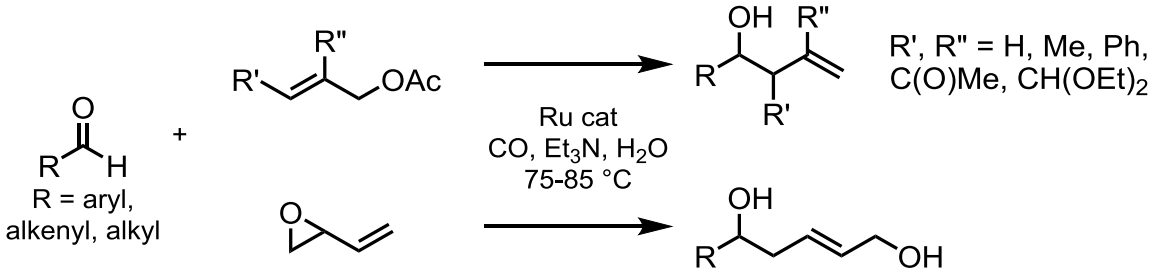
Carbon-Carbon Bond Formation Driven by the Water-Gas Shift Reaction

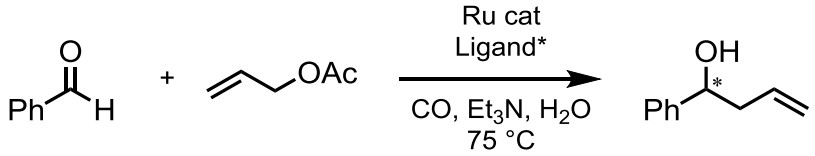
Zachery Matesich 28 March 2017

Projects

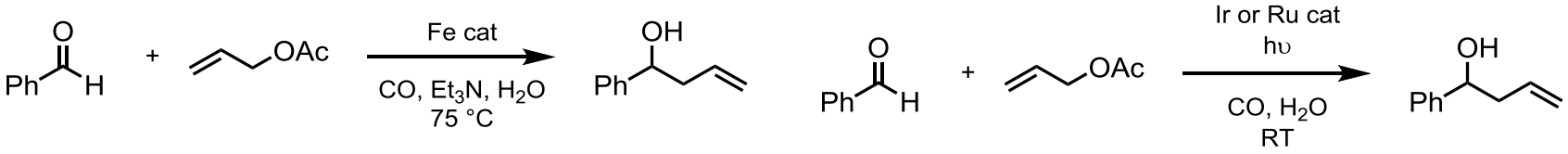
- Allyl electrophile scope



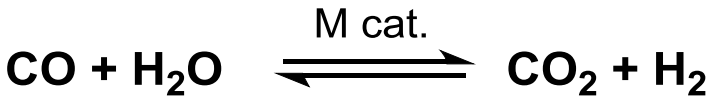
- Asymmetric allylation



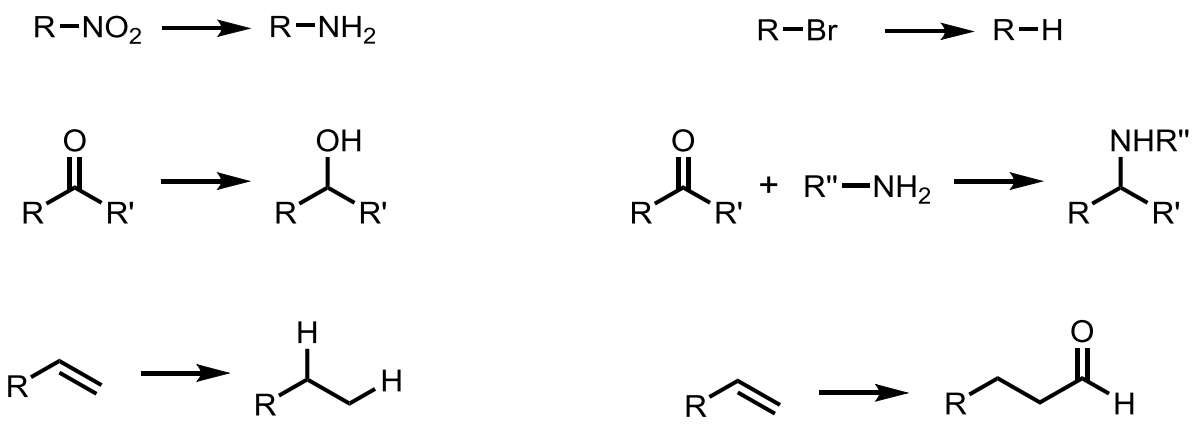
- Alternative approaches



Water-Gas Shift Reaction



- Traditionally used in industry to purify H_2 via removal of CO
- Organic synthesis use as H_2 surrogate

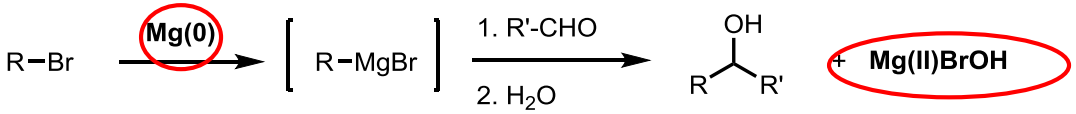


Ambrosi, A.; Denmark, S. E. *ACIEE* **2016**, *55*, 12164-12189.

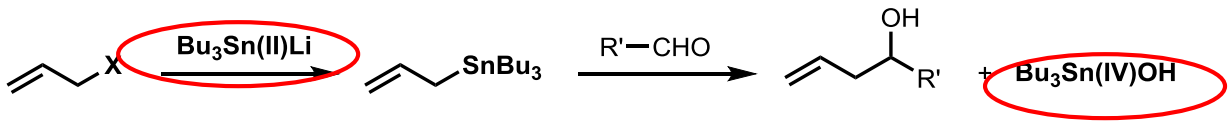
Why use the WGSR

- Significant number of organic reactions require pre-reduced starting materials and are therefore, overall a reductive process

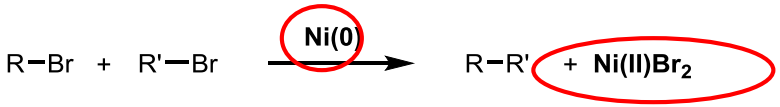
Grignard



Stannane allylation



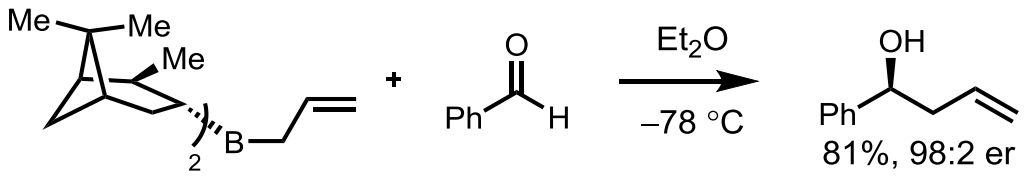
Reductive coupling



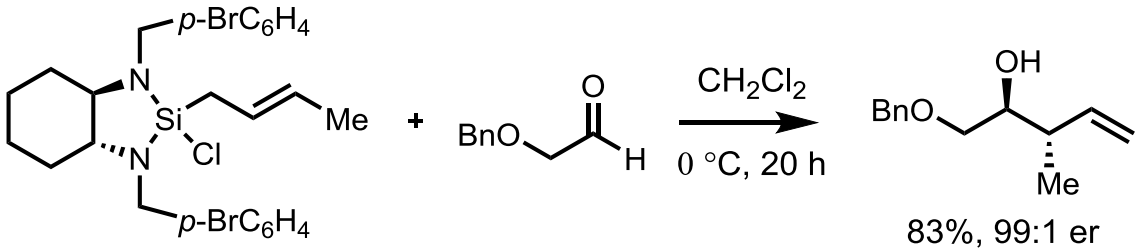
- This generates a waste stream and involves poor atom economy

Carbonyl Allylation – Pre-formed/catalytic allylation reagents

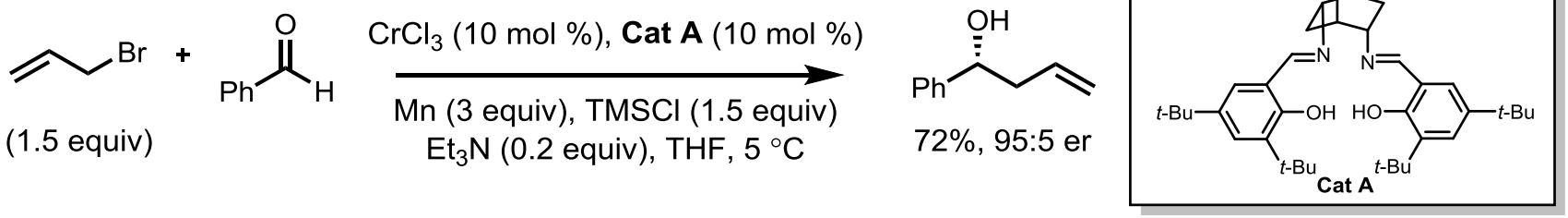
- Brown (1983)



- Leighton (2004)



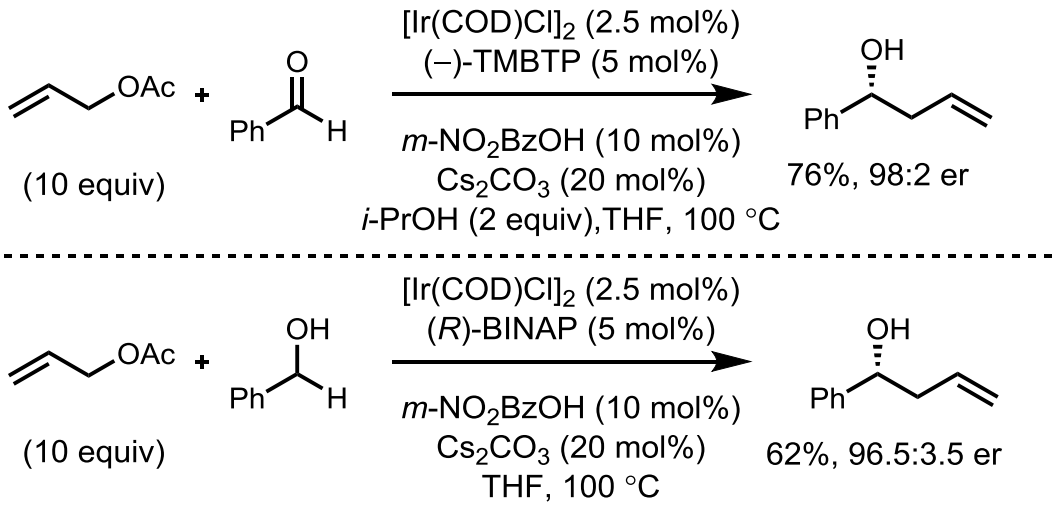
- Paterson (2003)

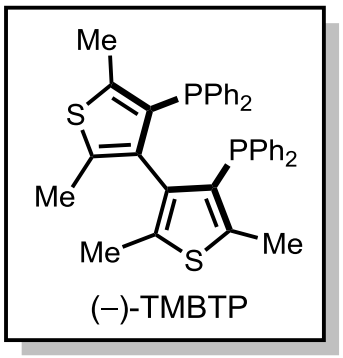


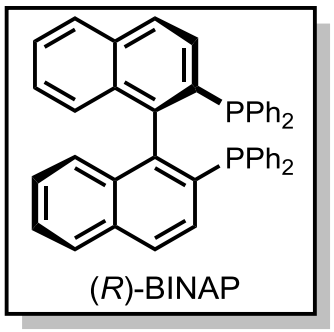
Brown, H. C.; *et al. J. Am. Chem. Soc.* **1983**, *105 (7)*, 2092-2093.
Leighton, J. L. *et al Org. Lett.* **2004**, *6*, 4375-4377.
Paterson, I. *et al. Angew. Chem. Int. Ed.* **2003**, *42 (9)*, 1032-1035.

Carbonyl Allylation – Transfer Hydrogenation

- Krische (2008)





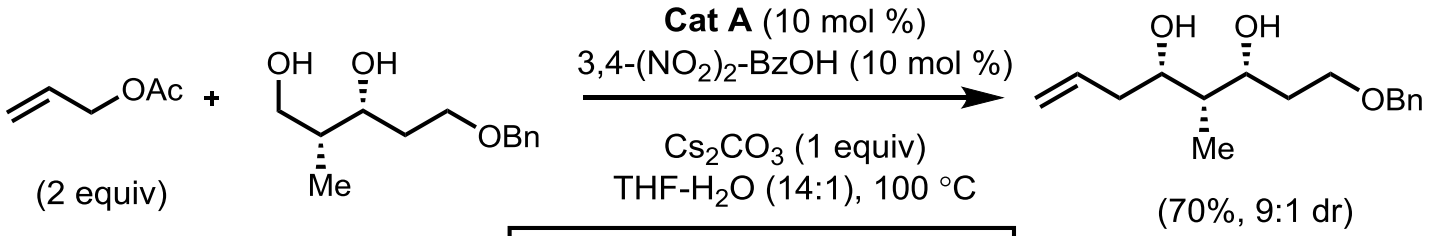


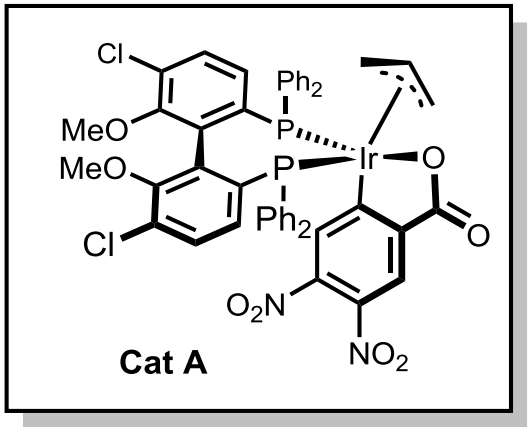
- Starting material can be aldehyde or alcohol

Krische, M. J., *et al. J. Am. Chem. Soc.* **2008**, *130* (20), 6340-6341.

