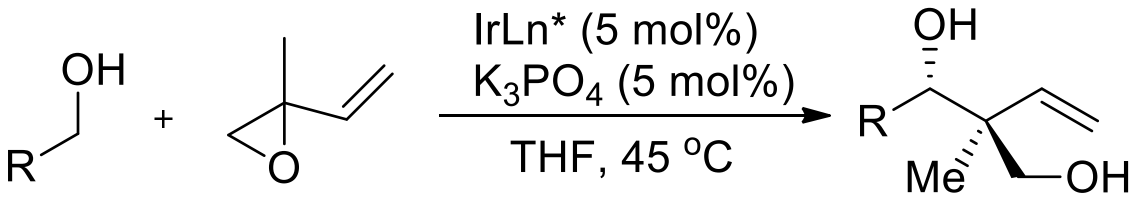
Redox-Triggered C-C Coupling of Alcohols and Vinyl Epoxides

Jiajie Feng, Victoria J. Garza, and Michael J. Krische

J. Am. Chem. Soc., **2014**, *136* (25), pp 8911–8914



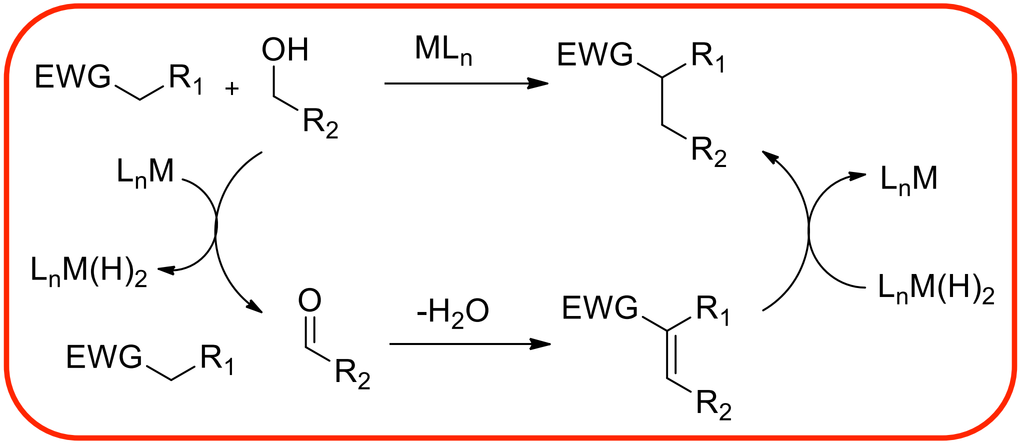
73-91% yield
30 - >99:1 dr
91-99%

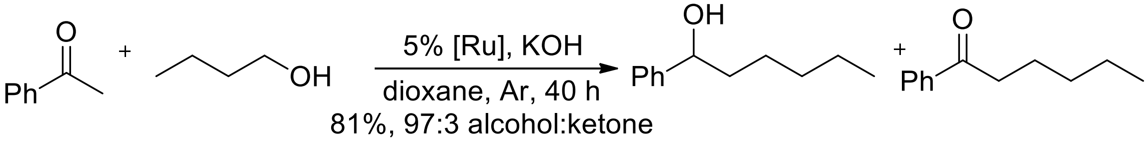
Nicholas Reed
Wipf Group Current Literature
July 5, 2014
Happy (Belated) Birthday America!

Development of Redox Triggered Catalysis

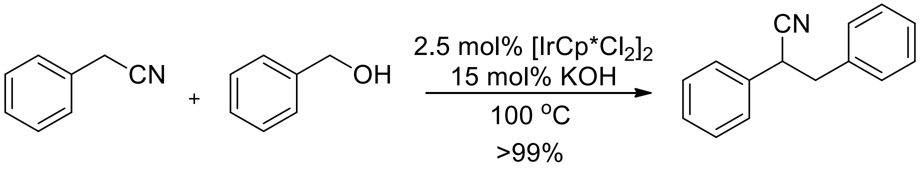
- Traditional Methods – Hydrogen Autotransfer Involving Condensation/Olefination
  1. Alcohol Dehydrogenation
  2. Condensation/Olefination
  3. Hydrogenation

