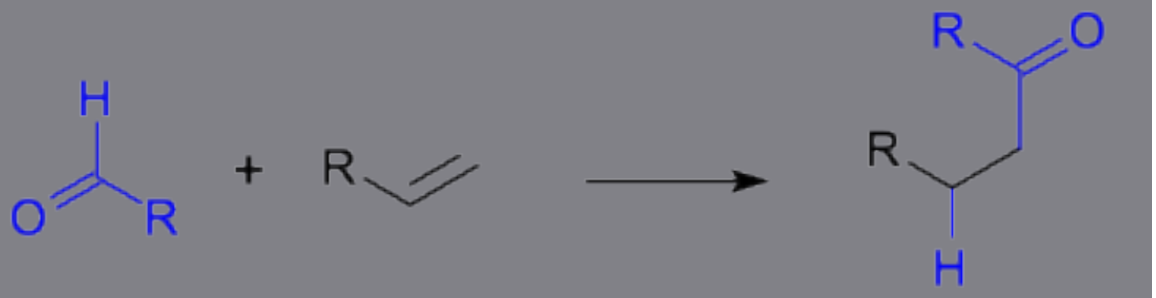
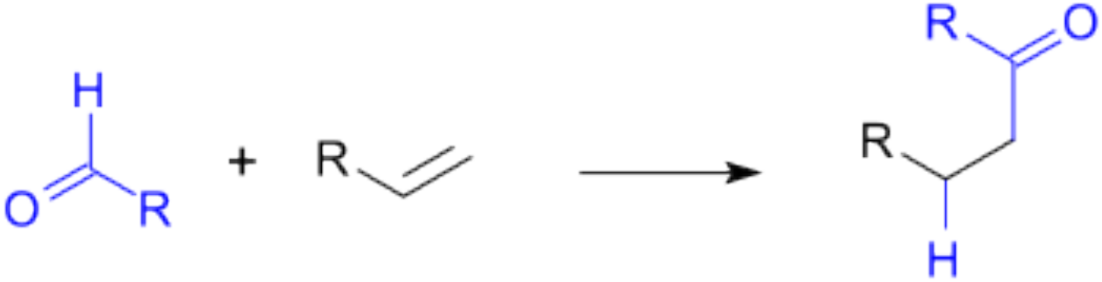


Hydroacylation and Related Topics

Dong Group Seminar

Brandon Reinus

Wed, Sept. 5th 2012



Why?

- Looking at the reaction, it is a highly atom-economical approach to synthesizing ketones
- Umpolung (ex: deprotonating dithioacetals)
- Using acrylate derivatives generates a 1,4 diketone relationship, a hard relationship to establish using classical organic synthesis.

Presentation Overview

1. Hydroformylation (extremely brief)
2. Rh-Catalyzed Hydroacylation
   - Intramolecular
   - Intermolecular
   - Other
3. NHC Catalyzed Hydroacylation
   - Benzoin reaction
   - Stetter reaction
   - other

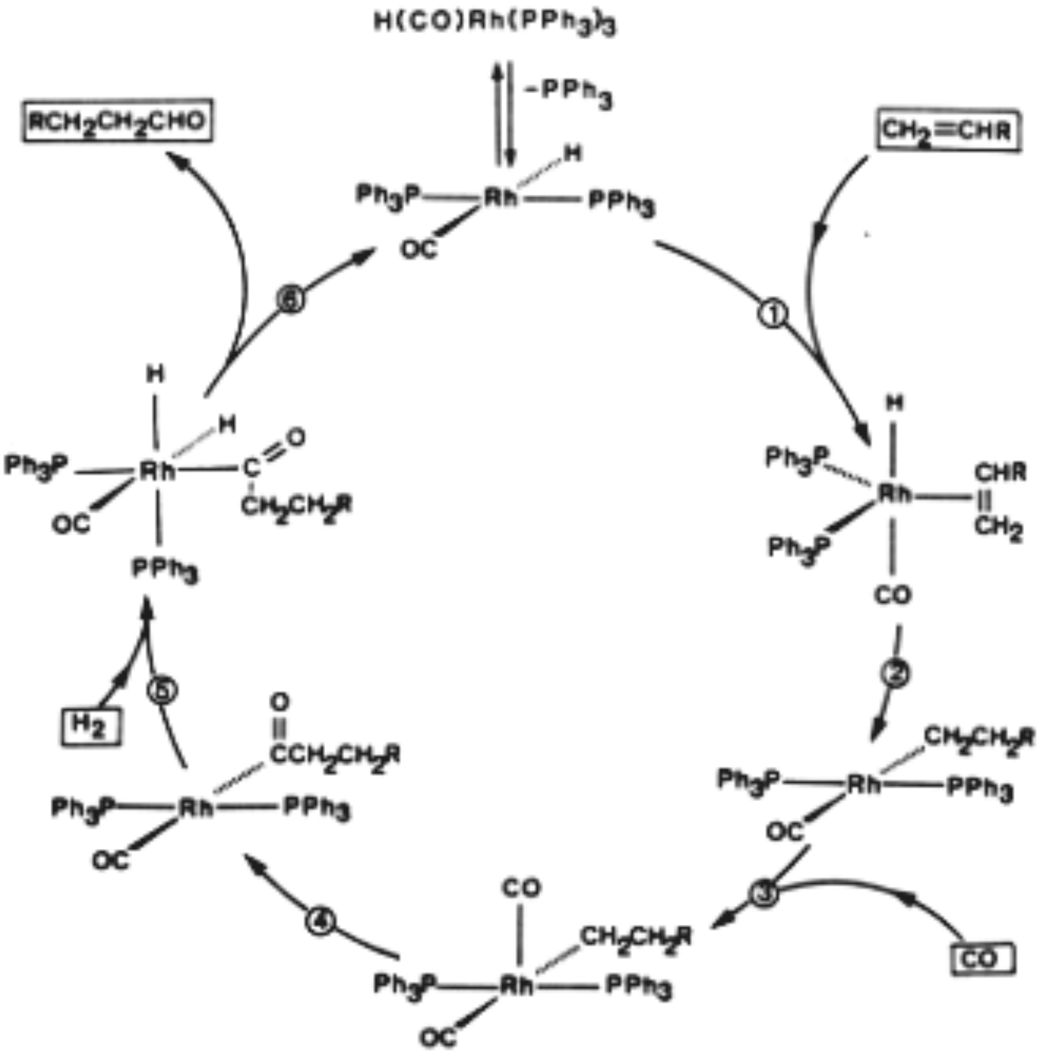
Part 1 : Background

Reppe

Roelen

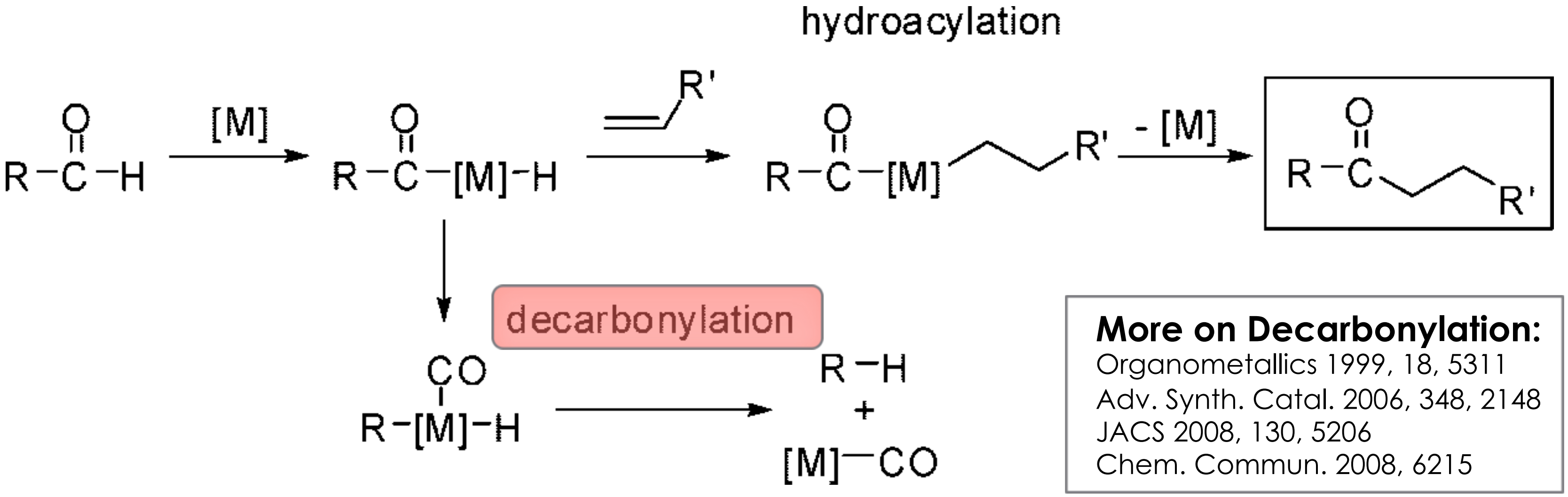
Science of Synthesis, Stereoselective Synthesis 1, 2011, pg.409

Hydroformylation



Union Carbide hydroformylation process

Part 2 : Rh-Catalyzed Hydroacylation



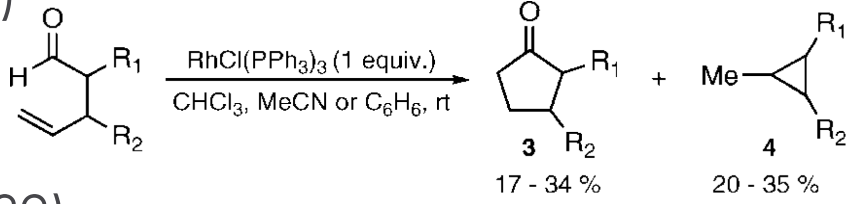
More on Decarbonylation:
Organometallics 1999, 18, 5311
Adv. Synth. Catal. 2006, 348, 2148
JACS 2008, 130, 5206
Chem. Commun. 2008, 6215

