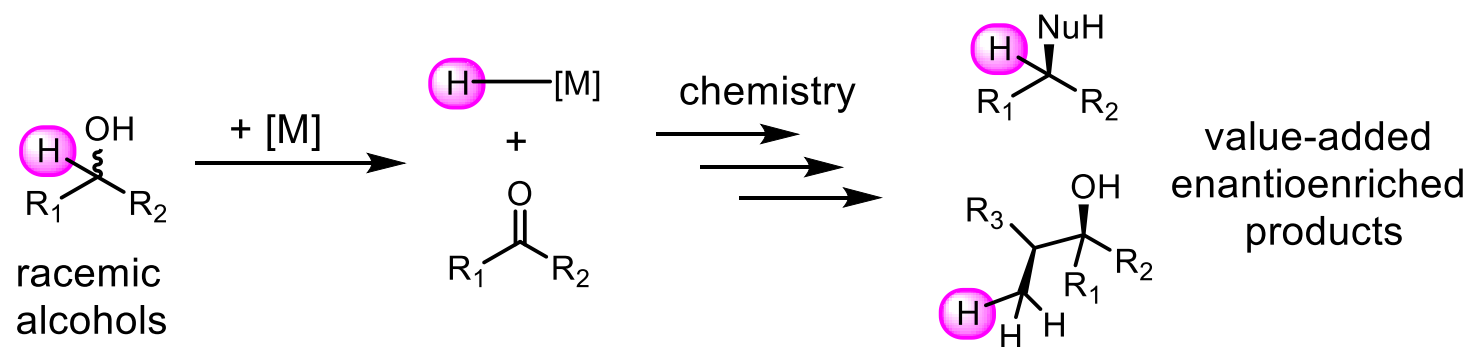


# Borrowing Hydrogen in Asymmetric Catalysis

Casey Olen  
Denmark Group Meeting  
September 26<sup>th</sup>, 2023





# Overview

**Part 1:** Historical overview, mechanism, and note on nomenclature.

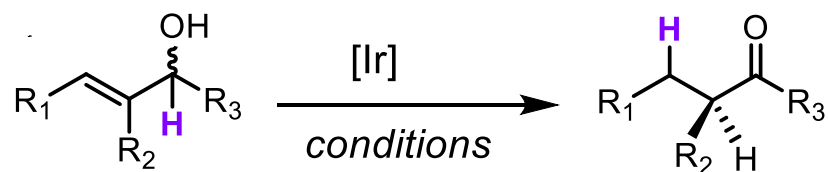
**Part 2:** Borrowing hydrogen/returning carbon for C-C bond formation: *In situ* nucleophile generation by hydrometallation or reductive C-X bond cleavage.

**Part 3:** Borrowing hydrogen/returning hydrogen for enantioconvergent functionalization of racemic 2° alcohols.

Not covered in this talk:

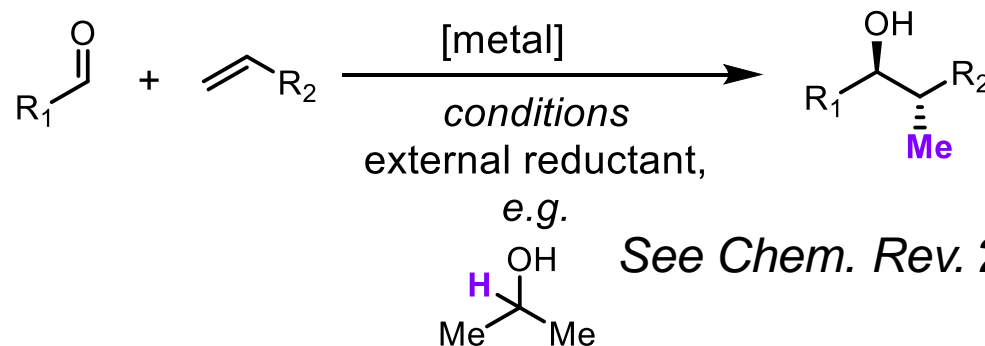
- Enantioselective isomerization
- Reductive couplings/transfer hydrogenation

**Not covered:**



See *Chem. Soc. Rev.*, **2023**, 52, 5541.

**Not covered:**

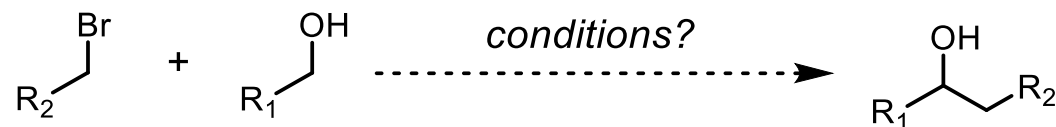


See *Chem. Rev.* **2018**, 118, 6026

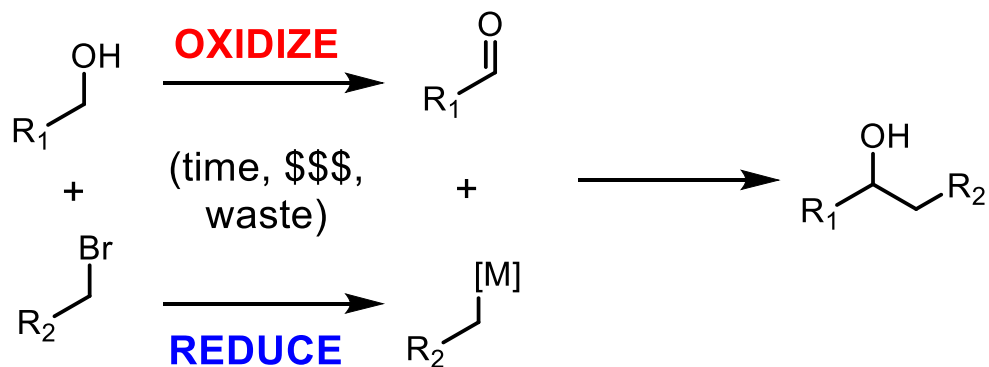


# Motivation for Borrowing Hydrogen Reaction Development

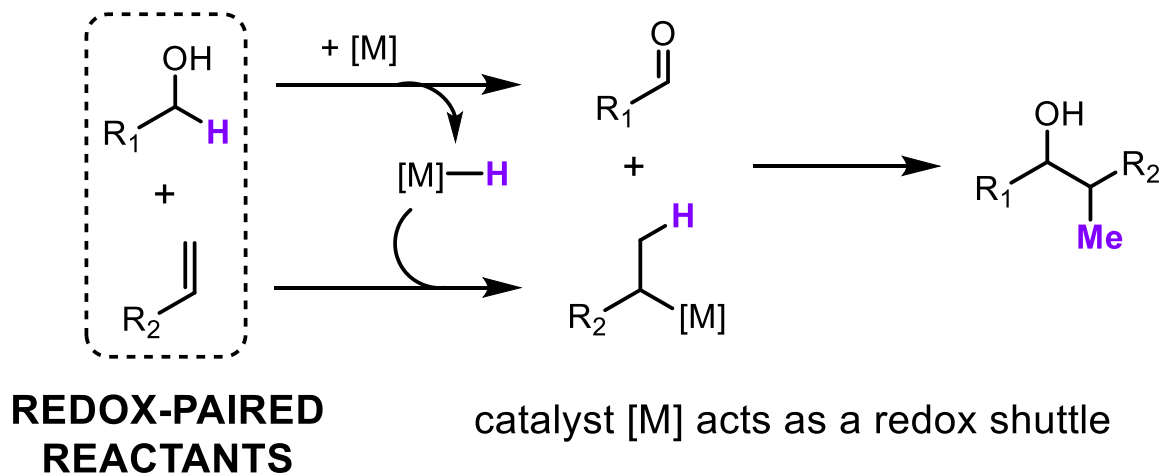
1. Avoid discrete redox manipulations to produce activated nucleophile/electrophile reactant pairs.



Classically, separate redox events to generate nucleophile/electrophile *ex situ*.



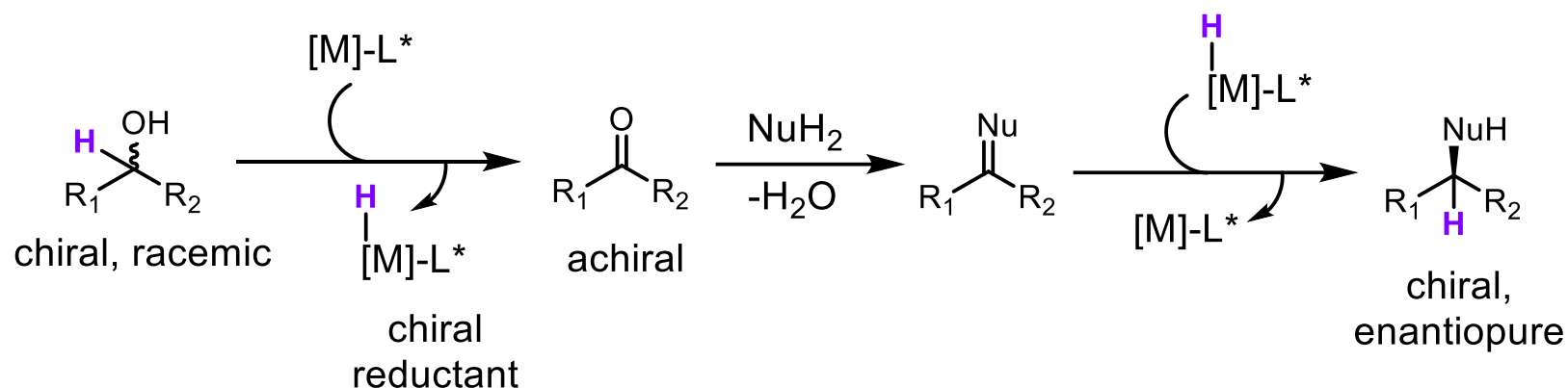
The borrowing hydrogen strategy: redox-paired reactants and have a catalyst shuffle around the electrons.





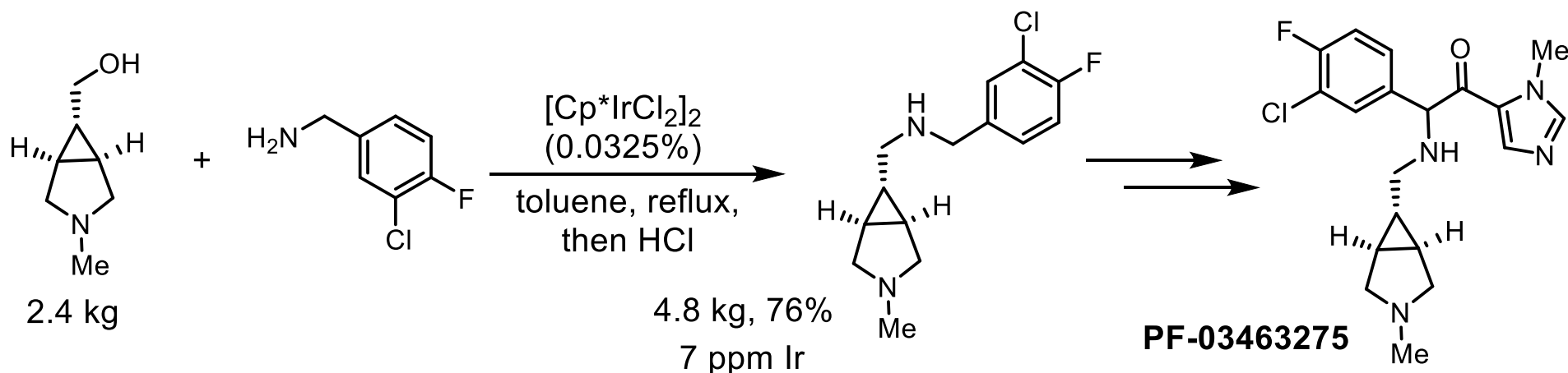
# Motivation for Borrowing Hydrogen Reaction Development

2. Borrowing hydrogen mechanistic step ablates alcohol stereochemistry.



If the alcohol is only used as a reactive handle, then there is no need to make it in an enantiopure form.

3. Green chemistry – borrowing hydrogen reactions are highly redox- and atom-economical.



Increasing interest in borrowing hydrogen applications in process development.



# Historical Overview: Pioneering Work from the 20<sup>th</sup> Century

← Heterogeneous catalysis → ← Homogeneous catalysis →

1899

1930

...

1970

1980

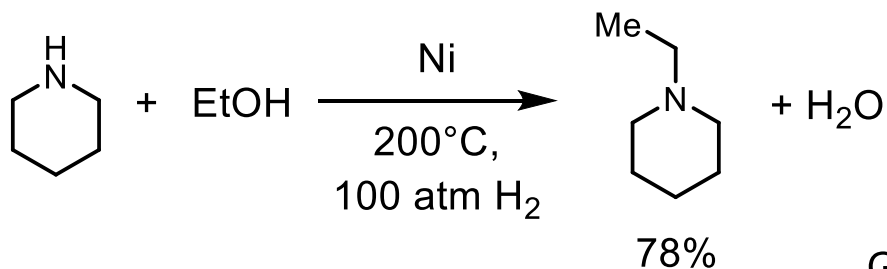
1990

2000

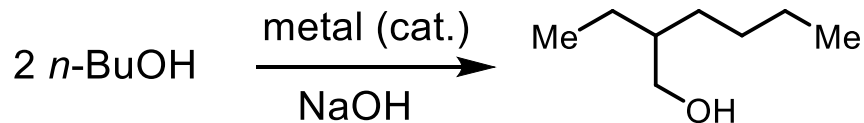
2010

2020

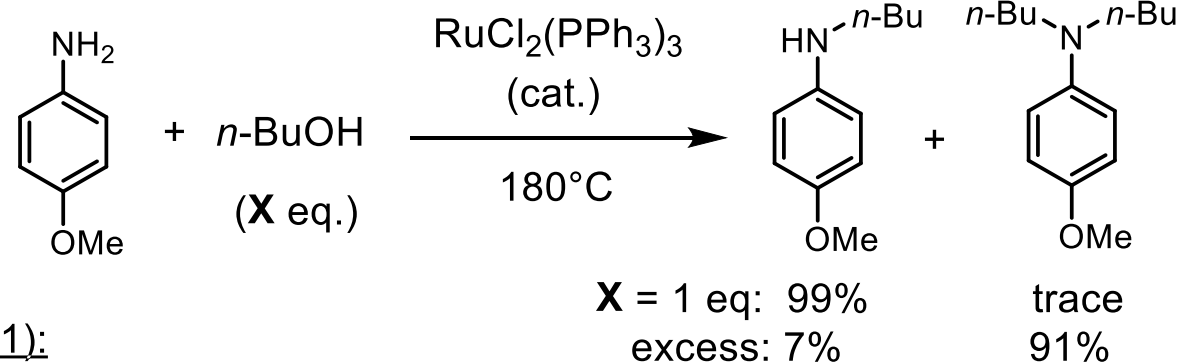
Winan and Adkins (1932):



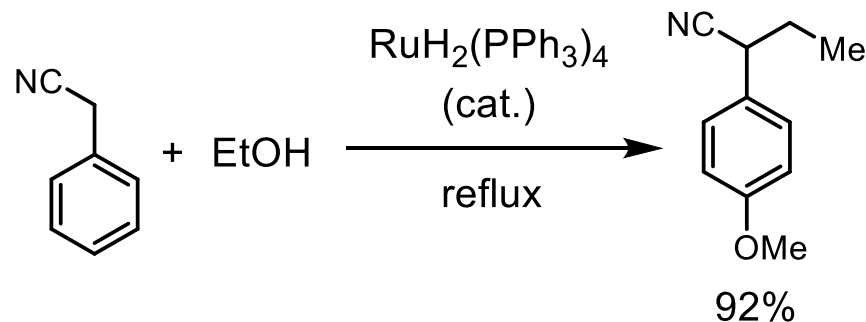
Guerbet (1899):



Watanabe *et al* (1984):

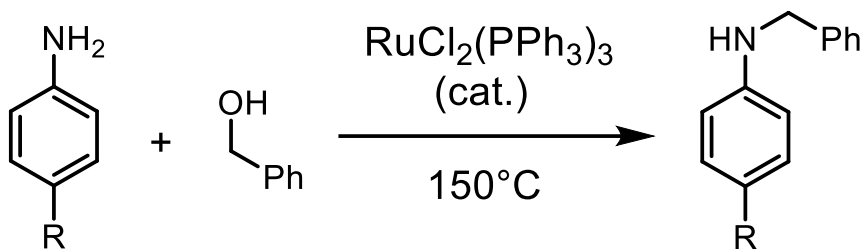


Grigg *et al.* (1981):



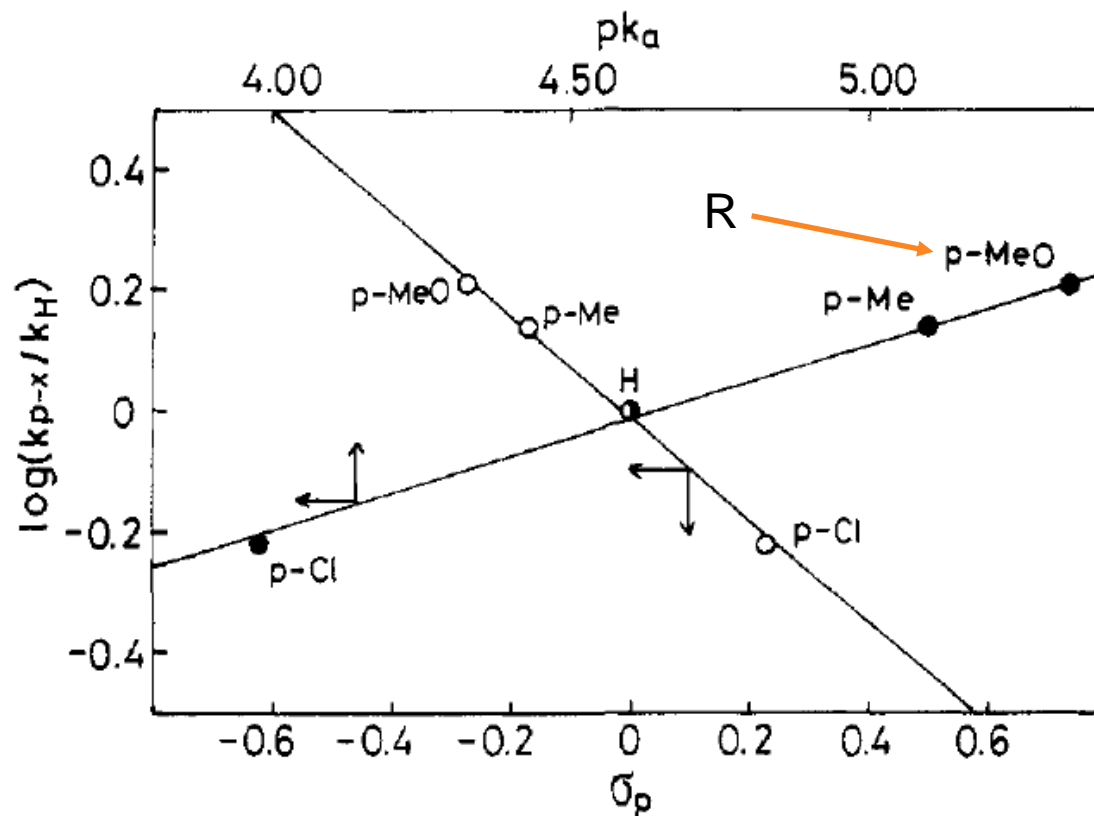
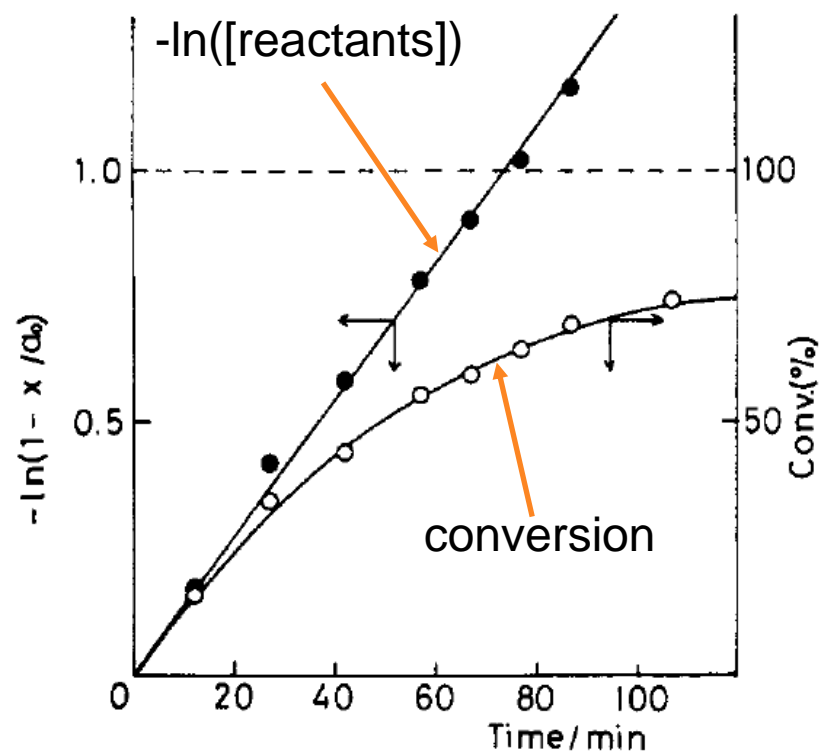


# Early Kinetic Analysis with Aniline Alkylation



R = OMe, Me, H, Cl

- First-order kinetic model for total reaction order in aniline and BnOH.
- Pseudo-first order swamping studies suggested zero-order in aniline.
- First-order in catalyst loading.
- Hammett study shows EDG on aniline enhances rate.