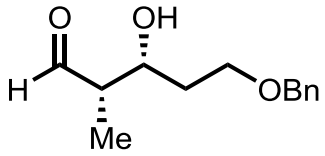
Carbonyl Allylation – Transfer Hydrogenation

- Use of alpha-branched alcohols





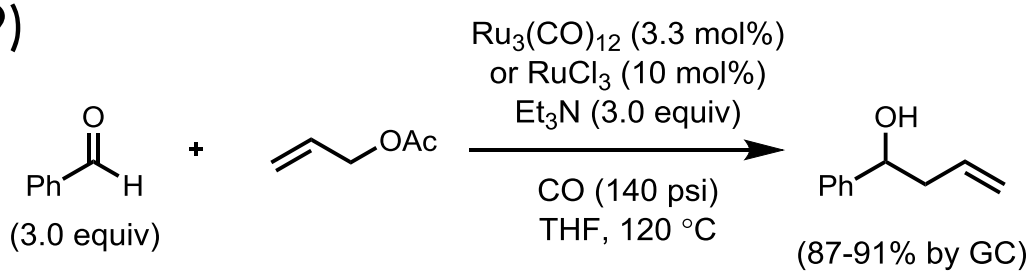
- Avoids use of:



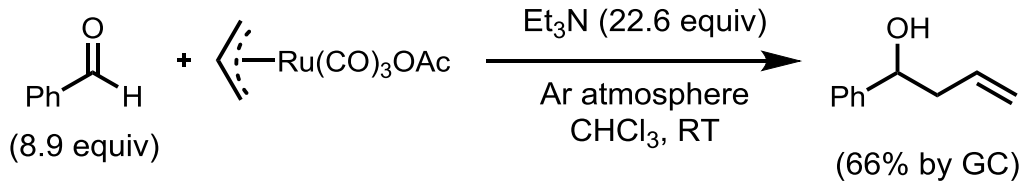
Krische, M. J., *et al. Angew. Chem. Int. Ed.* **2013**, *52* (11), 3195-3198.

Ruthenium-catalyzed Allylation – Et_3N as Stoichiometric Reductant

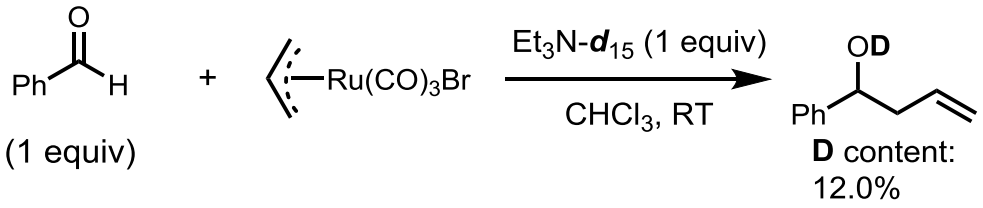
- Kondo (1989)



- Stoichiometric reaction



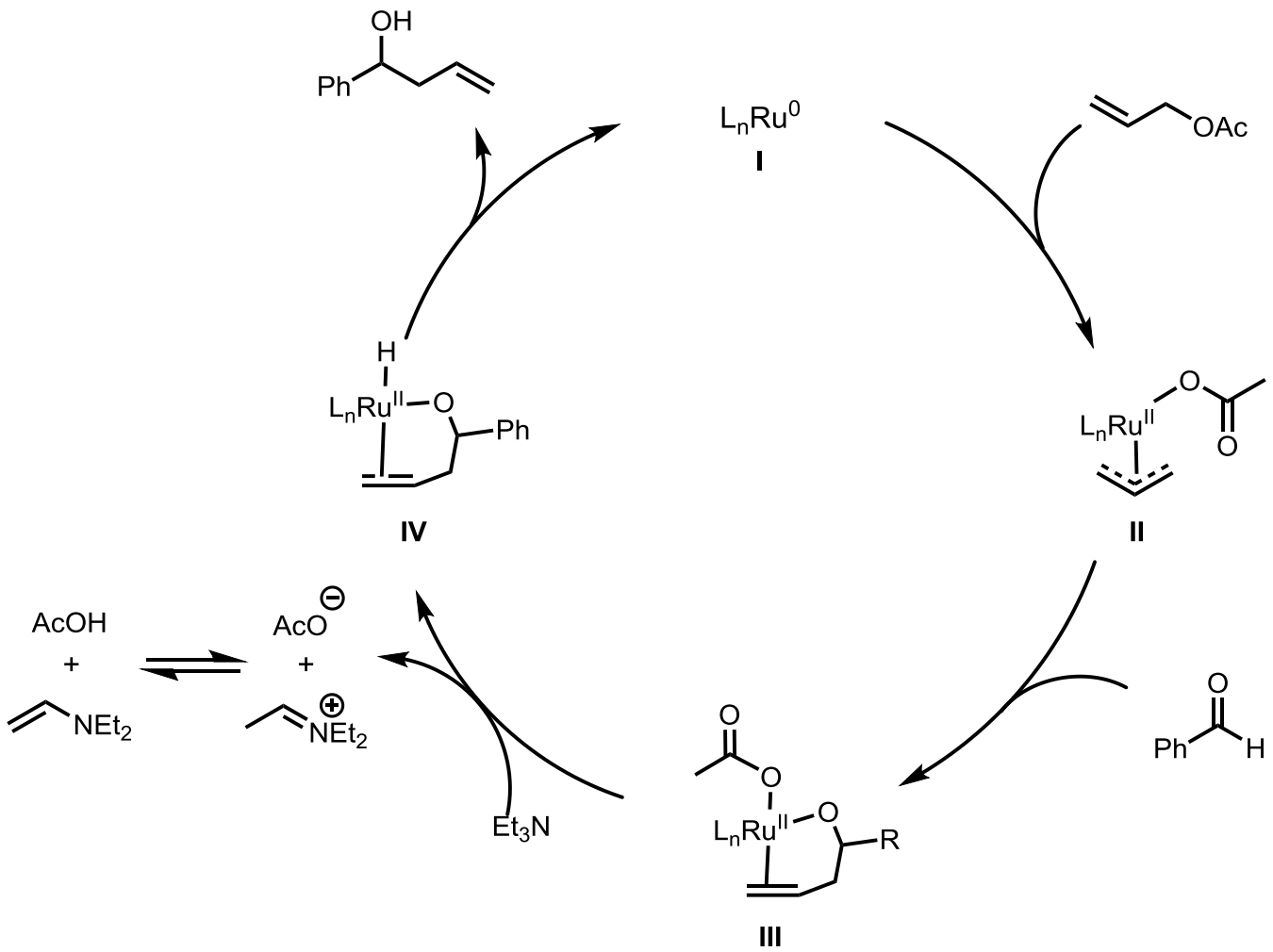
- Deuterium study



- Amine is the hydride source
- CO thought to only serve to stabilize the ruthenium metal
- Further shown to be chemoselective for aldehydes over ketones

Kondo, T. *et al. Organometallics* **1995**, *14*, 1945-1953.

Et_3N as Stoichiometric Reductant – Mechanism

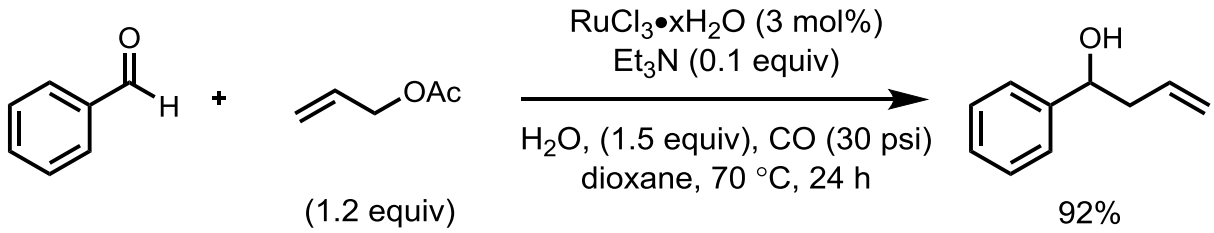


- Use of Et_3N for catalyst turnover

Kondo, T. *et al. Organometallics* **1995**, *14*, 1945-1953.

Ruthenium-catalyzed Allylation – CO as Stoichiometric Reductant

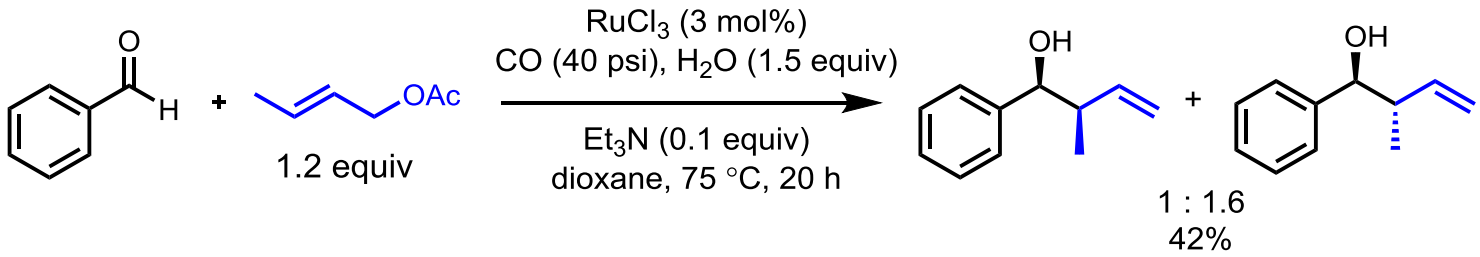
- Denmark (2008)

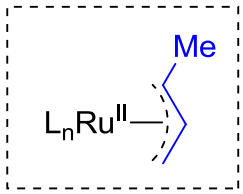


- Improvements:
  - CO pressure lowered to 30 psi
  - Aldehyde limiting reagent
  - Et_3N only 0.1 equiv
  - Temperature lowered to 70 °C

Denmark, S. E. *et al. Org. Lett.* **2008,** *11 (3),* 781-784.

CO as Stoichiometric Reductant – π-allyl formation

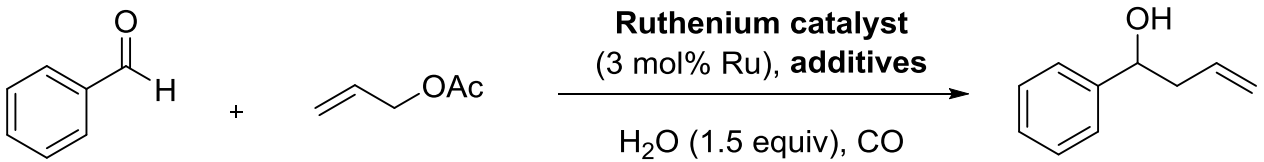




- Same formation of products from constitutional isomers
- Evidence for formation of same π-allyl complex

Milicevic, S. D. Postdoctoral Report, University of Illinois - Urbana/Champaign, 2009.

CO as Stoichiometric Reductant – Ruthenium Catalyst Survey

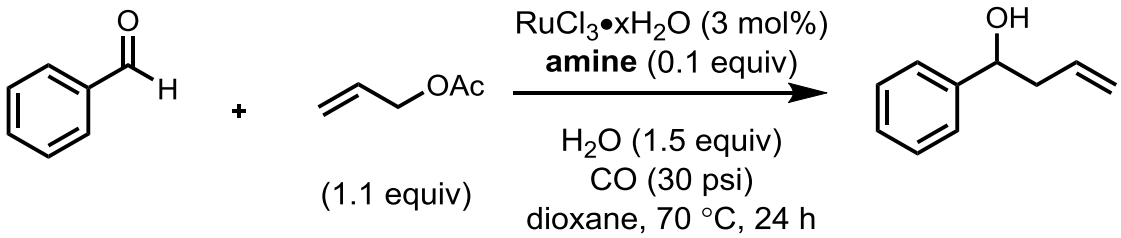


Entry	Ruthenium Catalyst	Et_3N (equiv)	TBACl (equiv)	Product Yield (%)
1	$RuCl_3 \cdot nH_2O$	0.03	0	0
2	$RuCl_3 \cdot nH_2O$	0.10	0	100
3	$RuCl_3 \cdot nH_2O$	1.0	0	68
4	allyl$Ru(CO)_3Br$	0	0	12
5	allyl$Ru(CO)_3Br$	0.1	0	93
6	allyl$Ru(CO)_3OAc$	0	0	43
7	allyl$Ru(CO)_3OAc$	0.1	0	70
8	allyl$Ru(CO)_3OAc$	0	0.03	84
9	$Ru_3(CO)_{12}$	0.1	0	15
10	$Ru_3(CO)_{12}$	0.1	0.03	8
11	$Ru_3(CO)_{12}$	0	0.1	80

- Amine required for Ru(III) precatalyst
- Use of amine can also increase product yields
- Halide has same effect or improved when using carbonyl

Nguyen, S. T. Postdoctoral Report, University of Illinois - Urbana/Chamapaign, 2008.