Decarbonylation can be surpressed by using high pressures of ethylene or CO or by generating a ***metallacycle***

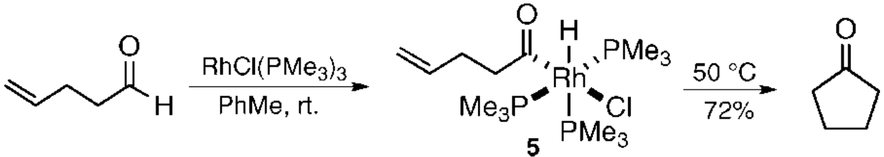
Accounts of Chemical Research p222, 2008

Historical Reactions

- Sakai (1972)

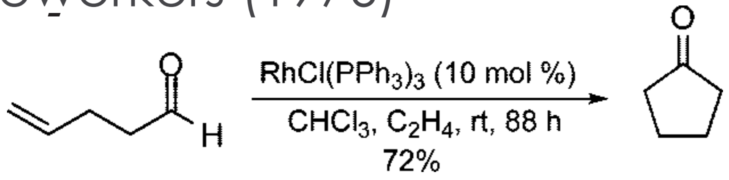


- Milstein (1982)



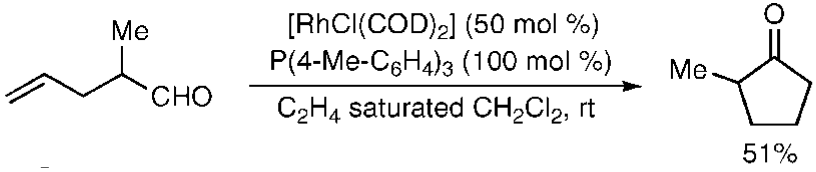
*Trimethyl phosphine is slow to dissociate

- Miller and Coworkers (1976)



*Also isolated ethylene insertion products

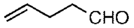
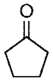
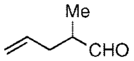
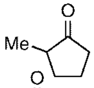
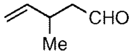
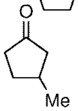
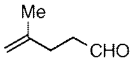
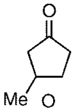
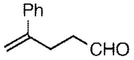
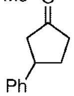
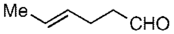
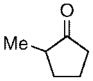
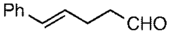
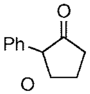
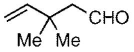
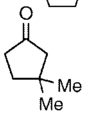
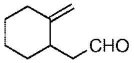
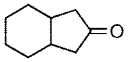
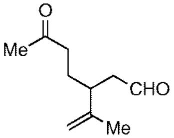
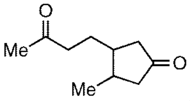
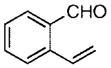
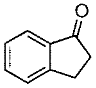
- Larock (1980)



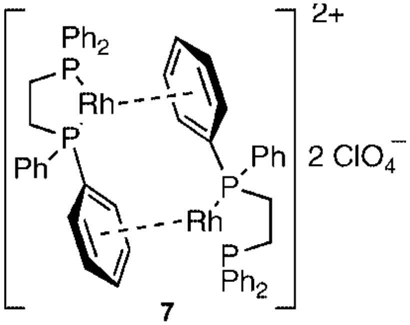
Chemical Reviews, 2010, p. 725

Intramolecular Reactions

Table 1. Scope of Bosnich's Cationic Rh(I) Cyclizations[a]

entry	aldehyde	catalyst mol %	product	yield (%)[b]
1		1		95
2		1		88
3		1		98
4		1		98
5		2		92
6		4		89
7[c]		10		70
8		1		100
9		1		90 35 : 65 *cis : trans*
10		2		94 42 : 58 *cis : trans*
11		2		30

[a] $[Rh(dppe)]_2(ClO_4)_2$, CD_3NO_2, 20 °C. [b] Determined by GC and ^1H NMR methods. [c] 65 °C.



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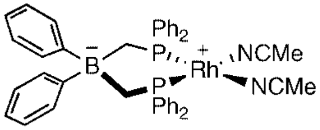

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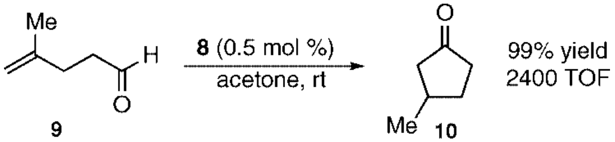
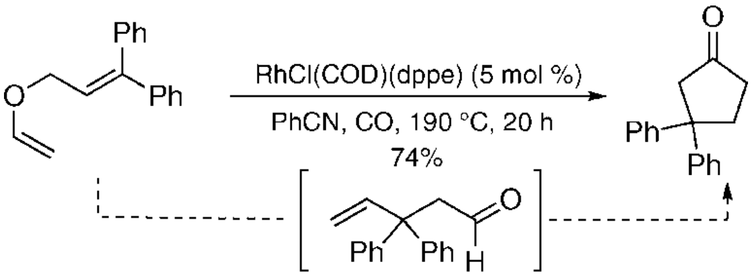
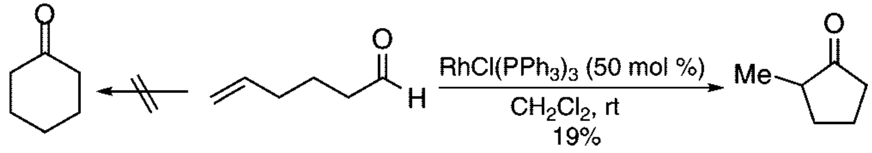


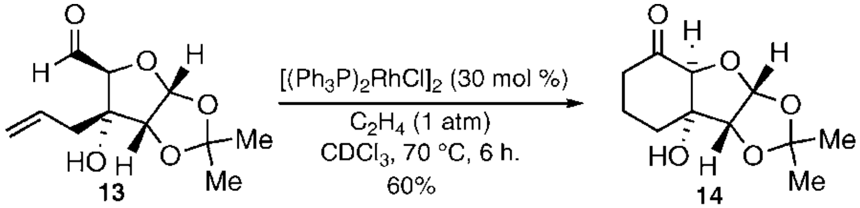
Tandem Reaction:

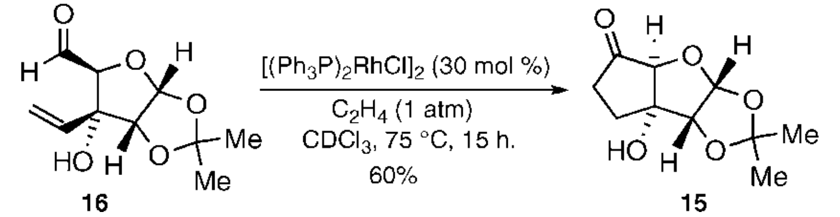


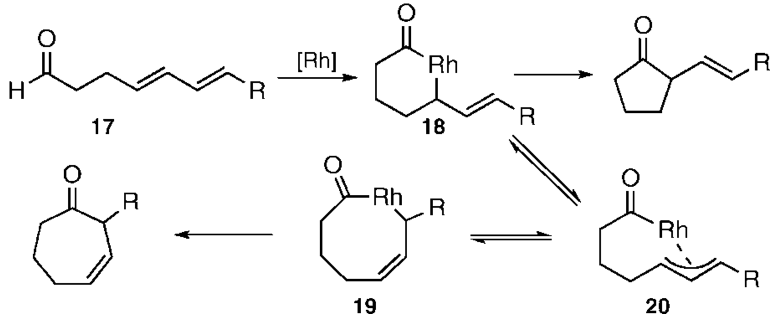
Organometallics 1988, 7, 936-945
Angew Chem, Int. Ed. 2003, 42, 2385

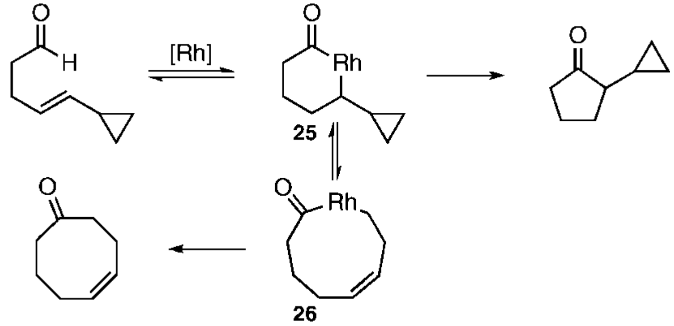
Larger Rings

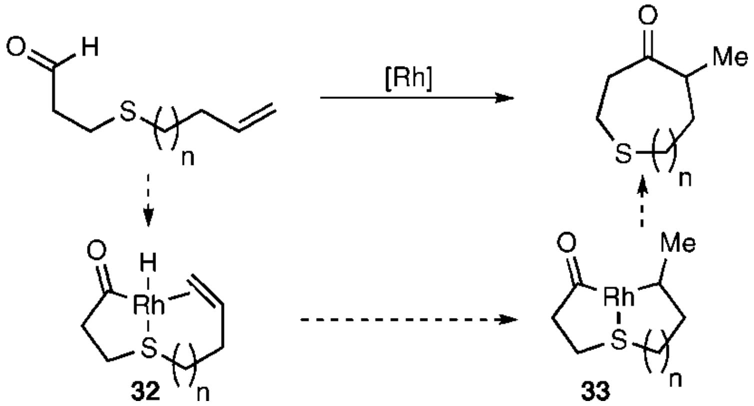






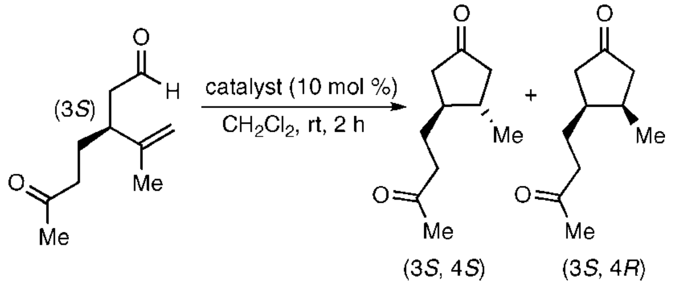




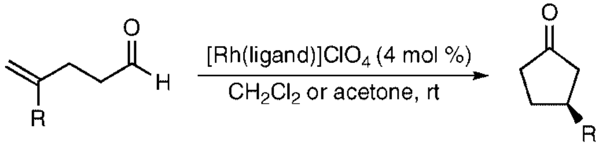


Chem reviews 2010, p.725

Diastereo and Enantioselective



entry	substrate	catalyst	time (h)	yield (%)	*cis*/*trans*
1	3*R*	Rh[(*S*)-BINAP]ClO_4	1.5	85	<1:>99
2	3*R*	Rh[(*R*)-BINAP]ClO_4	4	74	97:3
3	3*S*	Rh[(*R*)-BINAP]ClO_4	2	86	<1:>99
4	3*S*	Rh[(*S*)-BINAP]ClO_4	5	82	96:4

