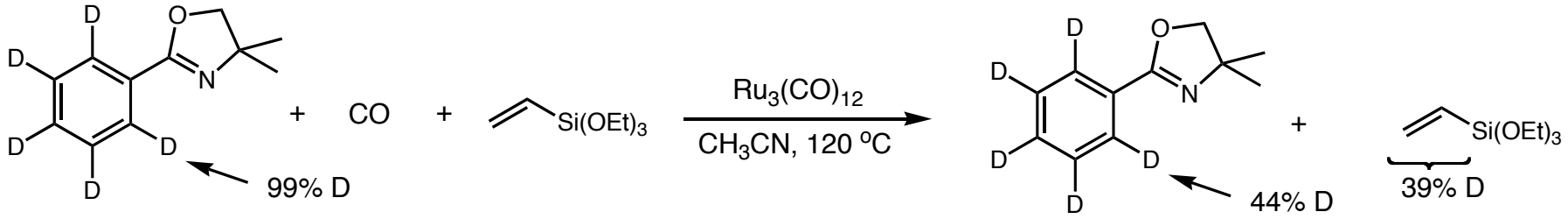
Watanabe, JOMC, 1989, 369, C51.

Activation of Aromatic C-H Bonds: Mechanism



Murai, Pure Appl. Chem., 1997, 589 and JOC, 2000, 1475.