CO as Stoichiometric Reductant – Amine Survey

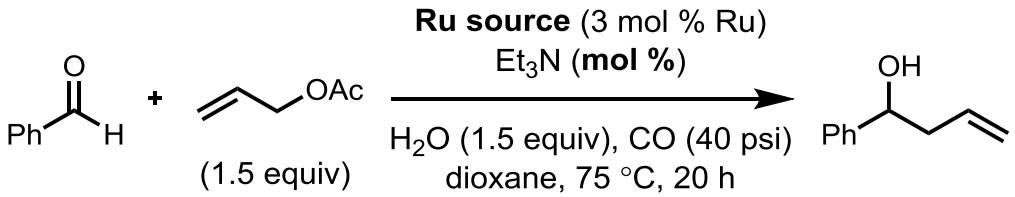


Entry	Amine	Product Yield (%)
1	Pyridine	0
2	DIPA	89
3	Quinuclidine	94
4	Quinine	62
5	Sparteine	97

- Amine not a hydride donor
- Use of chiral amines gave no product enantioenrichment

Denmark, S. E. *et al. Org. Lett.* **2008,** *11 (3),* 781-784.

CO as Stoichiometric Reductant – Role of Amine



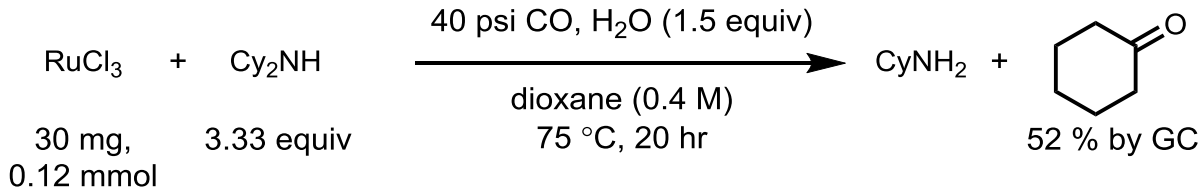
$RuCl_3$

Entry	Et_3N (mol %)	Aldehyde Remaining (% GC)	Product Conversion (% GC)
1	0	94	0
2	3.0	97	3
3	3.5	98	2
4	4.0	18	85
5	4.5	6	94

$[RuCl_2(p\text{-cymene})]_2$

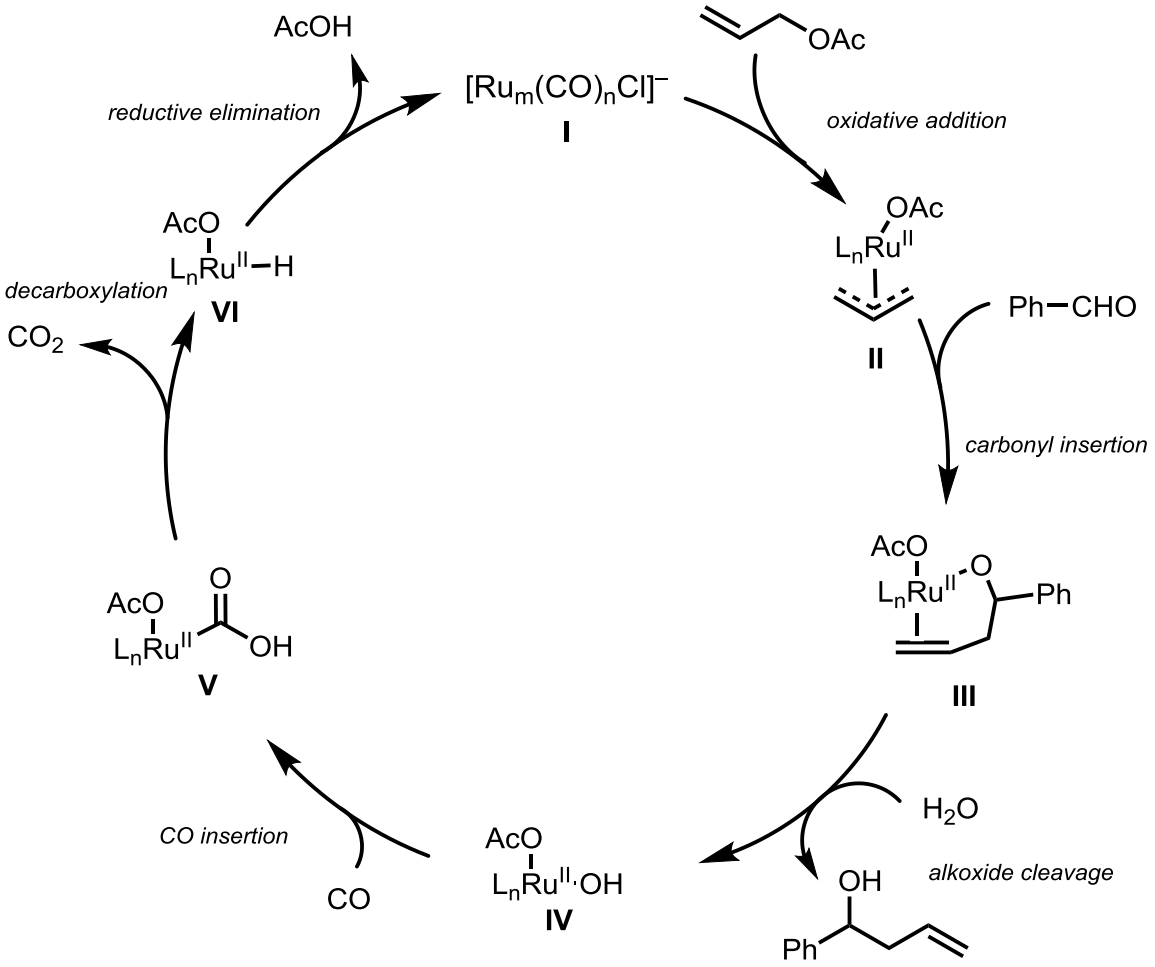
Entry	Et_3N (mol %)	Aldehyde Remaining (% GC)	Product Conversion (% GC)
6	0	94	<1
7	1.0	80	10
8	1.5	75	15
9	2.0	80	16
10	2.5	1	83

- $RuCl_3$ requires 3 e^- ~3.5-4.0 mol % Et_3N
- $[RuCl_2(p\text{-cymene})]_2$ requires 2 e^- ~2.5-3.0 mol % Et_3N



- Amine acts to reduce the higher oxidation ruthenium sources to $Ru(CO)_x$

CO as Stoichiometric Reductant – Proposed Catalytic Cycle

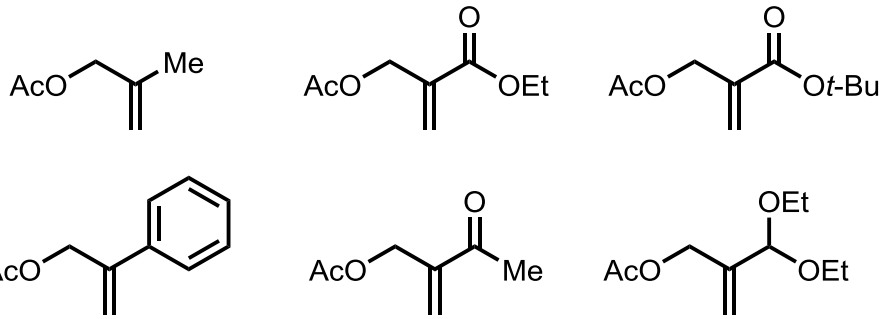


- Action of WGSR to turnover catalyst

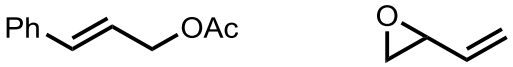
Denmark, S. E. *et al. Org. Lett.* **2008,** *11 (3),* 781-784.

Research Objectives for Allyl Electrophiles

- Determine effect of 2-substitutions on allylic acetates on reaction efficiency and mechanism

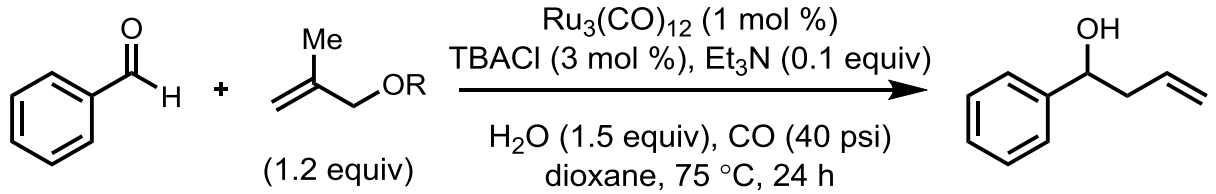


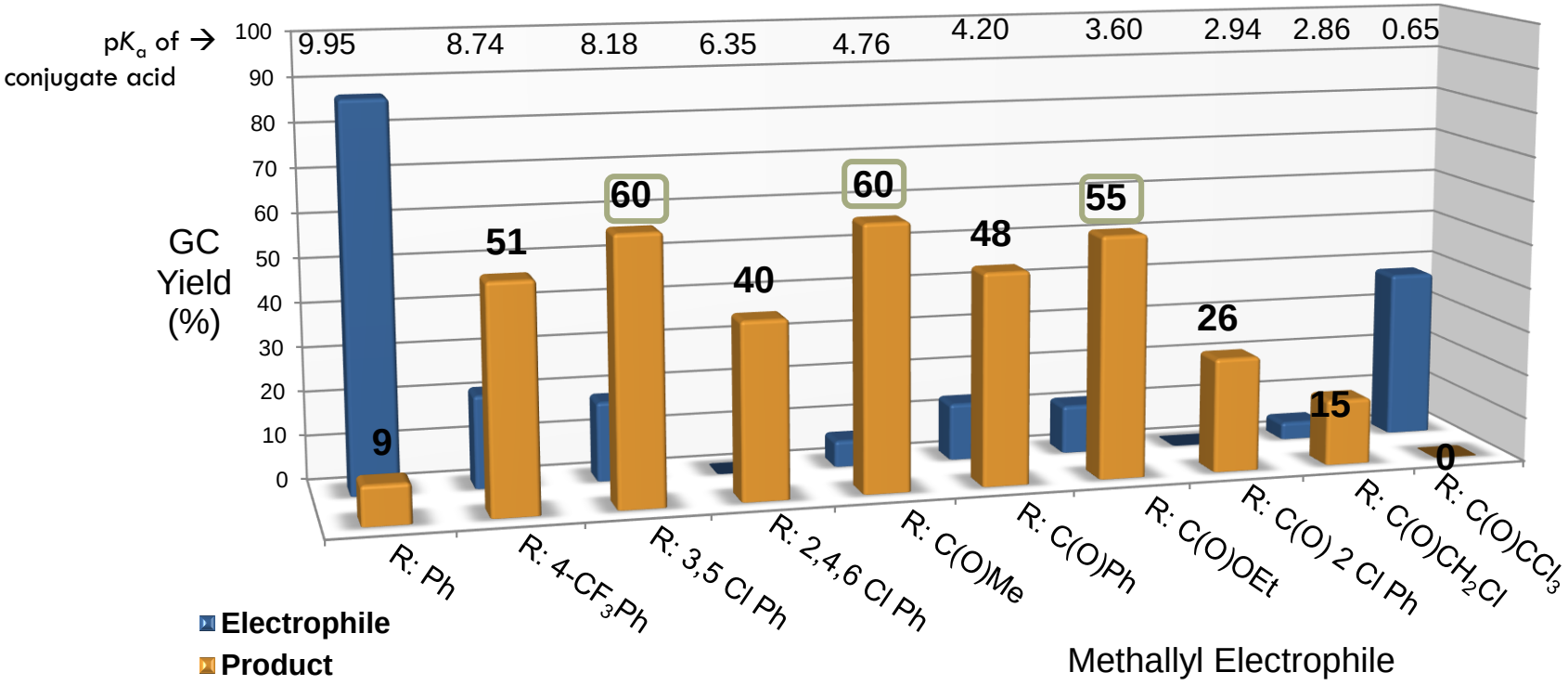
- Explore the ability of non-symmetrical allyl electrophiles and reaction conditions that can affect product distribution



- Explore reaction conditions and roles of other reagents in carbonyl allylation reaction

Nucleofuge on 2-Methallyl Electrophile Survey

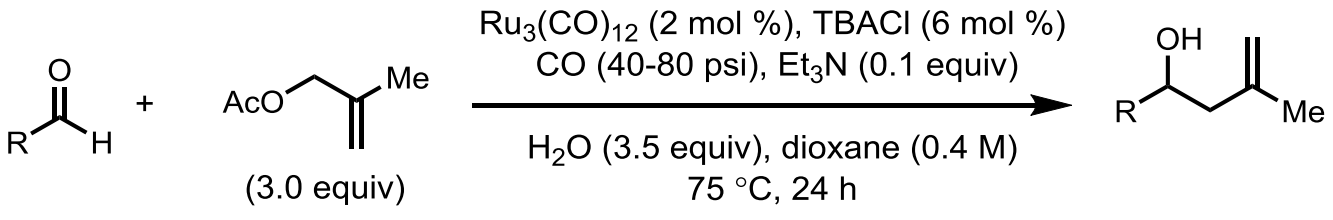




- pK_a values near AcOH appear to be most beneficial

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

Aldehyde Scope for 2-Methylallyl acetate

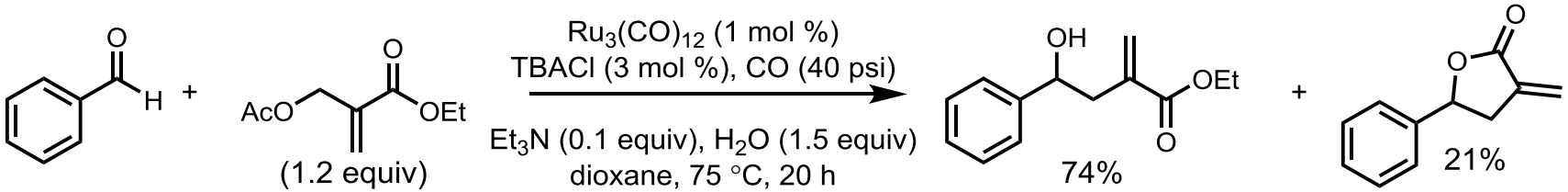


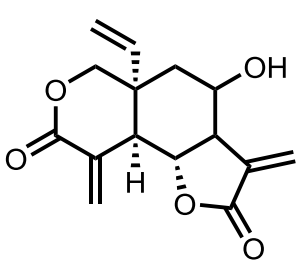
[a]Reaction conditions: (A) 40 psi CO; (B) 80 psi CO.