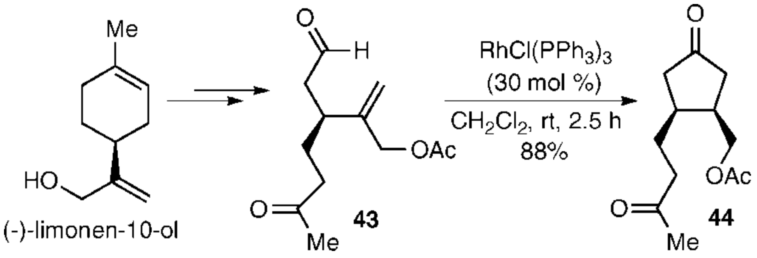


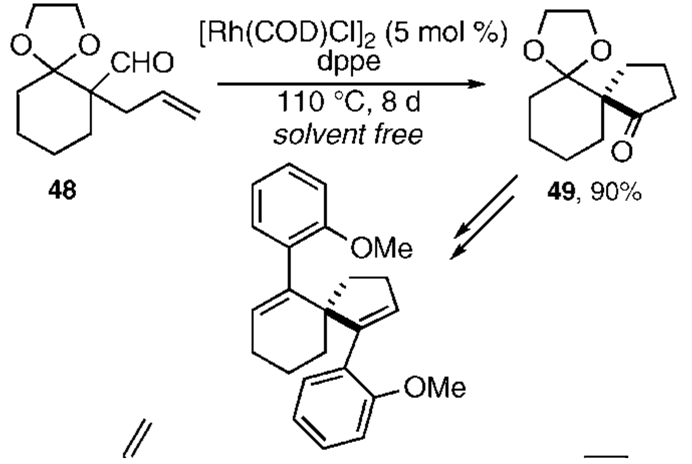
entry	R	ligand	ee (%)
1[a,b]	Me	(*S*,*S*)-MeDuphos	94
2[a,b]	*i*Pr	(*S*,*S*)-MeDuphos	96
3[a,b]	cyclopentyl	(*S*,*S*)-MeDuphos	96
4[c]	*t*Bu	(*S*)-BINAP	>99
5[c]	$SiMe_3$	(*S*)-BINAP	>99
6[c]	Ph	(*S*,*S*)-chiraphos	78
7[c]	4-MeO-Ph	(*S*,*S*)-chiraphos	75
8[c]	C(O)Me	(*S*)-BINAP	87
9[c]	C(O)Ph	(*S*)-BINAP	94
10[b]	CO_2Et	(*S*)-BINAP	>99
11[b]	CO_2*i*Pr	(*S*)-BINAP	>99

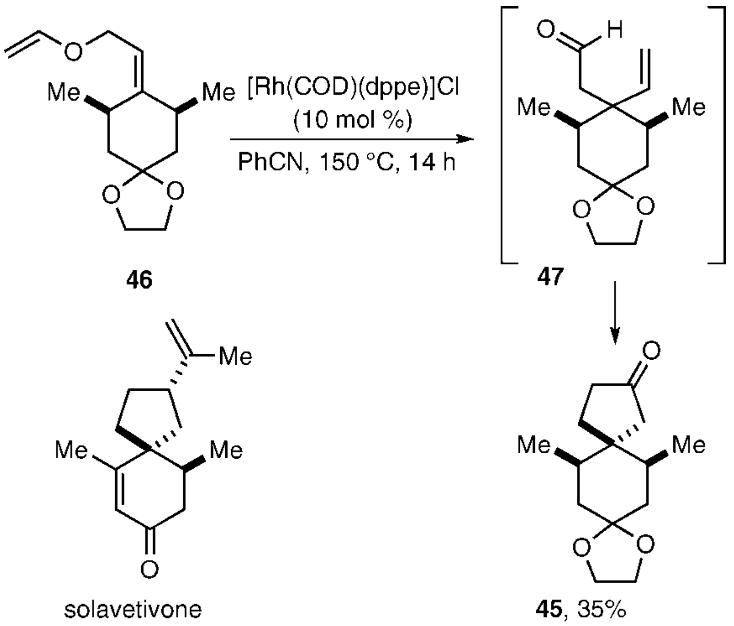
[a] PF_6^- salt (5 mol %) used. [b] Acetone. [c] CH_2Cl_2.

