

# Nickel Catalyzed $sp^3$ - $sp^3$ Couplings

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# Difficulties in $sp^3$ - $sp^3$ Cross Coupling

- Difficult oxidative addition
  - Sterics - three substituents prevent access to the C-X bond
  - Electronics - electrons are more equally shared in an  $sp^3$  C-halide bond than in  $sp^2$  C-halide bond.
- Slow reductive eliminations
  - Increases reaction time
  - Increases amount of  $\beta$ -Hydride elimination
  - Increases amount of reduction of alkylhalide

# Outline

## Part I: Knochel

Development of alkylzinc reagents for coupling

## Part II: Fu

Elaboration of nickel catalyzed alkylzinc couplings

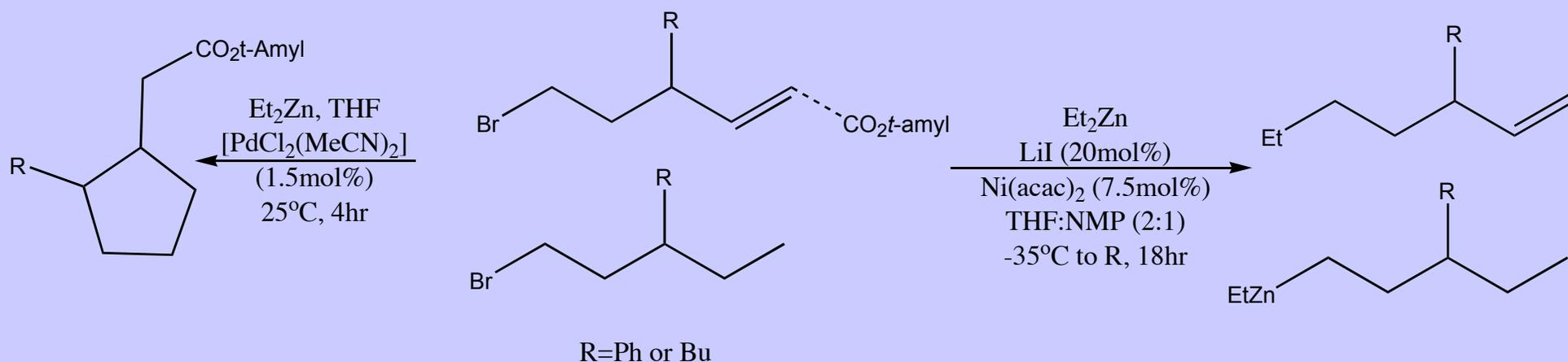
## Part III: Vicic

Mechanistic studies of alkyl zinc couplings

## Part IV: Kumada

Alkyl grignards as the organometallic donor

# First Example



Initial substrate scope:

Homoallylic and bishomoallylic primary iodides  
Alkene or  $\alpha,\beta$ -unsaturated ester.