Marcel Guerbet





JOC **2001**, *66*, 9020

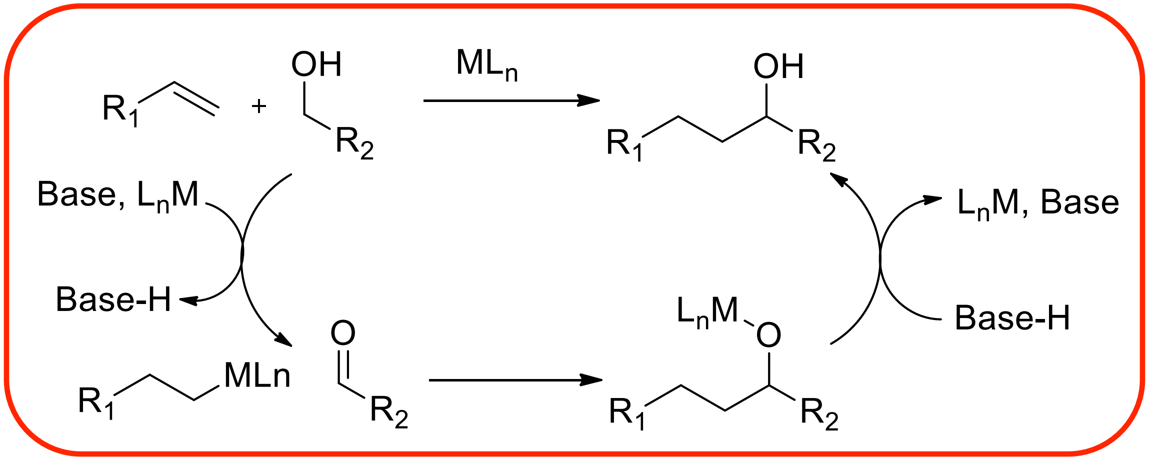


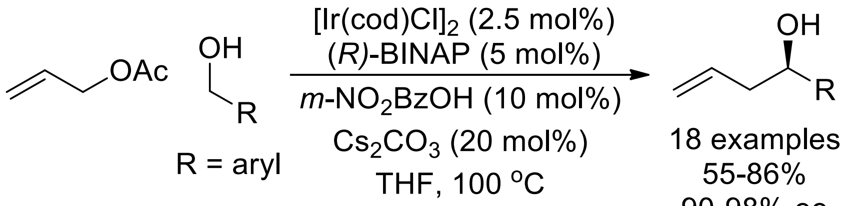
JOC **2006**, *71*, 8023

Seminal Paper: *C. R. Chim.* **1908**, *146*, 298

Development of Redox Triggered Catalysis

- Carbonyl Addition via Hydrogen Auto-Transfer

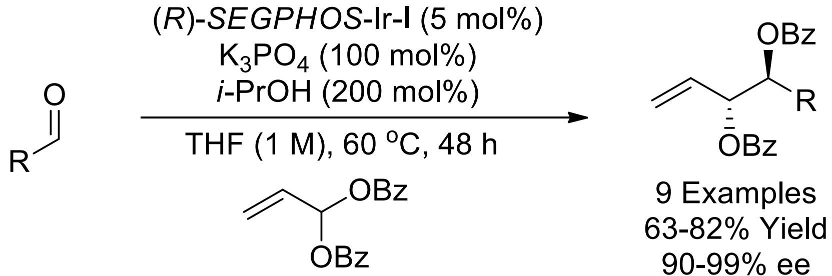




$[Ir(cod)Cl]_2$ (2.5 mol%)
(*R*)-BINAP (5 mol%)
m-NO_2BzOH (10 mol%)
Cs_2CO_3 (20 mol%)
THF, 100 °C

18 examples
55-86%
90-98% ee

JACS **2008**, *130*, 6340



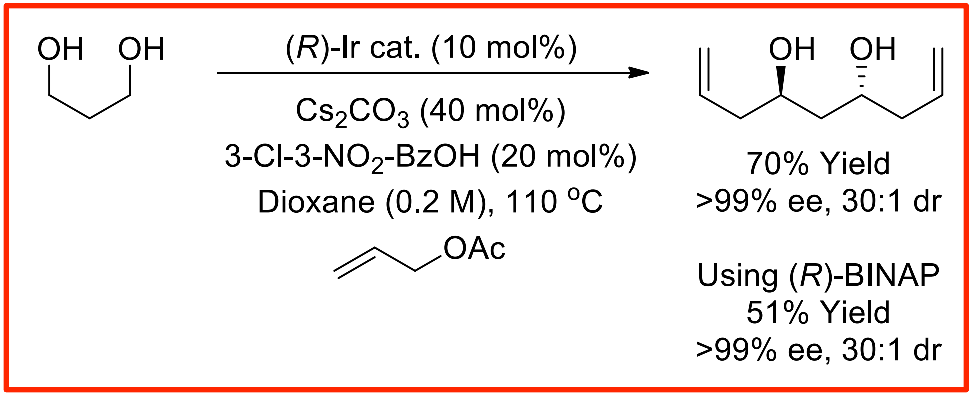
(*R*)-*SEGPHOS*-Ir-**I** (5 mol%)
K_3PO_4 (100 mol%)
i-PrOH (200 mol%)
THF (1 M), 60 °C, 48 h
then BzCl, TEA, DMAP

9 Examples
63-82% Yield
90-99% ee

JACS **2010**, *132*, 1760

For the full developmental story by the Krische Group: *JOC* **2007**, *72*, 1063

Hydrogen Auto-Transfer in Total Synthesis



(*R*)-Ir cat. (10 mol%)

Cs_2CO_3 (40 mol%)

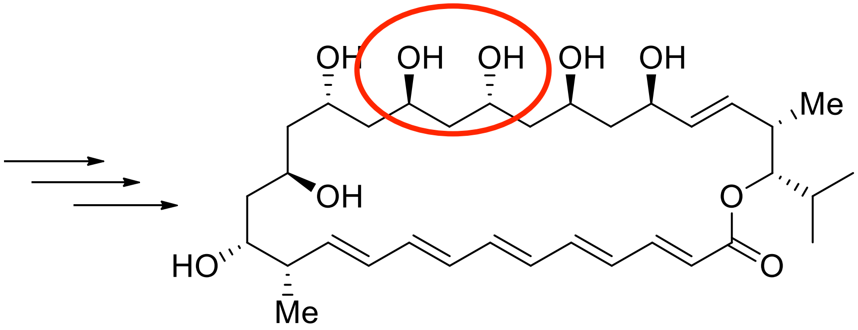
3-Cl-3-NO_2-BzOH (20 mol%)