Chem reviews 2010, p.725

Application

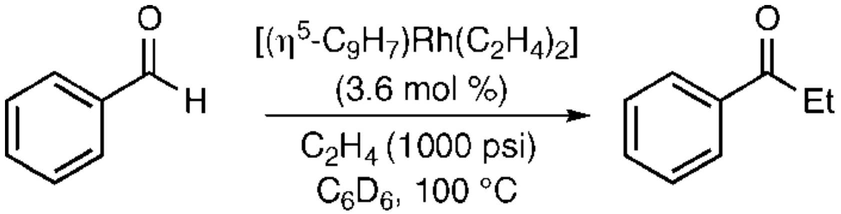


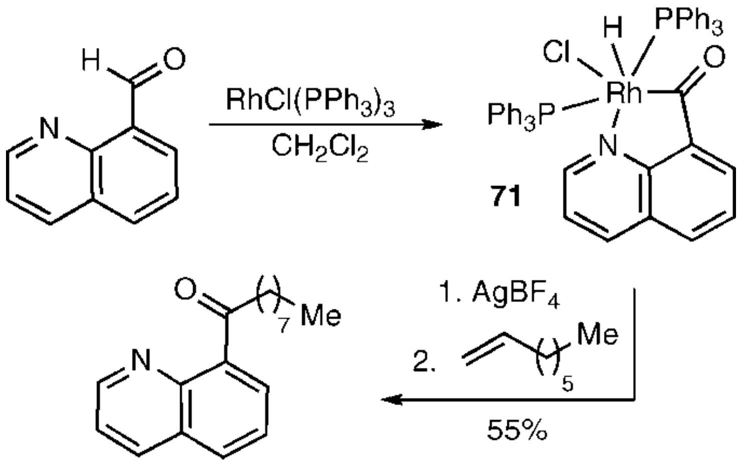




Chem reviews 2010, p.725

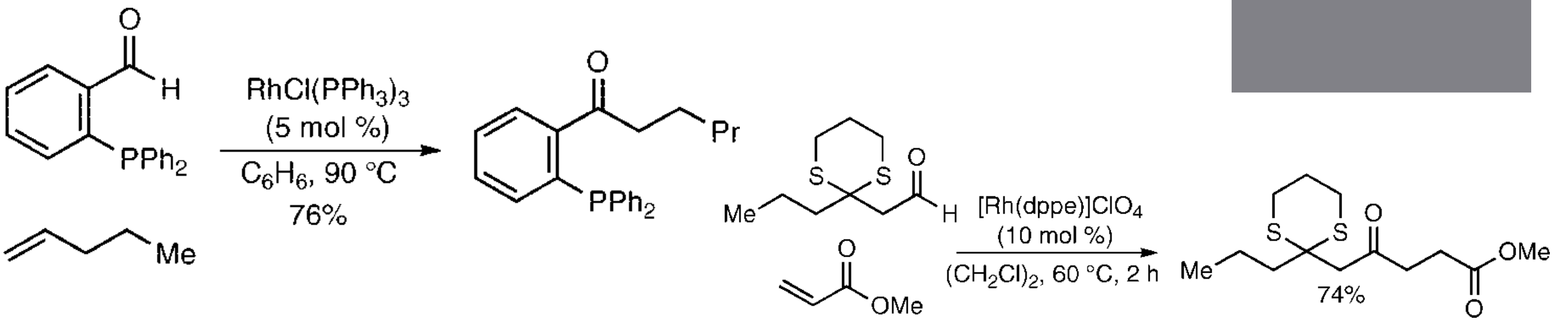
Intermolecular Hydroacylation

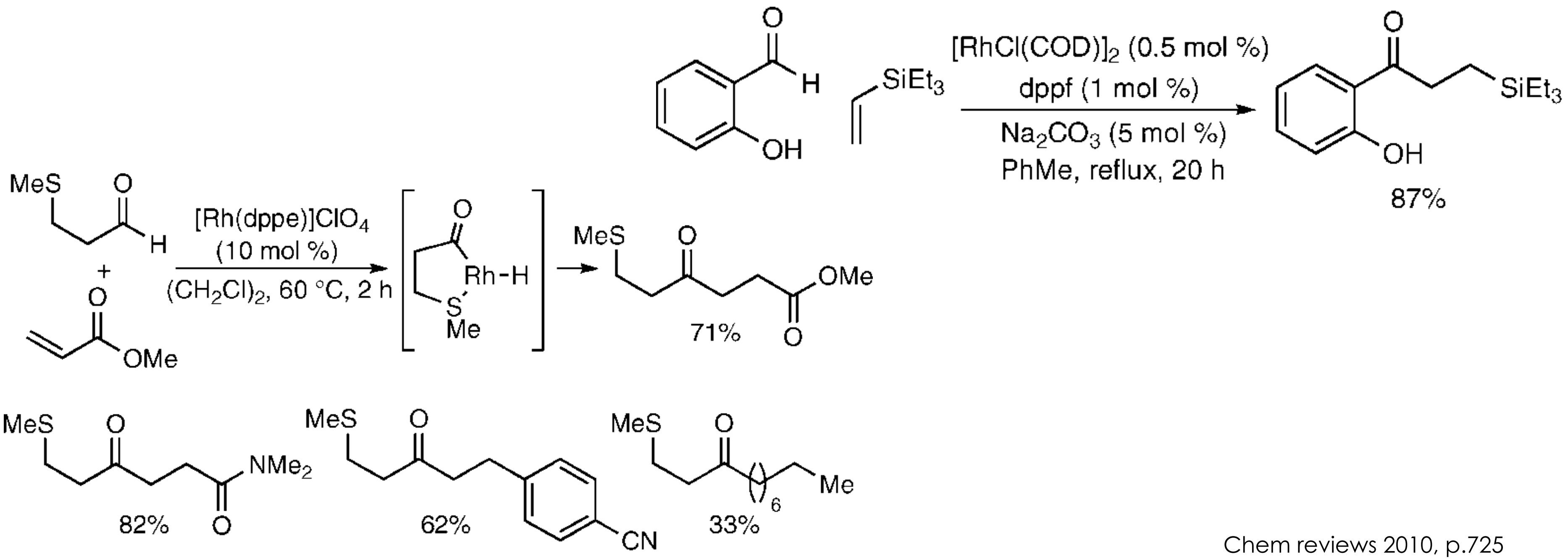




Chem reviews 2010, p.725

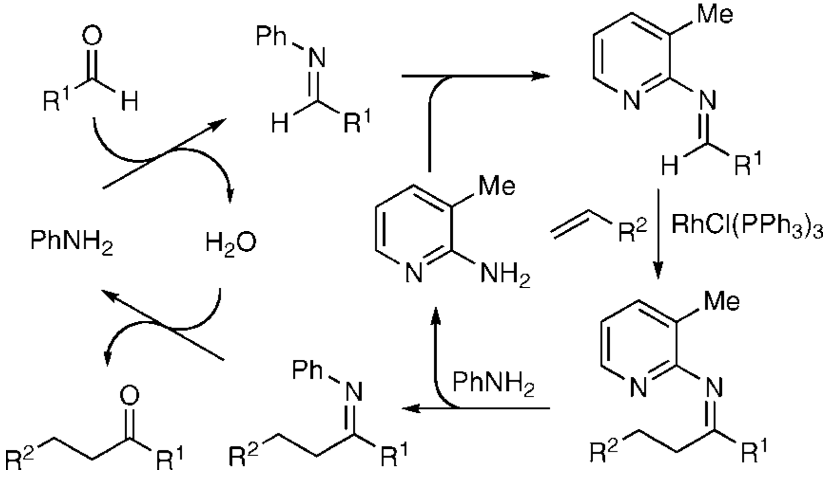
Chelation Assisted

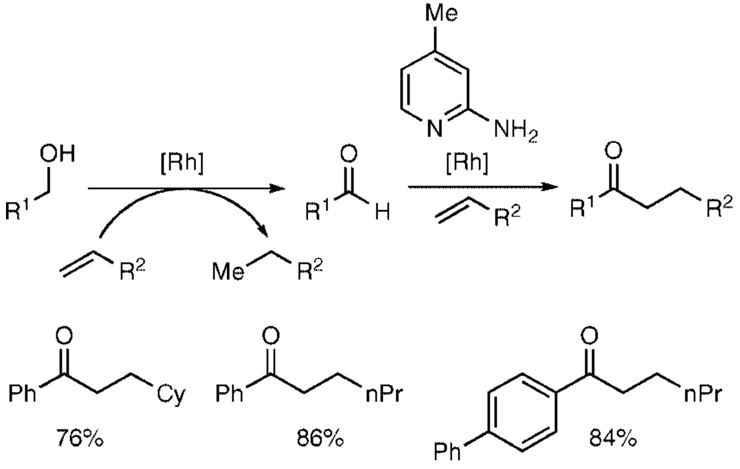


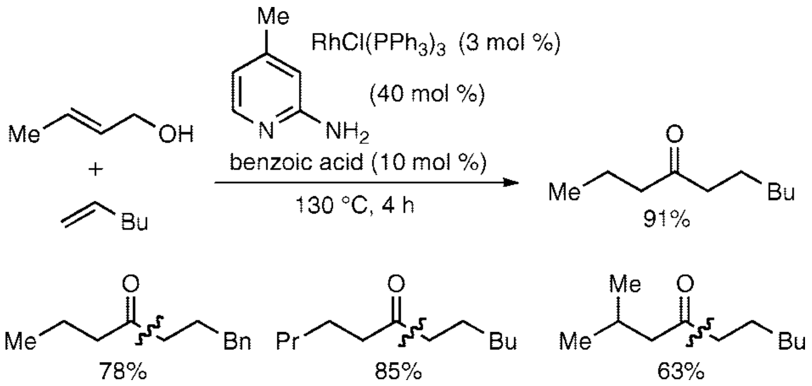


Chem reviews 2010, p.725

Aldimines

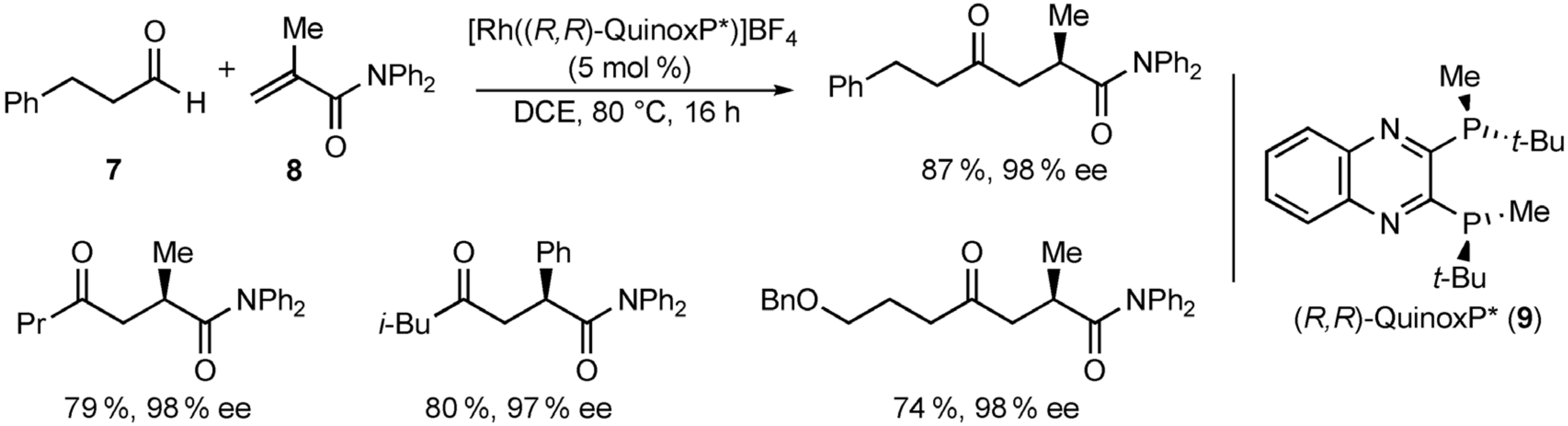






Chem reviews 2010, p.725

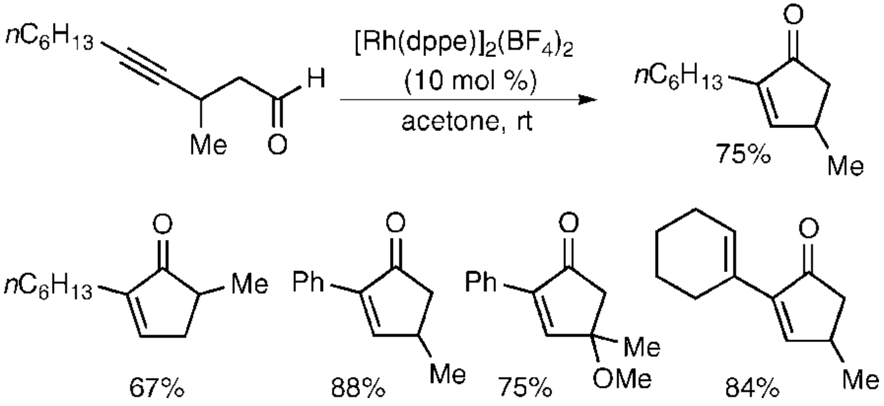
Stereoselective Intermolecular reactions

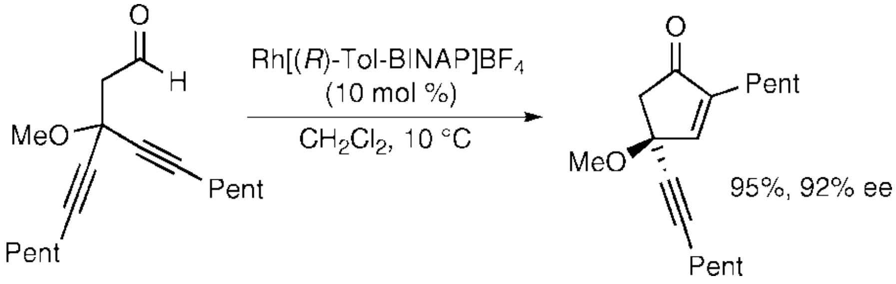


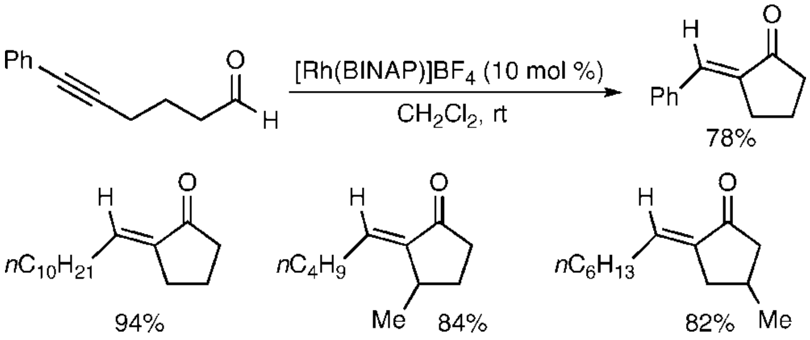
Very limited in scope, still needs a lot of work