- Moderate yields with ED allylic acetate
- Oxidative addition would be slower in more electron rich allyl

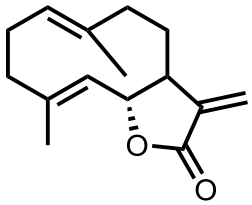
Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

Formation of Lactone

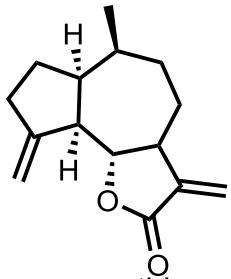




vernolepin



costunolide

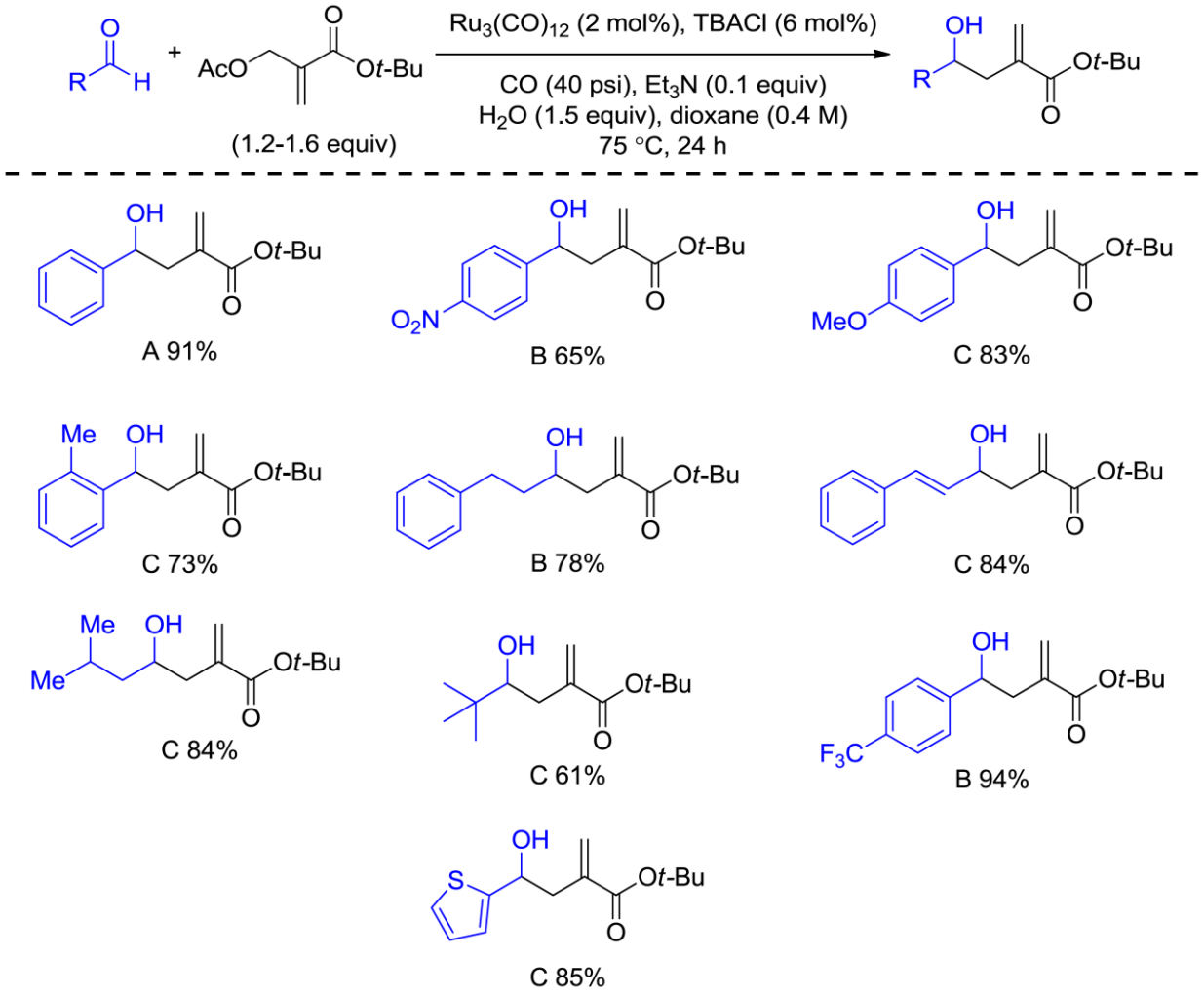


erematin

- Lactone formed *in situ*
- Workup with CF_3CO_2H could induce lactone formation
- Motif present in 10% of natural products

Hoffmann, H. M. R., *et al. Angew Chem Int Ed* **1985**, *24 (2)*, 94-110.

Aldehyde Scope for *t*-Butyl 2-(acetoxymethyl) acrylate

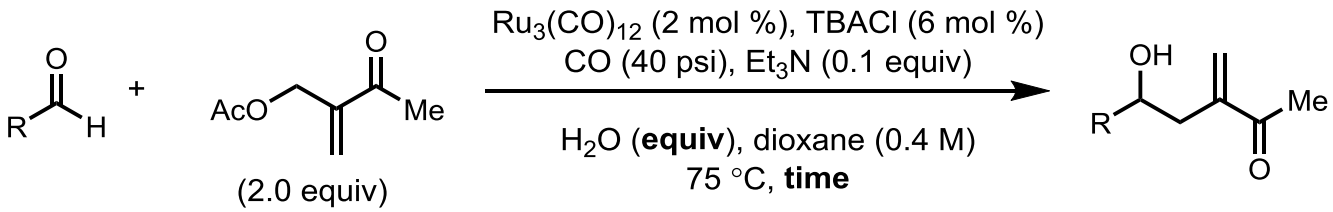


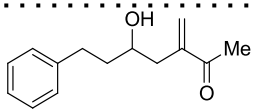
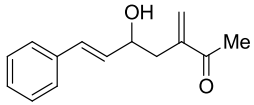
Reaction conditions: (A) 1.6 equiv of acetate; (B) 1.2 equiv of acetate; (C) 1.4 equiv of acetate.

- Similar yields to ethyl ester without lactone formation

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

H_2O Optimization – 2-methylene-3-oxobutyl Acetate

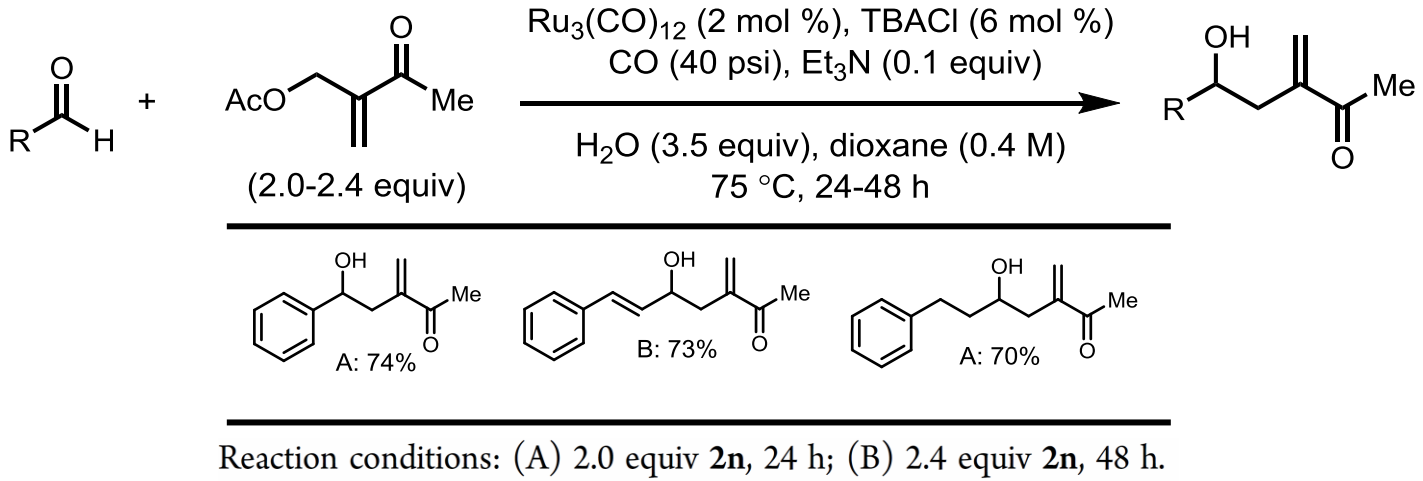


Entry	Product	Time (hours)	H_2O (equiv)	Benzaldehyde Recovery GC (%)	Acetate Recovery GC (%)
1		24	**3.0**	11	4
2		24	**3.5**	2	15
3		24	**3.0**	40	26
4		24	**3.5**	39	24
5		48	**2.5**	20	14
6		48	**3.5**	18	8

- Higher equivalents of H_2O and/or time increased aldehyde conversion

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

Aldehyde Scope for 2-methylene-3-oxobutyl acetate

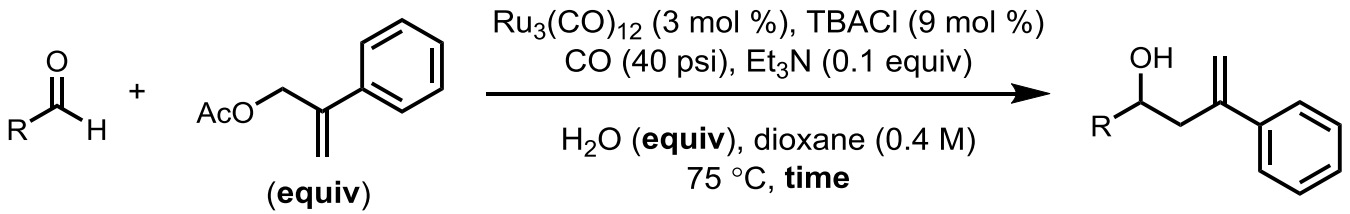


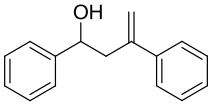
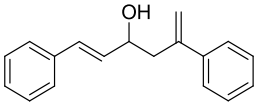
Reaction conditions: (A) 2.0 equiv **2n**, 24 h; (B) 2.4 equiv **2n**, 48 h.

- Good to moderate yields with EW allylic acetate

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

H_2O Optimization – 2-Phenylallyl Acetate

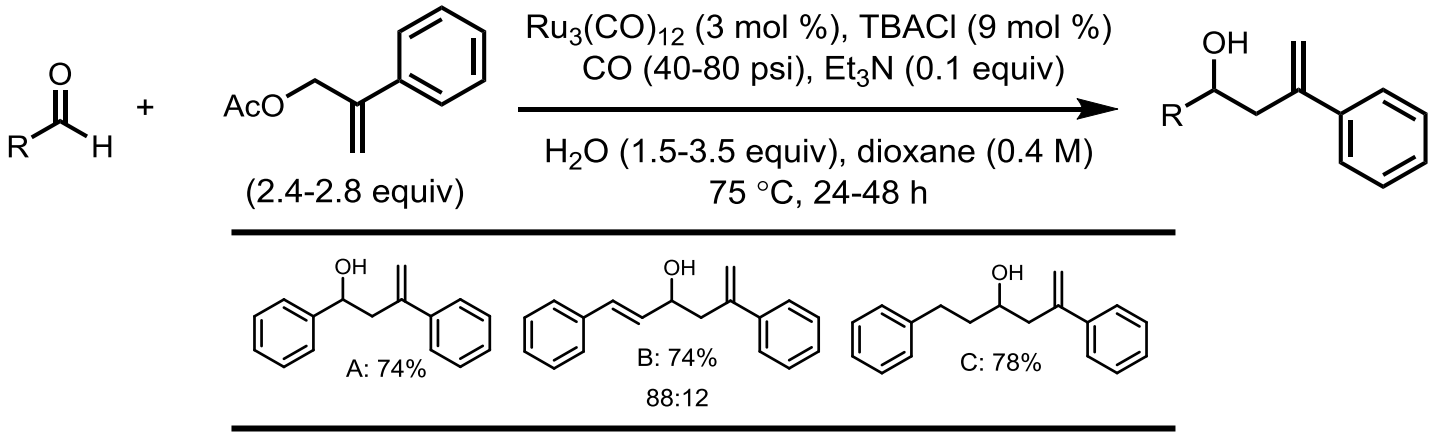


Entry	Product	Time (hours)	Acetate (equiv)	H_2O (equiv)	Benzaldehyde Recovery (% by GC)	Acetate Recovery (% by GC)
1		24	2.4	3.0	17	0
2		24	2.4	3.5	19	1
3		24	2.8	2.0	16	40
4		24	2.8	2.5	12	11
5		48	2.8	2.0	17	37
6		48	2.8	2.5	11	7
7		24	2.4	3.5	18	0
8		24	2.8	2.5	22	12
9		24	2.8	3.5	22	0
10		48	2.8	3.5	18	0