Dioxane (0.2 M), 110 ^oC

OAc

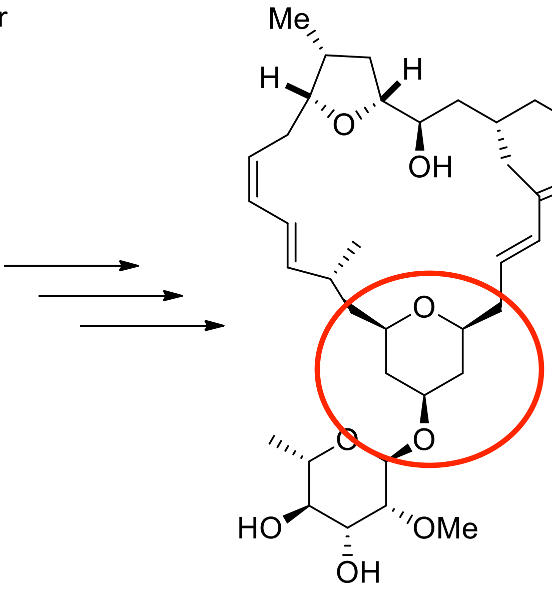
70% Yield
>99% ee, 30:1 dr

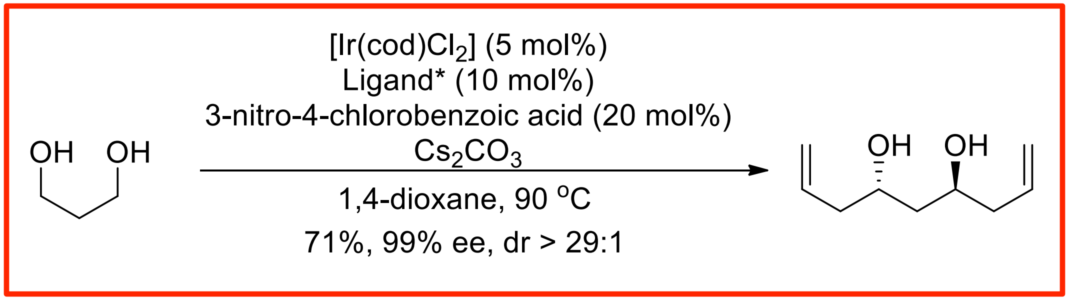
Using (*R*)-BINAP
51% Yield
>99% ee, 30:1 dr



(+)-Roxaticin (20 steps LLS, 29 steps total)

JACS **2010**, *132*, 15559 / Also see: CL 3/23/13 “Total Synthesis of Cyanolide A” for another example from the Krische Group





$[Ir(cod)Cl_2]$ (5 mol%)
Ligand* (10 mol%)
3-nitro-4-chlorobenzoic acid (20 mol%)
Cs_2CO_3

1,4-dioxane, 90 ^oC

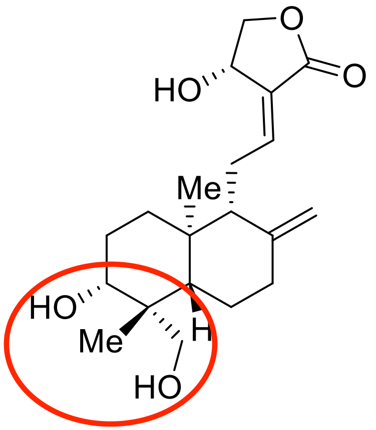
71%, 99% ee, dr > 29:1

ACIE **2014**, *53*, 4217

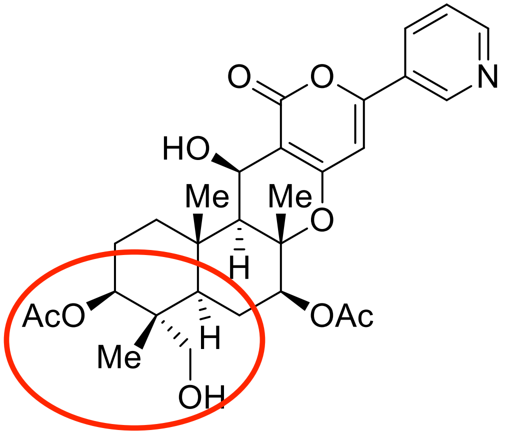
Mandelalide A (proposed)
21 steps LLS, 4.5% Overall Yield

Hydrogen Auto-Transfer in Total Synthesis

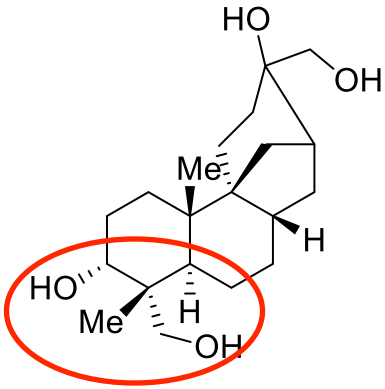
- Terpenoid natural products require *n*- and *tert*-prenylation