Organozinc

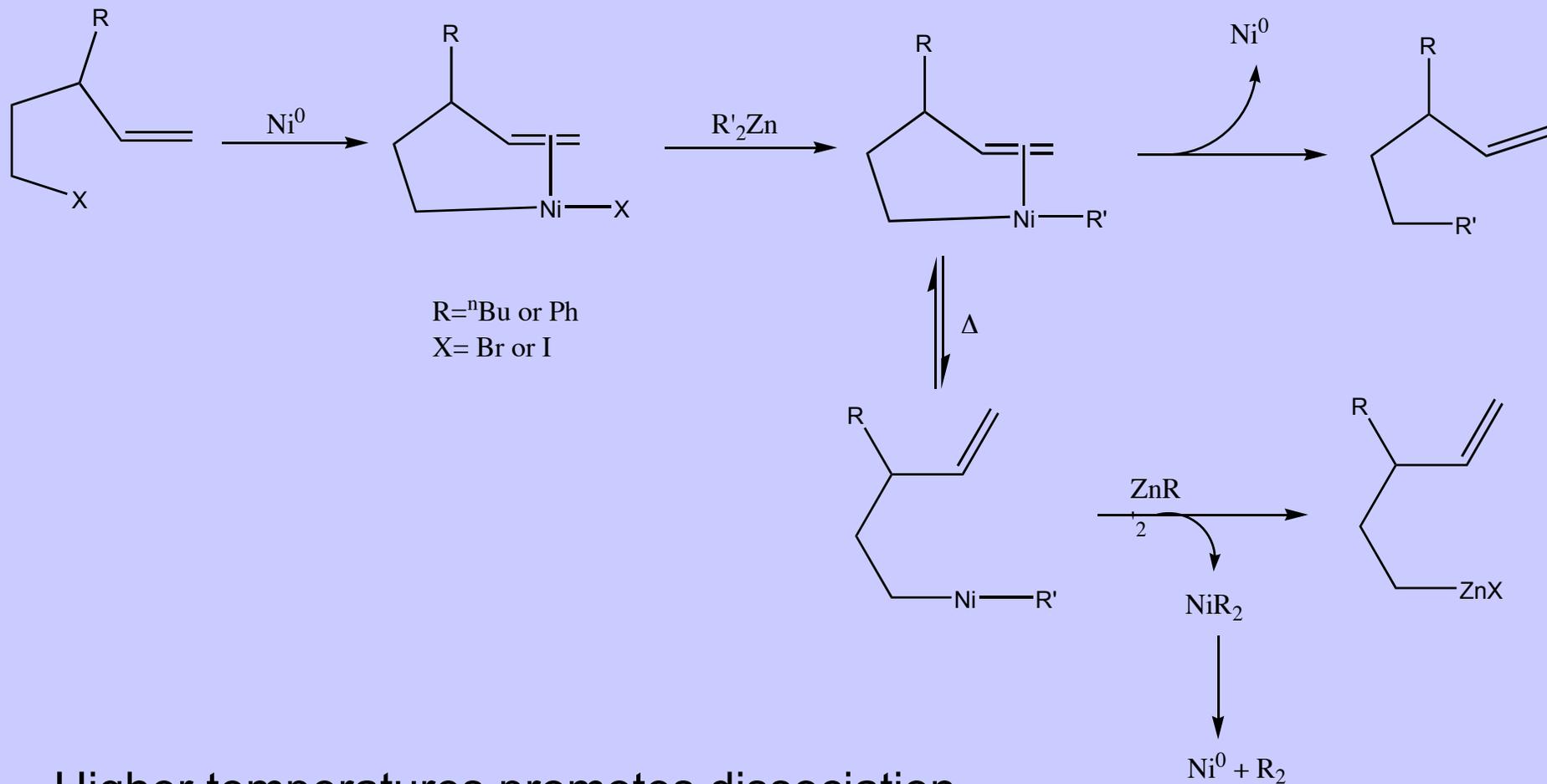
Symmetrical

$1^\circ$  and  $2^\circ$  Alkyl

TMS protected vinyl alcohols

Esters are tolerated

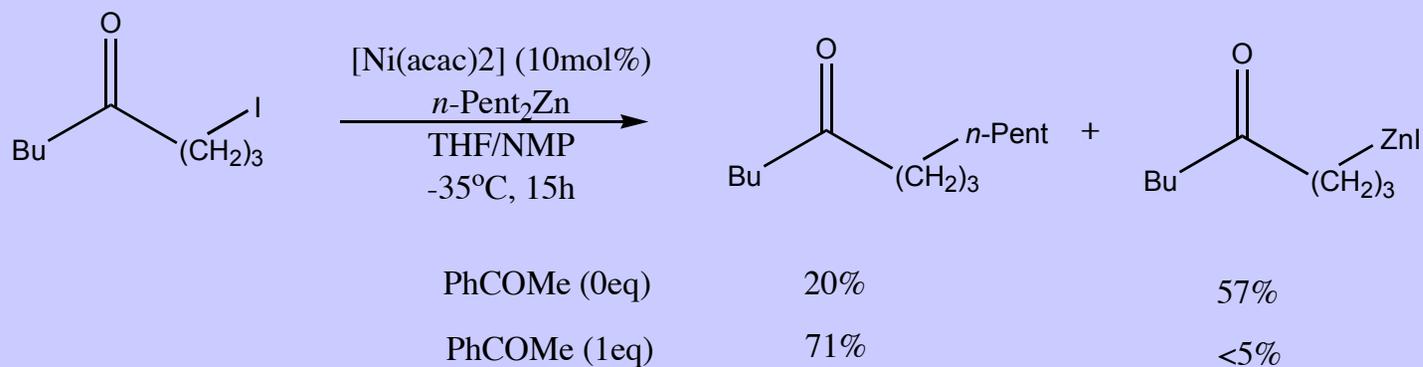
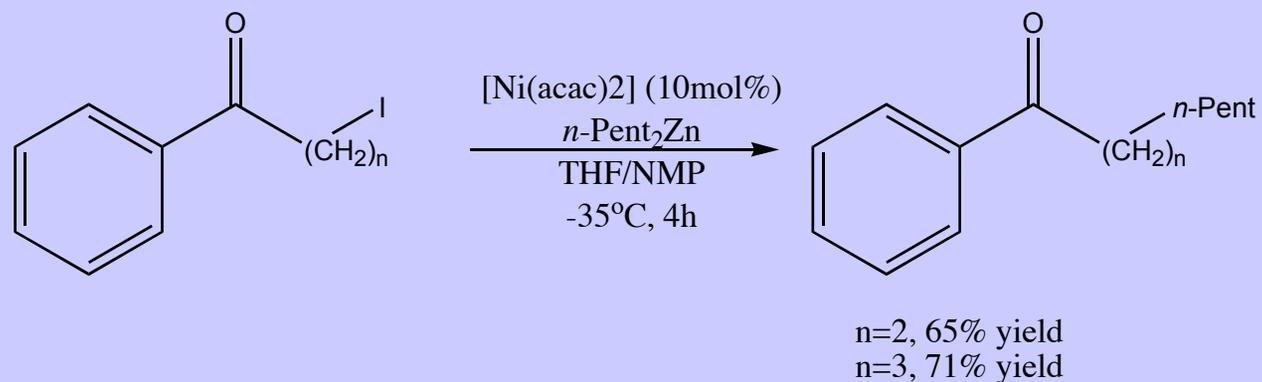
# Knochel Mechanistic Proposal