- Higher equivalents of H_2O increased aldehyde conversion with higher equivalents of allylic acetate

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

Aldehyde Scope for 2-Phenylallyl Acetate

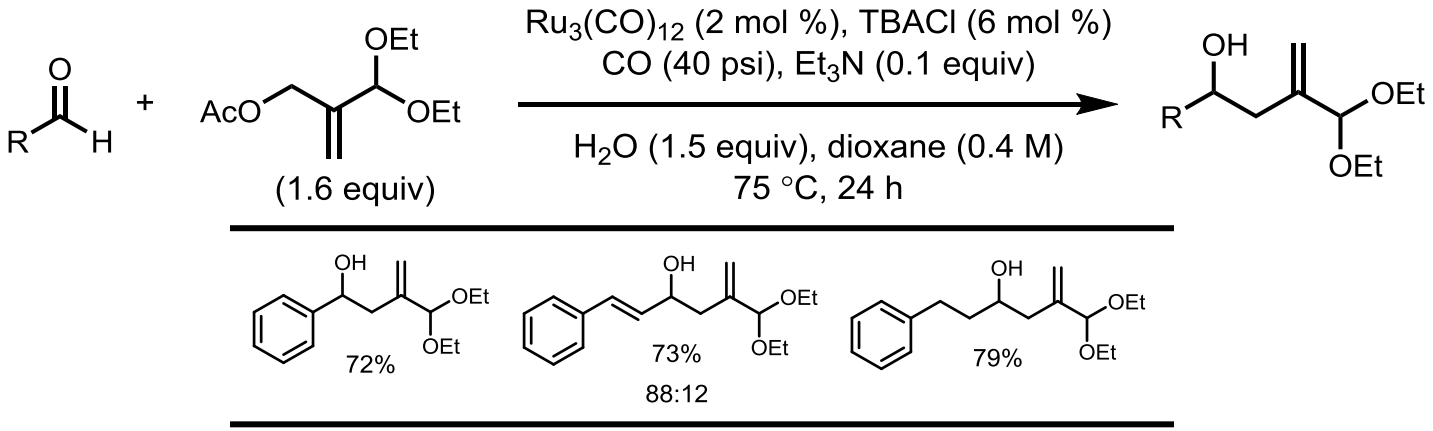


Reaction conditions: (A) 2.8 equiv of acetate, 2.5 equiv H_2O, 48 hours; (B) 2.4 equiv of acetate, 1.5 equiv H_2O, 24 hours; (C) 2.8 equiv of acetate, 3.5 equiv H_2O, 24 hours.

- Yield somewhat lower compared to EW allylic acetates

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014,** *79,* 5970-5986.

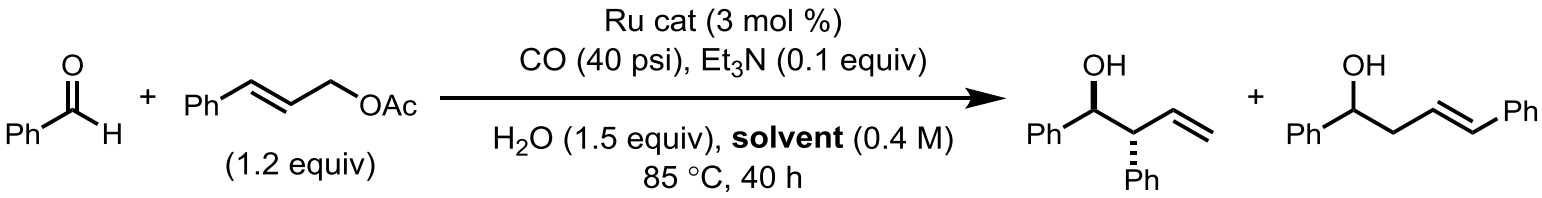
Aldehyde Scope for 2-(diethoxymethyl)allyl acetate



- Initial experiments showed near total conversion of aldehyde under classic conditions
- Required basic workup to remove acid that hydrolyzed on removal of solvent

Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970-5986.

Initial Screen – Cinnamyl Acetate

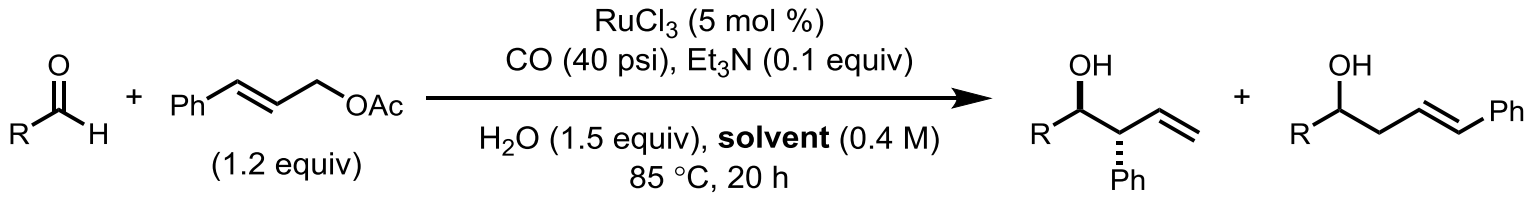


Entry	Ru cat	Solvent	Aldehyde Remaining (% GC)
1	$RuCl_3$	dioxane	49
2	$Ru_3(CO)_{12}$ / TBACl	dioxane	76
3	$Ru(bpy)(CO)_2Cl_2$	dioxane	73
4	$RuCl_3$	EtOH	28
5	$Ru_3(CO)_{12}$ / TBACl	EtOH	23
6	$Ru(bpy)(CO)_2Cl_2$	EtOH	22

- Use of EtOH gave improved yield over dioxane
- Furthermore, significant linear product observed with dioxane reactions
- As ruthenium catalysts gave similar results, move forward with RuCl3
- Later experiments revealed 5 mol % catalyst gave sufficient conversion in 20 h

Acetal Formation – Cinnamyl Acetate

- In case of aliphatic aldehydes, acetal formation became problem with EtOH

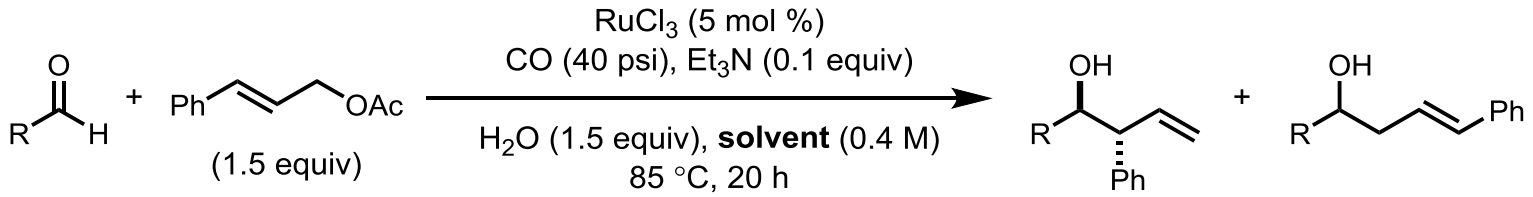


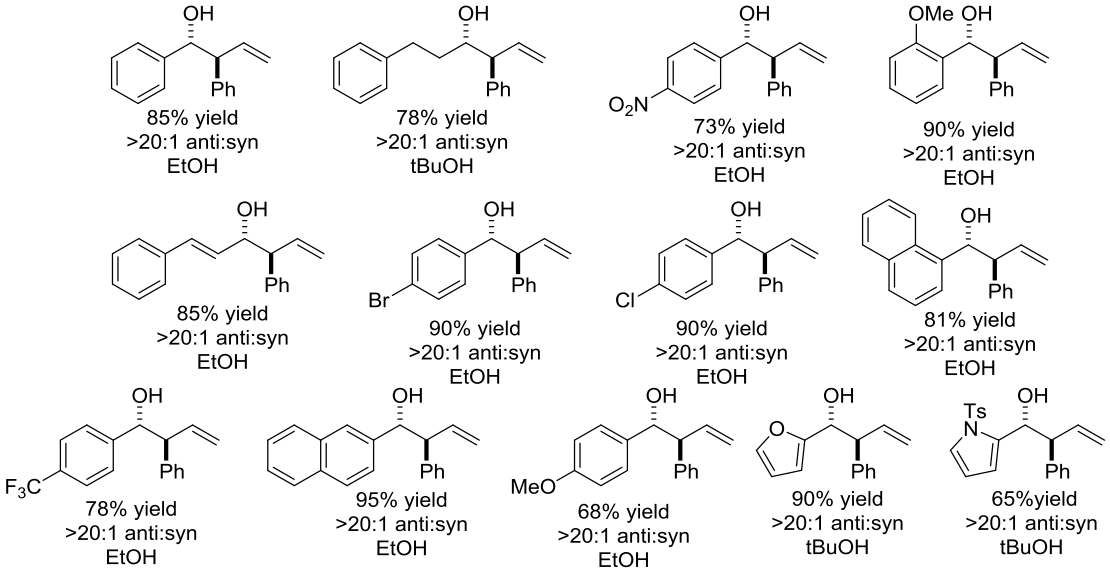
Entry	Aldehyde	Solvent 1	Solvent 2	Aldehyde Remaining (% ^{1}H NMR)	γ-*anti* (% ^{1}H NMR)	γ-*syn* (% ^{1}H NMR)	α Product (% ^{1}H NMR)	Acetal (% ^{1}H NMR)
1	$Ph(CH_2)_2$	EtOH	--	0	37	0	1	60
2	$Ph(CH_2)_2$	tBuOH	--	2	91	1	1	0
3	$Ph(CH_2)_2$	t-amyl	--	10	77	1	2	0
4	$Ph(CH_2)_2$	HFIP	--	90	7	3	0	0
5	$Ph(CH_2)_2$	DME	--	0	94	5	4	0
6	$Ph(CH_2)_2$	Dioxane	EtOH	5	97	3	0	0
7	Ph	tBuOH	--	3	73	3	8	1
8	4-MeOPh	tBuOH	--	20	70	5	5	0

- Use of tBuOH worked best for hydrocinnamaldehyde
- However, with other aldehydes, increased γ-syn and α products
- Aliphatic aldehydes to use tBuOH, otherwise use EtOH

Aldehyde Scope – Cinnamyl Acetate

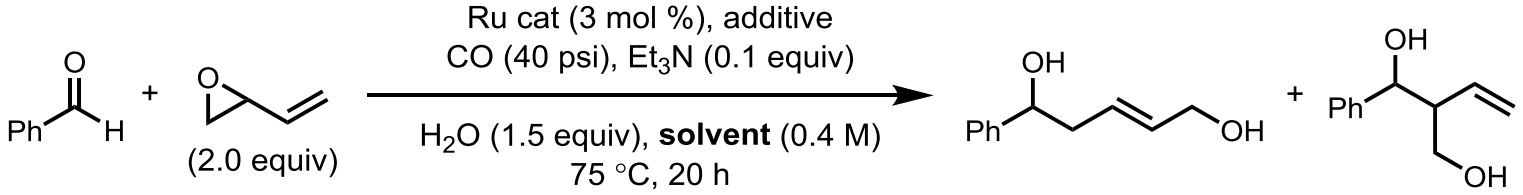
- Scope of aldehydes was next examined





- Yields of around 70-90%
- Heterocycles also required used of tBuOH for good selectivity
  - In case of EtOH, N-Ts pyrrolaldehyde had *anti*:*syn* ration closet to 8:1

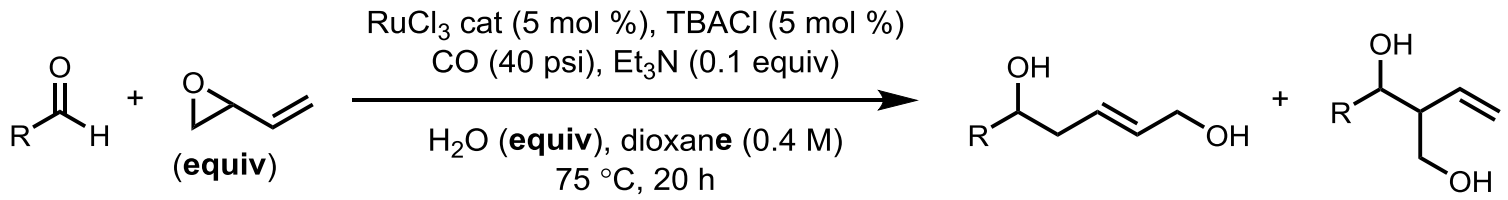
Initial Screen – Vinyl Oxirane



Reaction	Ru Cat	Solvent	Additive	Aldehyde Remaining (% ^{1}H NMR)	γ Product (% ^{1}H NMR)	α Product (% ^{1}H NMR)
1	$Ru_3(CO)_{12}$ / TBACl	nBuOH	--	78	1	7
2	$RuCl_3$	nBuOH	--	81	8	4
3	$[RuCl_2(pcymene)]_2$	nBuOH	--	86	6	4
4	$RuCl_3$ (5 mol %)	nBuOH	--	56	0	33
5	$Ru_3(CO)_{12}$ / TBACl	dioxane	TBACl (3 mol %)	7	93	0
6	$[RuCl_2(pcymene)]_2$	$RuCl_3$	--	15	62	19
7	$[RuCl_2(pcymene)]_2$	dioxane	TBACl (3 mol %)	8	90	0
8	$RuCl_3$	dioxane	TBACl (3 mol %)	5	91	0

- Alcohol solvent gave poor yield and selectivity
- Dioxane with Ru(0) catalyst gave great yield and selectivity
- Soluble chloride shown to be a necessity, even with $RuCl_x$ catalysts