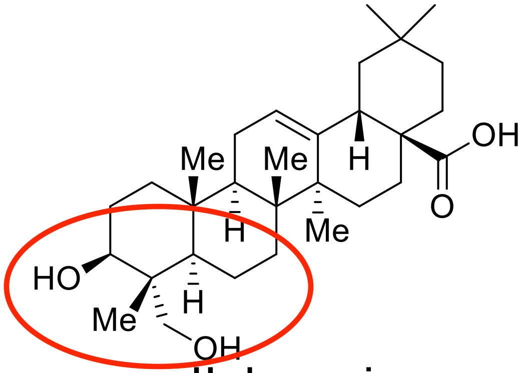
Andrographolide



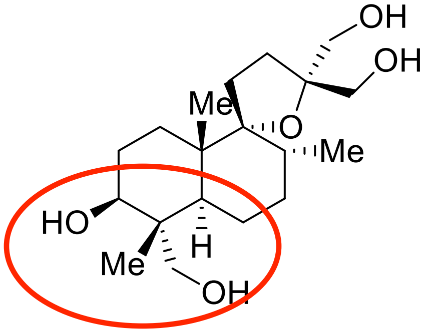
Pyripyropene A



Aphidicolin

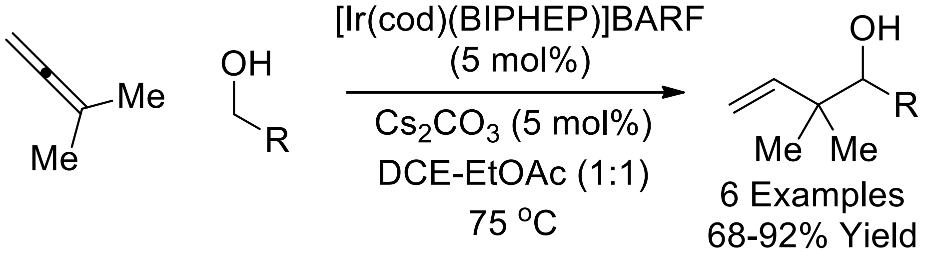


Hederagenin



Lagochilin

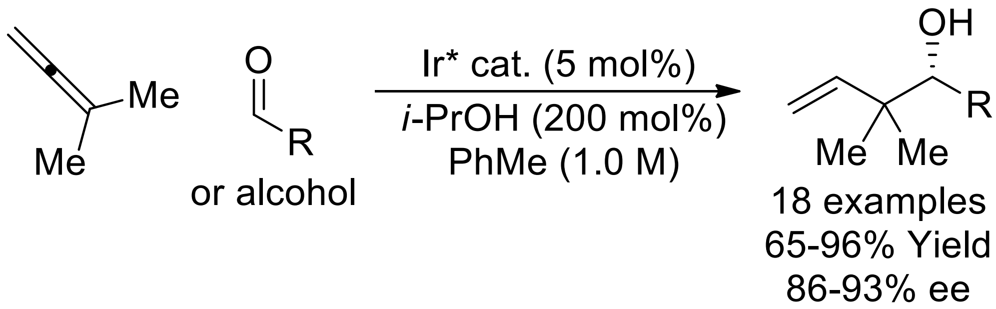
Early Developments



JACS **2007**, *129*, 15134

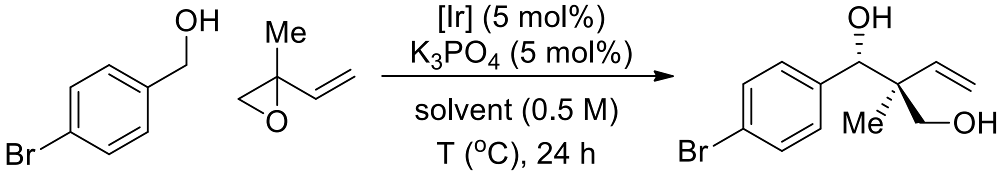
Reverse prenylation possible using iridium catalyst. Presumably forms allyl metal species *in situ*

Enantioselective reverse prenylation from either aldehyde or alcohol oxidation state



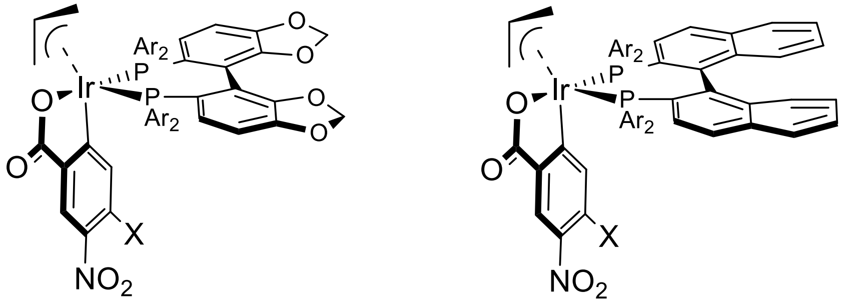
JACS **2009**, *131*, 6916-6917

Optimization and Catalyst Screening



Entry	**3a** (mol%)	T (^oC)	[Ir]	solvent	**4a** yield (dr, ee%)
1[a]	200	60	(*R*)-Ir-**Ib**	THF	37% (2:1, 93)
2	200	60	(*R*)-Ir-**Ib**	THF	90% (4:1, 93)
3[b]	200	25	(*R*)-Ir-**Ib**	THF	trace
4	200	45	(*R*)-Ir-**Ib**	THF	95% (2.5:1, 93)
	200	90	(*R*)-Ir-**Ib**	THF	60% (4:1, 75)
5	200	45	(*R*)-Ir-**IVb**	THF	71% (30:1, 93)
6	300	**45**	(*R*)-Ir-**IVb**	THF	91% (40:1, 94)