Pure Appl. Chem. Vol. 83, p. 577, 2011

Alkynes Intramolecular

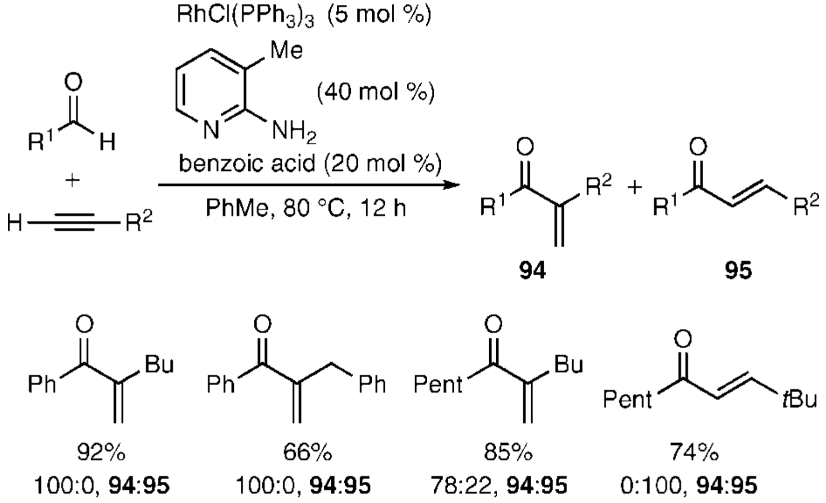




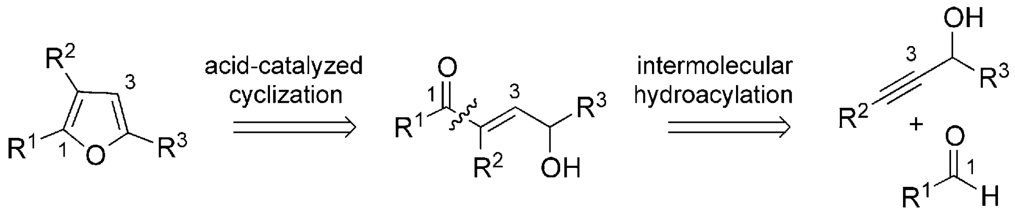


Chem reviews 2010, p.725

Alkynes Intermolecular

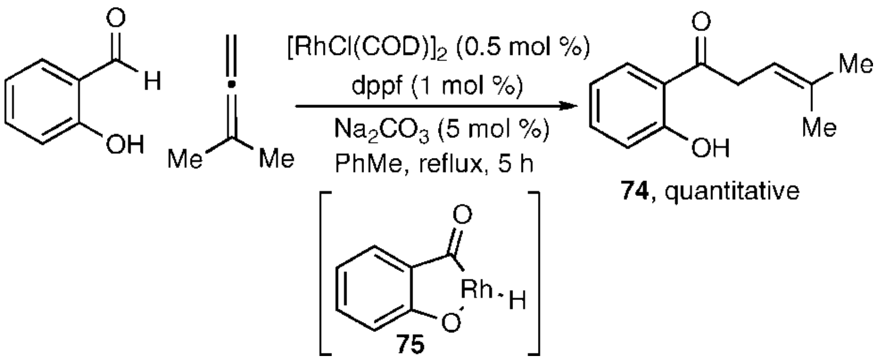


Application:



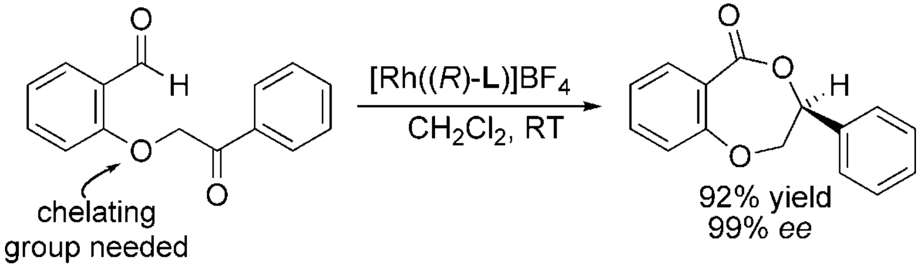
Chem reviews 2010, p.725
Angew. Chem. Int. Ed. 2011, 50, 10657

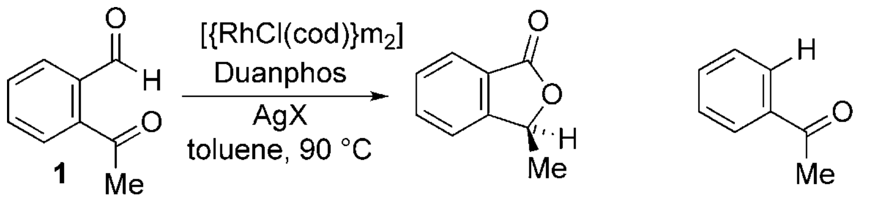
Other substrates



74, quantitative

75





1

2
phthalide product

3
decarbonylation-
derived by-produc

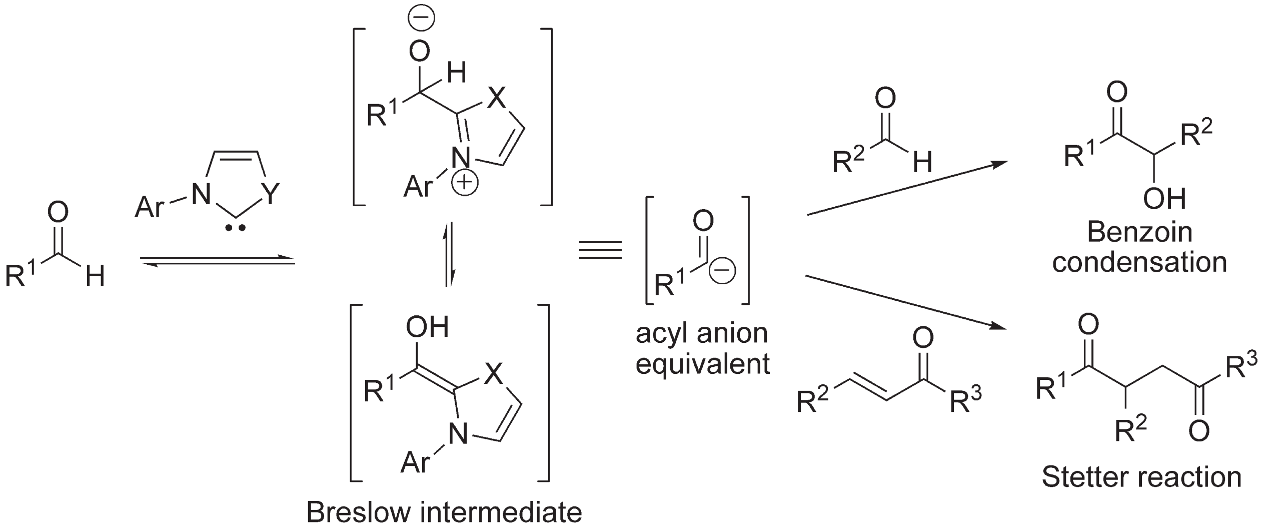
Few examples, C-O bond formation

Chem reviews 2010, p.725
Angew. Chem. Int. Ed. 2010,49,6026-6027

My take:

- **Intramolecular**- start with cationic or other coordinatively unsaturated Rh(I)
- **Intermolecular**
  - **Chelation**- toss-up both are used in the literature, see if anyone has used similar substrates, if not lean towards starting with cationic Rh(I)
  - **Aldimines** – start with Wilkinson's catalyst or other neutral Rh (I)