Electrophile/Water Loading – Vinyl Oxirane



Reaction	Aldehyde	VO / H_2O (equiv)	Aldehyde Remaining (% ^{1}H NMR)	γ Product (% ^{1}H NMR)	VO Remaining (% ^{1}H NMR)
1	Benzaldehyde	2.0 / 1.5	8	82	0
2	Hydrocinammal		8	85	0
3	4-MeO		39	62	0
4	Benzaldehyde	2.5 / 2.5	2	84	0
5	Hydrocinammal		3	100	0
6	4-MeO		31	68	0

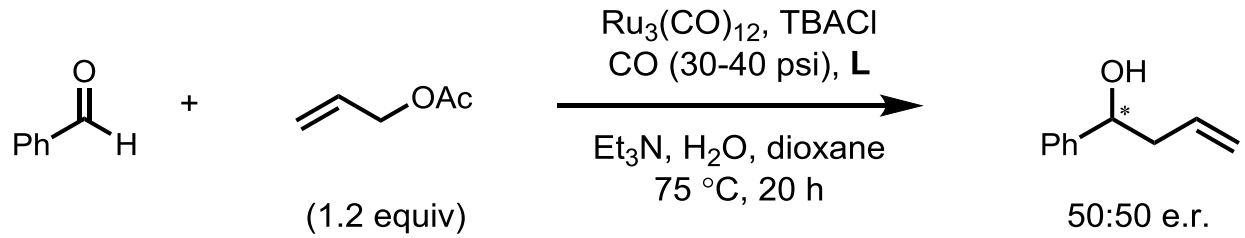
- Full consumption of vinyl oxirane shows significant unproductive protonolysis
- Increased equivalents was able to further increase yield, still with full consumption

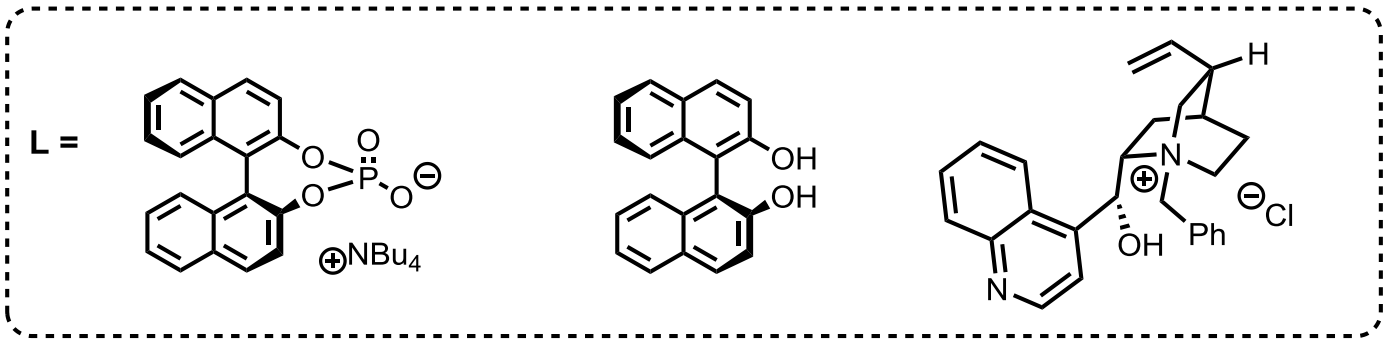
- Aldehyde scope is ongoing

Conclusions

- Successful extension of ruthenium-catalyzed nucleophilic allylation of aldehydes to 2-substituted allylic acetates
- Selective use of solvent and additives can improve selectivity on non-symmetrical allyl electrophiles
- Reaction conditions compatible for diverse substituents on allylic acetate pro-nucleophiles
- Balance of equivalents of allyl electrophile and H_2O resulted in increased product yields

Asymmetric Allylation – Prior Work

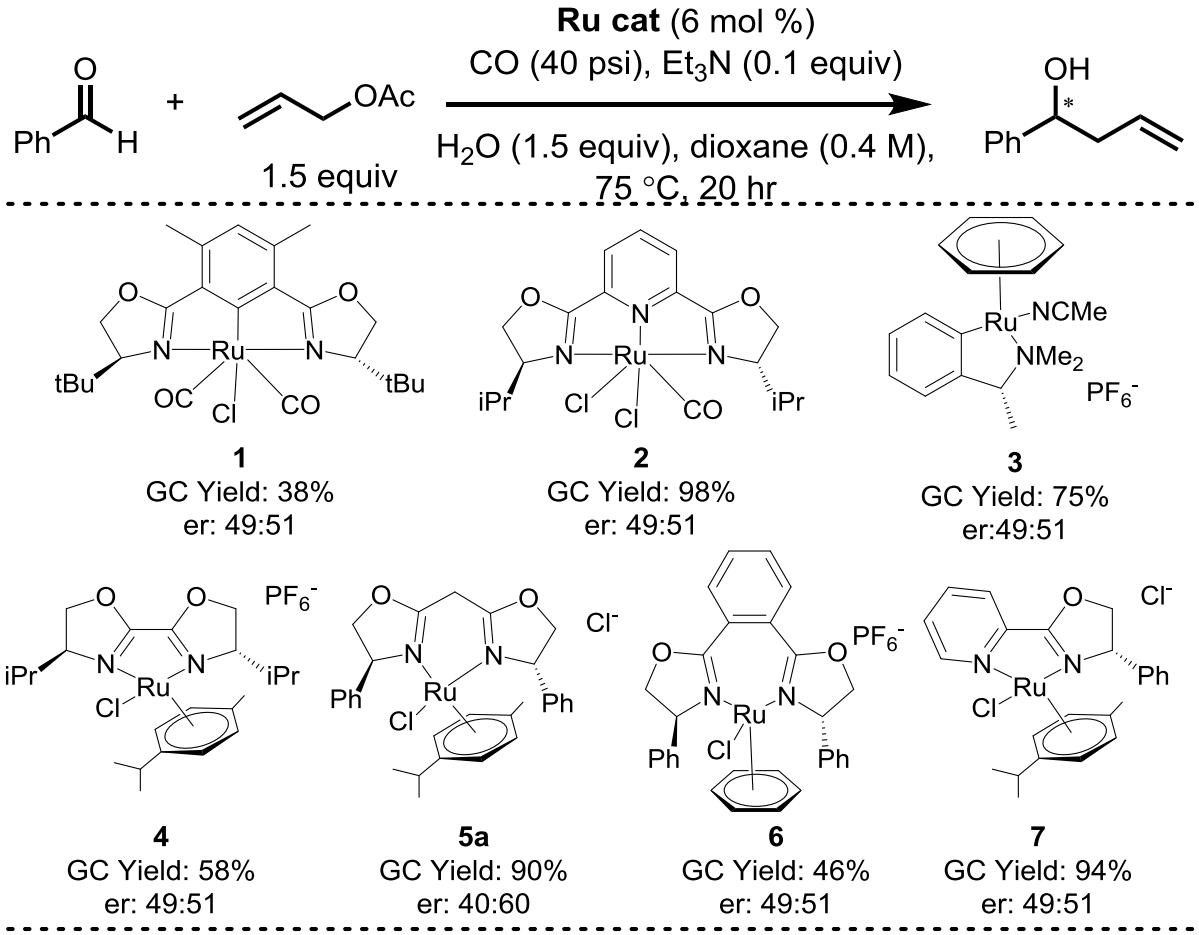




- Initial attempts to render reaction enantioselective were unsuccessful
- Thought to be result of ligand not coordinating to ruthenium

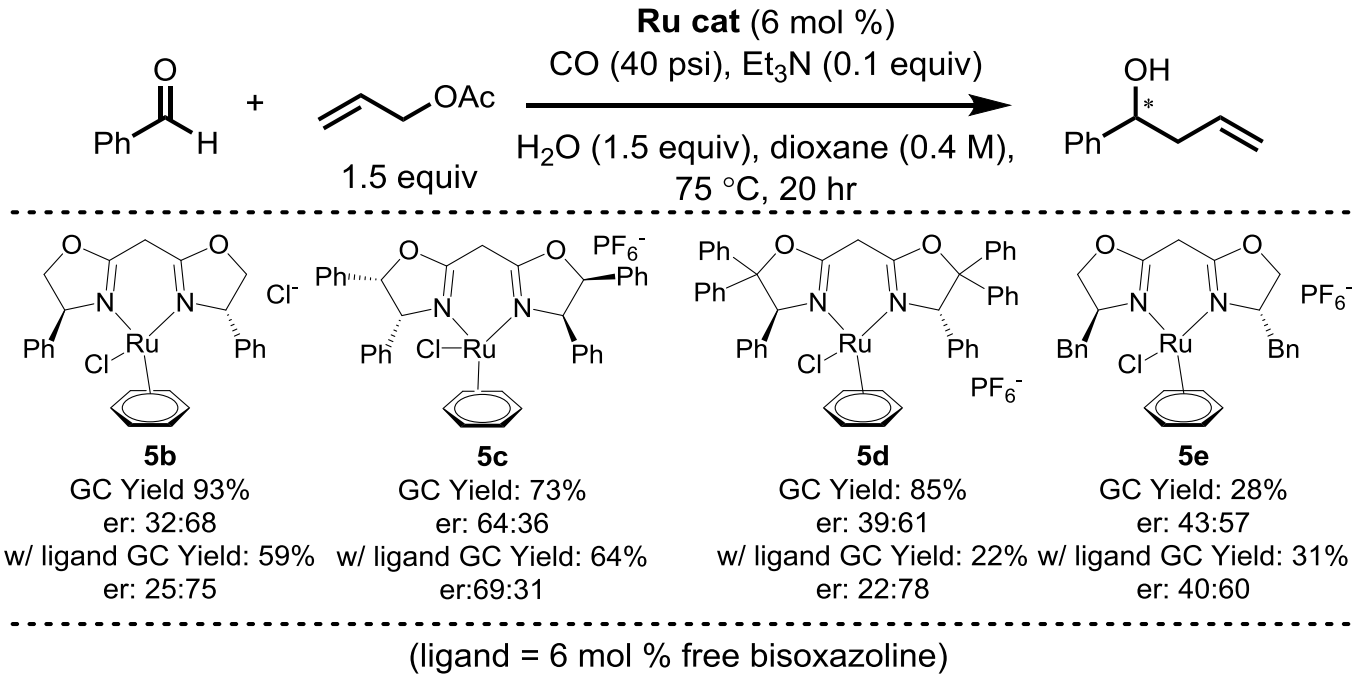
Milicevic, S. D. Postdoctoral Report, University of Illinois - Urbana/Champaign, 2009.

Asymmetric Allylation – Pre-formed Ru-catalysts



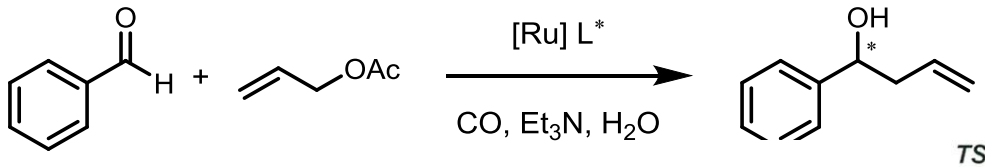
- Tridentate and/or C-Ru bound complexes give no enantioenrichment
- Use of bidentate oxazoline ligands with different backbones gave a hit

Asymmetric Allylation – Bisoxazoline Ru-catalysts

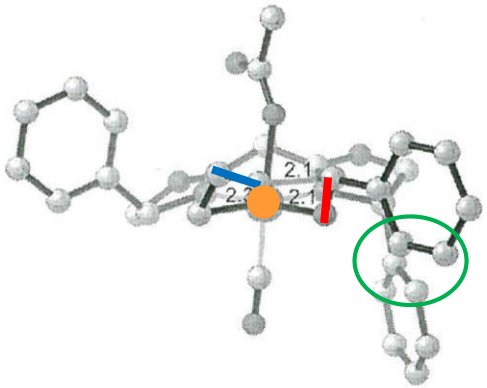


- Variable er values, but close to 30:70
- Additional ligand improved er, up to 22:78, at cost of lower yields
- Highly efficient background causing lower er values

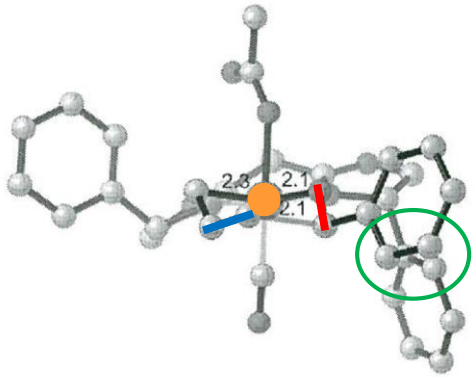
Asymmetric Allylation – Computational Study