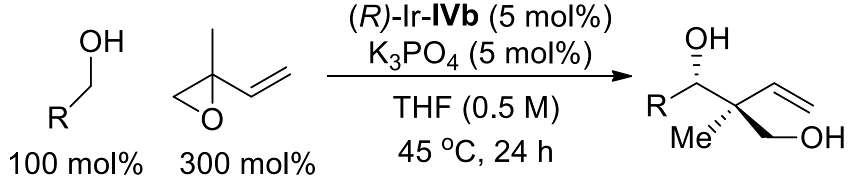
[a] K_3PO_4 omitted from the reaction mixture [b] 48 h



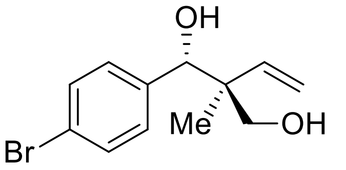
(*R*)-Ir-**Ia**, Ar = Ph, X = H
(*R*)-Ir-**Ib**, Ar = Ph, X = CN
(*R*)-Ir-**IIa**, Ar = 3,5-Me_2Ph, X = H
(*R*)-Ir-**IIb**, Ar = 3,5-Me_2Ph, X = CN

(*R*)-Ir-**IIIa**, Ar = Ph, X = H
(*R*)-Ir-**IIIb**, Ar = Ph, X = CN
(*R*)-Ir-**IVa**, Ar = 4-MePh, X = H
(*R*)-Ir-**IVb**, Ar = 4-MePh, X = CN

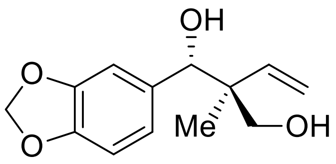
tert-(Hydroxy)-Prenylation of Alcohols



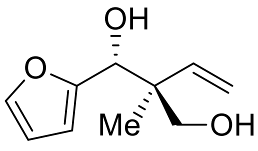
a, R = 4-Br-Ph
b, R = piperonyl
c, R = 2-furyl
d, geraniol
e, R = prenyl alcohol
f, cinnamyl alcohol
g, R = n-hexyl
h, R = 2-phenethyl
i, R = *c*-hexylmethyl



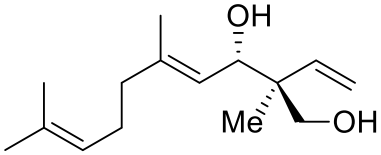
a, 91% Yield
40:1 dr, 94% ee (X-ray)



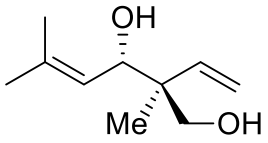
b, 89% Yield
60:1 dr, 91% ee



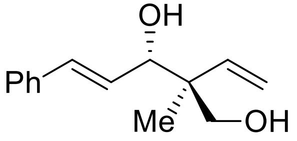
c, 91% Yield
30:1 dr, 98% ee



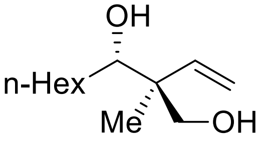
d, 73% Yield
30:1 dr, 91% ee



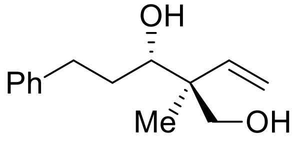
e, 85% Yield
>99:1 dr, 93% ee



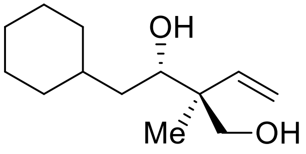
f, 85% Yield
40:1, dr, 93% ee



g, 74% Yield
40:1 dr, 93% ee

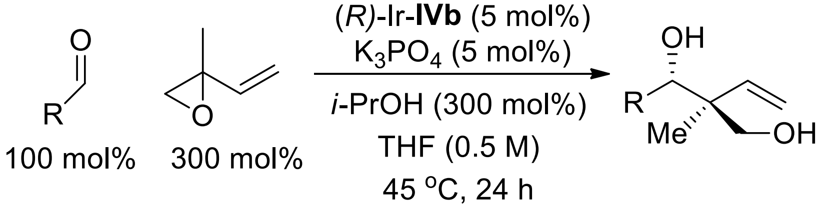


h, 76% Yield
30:1 dr, 93% ee

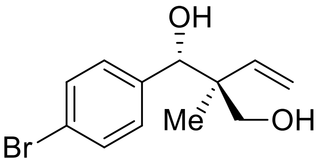


i, 76% Yield
30:1 dr, 99% ee

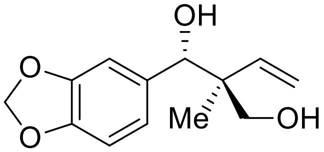
tert-(Hydroxy)-Prenylation of Aldehydes



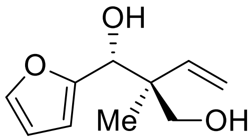
a, R = 4-Br-Ph
b, R = piperonyl
c, R = 2-furyl
d, geranial
e, R = CH=CMe_2
f, cinnamaldehyde
g, R = n-hexyl
h, R = 2-phenethyl
i, R = *c*-hexylmethyl