■ Deuterium labelling experiment shows C-H / olefin insertions are reversible



1 mmol 1 atm 1 mmol

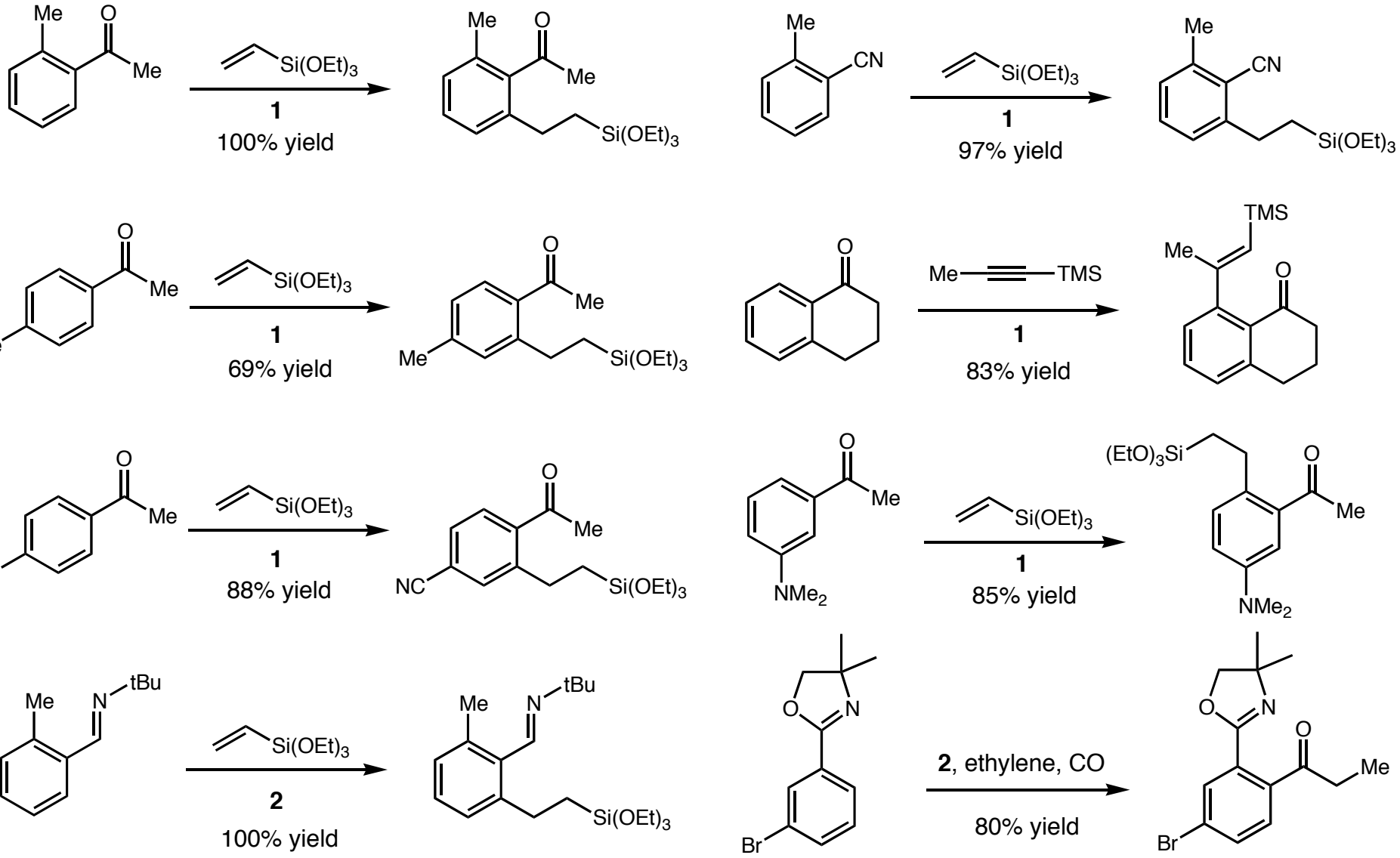
94% recovered 57% recovered

(40% theoretical D at each of 5 positions)

Activation of Aromatic C-H Bonds: Scope

1 = $Ru(H)_2(CO)(PPh_3)_3$

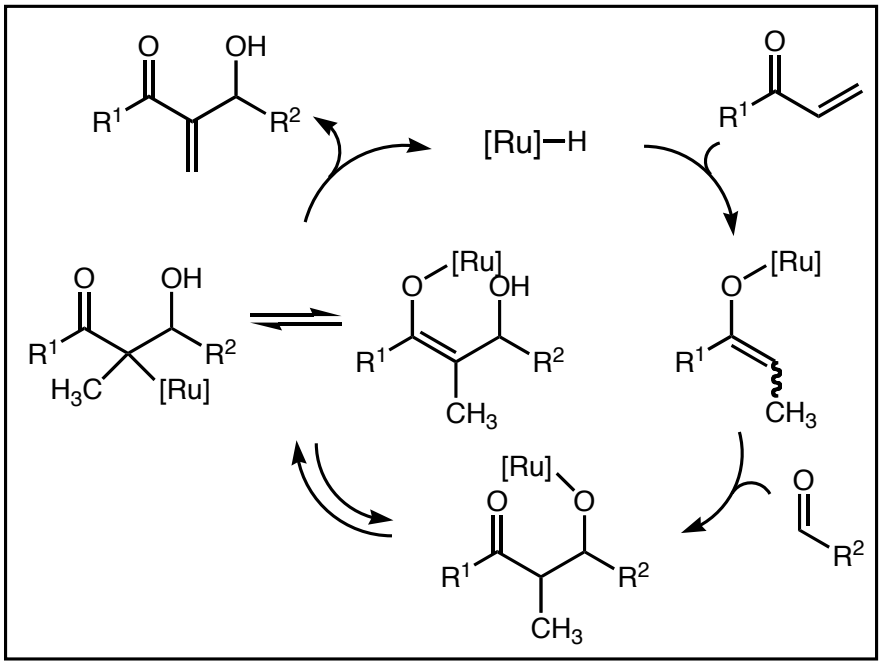
2 = $Ru_3(CO)_{12}$

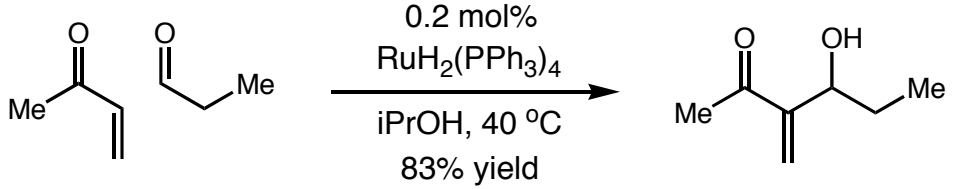


Trost, Chem. Rev., 2001, 2067.