Empirical rate law:

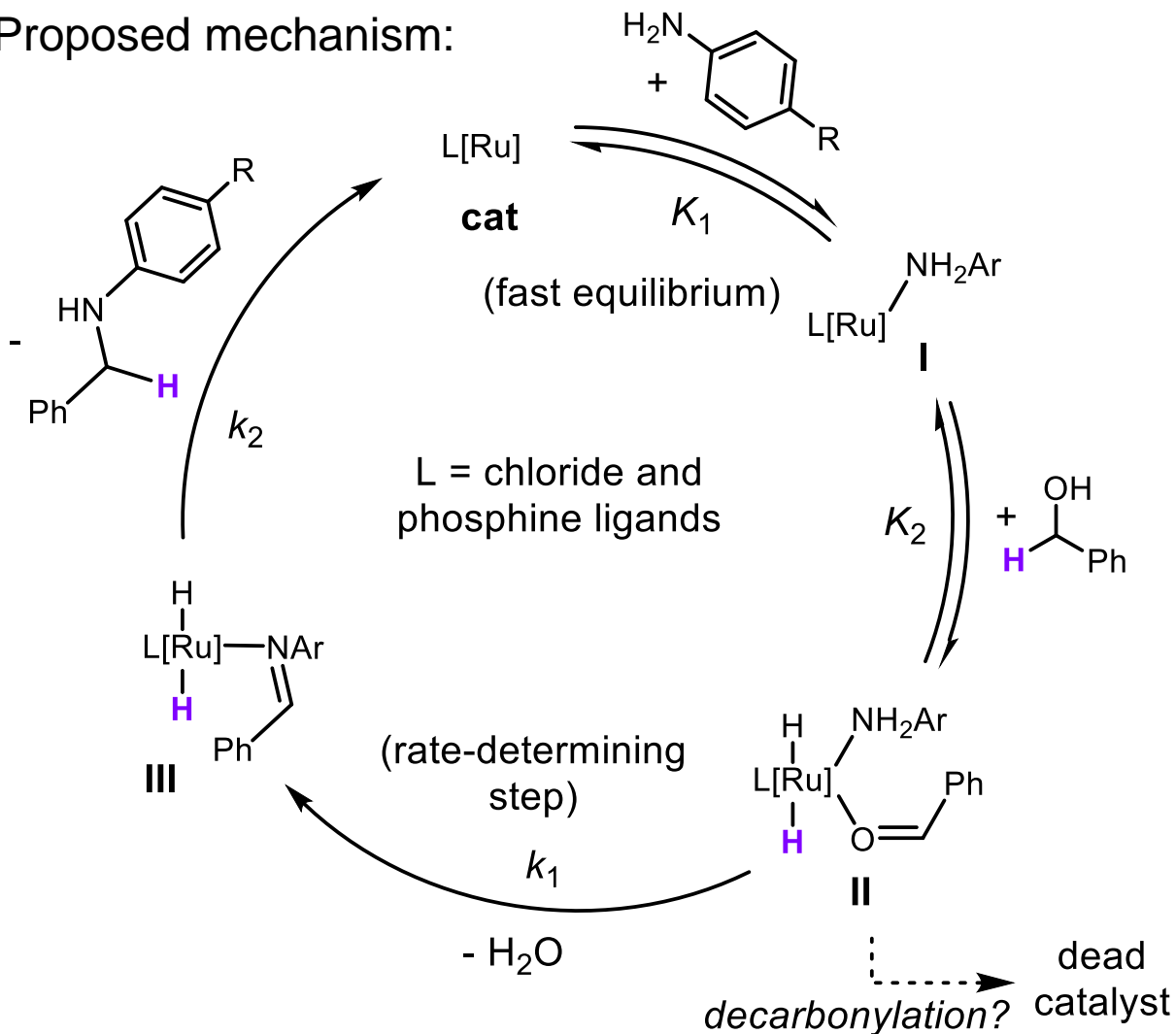
$$rate = k [\text{Ru}]_0 [\text{alcohol}]$$

$[\text{Ru}]_0$  is catalyst loading (constant).



# Early Kinetic Analysis with Aniline Alkylation

Proposed mechanism:

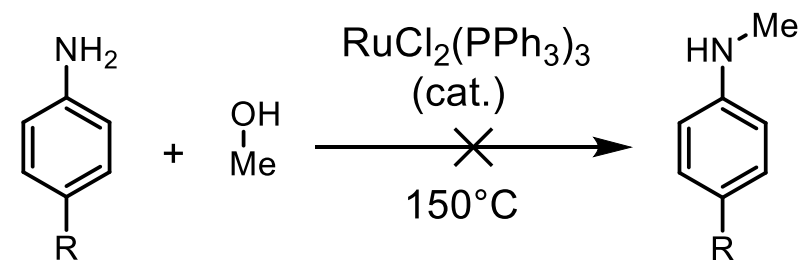


$$\text{rate} = k_1 K_2 [\text{Ru}]_0 [\text{alcohol}]$$

Assumptions:

- Steady-state concentration of **III**.
- $k_2 \gg k_1$ .
- $K_1 \gg 1$  and  $K_2 \ll 1$ . This is supported by UV-Vis studies of amine/alcohol Ru ligation.
- Everything occurs within the Ru coordination sphere (unlike more contemporary proposals).

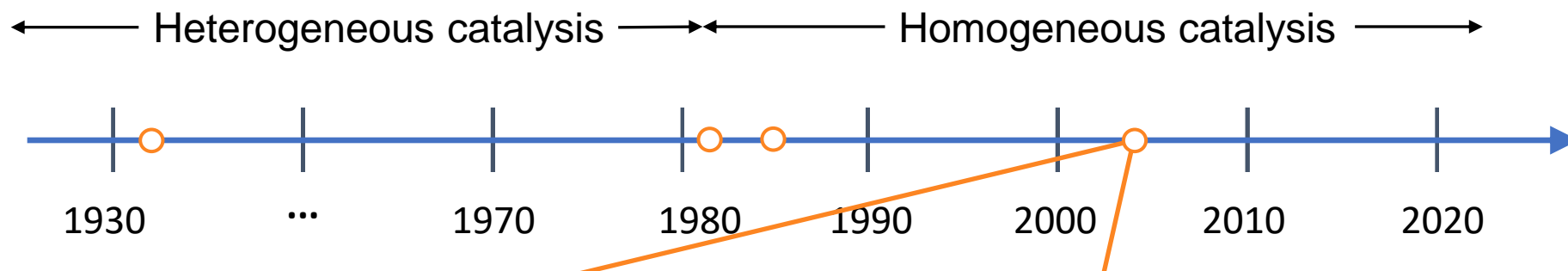
Catalyst deactivation through decarbonylation?



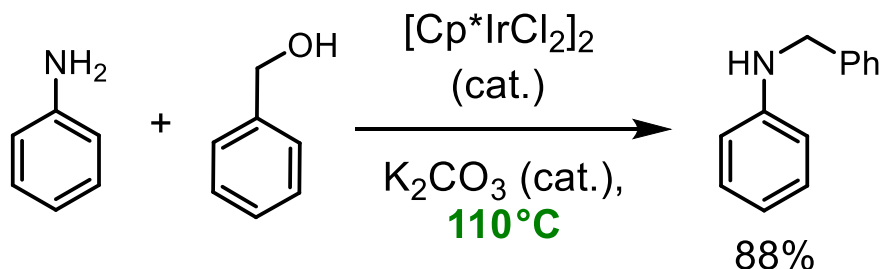
$\text{RuCl}_2(\text{CO})_2(\text{PPh}_3)_2$  isolated from reaction mixture, inactive catalyst



# Historical Overview: Modern Catalysts, Milder Conditions

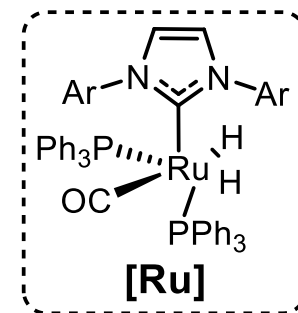
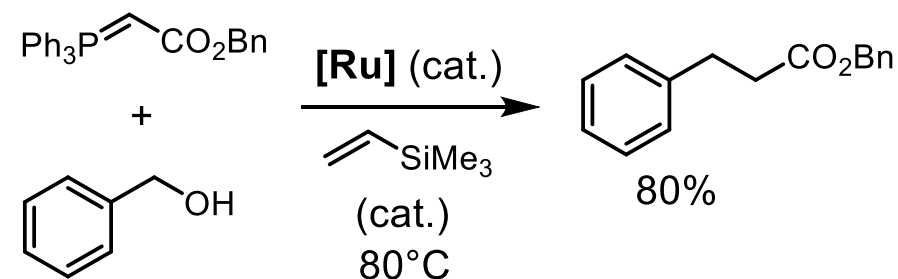


Yamaguchi *et al* (2003):



Introduction of iridium and ruthenium-NHC catalyst systems in 2003 revealed much more mild reactivity, essential for future asymmetric catalysis.

Edwards, Williams, *et al.* (2004):

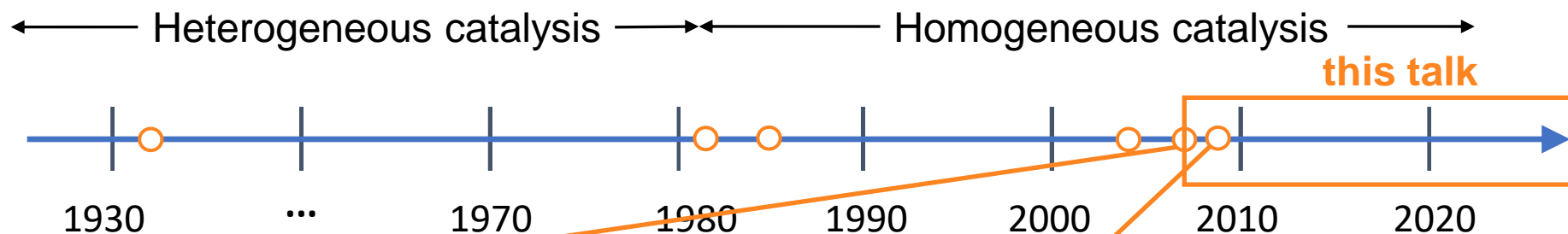


Williams coined the term “borrowing hydrogen” in 2004.

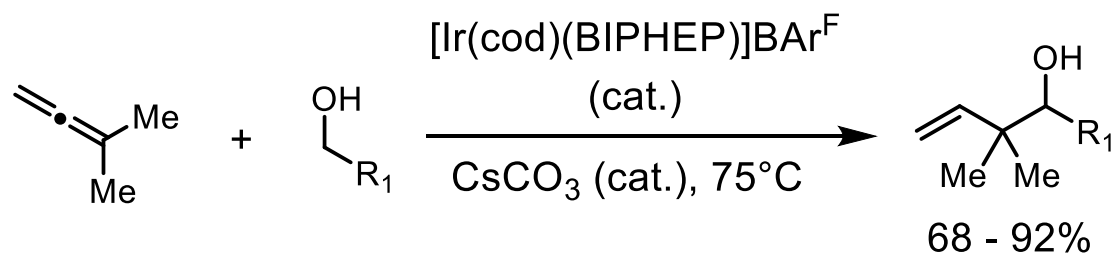
This foundational indirect Wittig olefination work was covered in a Denmark group meeting in 2004 by Edwards.



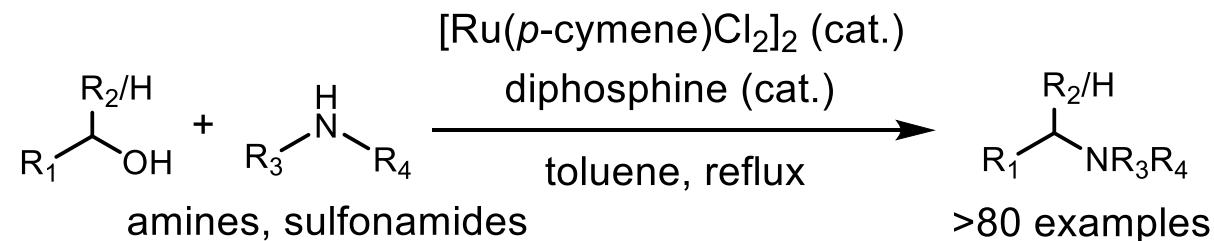
# Historical Overview: Modern Catalysts, Milder Conditions



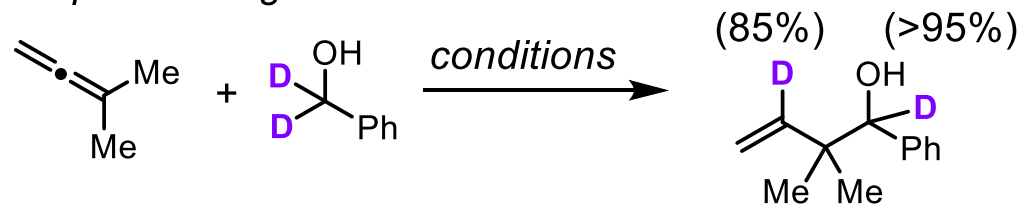
Krische *et al.* (2007):



Williams *et al.* (2009):

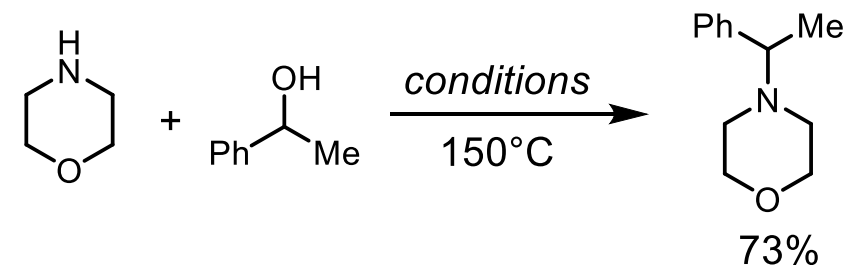


isotope labelling:



First borrowing hydrogen/returning carbon method.

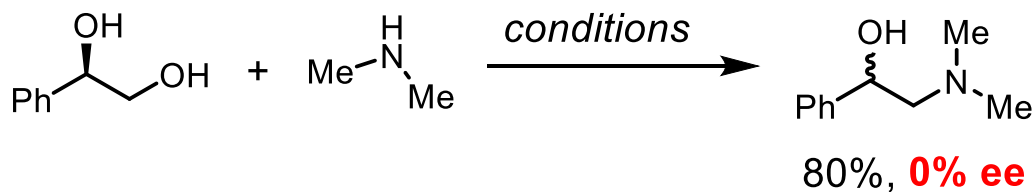
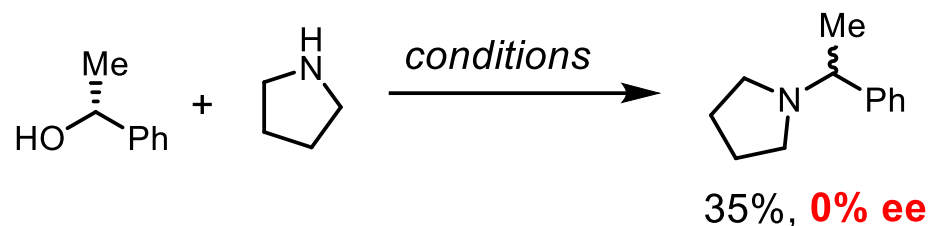
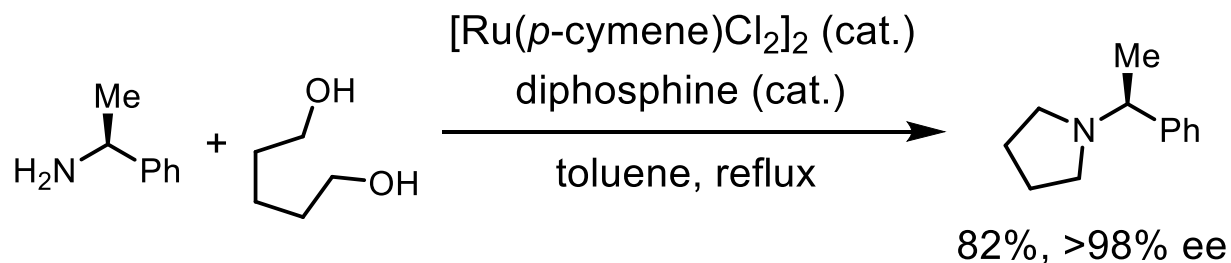
racemic reactions with 2° alcohol:





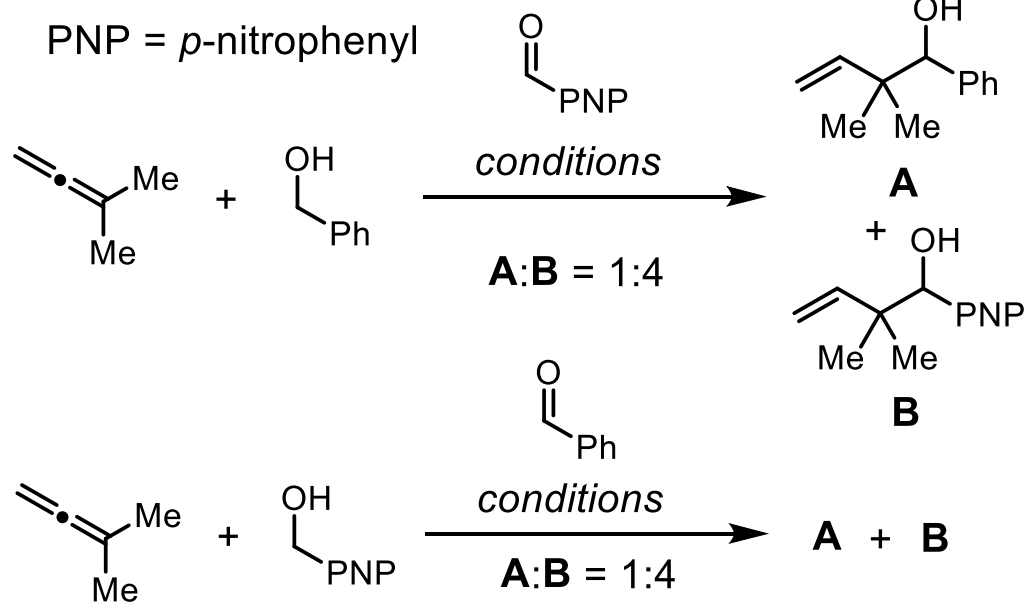
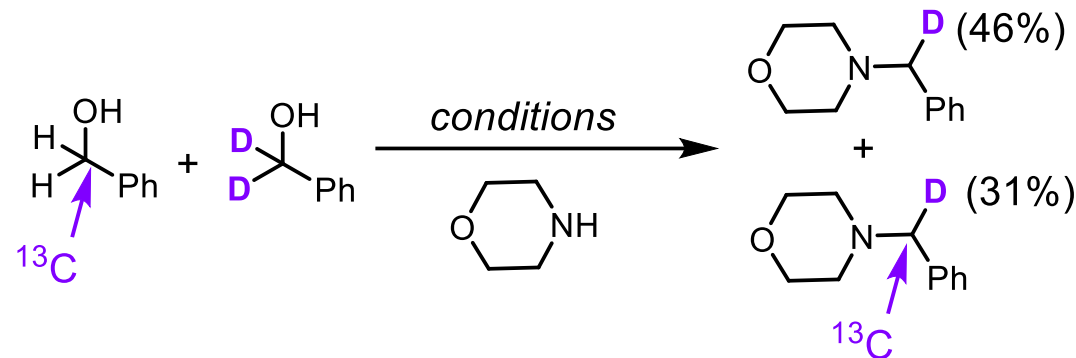
# Modern Mechanistic Studies: Where is the Aldehyde?

Substrate racemization studies (Williams):



Stereocenters bearing an alcohol are not preserved, while amine stereocenters are preserved.