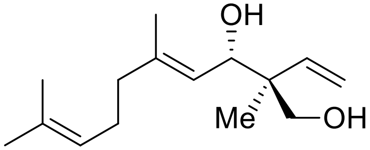
a, 87% Yield
10:1 dr, 94% ee (X-ray)



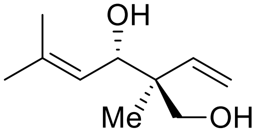
b, 90% Yield
50:1 dr, 90% ee



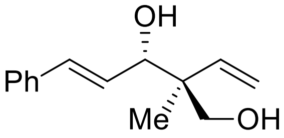
c, 91% Yield
5:1 dr, 94% ee



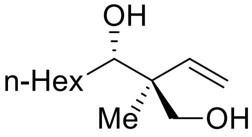
d, 77% Yield
20:1 dr, 91% ee



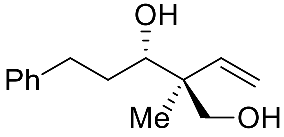
e, 81% Yield
20:1 dr, 86% ee



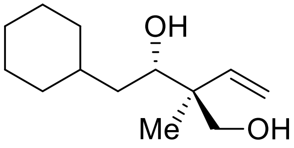
f, 76% Yield
10:1, dr, 91% ee



g, 73% Yield
12:1 dr, 93% ee

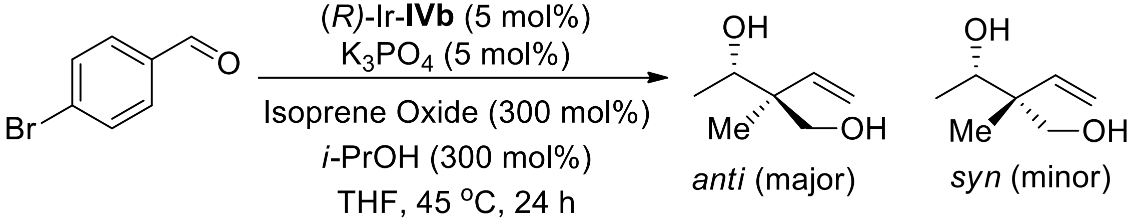