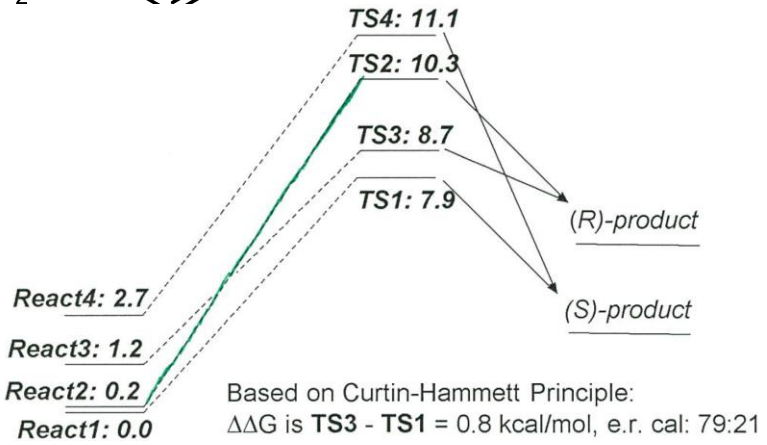
- Phenyl-substituent

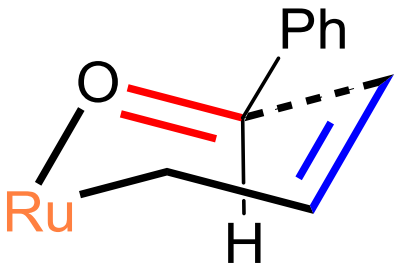


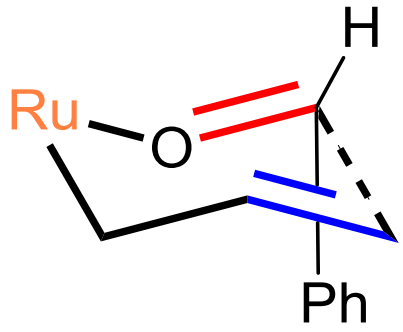
TS1: *7.9*



TS3: *8.7*







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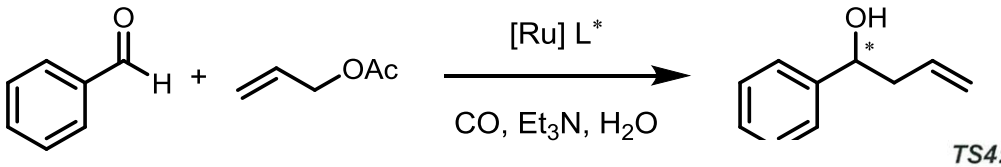
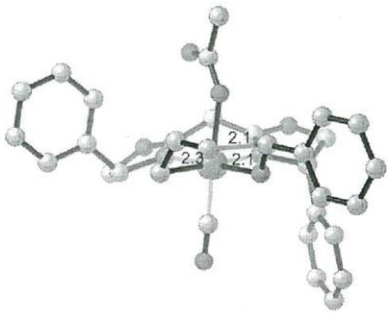
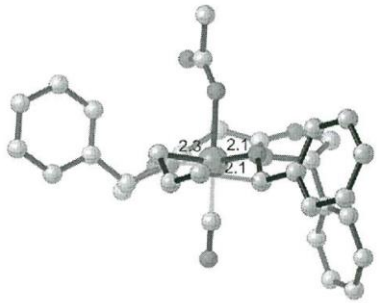
Asymmetric Allylation – Computational Study



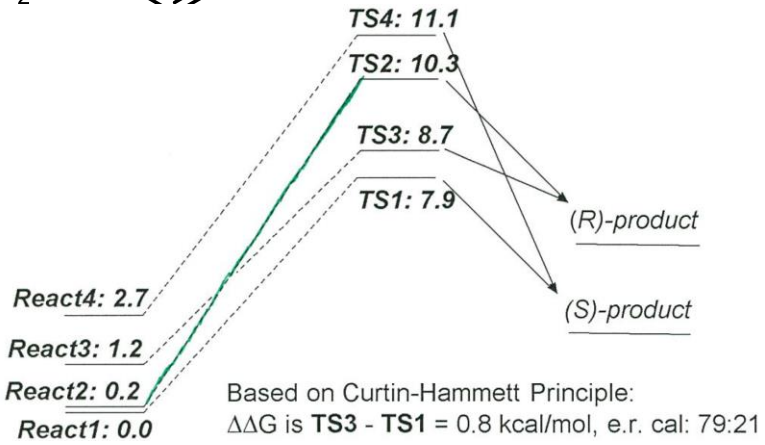
- Phenyl-substituent



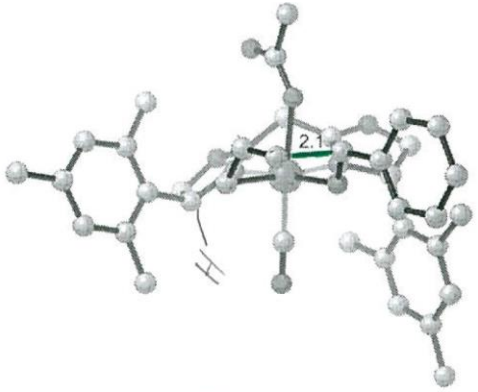
TS1: *7.9*



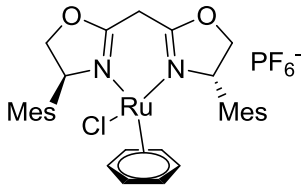
TS3: *8.7*



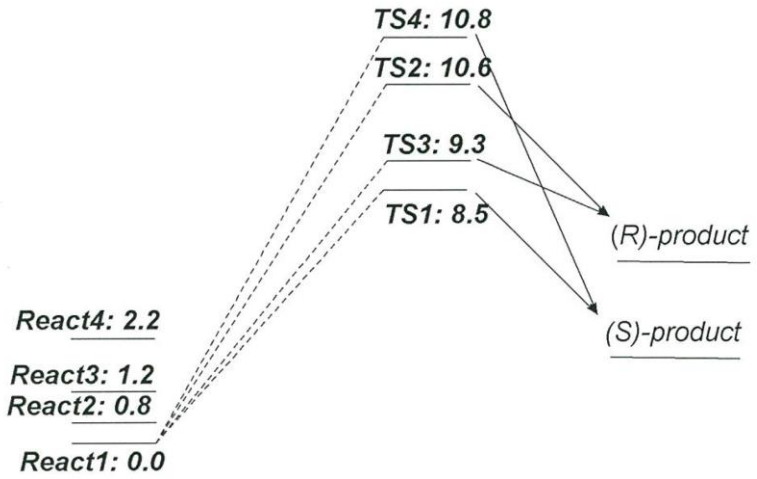
- Mesityl-substituent



TS1: *8.5*



72% Yield
44:56 e.r.



- Experimental attempt did not result in even same er as phenyl, despite similar energy differences

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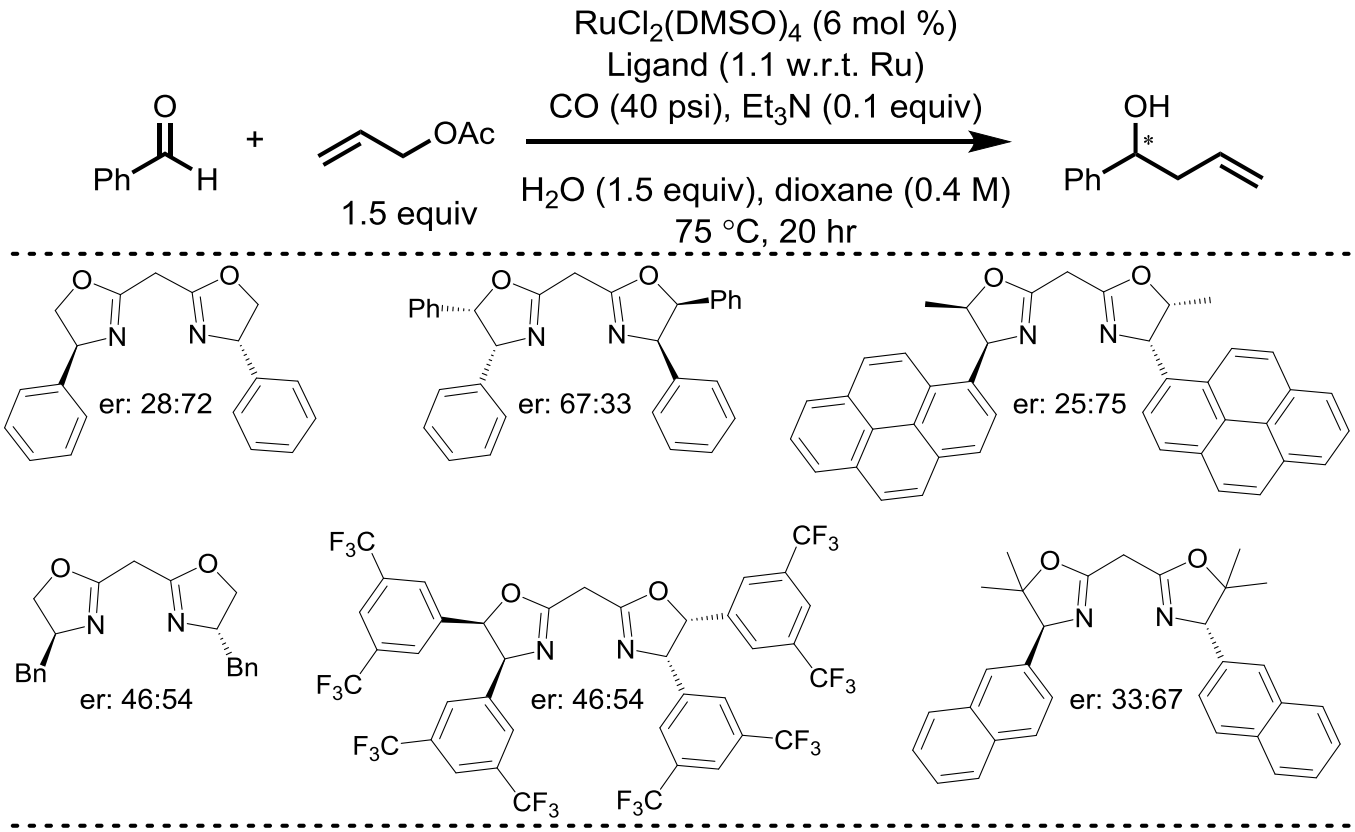
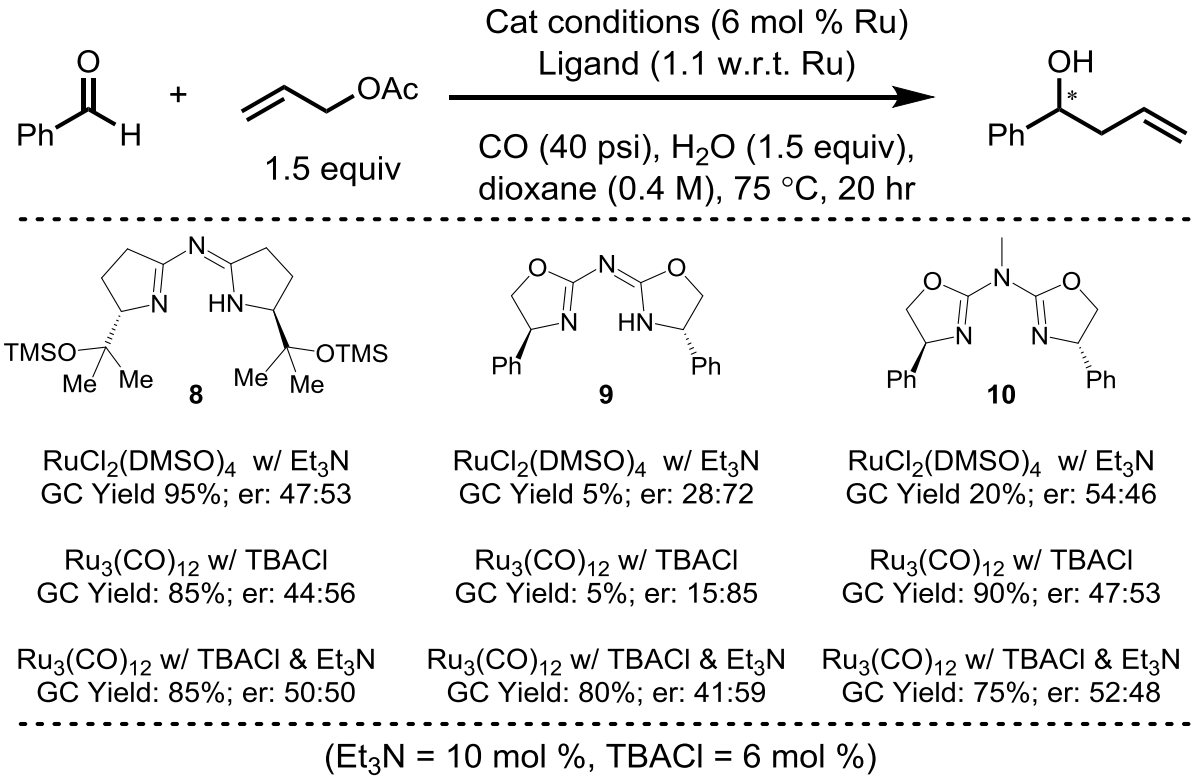
Asymmetric Allylation – Computer-guided Ligand Design



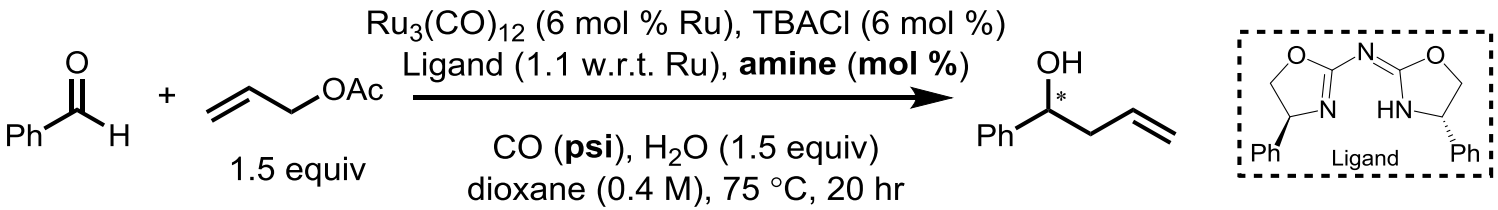
- Use of different ruthenium source allowed for use of free ligand
- Increased π-surface and steric bulk appeared to give high er value
- However, other increased π-surface or steric bulk ligands gave poor er