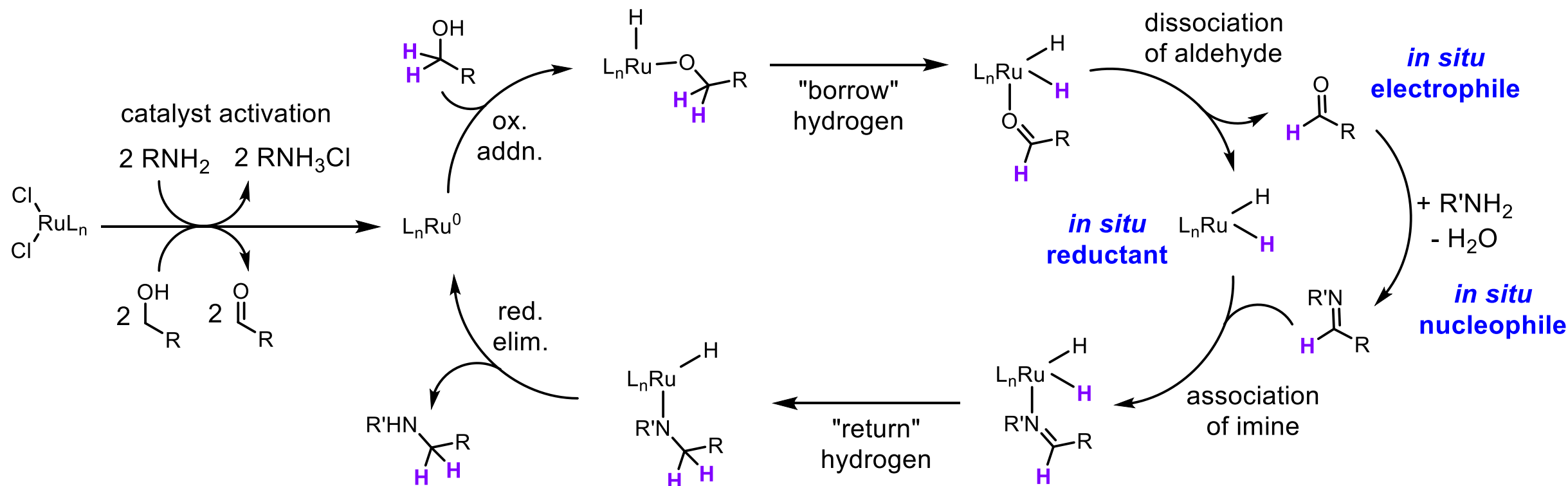
Crossover/competition experiments (Williams, Krische):





# Modern Mechanistic Studies: Where is the Aldehyde?

Mechanistic proposal with imine condensation outside of Ru coordination sphere (Williams, 2009):

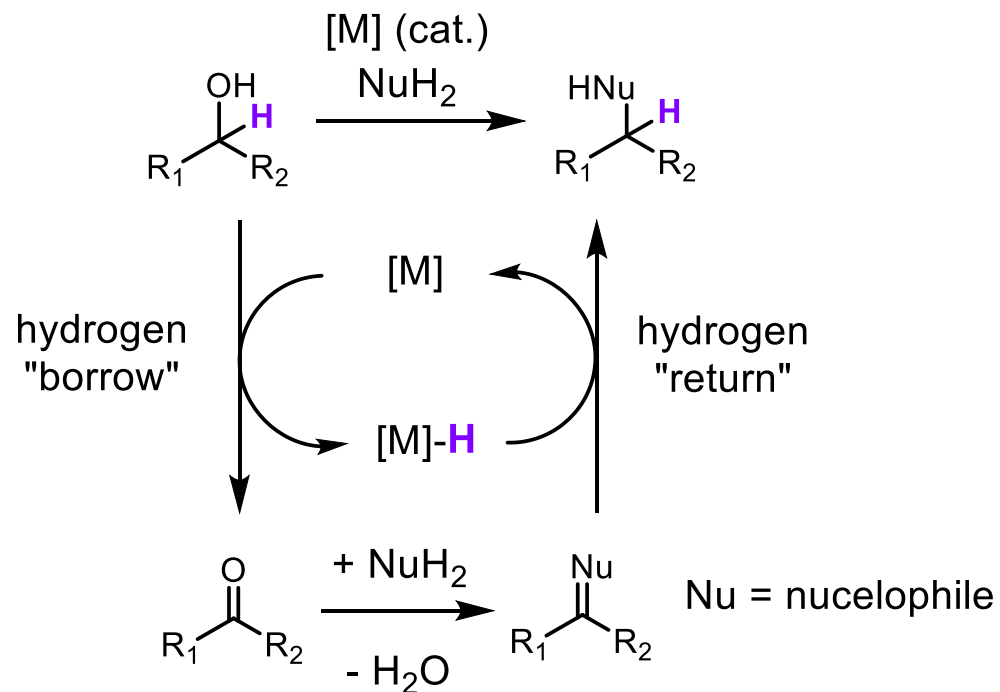


Dissociation of aldehyde before RDS explains the crossover result.

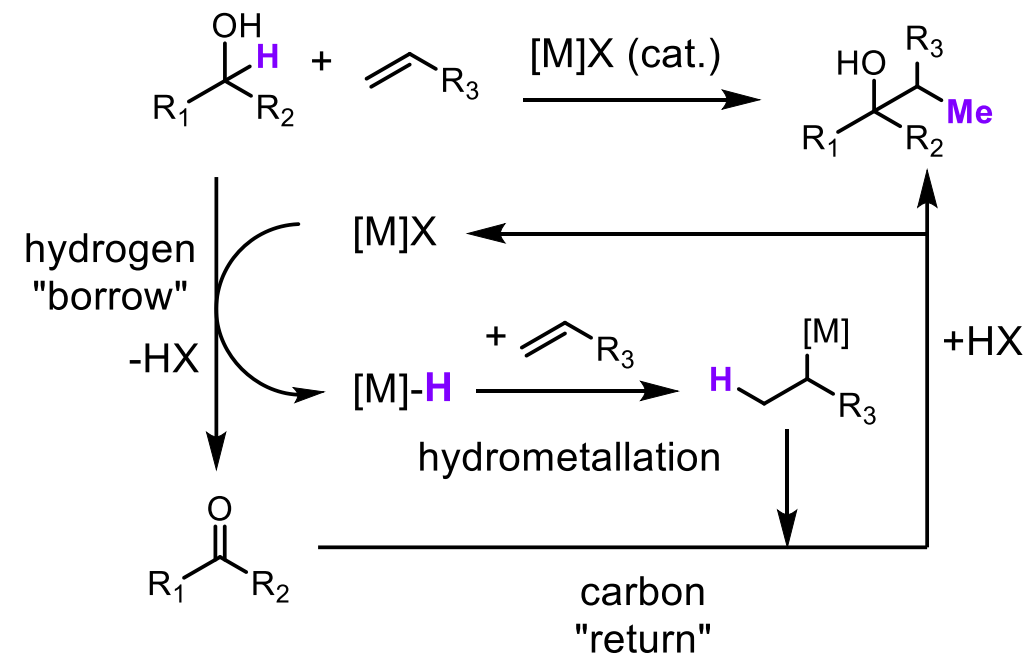


# Borrowing Hydrogen/Returning Hydrogen or Carbon

Borrowing hydrogen, returning hydrogen:



Borrowing hydrogen, returning carbon:



Most authors draw a distinction between "borrowing hydrogen" as a reaction class and as a mechanistic step.

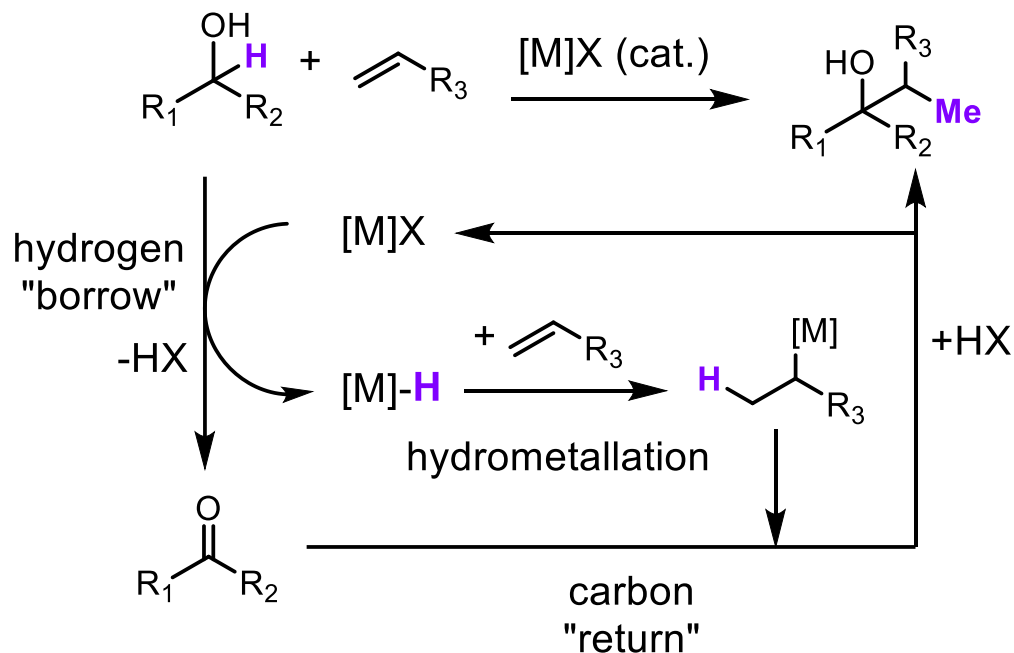
In "borrowing hydrogen" reactions, the borrowed hydrogen is returned to the same carbon in the product.



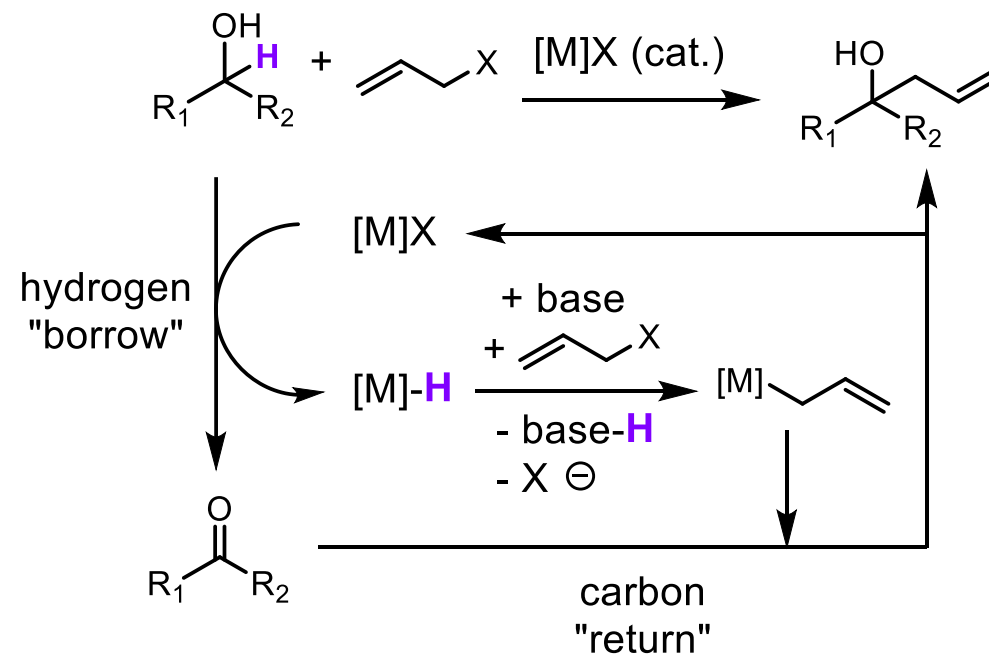
# Borrowing Hydrogen/Returning Carbon Overview

Three main mechanisms for borrowing hydrogen/returning carbon:

## 1. Hydrometallative pathways



## 2. C-X bond reductive cleavage:

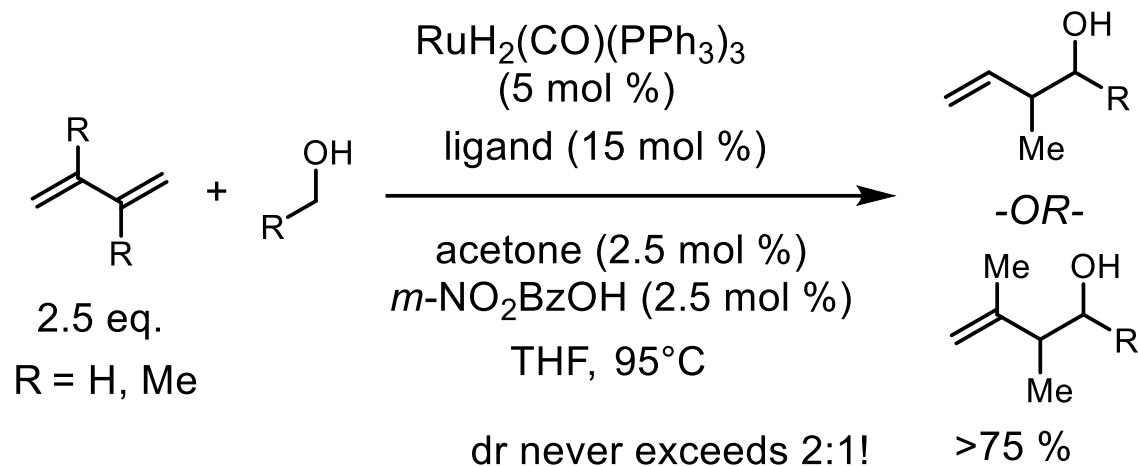


## 3. Hydrogenolysis of metallocyclic intermediates (not covered here).

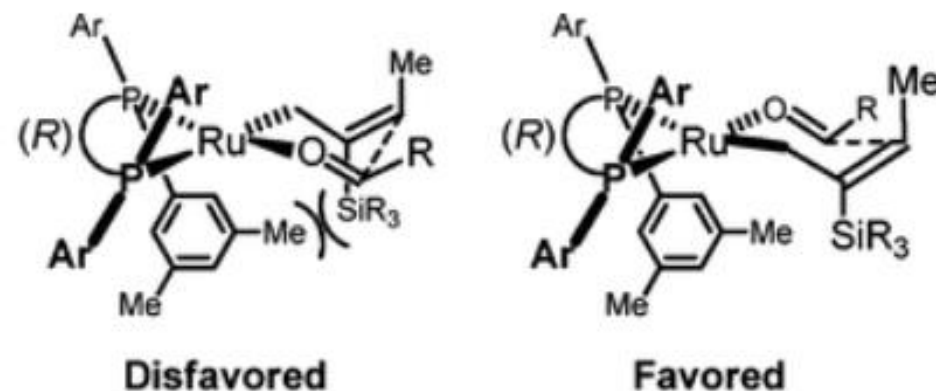


# Syn-Crotylation by Diene Hydrometallation

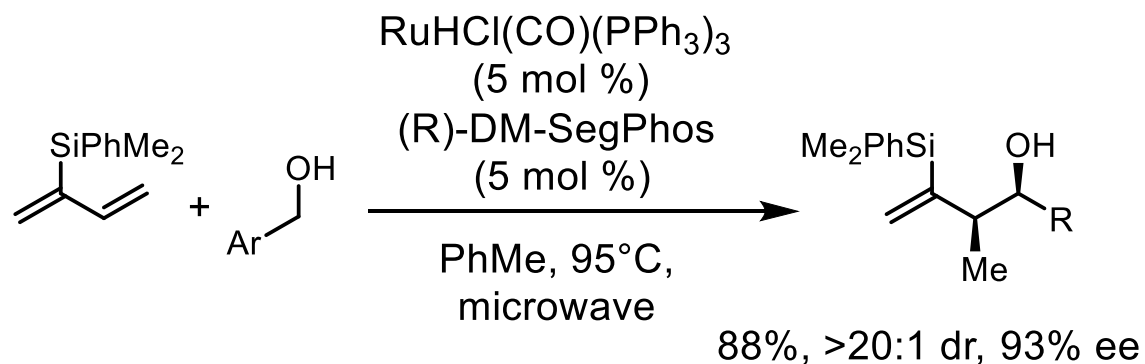
Initial report showed poor diastereoselectivity:



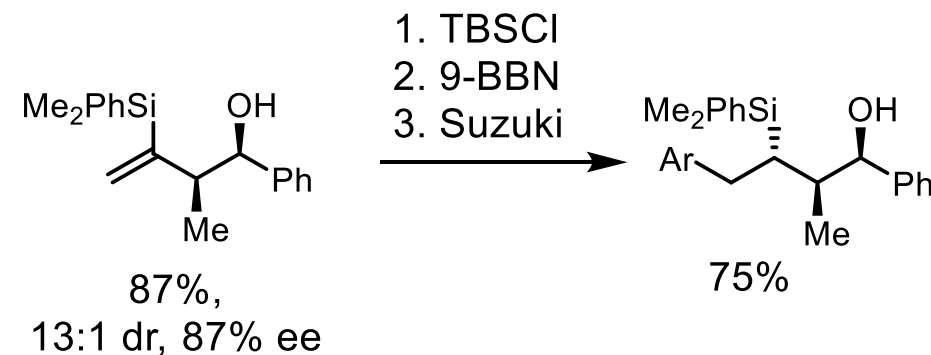
Stereochemistry is enforced by steric interactions of the Si group in transition state:



Incorporating a silicon group for enantioselective reaction:



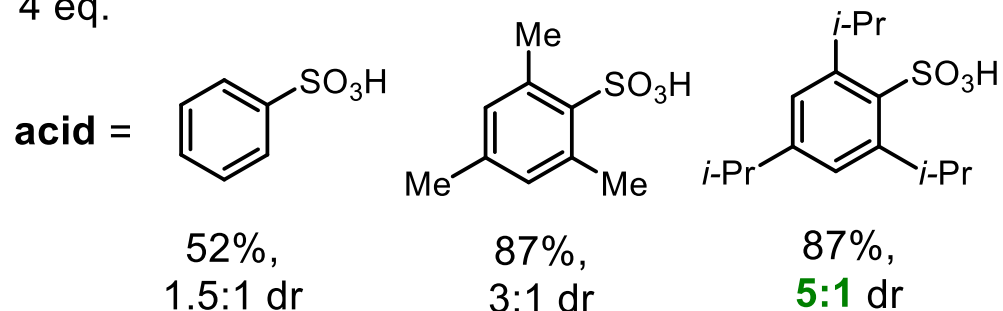
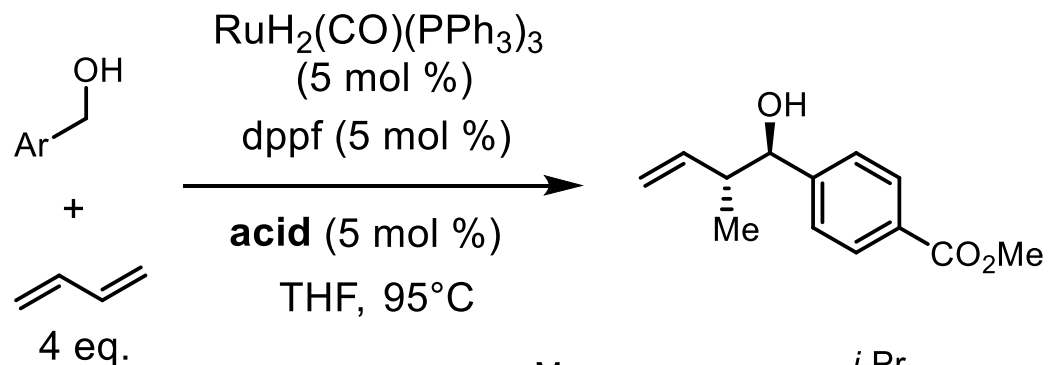
Product derivatization to introduce stereotriad:



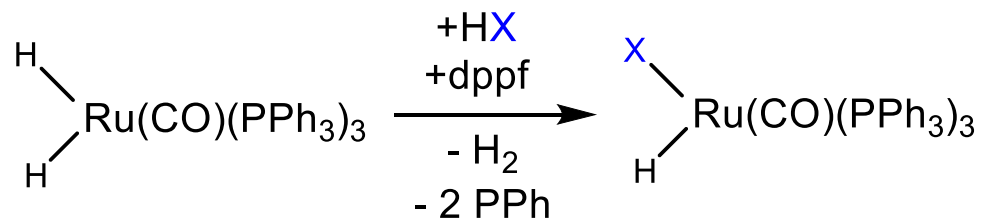


# Anti-Crotylation Using Chiral Acid Additive

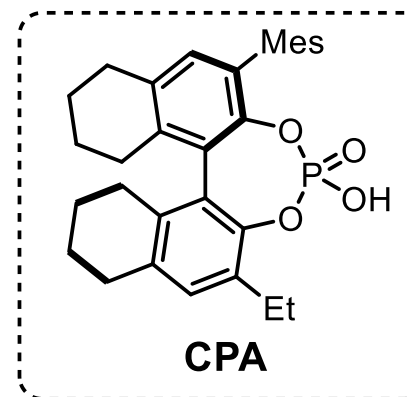
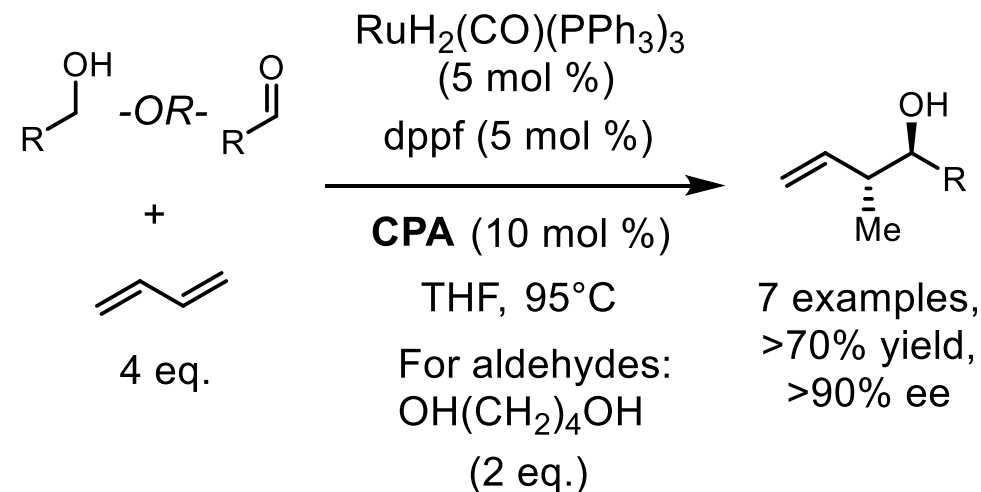
Ruthenium counterion effect on diastereoselectivity:



catalyst activation by acid additive:



Using a chiral acid for enantiomeric induction:

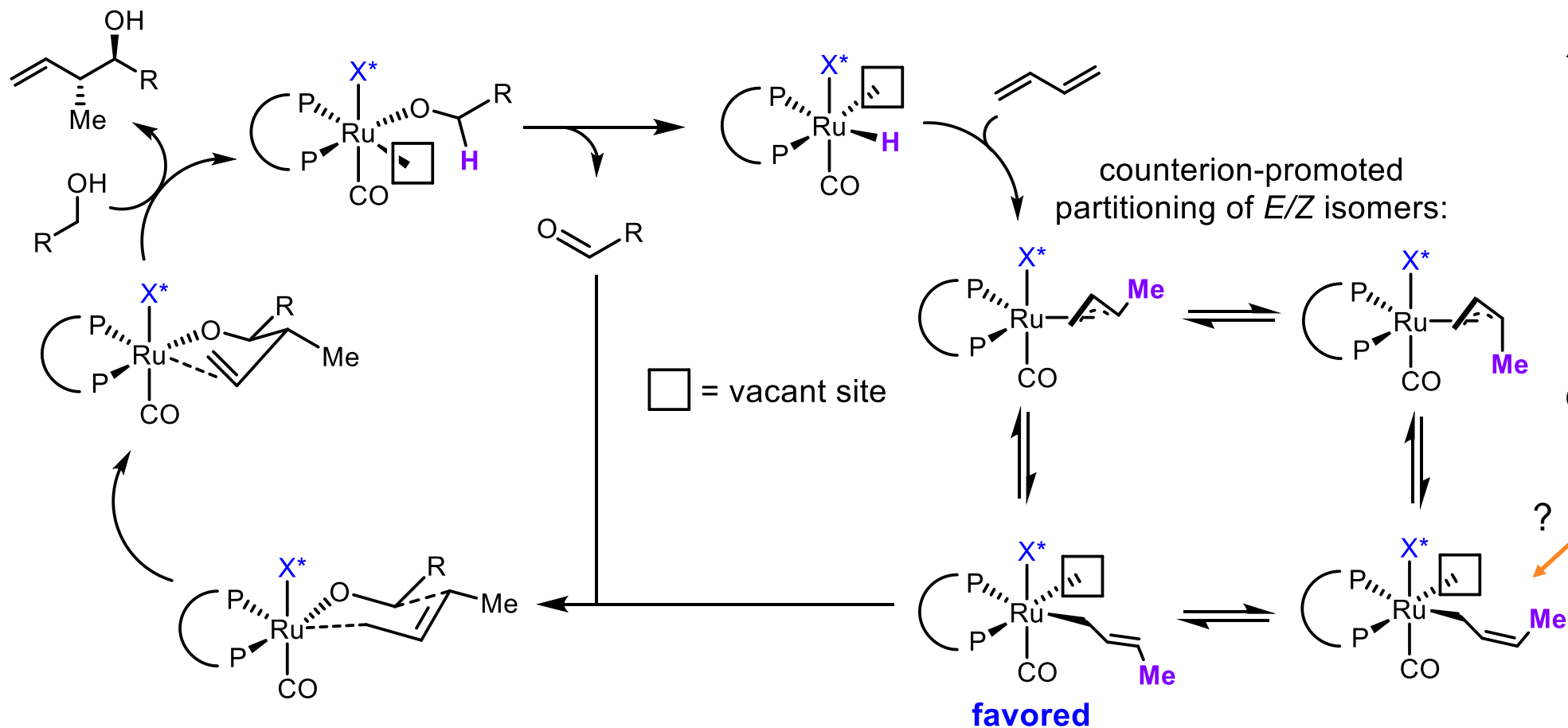


How does it work?



# Anti-Crotylation Using Chiral Acid Additive

Counterion-dependent partitioning of (*E*)- and (*Z*)- $\sigma$ -crotylruthenium haptomers:



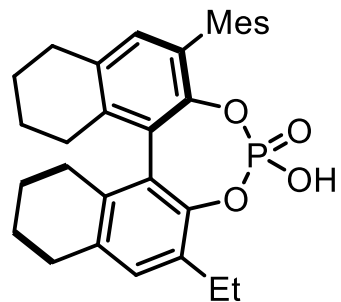
*Anti*-diastereoselectivity from 4:1 to 8:1 dr was achieved for 7 products

Can this counterion-dependence be exploited to access the *syn* isomers?

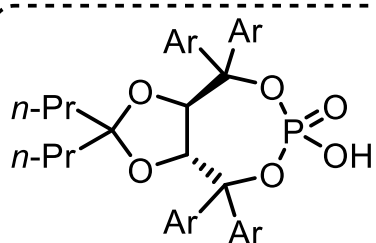


# Invertible Crotylation System Using Chiral Acid Additives

## Counterion-dependent partitioning of (*E*)- and (*Z*)- $\sigma$ -crotylruthenium haptomers:

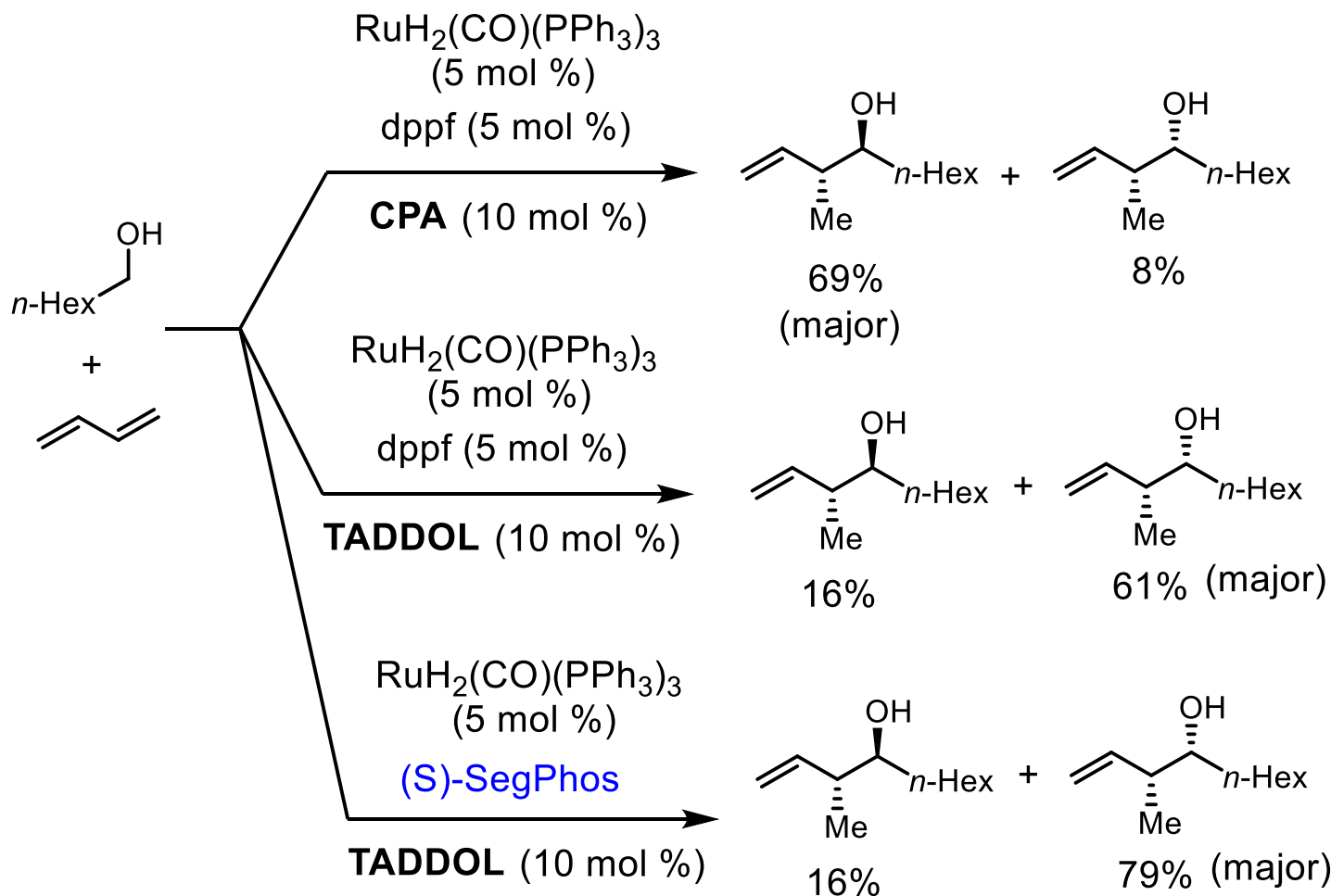


CPA

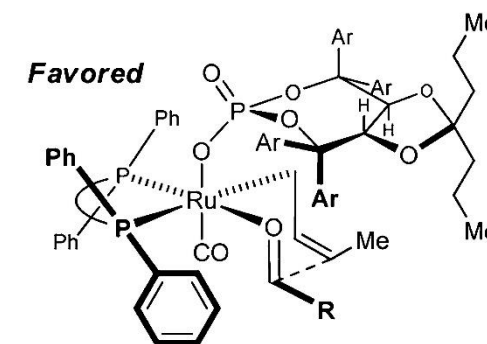


Ar = *m*-xylyl

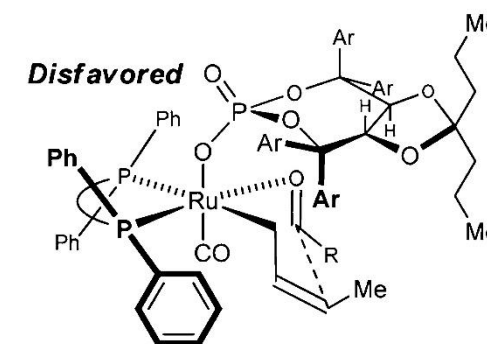
# TADDOL



Chiral SegPhos ligand enhances dr for TADDOL system and erodes dr for BINOL system.



**Favored**



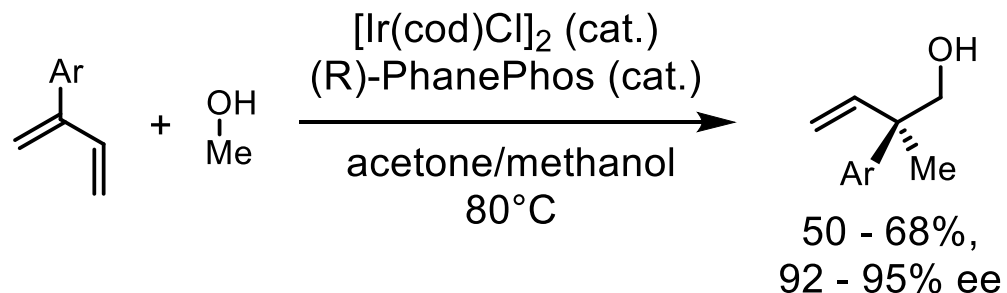
**Disfavored**



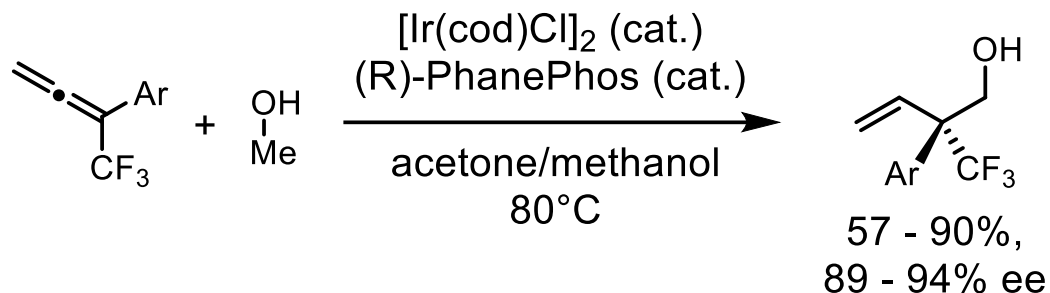
# Recent Methods with Hydrometallative Pathways

There are lots of reports exploiting the hydrometallative pathway, and it continues to be developed.

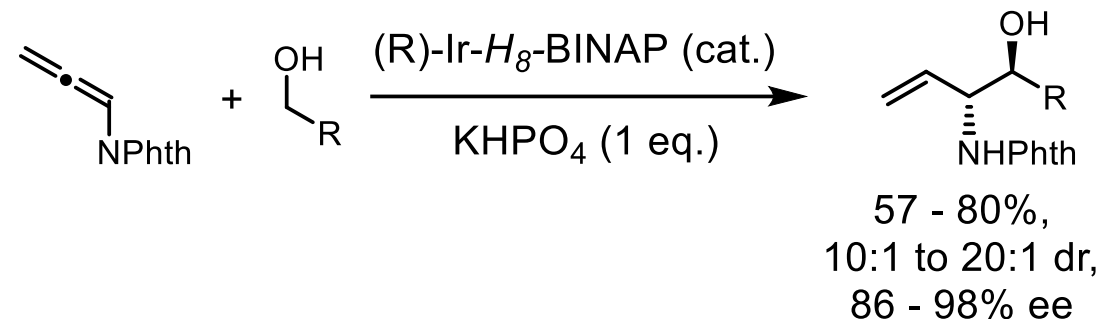
Direct coupling with methanol (Krische, 2016):



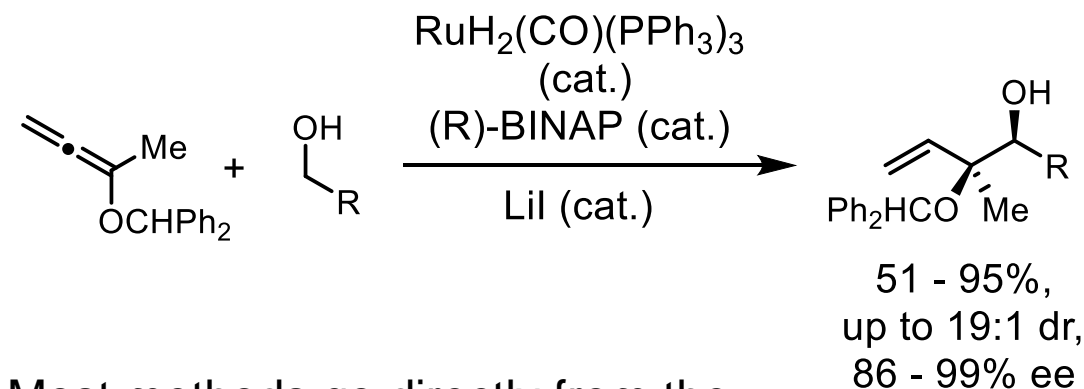
All-carbon quaternary centers from methanol (Krische, 2017):



Allylaminoalcohols (Krische, 2019):



Syn-sec,tert-diols (Krische, 2021):

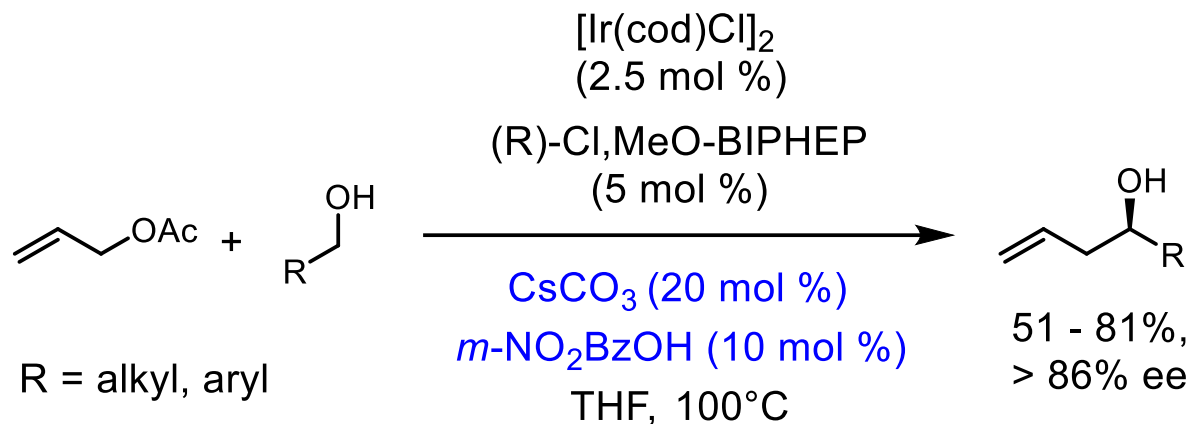


Limited examples of this methodology with  $2^\circ$  alcohols. Most methods go directly from the ketone and do a reductive coupling (*i.e.* Buchwald copper chemistry).

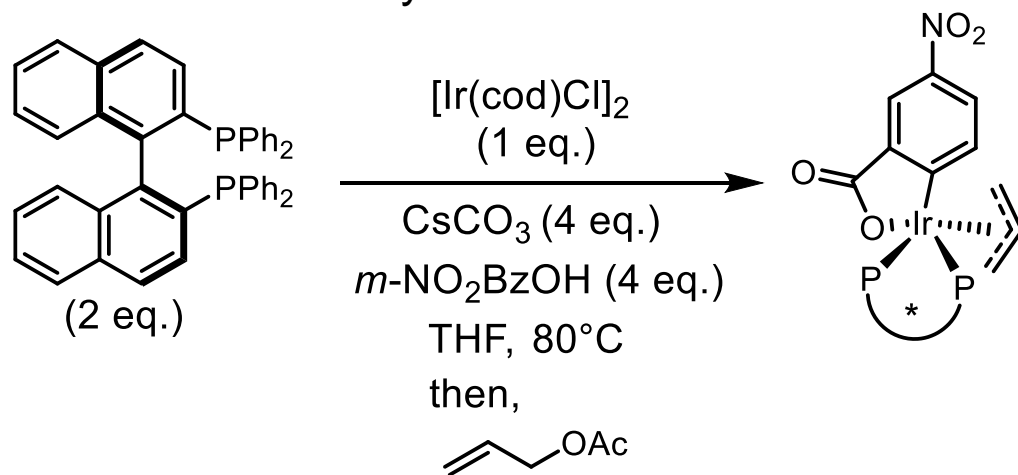


# Returning Carbon by C-X Bond Reductive Cleavage

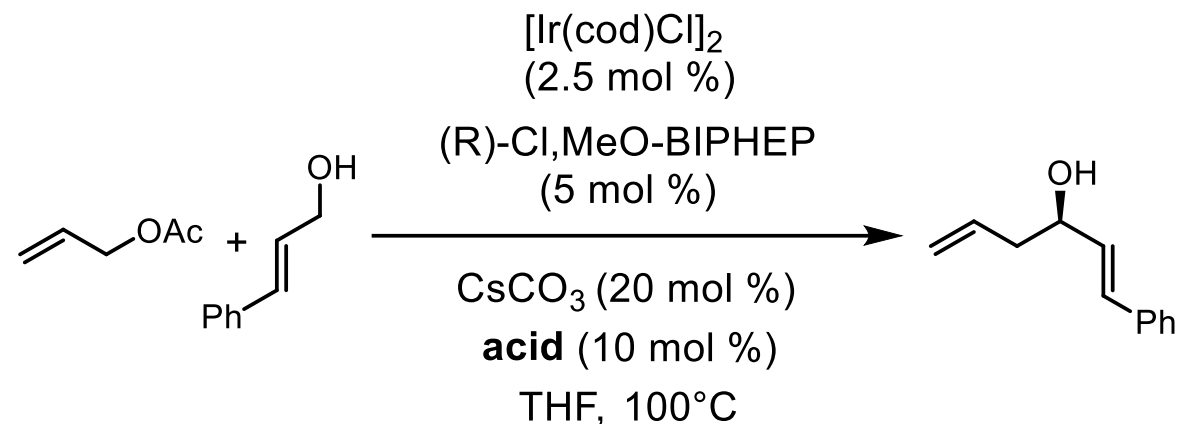
First allylation report (Krische, 2008):