h, 91% Yield
5:1 dr, 85% ee



i, 65% Yield
20:1 dr, 95% ee

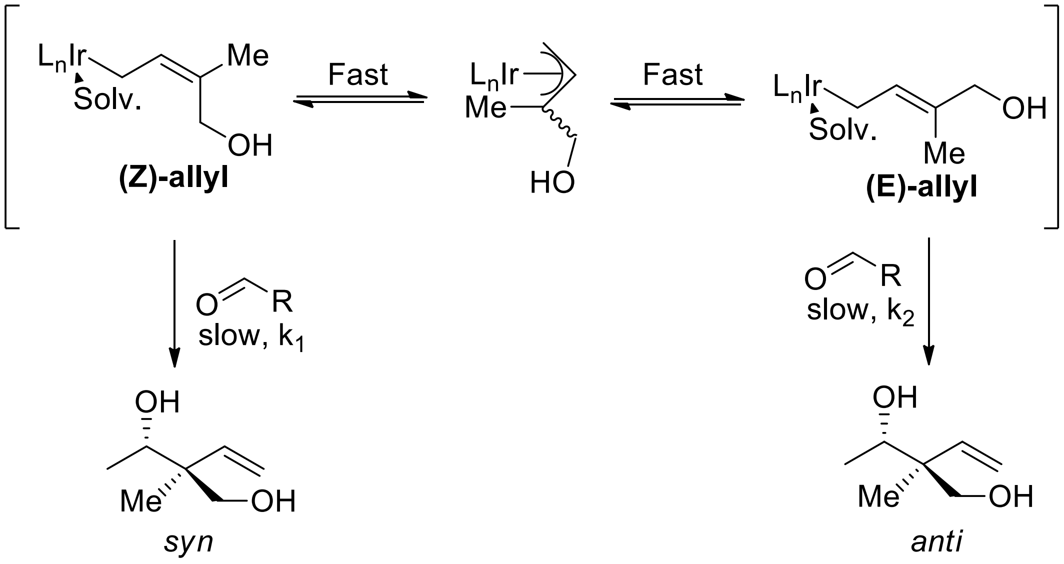
Concentration Dependent Selectivity



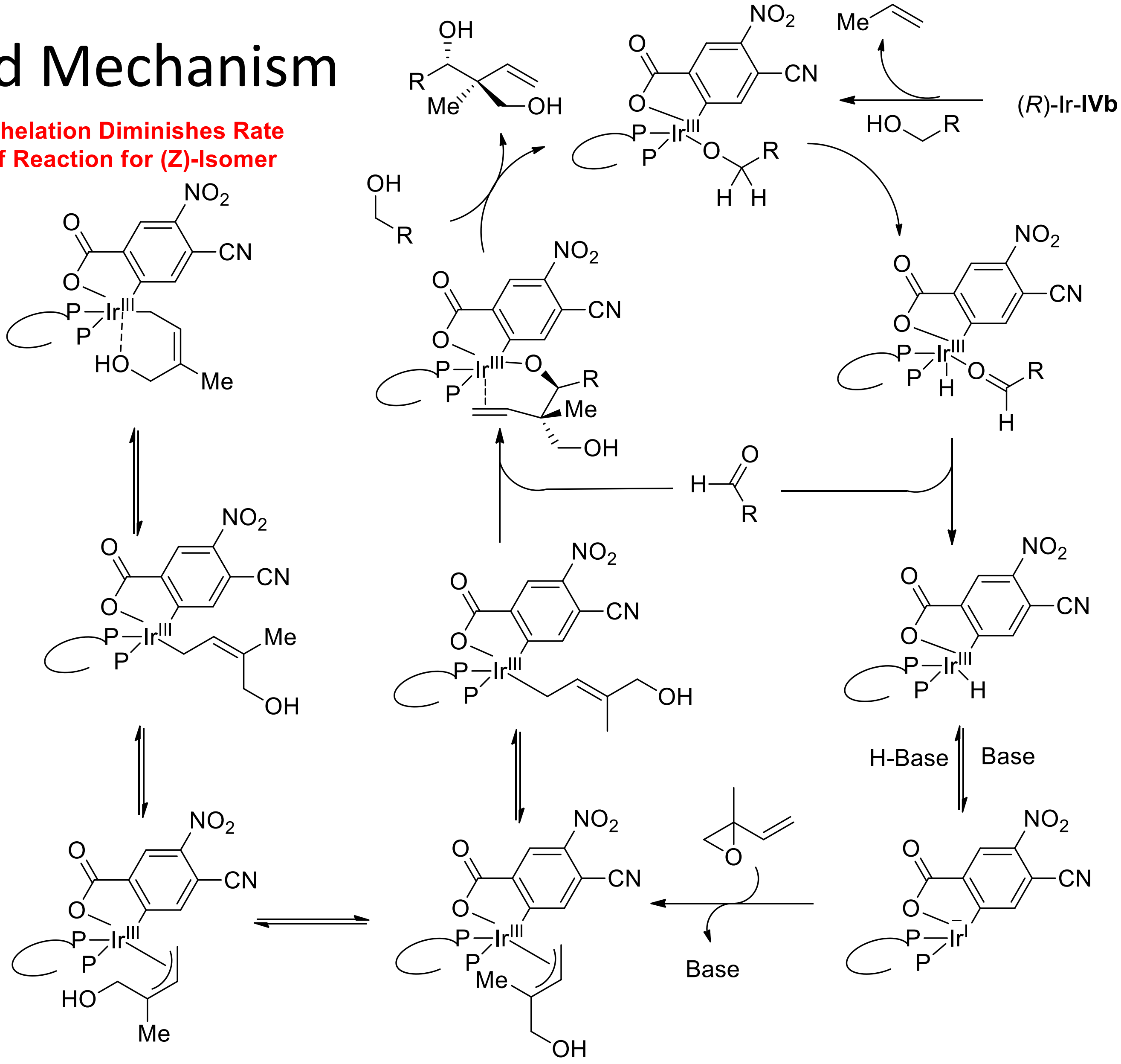
Entry	THF (conc.)	Yield	anti:syn (ee%)
1	1.0 M	92%	6:1 (92)
2	0.5 M	87%	10:1 (94)
3	0.33 M	84%	14:1 (90)
4	0.1 M	79%	17:1 (90)

Suggests Curtin-Hammett Principle is in Effect

- $k_1 < k_2$
- Lower concentration allows for replenishment of (E)-allyl-iridium species from less reactive (Z)-allyl isomer