Part 3 ; NHC Catalyzed RXNS



Part 1

Part 2

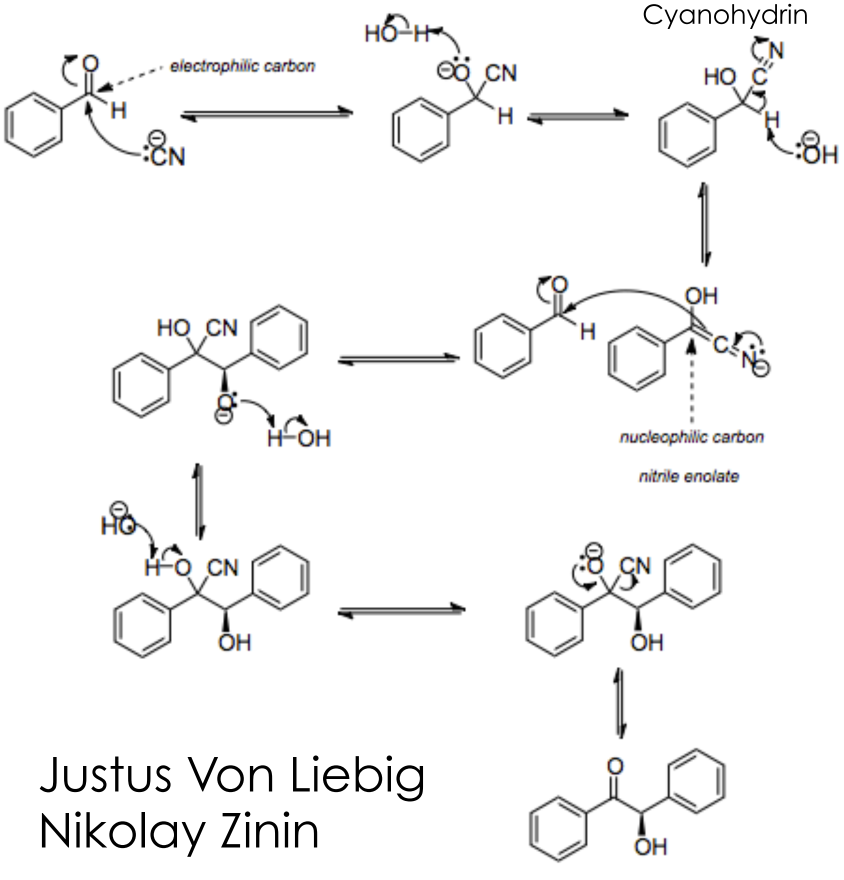
Unconventional reactions

Part 3

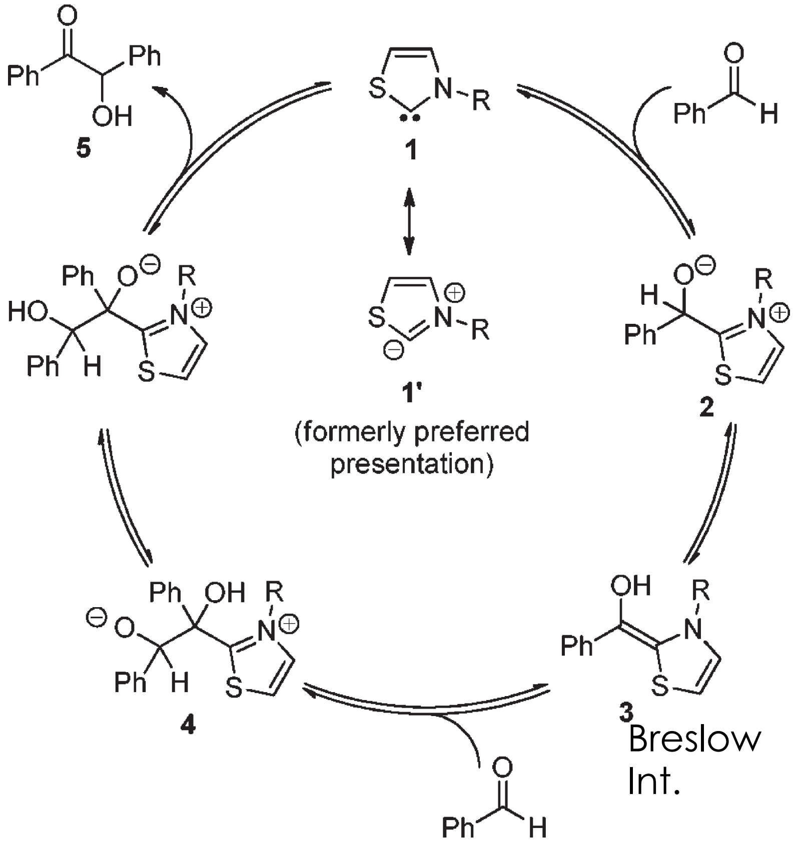
Benzoin Condensation

The Old

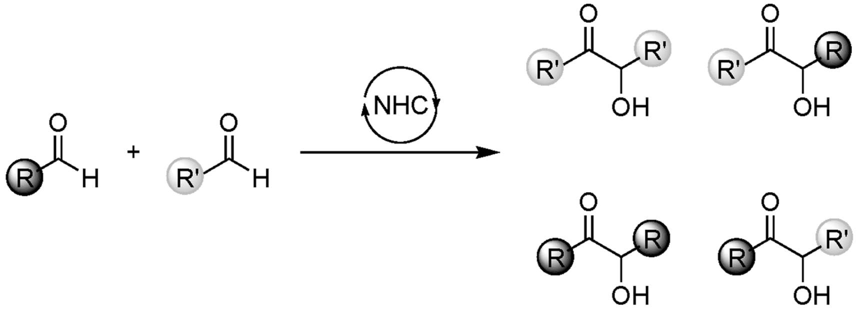
The New

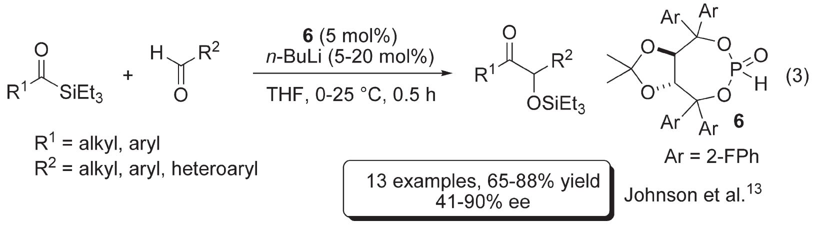


Justus Von Liebig
Nikolay Zinin



Cross-Benzoin

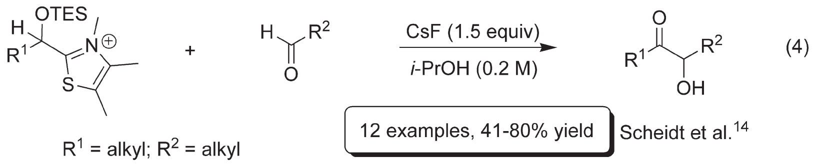




R^1 = alkyl, aryl
R^2 = alkyl, aryl, heteroaryl

13 examples, 65-88% yield
41-90% ee

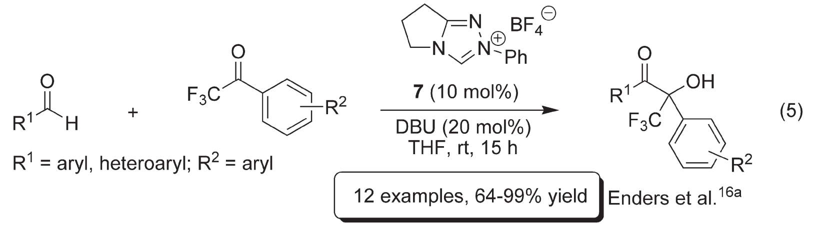
Johnson et al.[13]



R^1 = alkyl; R^2 = alkyl

12 examples, 41-80% yield

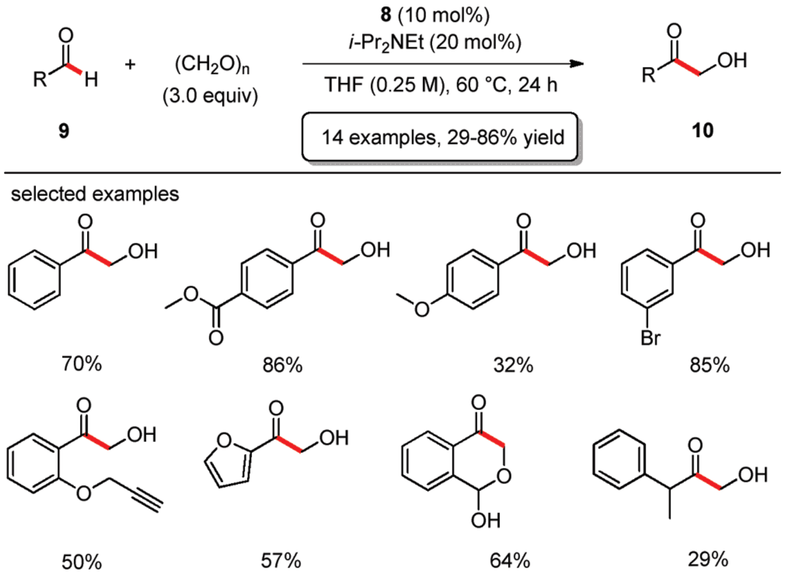
Scheidt et al.[14]



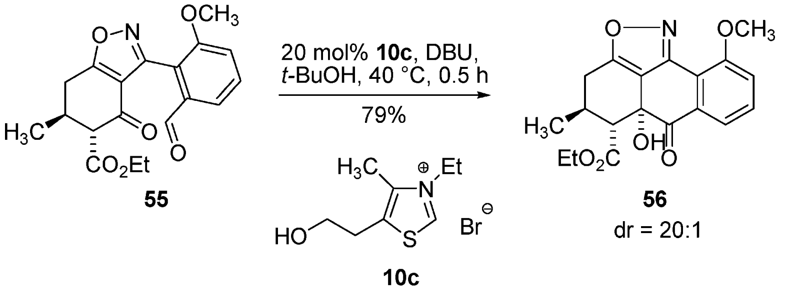
R^1 = aryl, heteroaryl; R^2 = aryl

12 examples, 64-99% yield

Enders et al.[16a]