Higher temperatures promotes dissociation

${}^n\text{Pentyl}_2\text{Zn}$  gives more halide-zinc exchange than  $\text{Et}_2\text{Zn}$

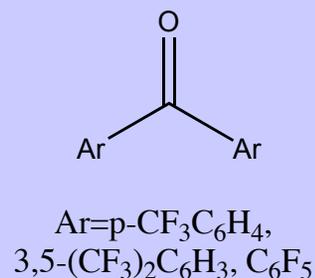
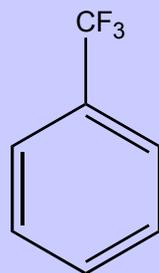
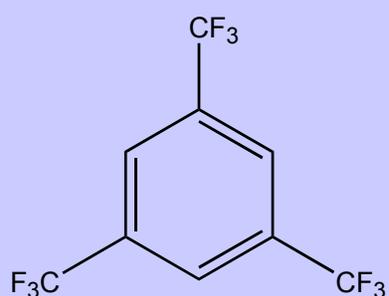
# Expanding the Scope



Conclusion: Stronger  $\pi$ -acids promote coupling

# Catalyst Development

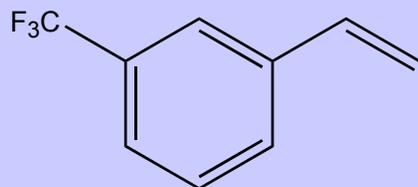
Can an external olefin be added as a co-catalyst to facilitate coupling?



All gave similar conversion times and a moderate amount of zinc-bromide exchange



Completely inhibits the coupling.



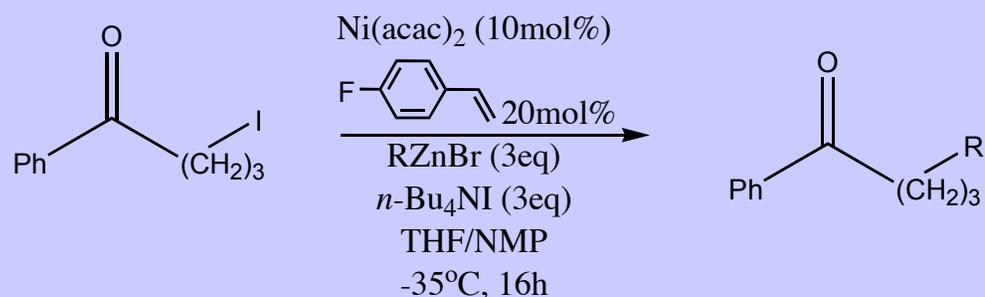
Gives fast conversion as well as suppresses formation of zinc halogen exchange.

Broad functional group tolerance

Notable exceptions: alcohols and amines

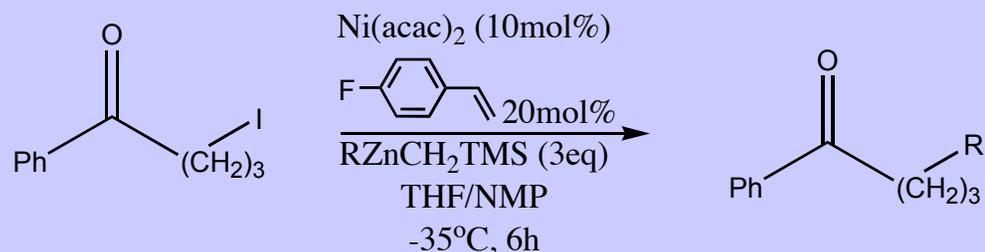
# Reducing Waste: AlkylZnX Reagents

2eq of Dialkylzinc reagents are typically used



Allows for more easily prepared  $\text{RZnI}$  reagents to be used.