Hydrometallation Initiated Reactions

■ Baylis-Hillman type reaction

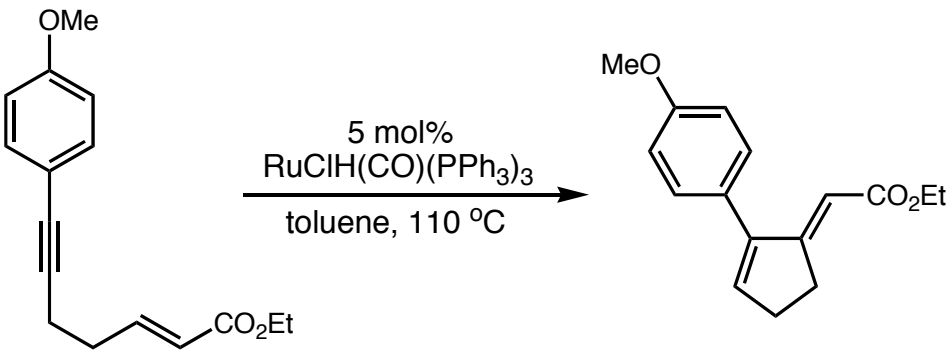




Matsuda, JOMC, 1989, 377, 347.

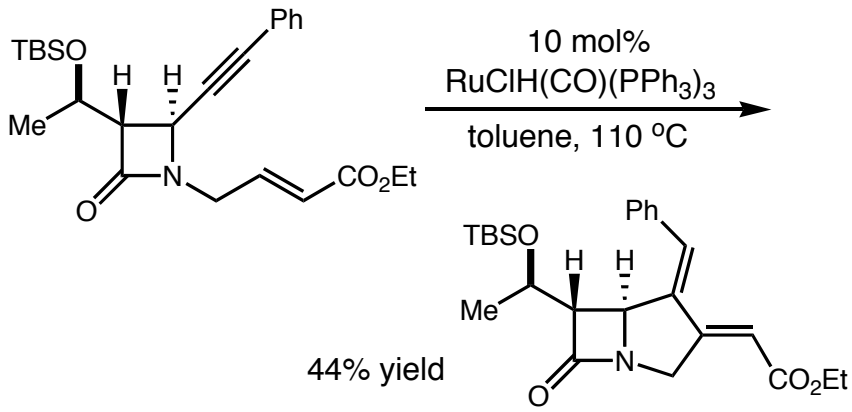
■ Substrate scope is very limited, Rh more effective

■ Cycloisomerization of ene-ynes



81% yield

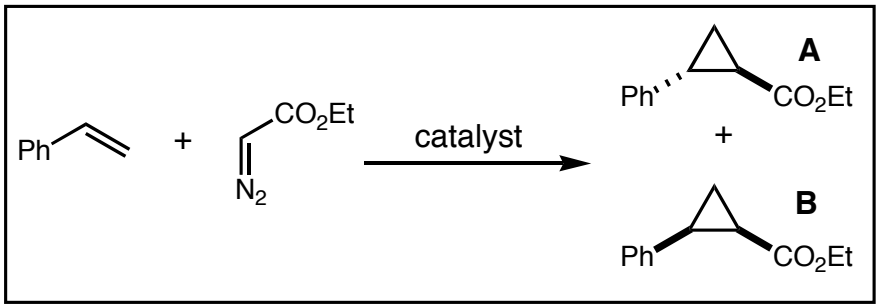
Mori, JOC, 1998, 9158.