Asymmetric Allylation – Nitrogen-bridged Ligands



- High er in case of **9**, but low yield
- Similar in the case of $Ru_3(CO)_{12}$ w/ TBACl
- Addition of Et_3N gave poor er in all cases but increased yield
- Gives evidence for competitive binding of amine and ligand

Asymmetric Allylation – Nitrogen-bridged Ligand Competition



Entry	Amine (mol %)	CO (psi)	Conversion (% by GC)	e.r
1	N-Me TMP (10)	40	5	20:80
2	Et_3N (5)	40	5	20:80
3	Et_3N (6)	40	20	14:85
4	Et_3N (7)	40	90	41:59
5	N/A	40	5	15:85
6	N/A	60	20	22:78
7	N/A	80	100	39:61
8	Et_3N (5)	60	20	38:62
9	Et_3N (5)	80	90	37:62

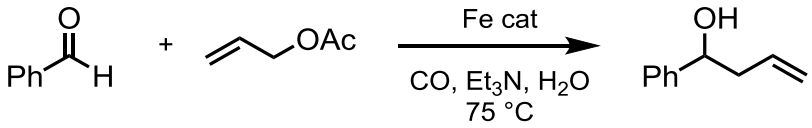
- Increasing amine equivalents decrease er/increase yield
- Similar trend for CO pressure with different amine loadings
- Reaffirms competitive binding
- Ligand-bound ruthenium is less reactive

Conclusions

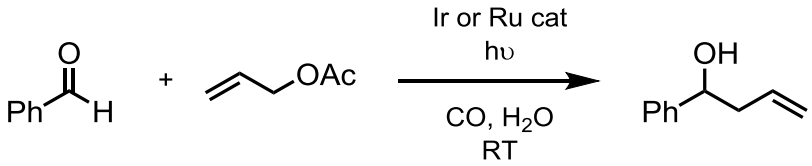
- Successfully able to design an asymmetric WGS allylation reaction
- The ligated-ruthenium appears to have a slower reaction rate, and highly efficient background lowers er
- Additional ligand or tighter-bound ligand increases er, but at cost of yield
- Competitive binding of ligand and additives observed
- Further enantioselective attempts should focus on a new ligand backbone

Alternative Approach

- Design a more efficient WGS allylation reaction
- Current drawbacks:
  - 1) Use of ruthenium – can we use a more abundant metal?



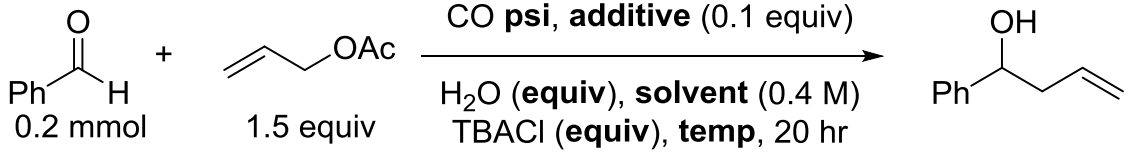
  - 2) Moderately high temperature – can we reduce to RT?



Alternative Approach – Iron DoE Study

- Carried out a Design of Experiment (DoE) approach

DoE Parameters



Fe Source	Additives	Solvent	CO Pressure
$Fe_3(CO)_{12}$	$AsPh_3$	Acetonitrile	30 to 210 psi
$[FeCp(CO)_2]_2$	PPh_3	Dioxane	**Temperature**
$FeCl_2$	BINAP	DMF	25 to 125 °C
$Fe(acac)_3$	2,2'-bipyridine	Ethanol	**H_2O Equivalents**
	Et_3N	Hexafluoro Isopropanol	0 to 10 equiv
		NMP	**TBACl Equivalents**
		Sulfolane	0 to 1 equiv
		THF	

- No turnover was observed
- Highest yield of product was 9% (by GC) with 10 mol % Fe
- One possibility is due to strong Fe-O bond strength as compared to Fe-COOH bond inhibiting the protonolysis step (93 kcal/mol vs 32 kcal/mol)

Electrochemical requirement

$CO + H_2O \longrightarrow CO_2 + 2H^+ + 2e^-$ $\quad E°_{ox} = +0.53\ V$

$M^{2+} + 2e^- \longrightarrow M^0$ $\quad E°_{red} = x$

$M^{2+} + CO + H_2O \longrightarrow M^0 + CO_2 + 2H^+$ $\quad \mathbf{\Delta E° = (x + 0.53)\ V}$

If $E°_{red} > -0.53$ V, the reaction can be driven by the WGSR

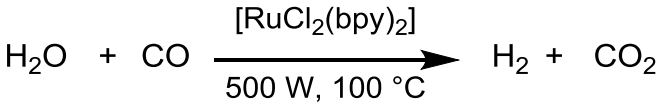
$M^{2+} + 2e^- \longrightarrow M^0$

$M^{2+} + CO + H_2O \longrightarrow M^0 + CO_2 + 2H^+$

Cr −0.91 **−0.38**	***Mn*** −1.19 **−0.66**	***Fe*** −0.45 **0.08**	***Co*** −0.28 **0.25**	***Ni*** −0.26 **0.27**	***Cu*** 0.34 **0.87**	***Zn*** −0.76 **−0.23**
Mo	***Tc***	***Ru*** 0.45 **0.98**	***Rh*** 0.60 **1.13**	***Pd*** 0.95 **1.48**	***Ag***	***Cd*** −0.40 **0.13**
W	***Re***	***Os***	***Ir***	***Pt*** 1.18 **1.71**	***Au***	***Hg*** 0.85 **1.38**

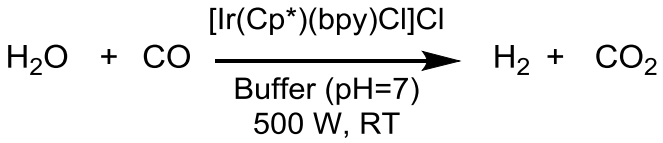
Alternative Approach – Photochemical WGS Allylation

- Ruthenium-based catalysts



- Light irradiation required to generate H_2 from $[RuClH_2(bpy)_2]^+$

- Iridium-based catalysts

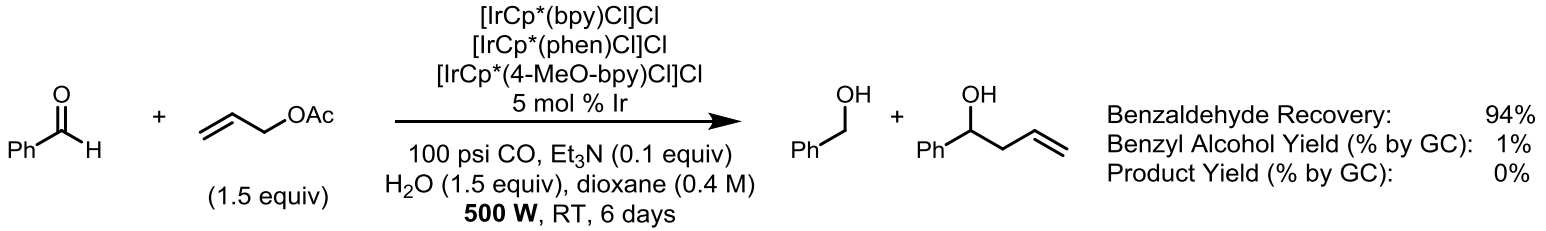


- pH of 7 required to balance CO_2 and H_2 formation preferences
- Activity of catalyst diminishes over time, but addition of bpy improves yield

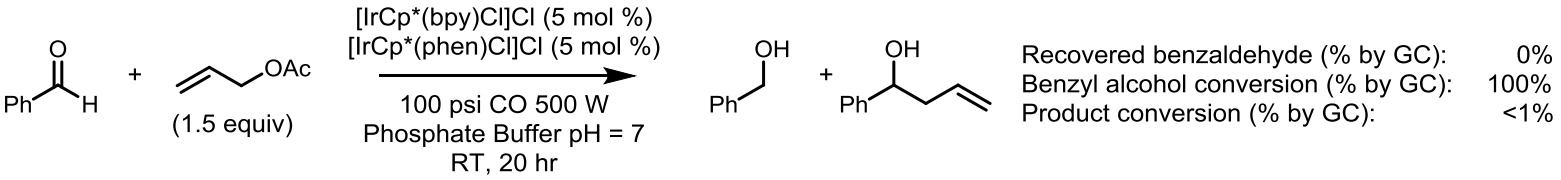
Cole-Hamilton, D. J. *et al J. Chem. Soc. Dalton Trans.* **1982,** 1885-1893
Ziessel, R. *J. Chem. Soc. Chem. Commun.* **1988,** 16-17

Alternative Approach – Ir Photochemical WGS Allylation

- Initial photochemical attempts with ruthenium catalysts



- No reaction in dioxane

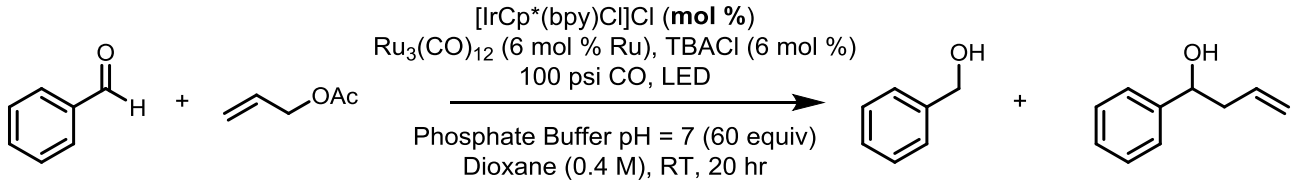


- Complete conversion to benzyl alcohol using phosphate buffer

- Iridium catalysts seem more suited to aldehyde reduction

Alternative Approach – Combined Ir and Ru Reaction

- Dual catalyst system

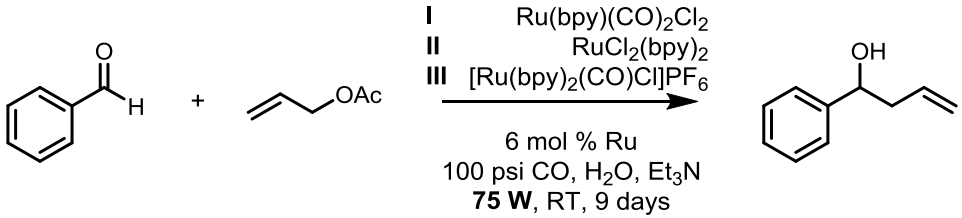


Ir cat (mol %)	Aldehyde Recovery (% GC)	Benzyl alcohol Conversion (% GC)	Product Conversion (% GC)
6	79	28	0
--	60	0	13

- Experiment showed that 60 equiv of buffer in dioxane allowed Ir reactivity
- Clear distinction of addition of Ir photocatalyst with Ru-allylation catalyst
- Additional reactions with other Ru-catalysts and bpy additives gave similar results
- In all cases, reduction of aldehyde was the dominant reaction

Alternative Approach – Ru Photochemical WGS Allylation

- Initial photochemical attempts with ruthenium catalysts

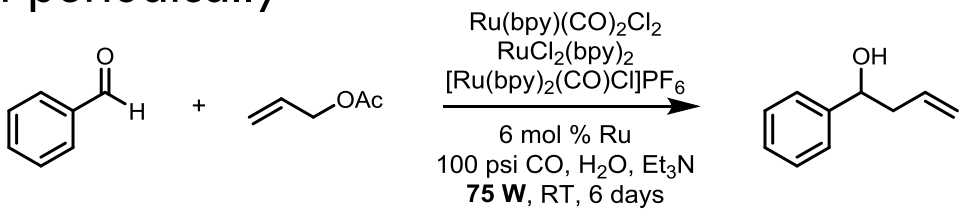


Catalyst	Light	Benzaldehyde Recovered (% by GC)	Benzyl Alcohol Yield (% by GC)	Product Yield (% by GC)
I / II / III	--	92	0	5
I	--	87	0	7
II	--	99	0	0
III	--	100	0	0
I / II / III	**75 W**	11	59	24

- Significant reactivity in light → revealed to be due to heat from lamp
- Formation of benzyl alcohol from aldehyde reduction

Alternative Approach – Ru Photochemical WGS Allylation

- Reaction rerun with better cooling in side by side with reaction cell that was opened to test periodically



Entry	Elapsed Time (hr)	Benzaldehyde Recovered (% by GC)	Benzyl Alcohol Yield (% by GC)	Product Yield (% by GC)
1	14	93	0	0
	24	94	0	1
	48	86	0	2
	72	77	0	2
	139	70	<1	3
2	139	77	14	4

- Divergence in yield of benzyl alcohols points towards possible buildup of H_2 from normal photochemical WGSR
- Yields of homoallylic alcohol similar in both experiments
- Subsequent reactions adjusting light intensity, solvent, additive gave at best 1:1 (total yield ~20%) reduction:allylation
- Most often, only increases in reduction were observed

Conclusions – Alternative Approaches

- Replacement of iron for ruthenium
  - Did not result in any turnover
  - Issue with electrochemical potential and Fe-O cleavage
- Photochemical reactions
  - Primary reaction was reduction of aldehyde
  - Iridium catalysts highly favored reduction
  - Ruthenium catalysts gave some allylation HOWEVER was usually observed in dark reactions to nearly same extent
  - RT activation of ruthenium shown viable (previous report used >80 °C)

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