Isolation of active catalyst:



Effect of carboxylic acid:



Entry	Carboxylic Acid	Yield (%)	ee (%)
1	$\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{H}$	71	91 (R)
2	No Acid Additive	8	47 (S)
3	$\text{R}_1 = \text{Me}, \text{R}_2 = \text{R}_3 = \text{H}$	18	65 (S)
4	$\text{R}_2 = \text{Me}, \text{R}_1 = \text{R}_3 = \text{H}$	50	67 (R)
5	$\text{R}_3 = \text{Me}, \text{R}_1 = \text{R}_2 = \text{H}$	69	91 (R)

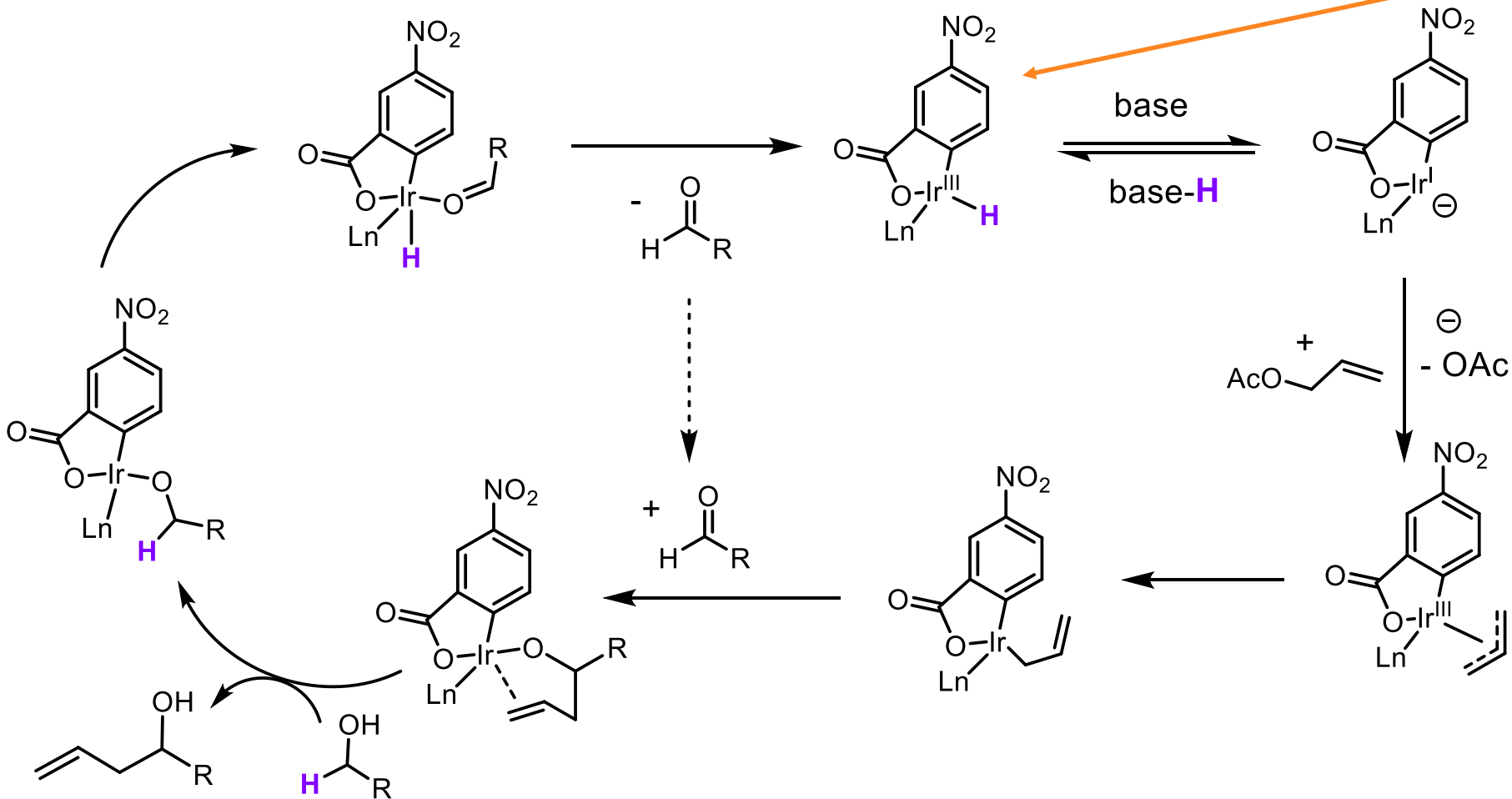
Acid additive can invert enantioselectivity, implying that it is present in stereodetermining step with metal.



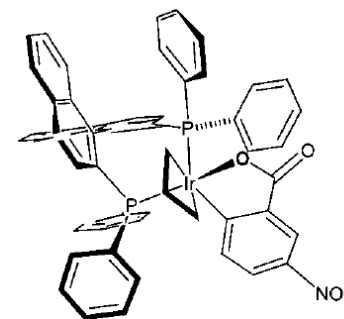
# Mechanism of Allylation via C-X Bond Reductive Cleavage

Mechanism for Ir-catalyzed borrowing hydrogen allylation:

C,O-benzoate-Ir complex is hypothesized to enhance acidity through EWG.



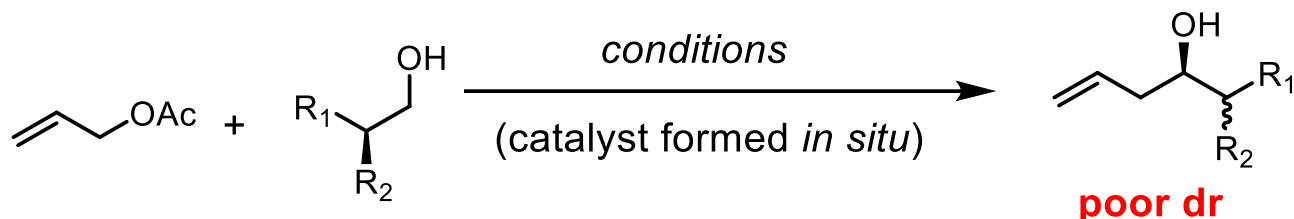
Crystal structure of Ir-allyl complex with BINAM:



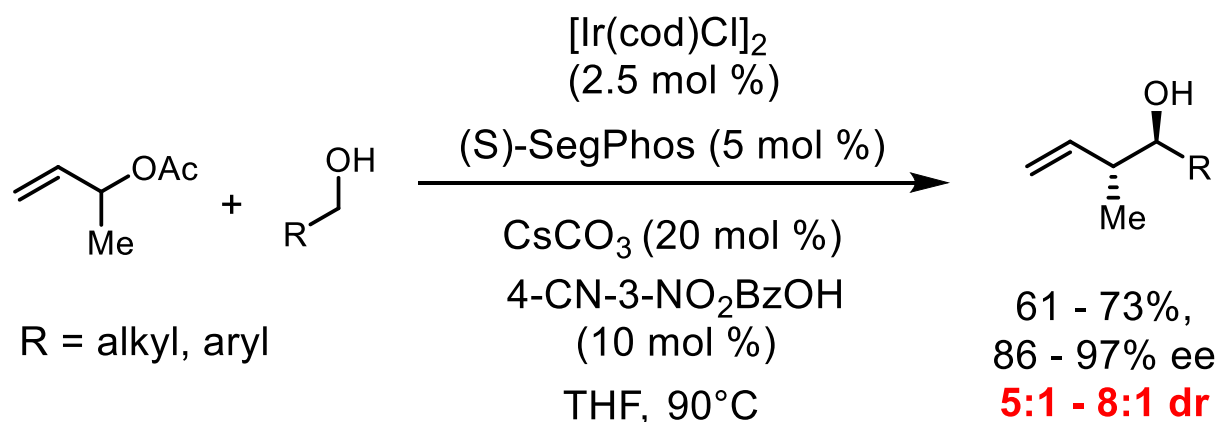


# Improved Catalyst Performance with C,O-Benzoate-Ir Complexes

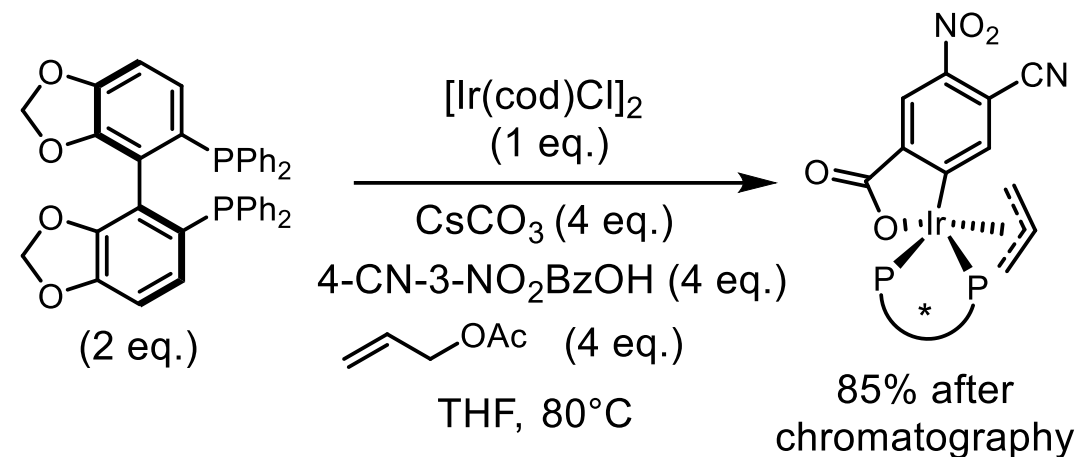
Attempted allylation of  $\beta$ -branched alcohols led to poor dr with *in situ* catalyst formation:



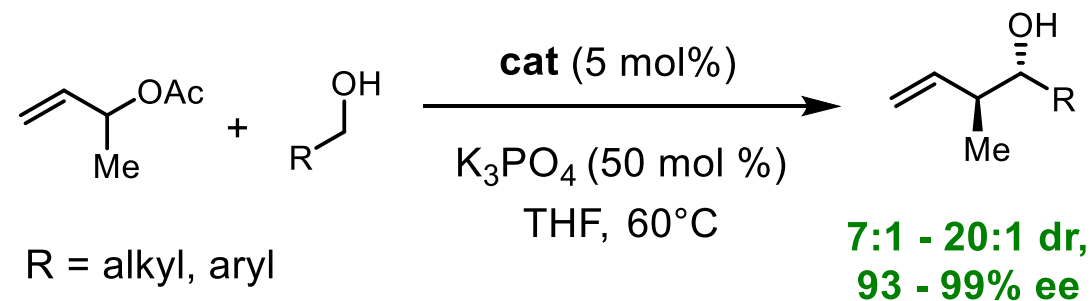
*Anti*-crotylation from the allyl acetate gives only moderate dr with *in situ* catalyst formation (Krische, 2009):



The solution: pre-form catalyst and isolate (Krische 2011):



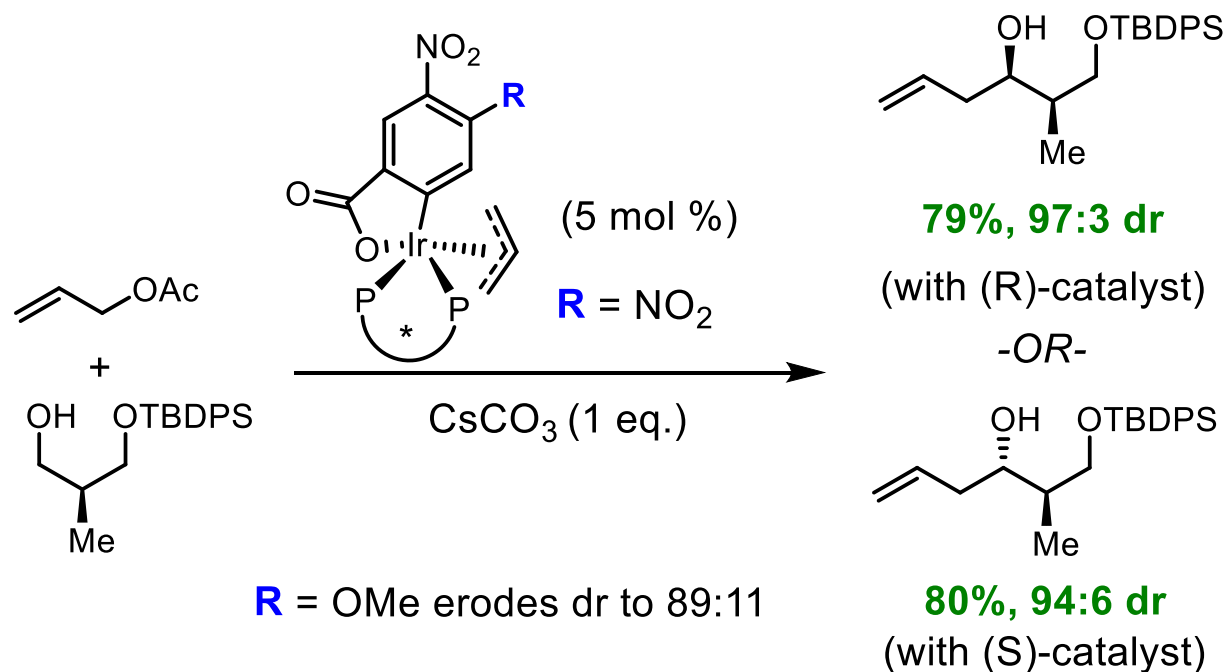
Better stereoselectivity and lower temperature with pre-formed catalyst:



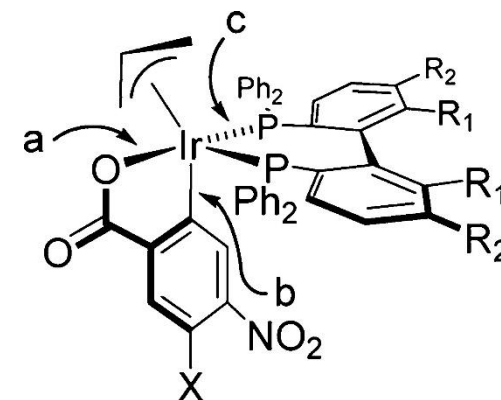


# Improved Catalyst Performance with C,O-Benzoate-Ir Complexes

Solving the  $\beta$ -branched alcohol problem by tuning the electronic effects of the C,O-benzoate complex (Krische 2012):



More electron-withdrawn C,O-benzoates give better dr due to enhanced Lewis acidity of Ir center (correlated with bond lengths in XRD crystal structures).

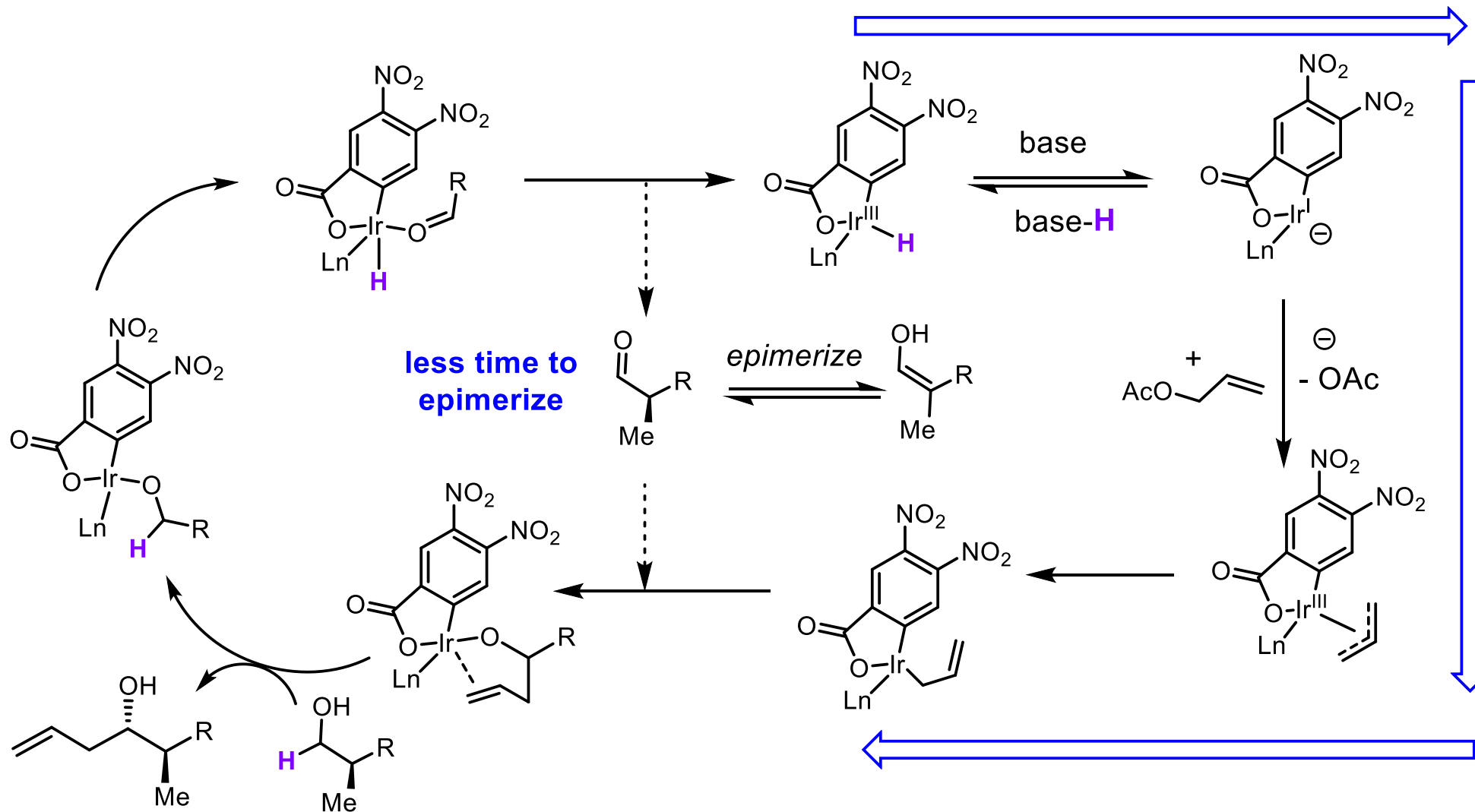


**Ir-a-X**  $\text{R}^1 = \text{R}^2 = -\text{OCH}_2\text{O}-$  (SEGPLHOS)  
**Ir-b-X**  $\text{R}^1 = \text{OMe}, \text{R}^2 = \text{Cl}$  (Cl,MeO-BIPHEP)

Ir-Complex	Bond a (Å)	Bond b (Å)	Bond c (Å)
(R)-Ir-a-OMe	2.107	2.068	2.260
(S)-Ir-a-H	2.112	2.074	2.262
(R)-Ir-a-NO <sub>2</sub>	2.121	2.072	2.277
(R)-Ir-b-NO <sub>2</sub>	2.131	2.088	2.329



# Improved Catalyst Performance with C,O-Benzoate-Ir Complexes



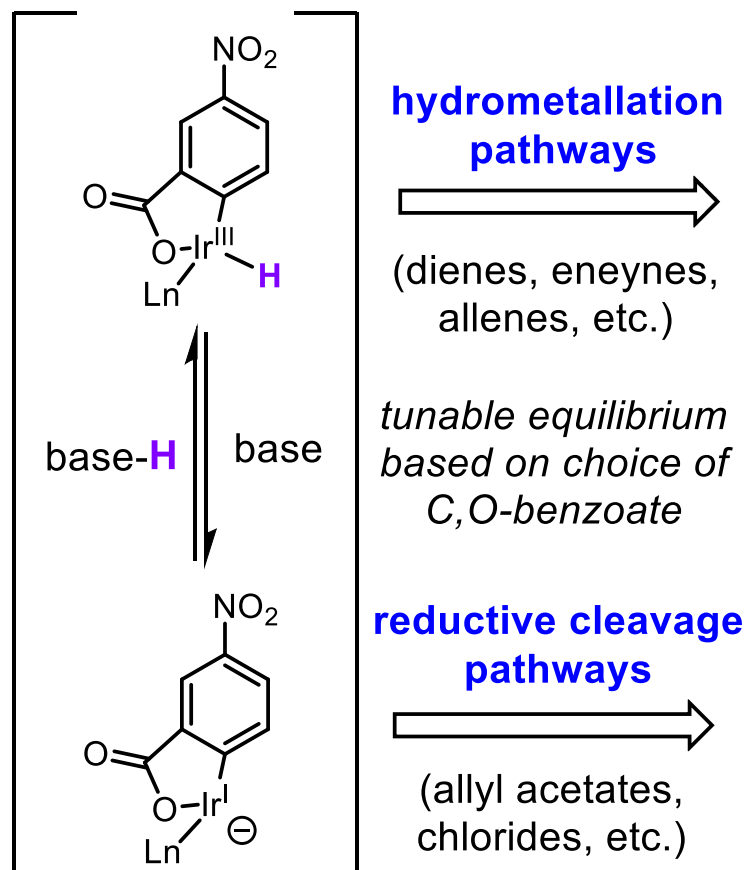
faster with more  
EWG on benzoate

C,O-benzoate  
complexes are not  
required for reductive  
activation of C-X  
bonds, but they are  
an extremely  
common additive.