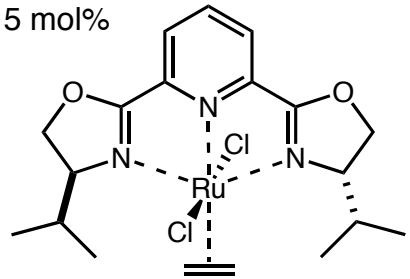
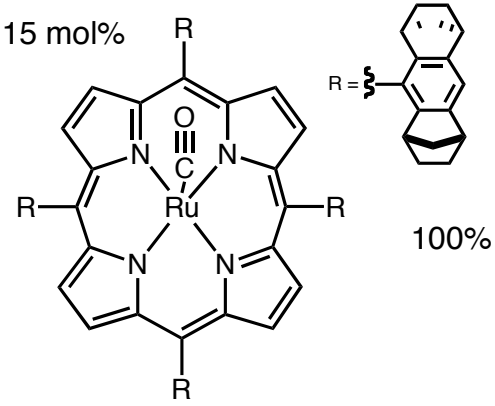
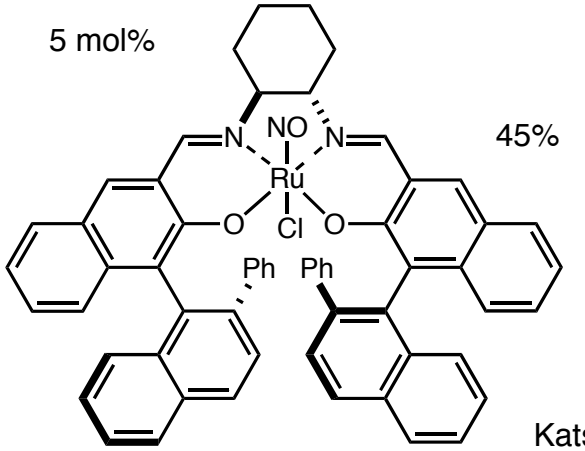


44% yield

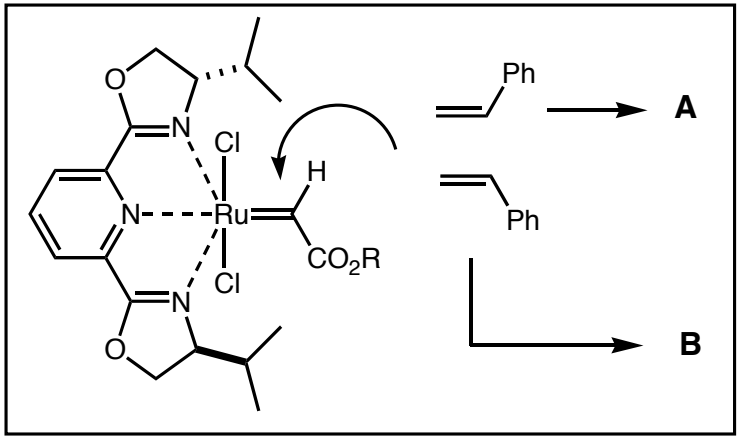
Mori, Org. Lett., 2000, 3245.

Cyclopropanation Using Diazo Esters



catalyst	yield	**A**(%ee) : **B**(%ee)
5 mol%  Nishiyama	73%	91(89) : 8(78)
0.15 mol% 	100%	95(91) : 5(27)
5 mol%  Katsuki	45%	7(15) : 93(97)

■ Stereochemical rational with pybox ligand



As expected, R = tBu gives higher dr and ee than R = Et

Trost, Chem. Rev., 2001, 2067 and ref. therein.

Conclusions

- Ruthenium catalyzes a tremendous range of organic transformations including hydrogenation of olefins, carbonyls, and imines; hydrogen transfer reactions; oxidation of olefins, alcohols, lactols, amines, amides, aromatics, and unactivated C-H bonds; epoxidations; olefin isomerizations; heteroatom addition to alkynes and nitriles; C-H activation; olefin metathesis and ene-yne metathesis; metallacycle formation; Pauson-Khand reactions; nucleophilic and electrophilic allylic substitutions; radical reactions;
and cyclopropanations among others.

- The field is relatively new and rapidly developing, especially in the area of C-C bond forming reactions. 50% of the articles sited in Trost, Chem. Rev., 2001, 2067 were published in 1997 or after.

- Ruthenium catalyzed chemistry promises to be an area of continuing development through the investigation of catalyst structure and the recognition and utilization of mechanistic intermediates.