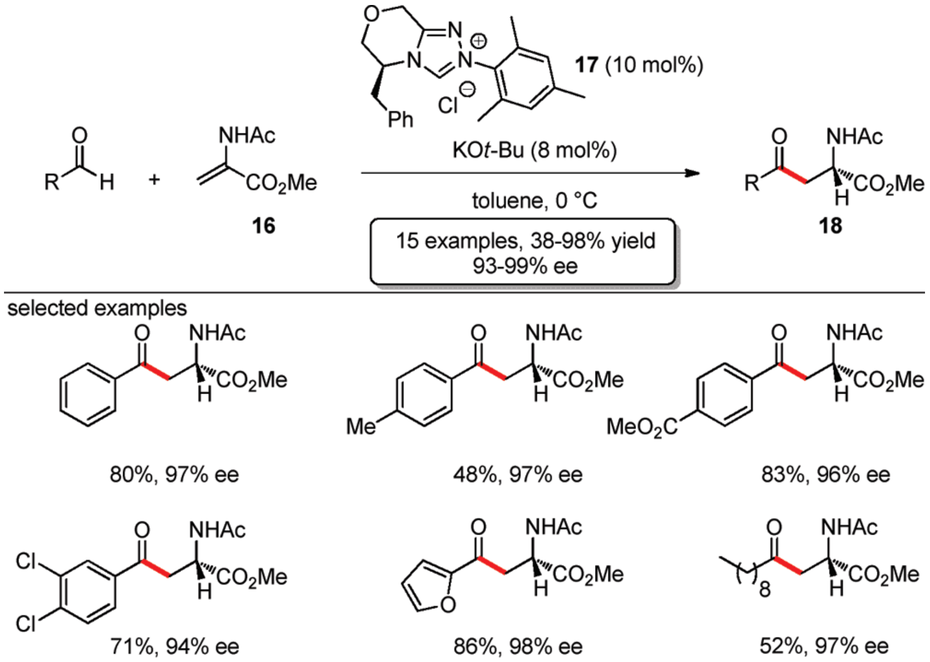
14 examples, 29-86% yield

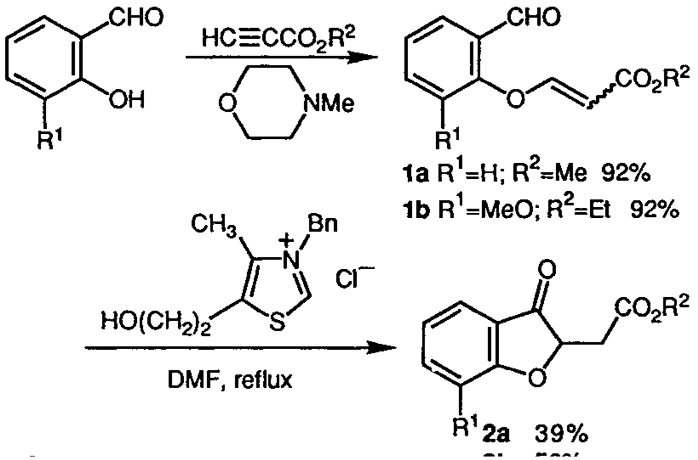


Suzuki and Coworkers

Chem. Rev. 2007, 107, 5606-5655
Accounts of Chem. Res. 1182-1195, 2011

Stetter Reaction

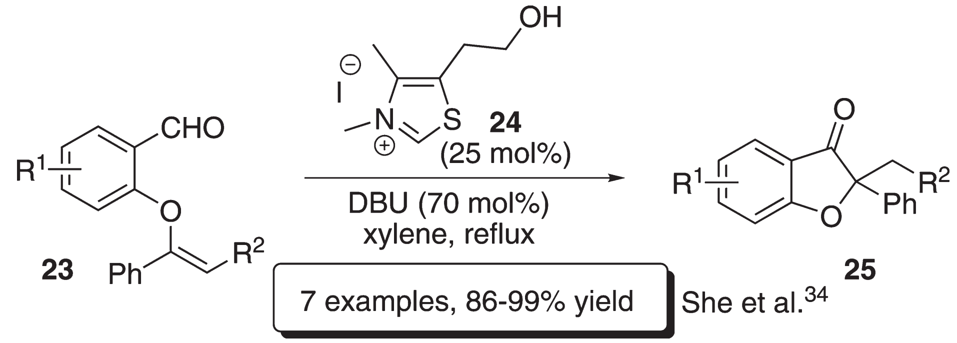




Michael acceptors with beta substituents usually are bad reaction partners

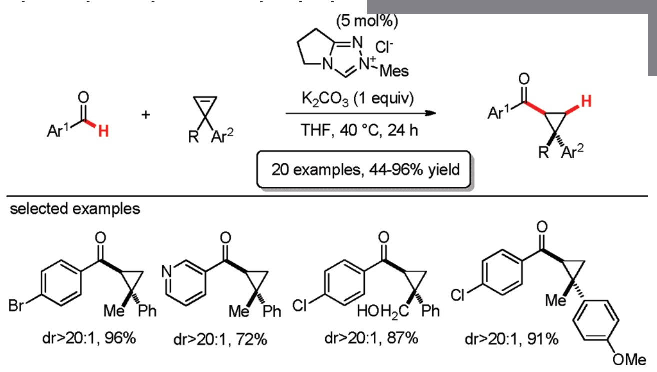
Ciganek, Synthesis, 1995, 1311
Accounts of Chemical Research, 2011, 1182

H-Acylation of Unactivated Compounds



7 examples, 86-99% yield

She et al.[34]