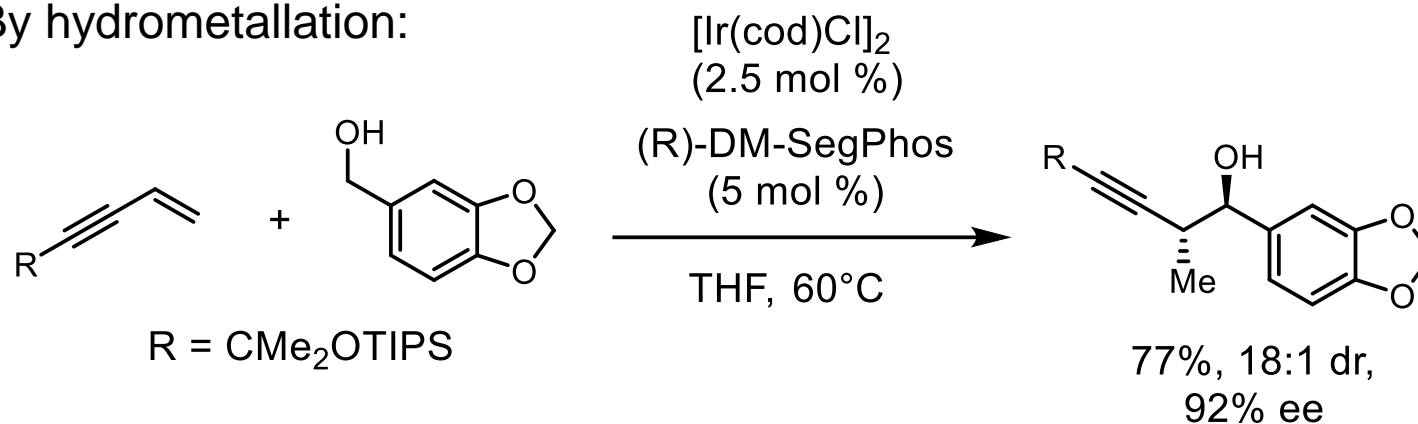


# Comparing Reductive Cleavage and Hydrometallation Mechanisms

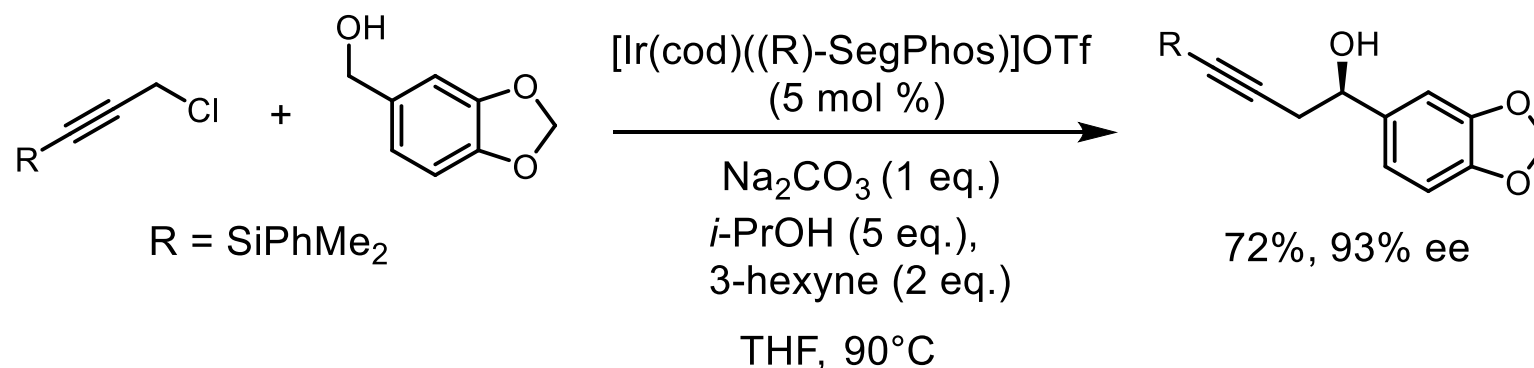
Homopropargyl arenes by two different borrowing hydrogen mechanisms.



By hydrometallation:



By reductive C-X bond activation:

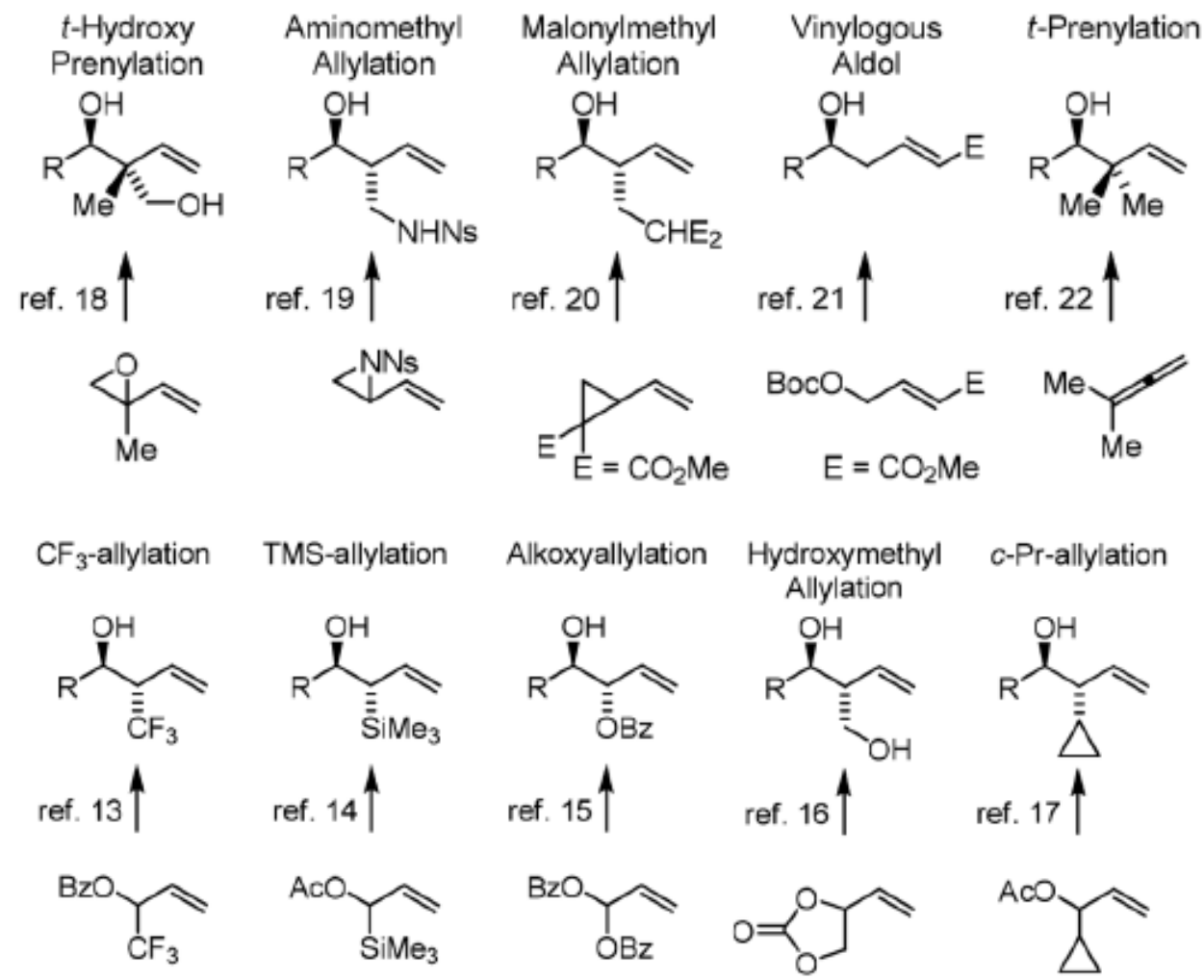




# Returning Carbon by C-X Bond Reductive Cleavage

A full paper comes out for every new substrate class, so there are a lot. The mechanism is basically the same for all of these, so I will not go over them.

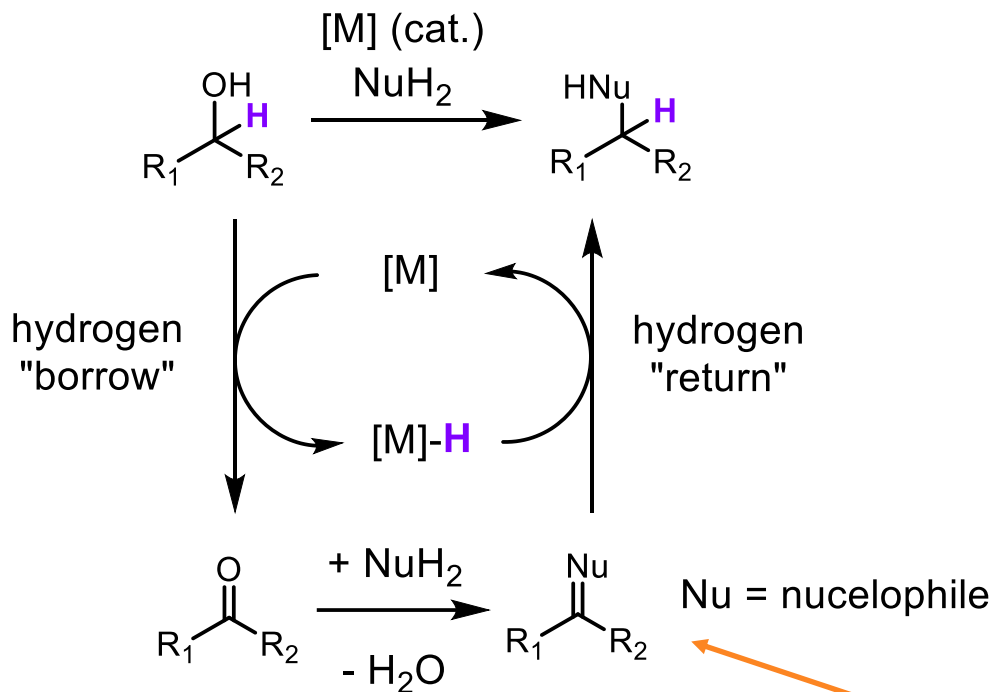
See *Acc. Chem. Res.* **2017**, 50, 2371–2380.





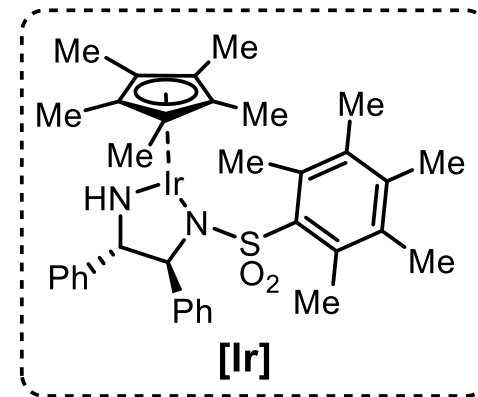
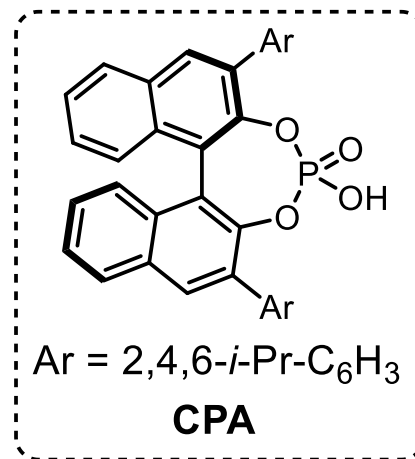
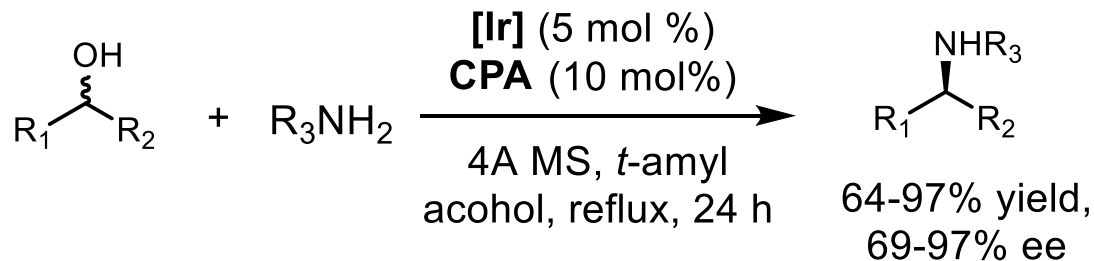
# Enantioconvergent Reactions by Borrowing/Returning Hydrogen

General reaction mechanism:



Borrowing hydrogen for enantioconvergent reactions are harder due to steric bulk of 2° alcohol

First example of enantioconvergent amination with racemic secondary alcohols (Zhao, 2014):

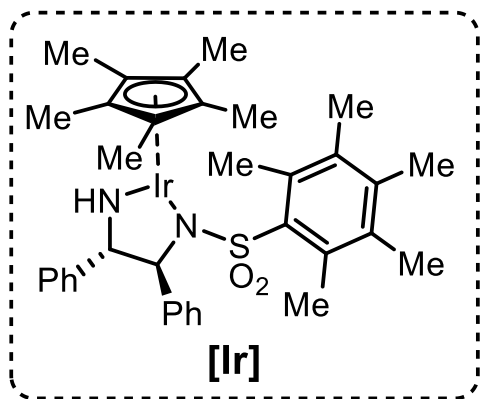
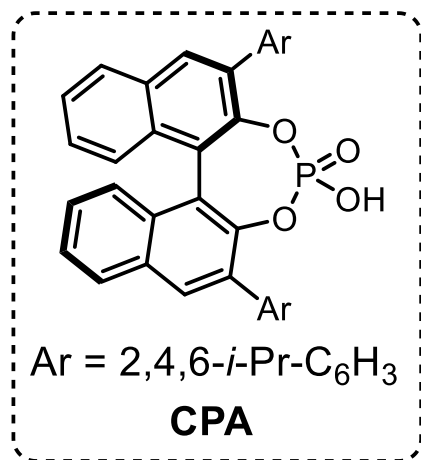
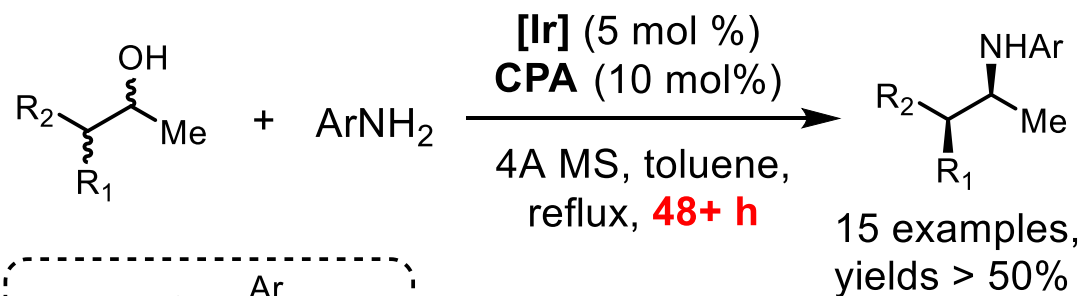


Acid additive is included to speed up imine condensation step.

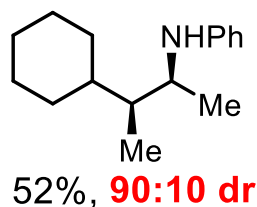


# DyKATs for Enantioconvergent Synthesis of $\beta$ -Branched Amines

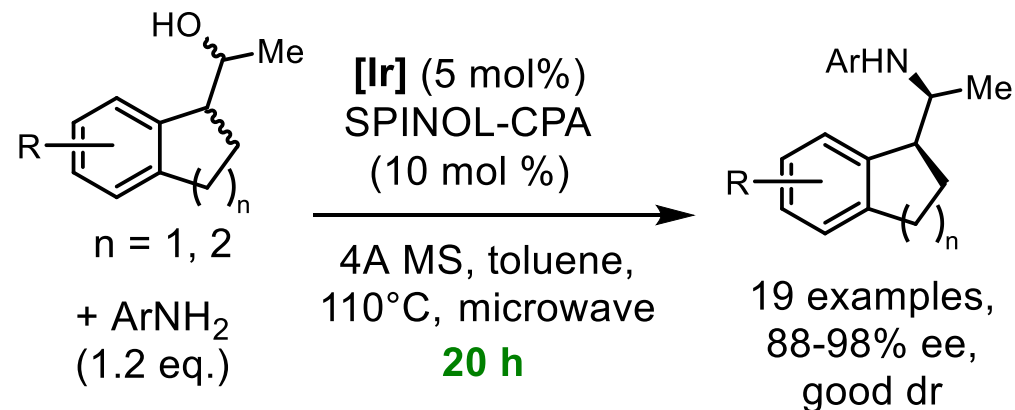
Borrowing hydrogen for dynamic kinetic asymmetric transformations (DyKATs) of racemic 1,2-diols (Zhao, 2015)



ee > 98% for all products.  
dr generally excellent (>90:10).  
Alkyl  $R_1$ ,  $R_2$  erodes dr.

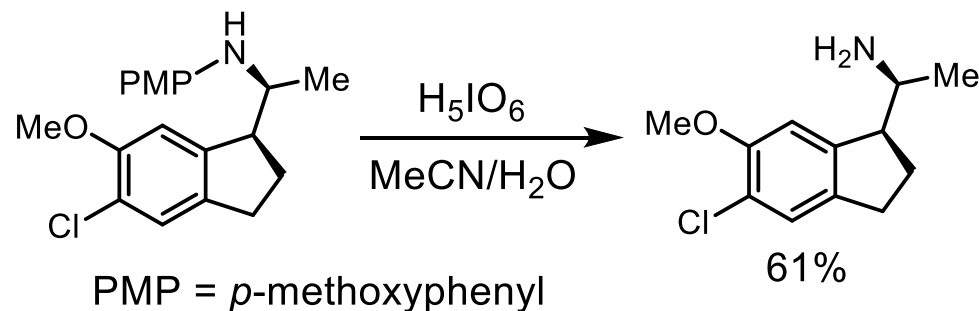


Extension to tetralins and indanes (2020):



Microwave conditions gave higher yield and shorter reaction times, similar ee/dr.