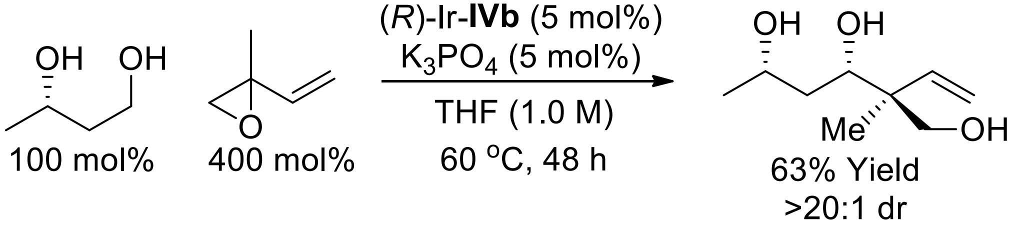
Proposed Mechanism

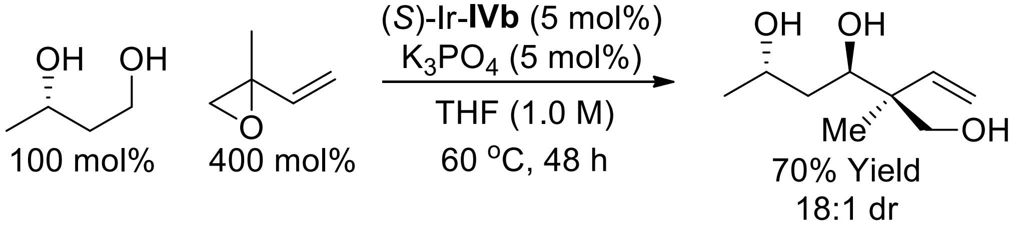


Chelation Diminishes Rate of Reaction for (Z)-Isomer

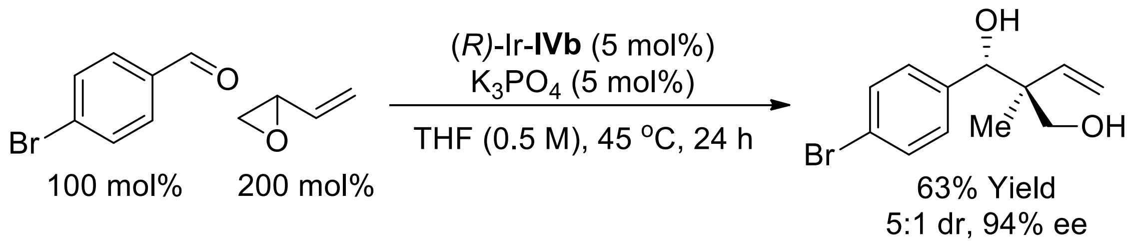
Alcohol Selectivity and Epoxide Scope

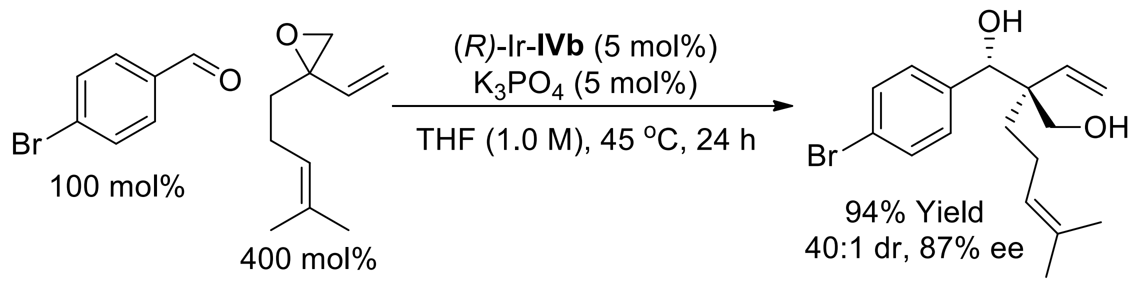
- Use of Malic Acid Derived Diols





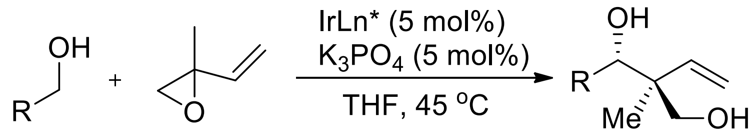
- Scope of Vinyl Epoxides





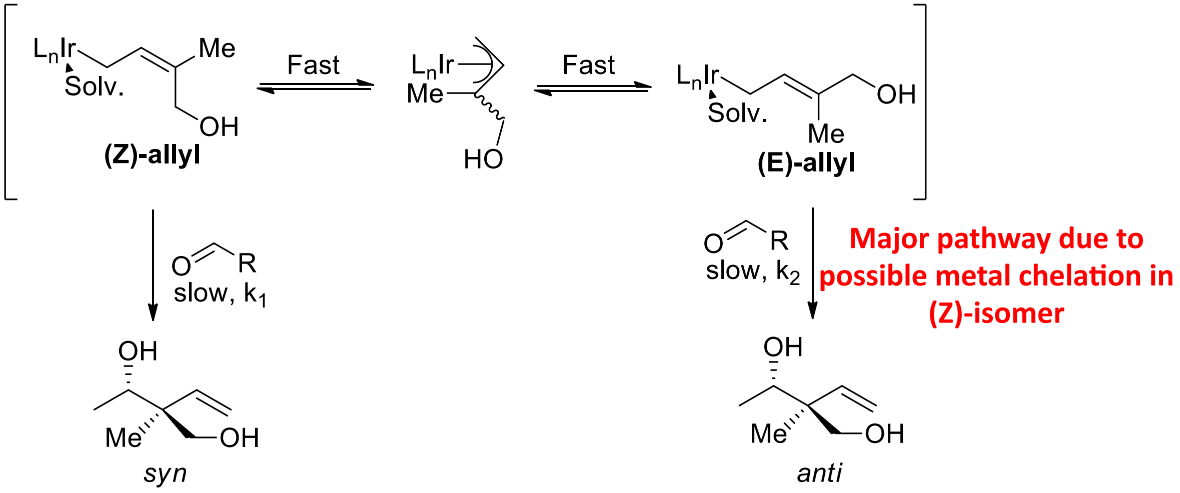
Conclusions

- Effective method to couple vinyl epoxides and alcohols with excellent enantio- and diastereoselectivity using redox-triggered catalysis



73-91% yield
30 - >99:1 dr
91-99%

- Expanded scope of vinyl epoxides and alcohols (potential natural product applications) and determined that Curtin-Hammett kinetics may be involved in the mechanism of this transformation



Major pathway due to possible metal chelation in (Z)-isomer