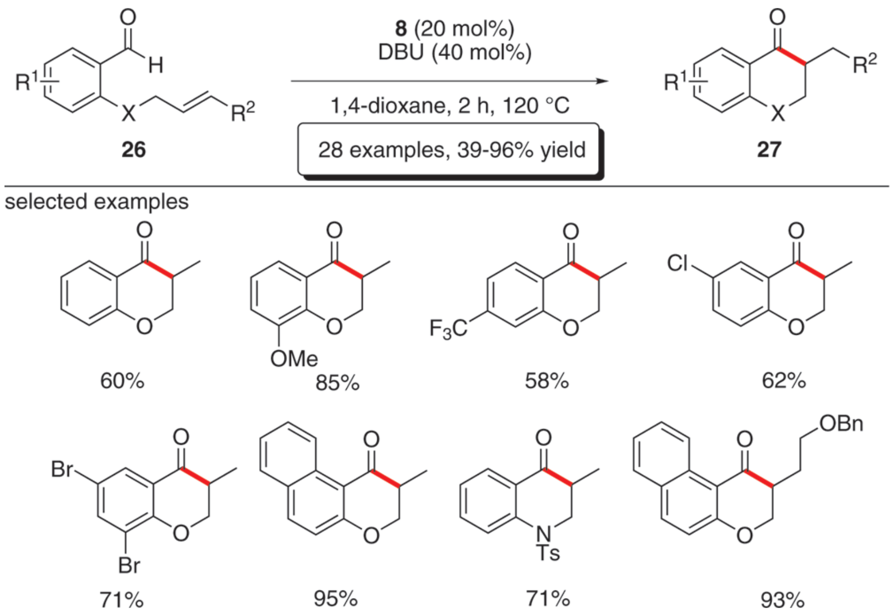
20 examples, 44-96% yield

dr>20:1, 96%

dr>20:1, 72%

dr>20:1, 87%

dr>20:1, 91%



28 examples, 39-96% yield

60%

85%

58%

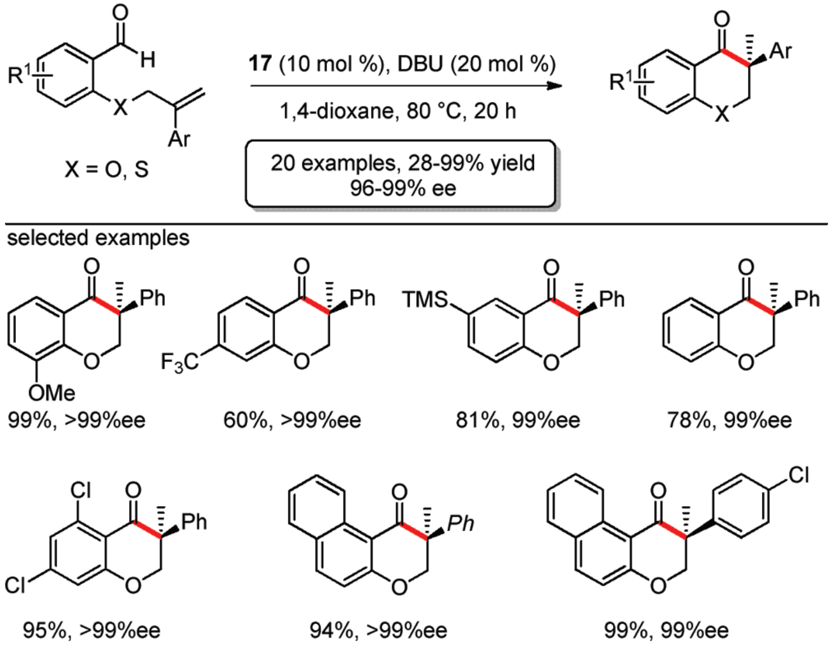
62%

71%

95%

71%

93%



20 examples, 28-99% yield
96-99% ee

99%, >99%ee

60%, >99%ee

81%, 99%ee

78%, 99%ee

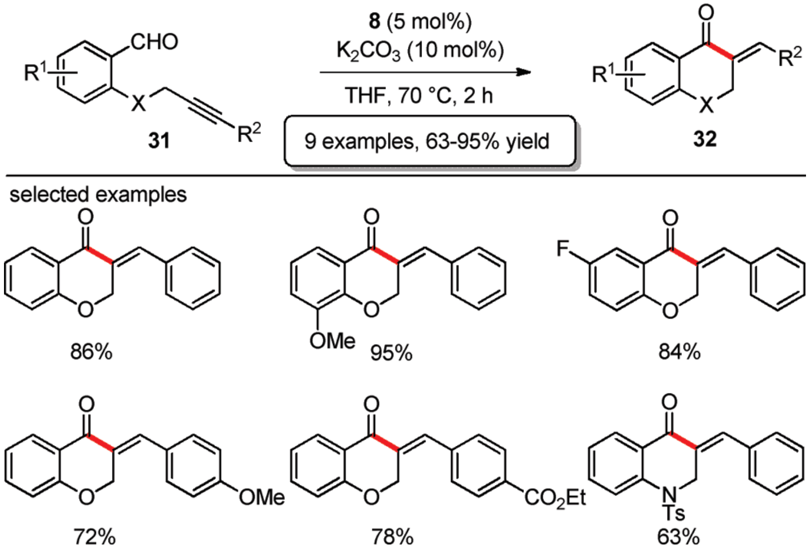
95%, >99%ee

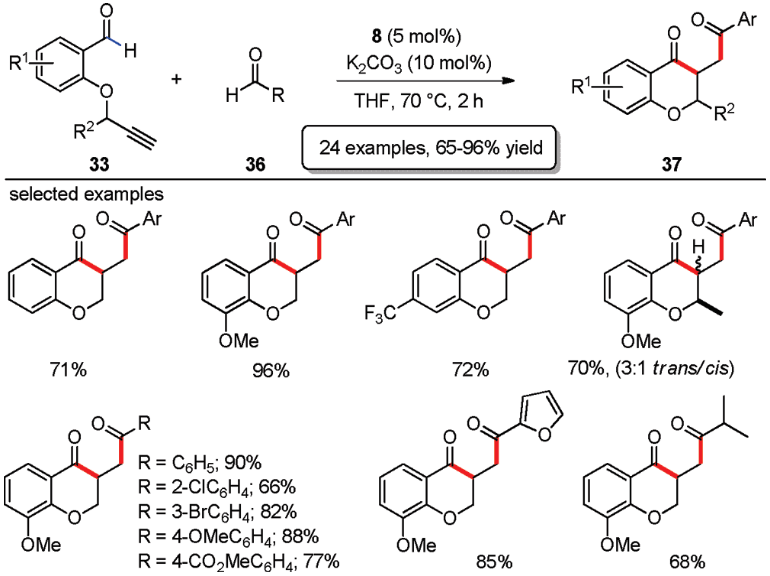
94%, >99%ee

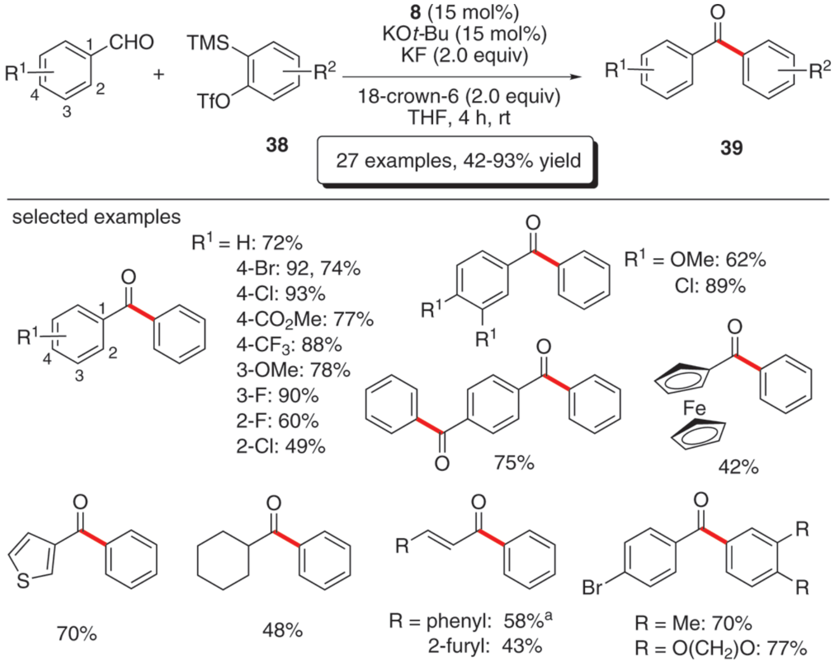
99%, 99%ee

Accounts of Chemical Research, 2011, 1182

Alkynes and Arynes







[a] Using 20 mol% of **8** and 20 mol% of KO*t*-Bu.

Accounts of Chemical Research, 2011, 1182

Metal Vs Organic

Metals:

- Have to worry about decarbonylation
- Rh is expensive, other metals are not as well documented
- Enantioselective reactions are pretty straightforward
- Screening catalysts is pretty straightforward

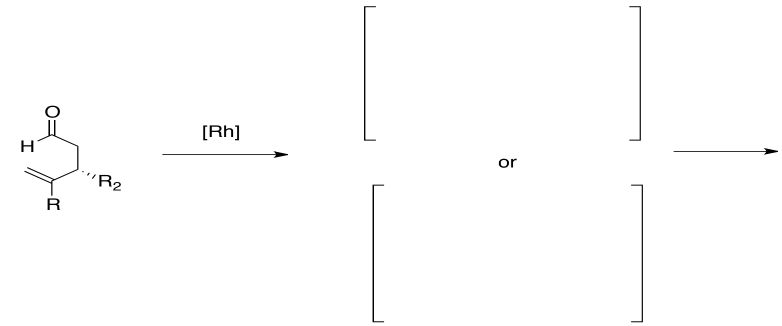
NHC:

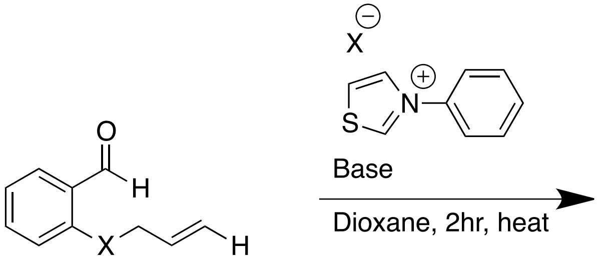
- Can react with a wider range of substrates (benzoin reaction, stetter, and other substrates)
- Made from very accessible materials.
- Catalyze many transformations, so you have to be aware of possible side reactivity, or use that to your advantage..
- **Have to find an NHC that works for you**

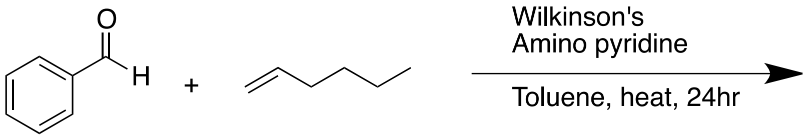
Thank You

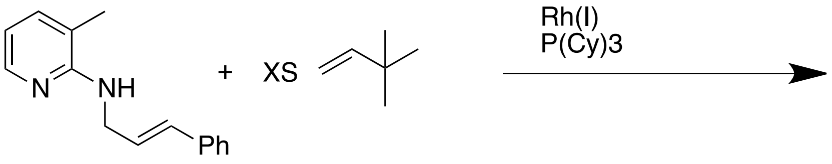
Questions for Me?

Questions for You..





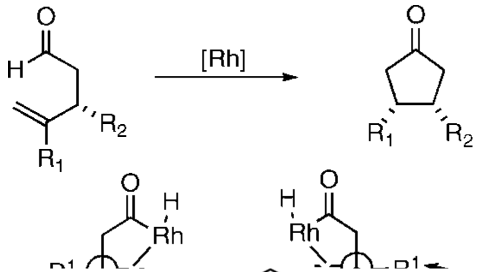


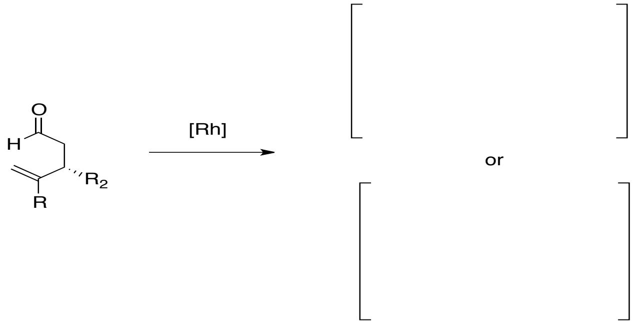


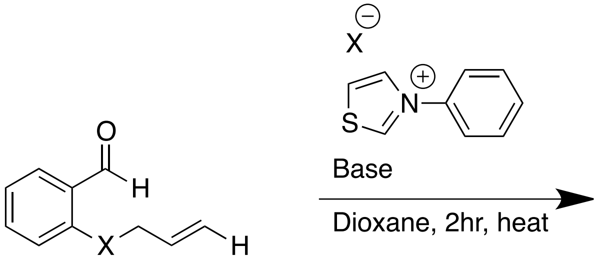
Assume Aq.
Workup

Questions for You..

Answers for You..

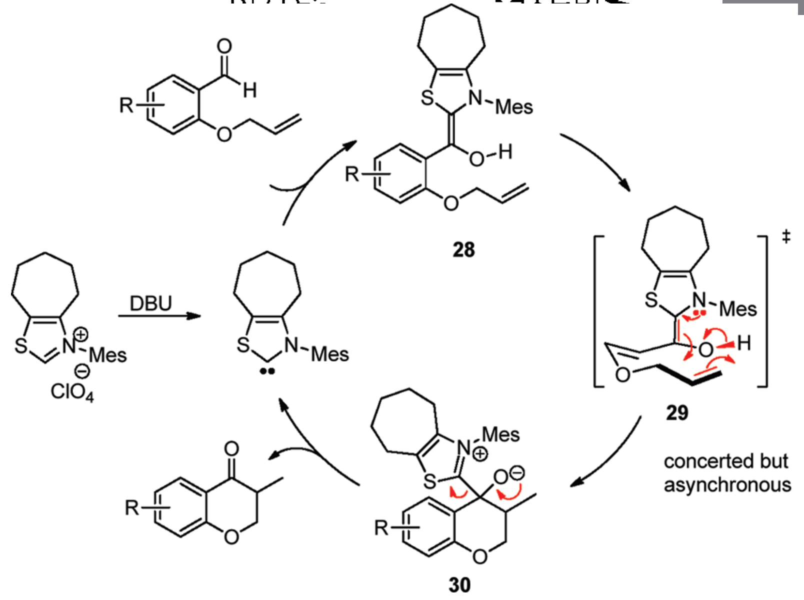




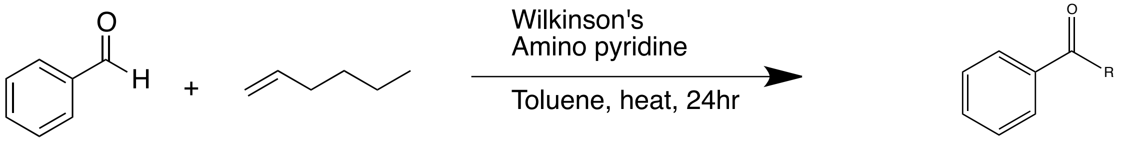


Base

Dioxane, 2hr, heat

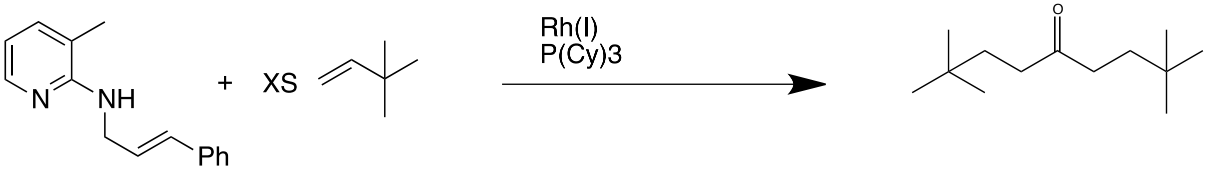


concerted but asynchronous



Wilkinson's
Amino pyridine

Toluene, heat, 24hr



Rh(I)
P(Cy)3

C-C meets C-H formaldehyde and acetaldehyde