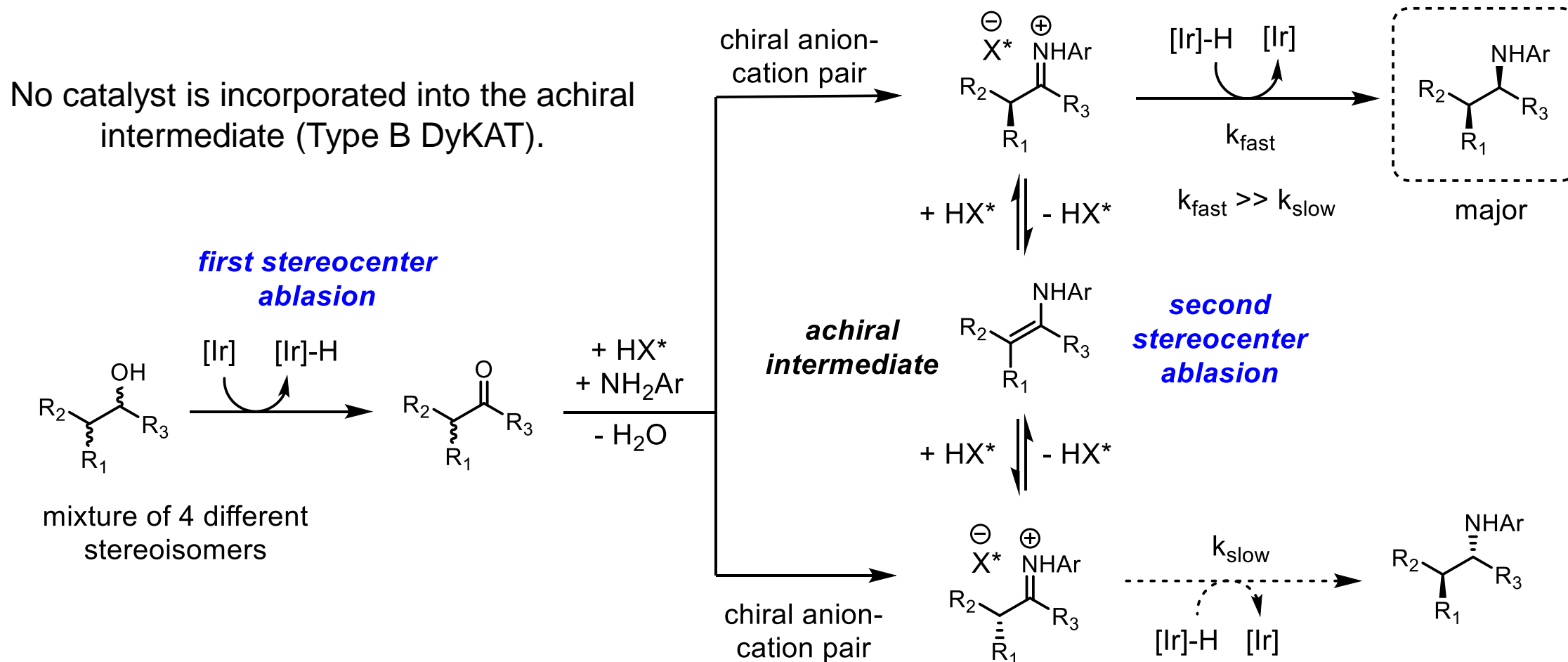
Deprotection to free amine:





# DyKATs for Enantioconvergent Synthesis of $\beta$ -Branched Amines

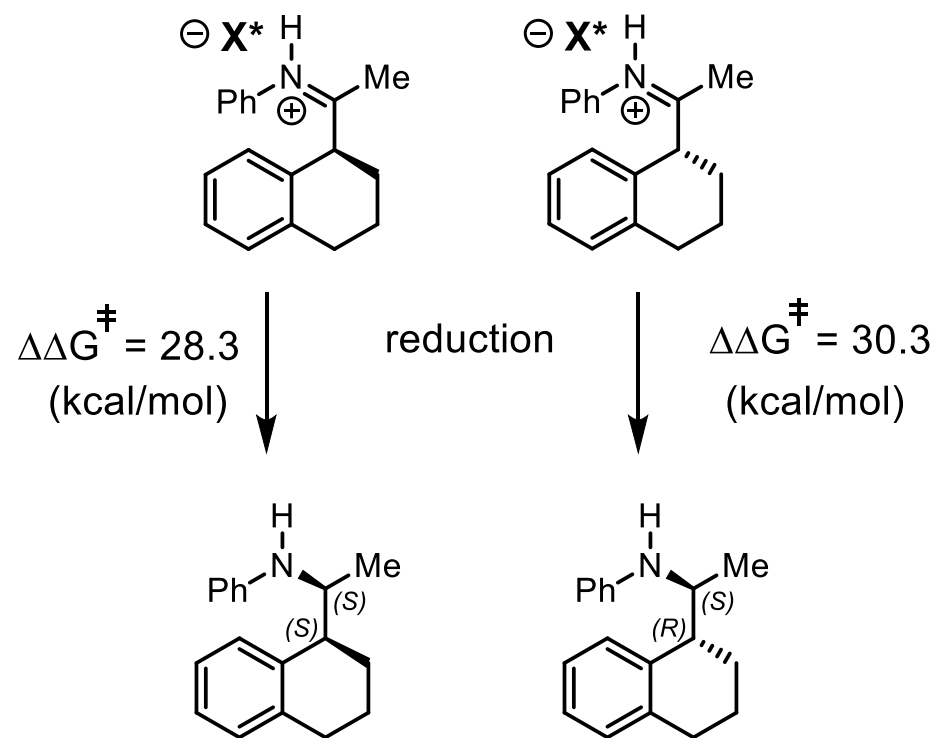
Two distinct mechanistic steps for stereoablation of starting material:



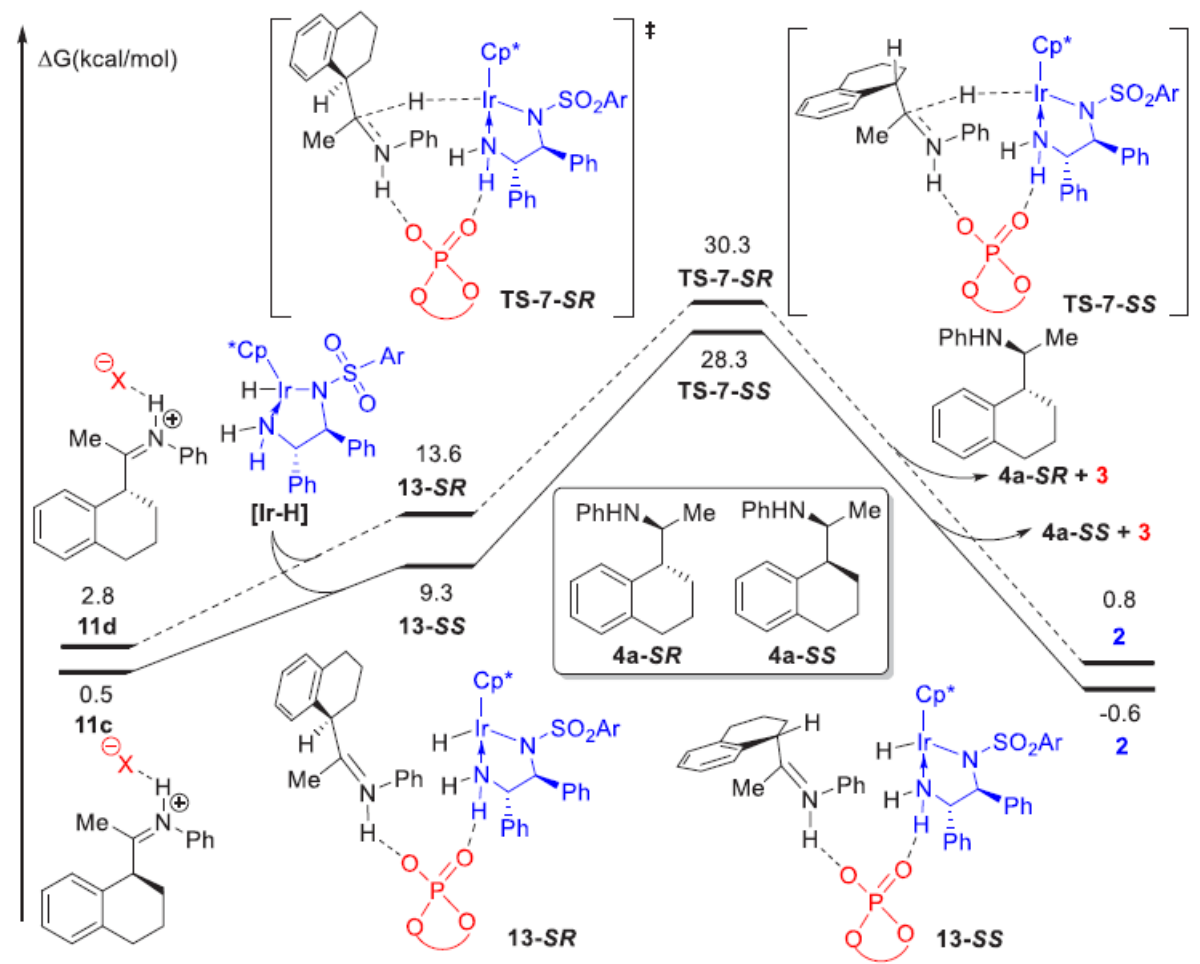


# DyKATs for Enantioconvergent Synthesis of $\beta$ -Branched Amines

DFT calculations provide insight into stereo-determining steps:

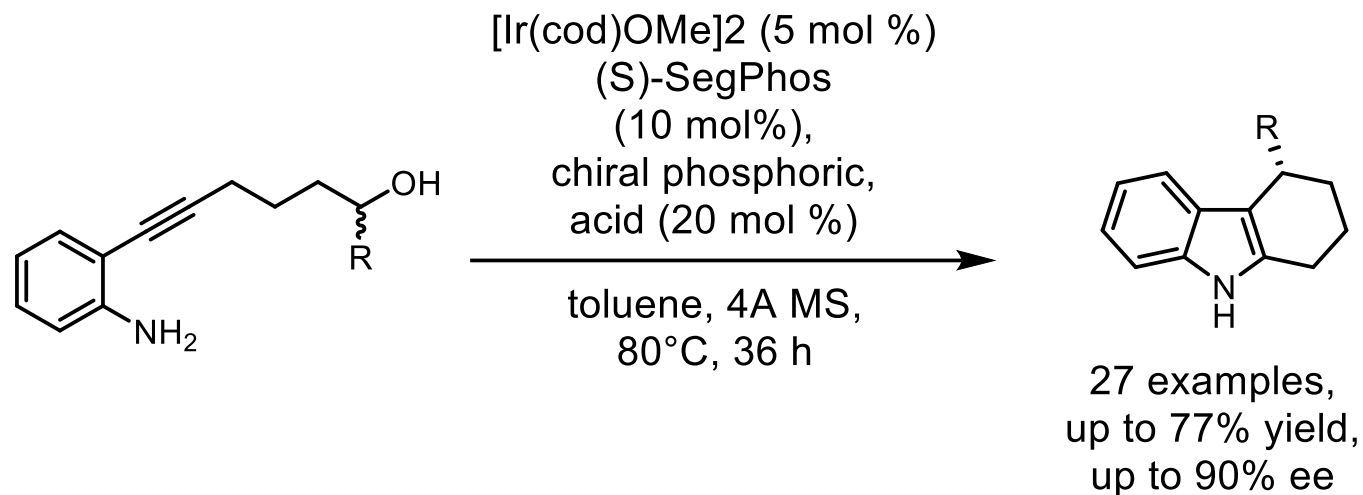


Delivery of H to pro-(*R*) face of iminium requires isomerization to (*Z*)-imine. These isomers are energetically disfavored by 6.9 kcal/mol or more





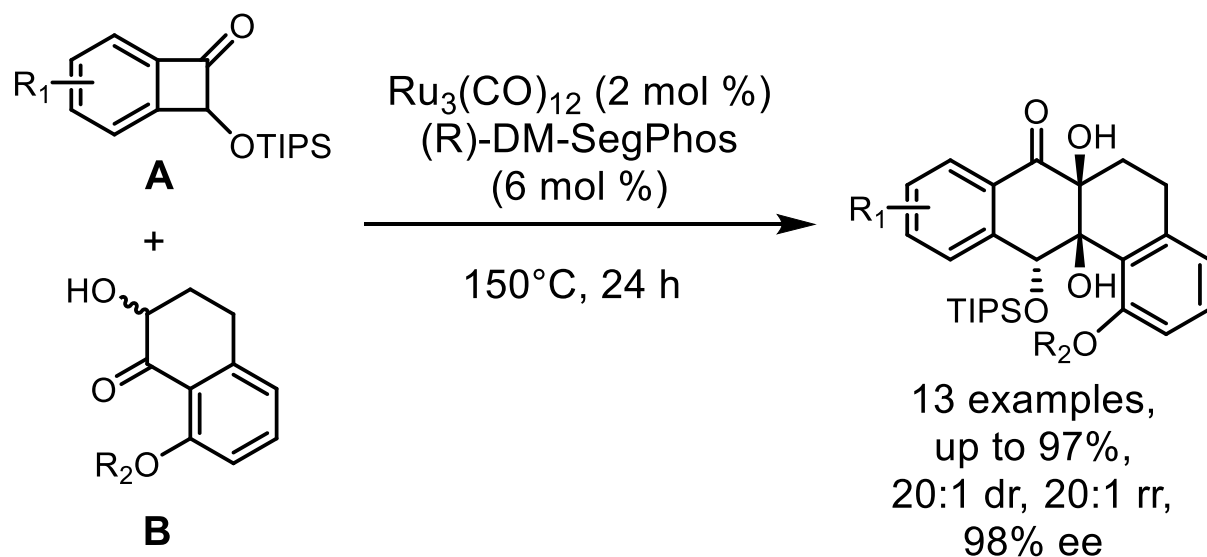
# Borrowing Hydrogen Coupled with Other Catalytic Steps



**GROUP PROBLEM:**

*Choose your adventure.*

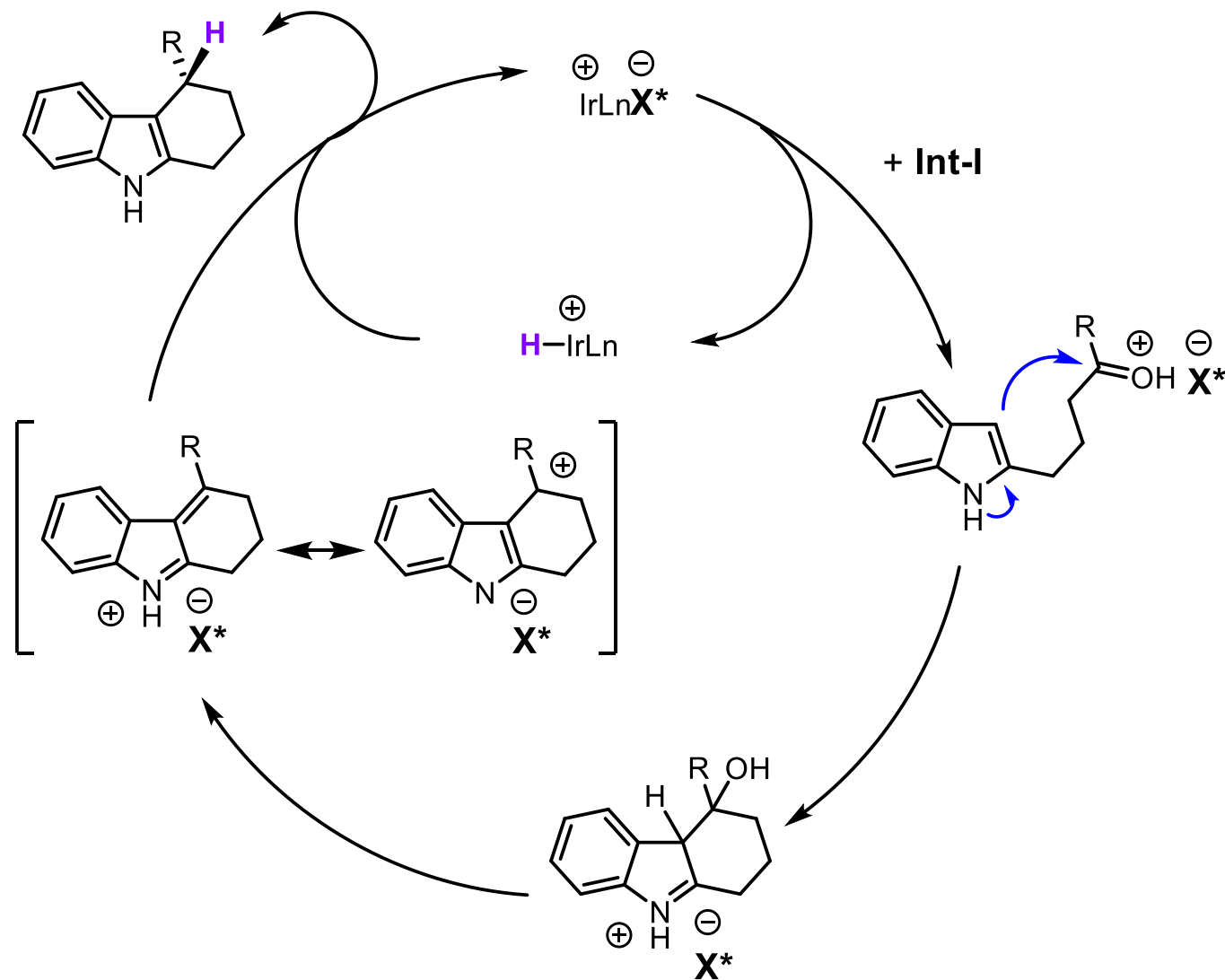
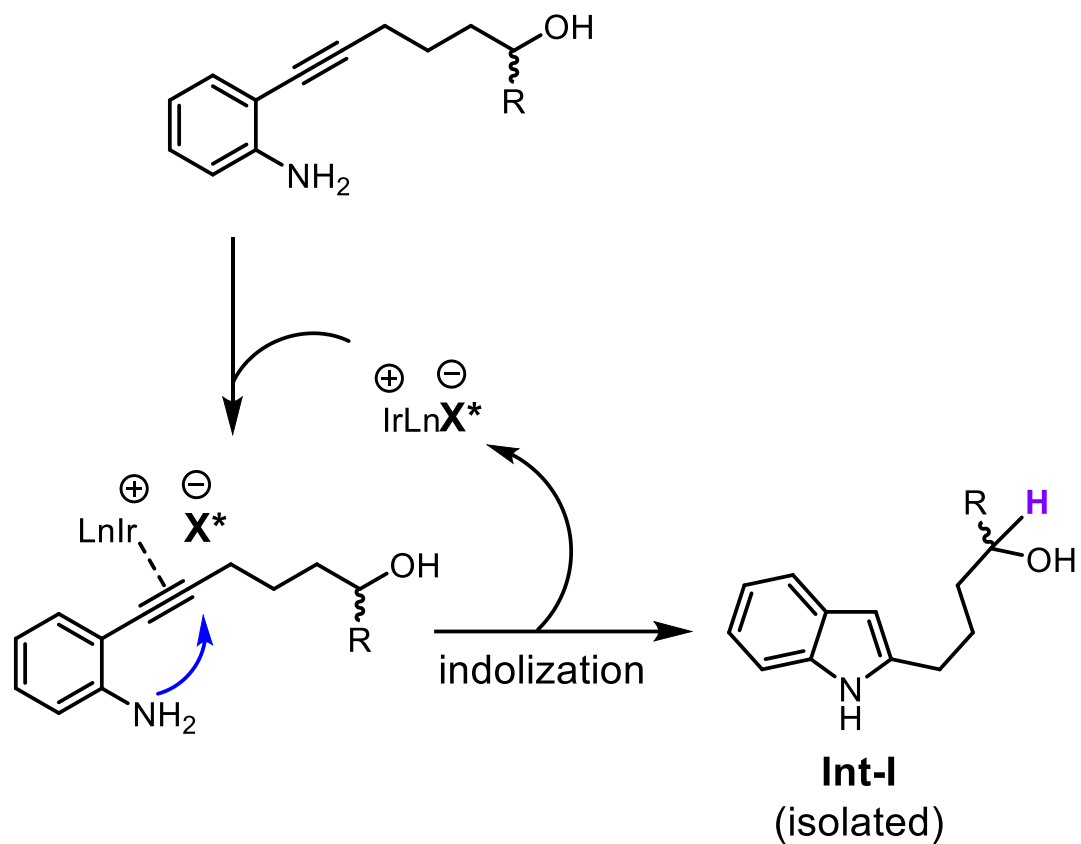
*Mechanism?*





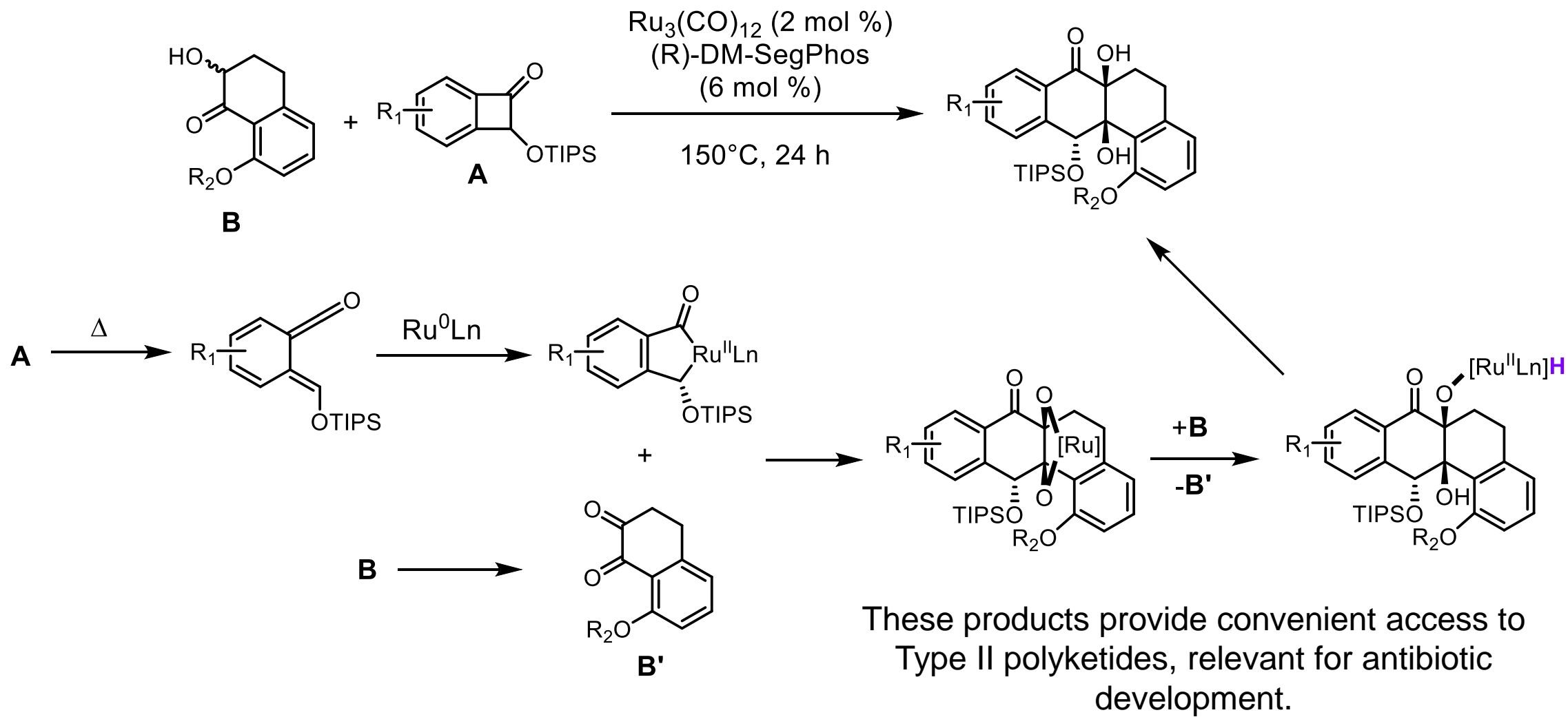
# Borrowing Hydrogen Coupled with Other Catalytic Steps

Sequential Ir-catalyzed indolization, borrowing hydrogen reactivity:





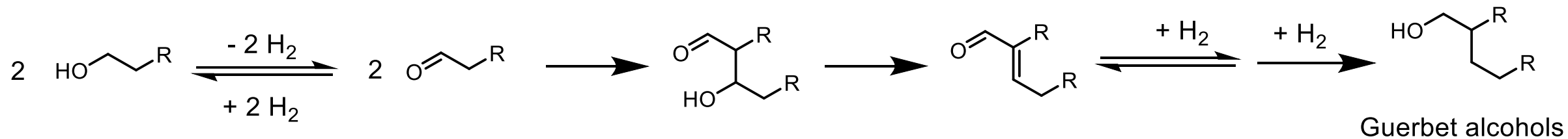
# Borrowing Hydrogen Coupled with Other Catalytic Steps



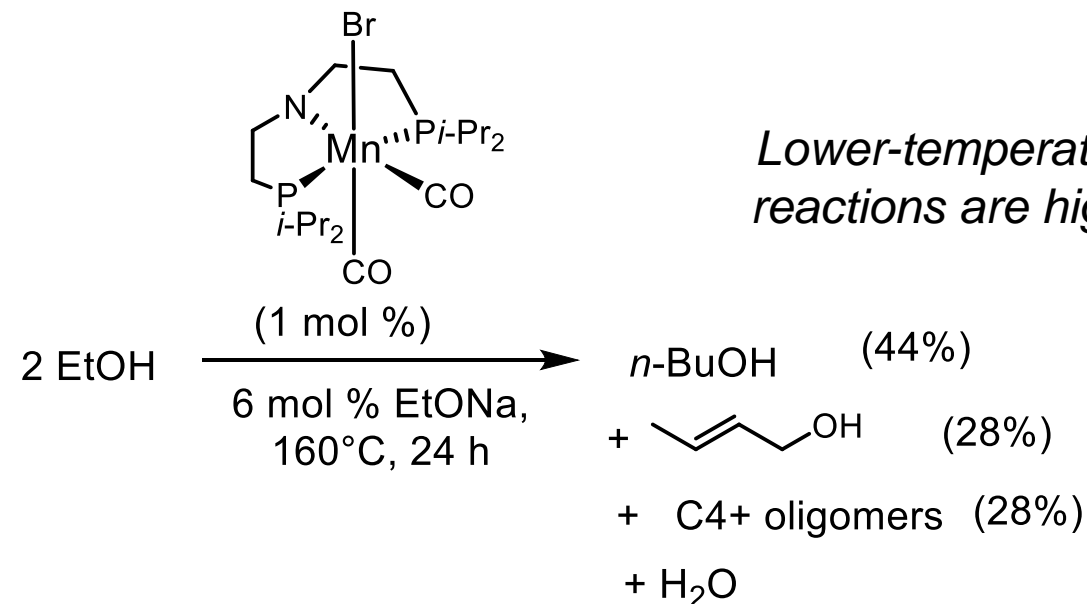


# Direct Alcohol Coupling: The Guerbet Reaction

The Guerbet reaction is a highly relevant reaction for industrial processes:

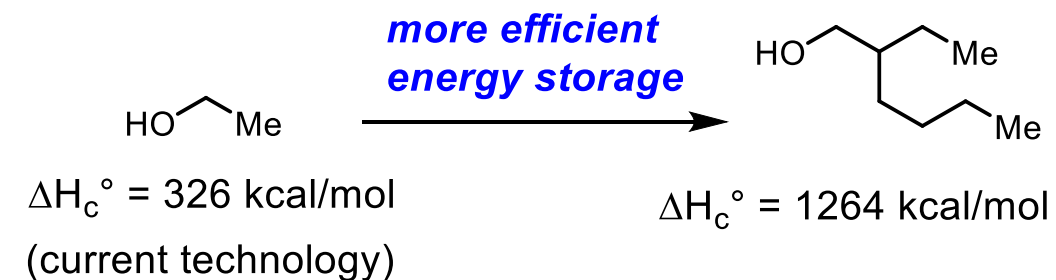


Recent Guerbet methods still require high temperatures (Liu 2017):



2-alkyl alcohol applications:

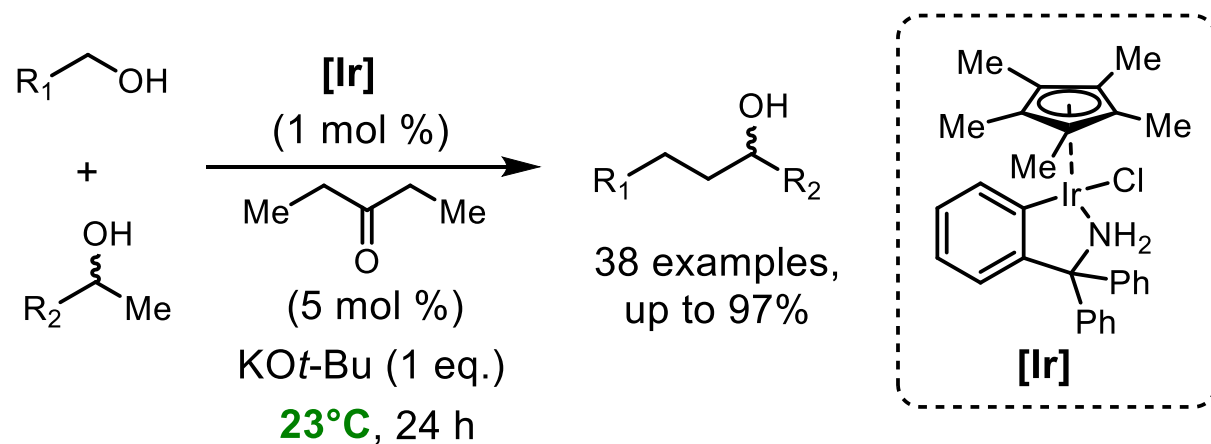
- Low-temperature lubricants and hydraulic fluids
- Cosmetic emollients
- Upgraded biofuels:



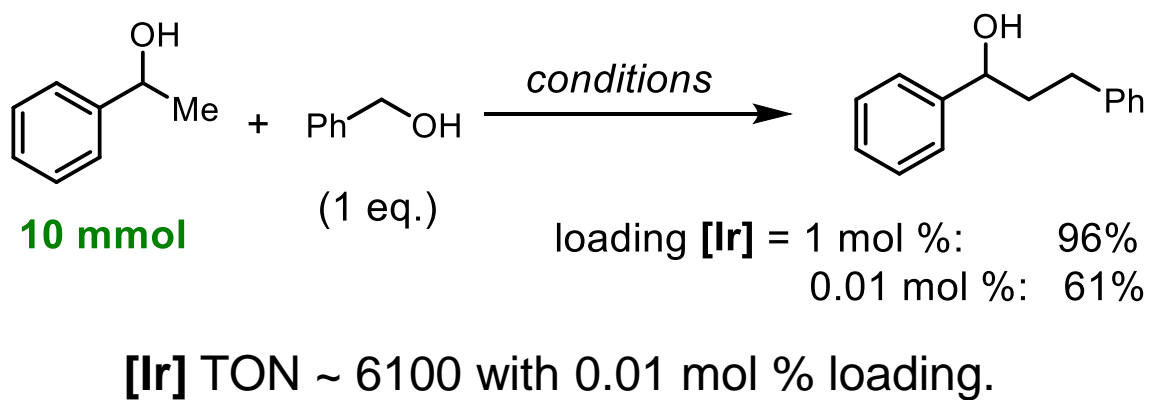


# Room-Temperature Enantioselective Guerbet Reaction

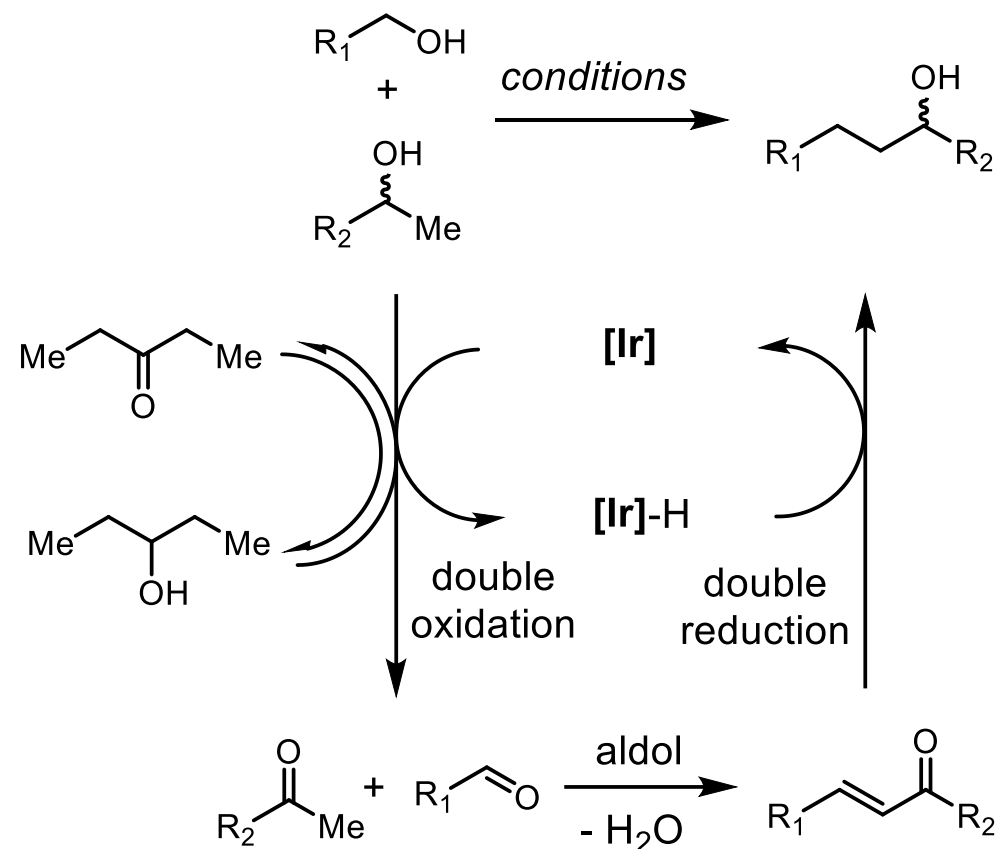
Development of a room-temperature (racemic) Guerbet reaction (Zhao 2020):



Scalable with lowered catalyst loading:



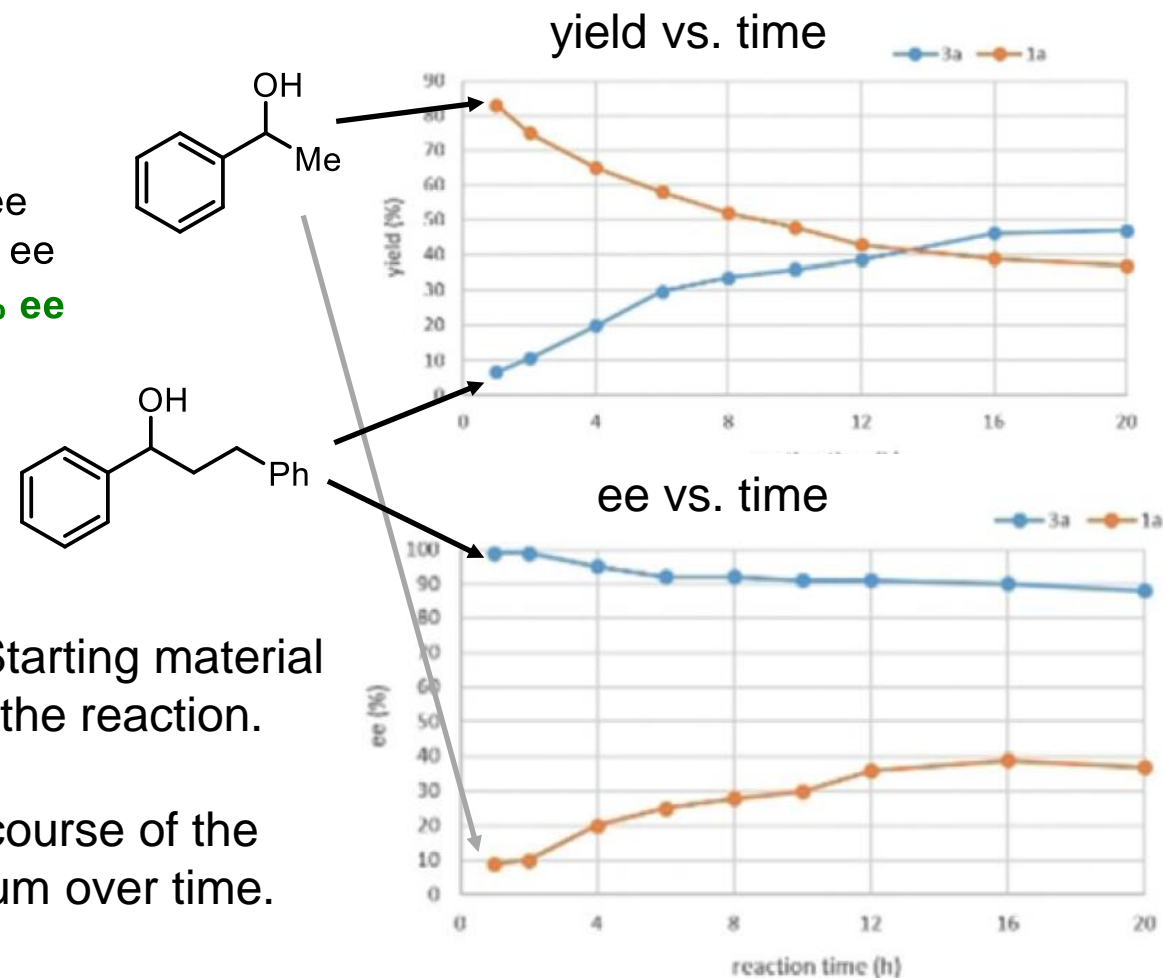
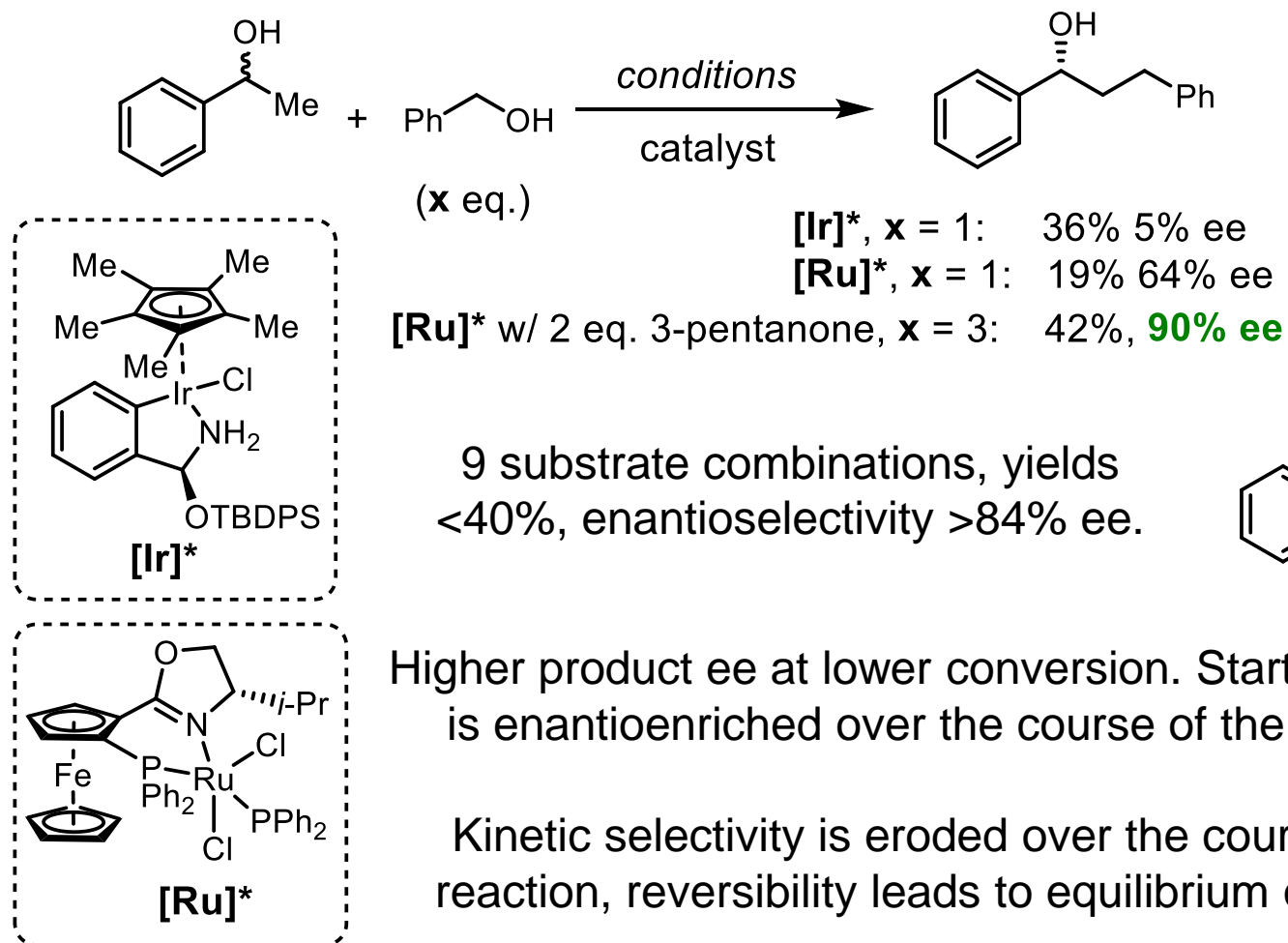
3-pentanone facilitates double oxidation equilibrium:





# Room-Temperature Enantioselective Guerbet Reaction

The same work describes the development of enantioselective conditions using Ru catalysis:





# Summary and Conclusion

## Borrowing H, Returning C or H:

- Borrowing H/ Returning C methods have seen much development. Both hydrometallative and reductive cleavage mechanisms to activate a pro-nucleophile have been realized.
- Systems are highly tunable based on choice of ligand, C,O-benzoate, and chiral additives.
- Switching between the two pathways depends on the Lewis acidity of the Ir center.
- Many pro-nucleophiles are tolerated, mostly 1° alcohols.

## Borrowing H/Returning H for Enantioconvergent Transformations:

- Enantioconvergent borrowing hydrogen methods from secondary alcohols have been developed in the last decade.
- DyKATs, kinetic resolutions, etc. are enabled by epimerizable intermediates.
- Can be coupled with other modes of catalysis for cascade/sequential processes.



# Useful Reviews

*Chem. Soc. Rev.*, **2023**, 52, 5541.

Chem Soc Rev



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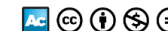
Cite this: *Chem. Soc. Rev.*, 2023, 52, 5541

## Enantioconvergent transformations of secondary alcohols through borrowing hydrogen catalysis

Yaru Gao,<sup>ab</sup> Guorong Hong,<sup>id</sup> Bin-Miao Yang<sup>\*a</sup> and Yu Zhao<sup>id</sup> <sup>\*ba</sup>



*ACS Cent. Sci.* **2021**, 7, 570–585.



Outlook

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## Borrowing Hydrogen for Organic Synthesis

Benjamin G. Reed-Berendt,<sup>#</sup> Daniel E. Latham,<sup>#</sup> Mubarak B. Dambatta, and Louis C. Morrill<sup>\*</sup>



Cite This: *ACS Cent. Sci.* 2021, 7, 570–585



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*Acc. Chem. Res.* **2017**, 50, 2371–2380.

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## Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier

Seung Wook Kim, Wandu Zhang, and Michael J. Krische<sup>\*id</sup>

Department of Chemistry, University of Texas at Austin, Welch Hall (A5300), 105 East 24th Street, Austin, Texas 78712, United States

*Angew. Chem. Int. Ed.* **2014**, 53, 9142 – 9150.

Angewandte  
Minireviews

M. J. Krische et al.

DOI: 10.1002/anie.201403873

Enantioselective Catalysis

## Catalytic Enantioselective C–H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon

John M. Ketcham, Inji Shin, T. Patrick Montgomery, and Michael J. Krische<sup>\*</sup>