$\text{RZnI}$  reacts with  $\text{TMSCH}_2\text{Li}$  to give  $\text{RZnCH}_2\text{TMS}$



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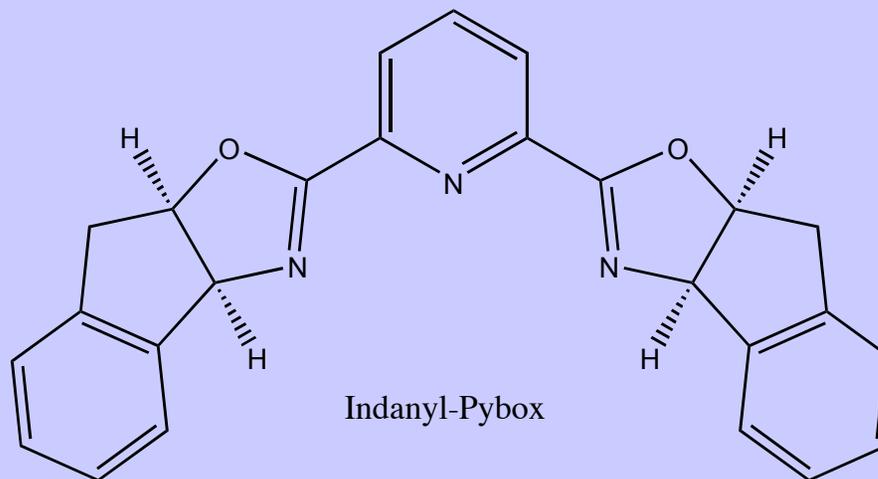
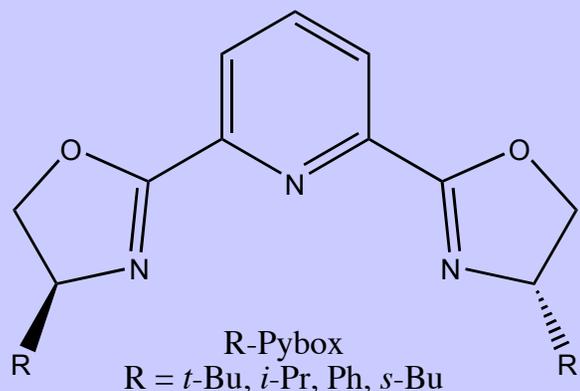
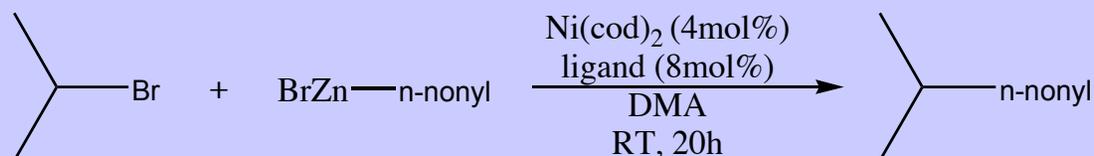
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Part IV: Kumada

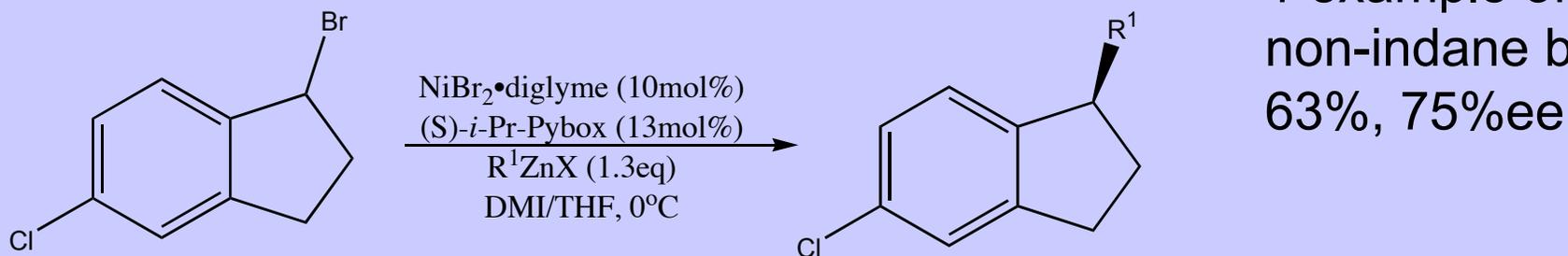
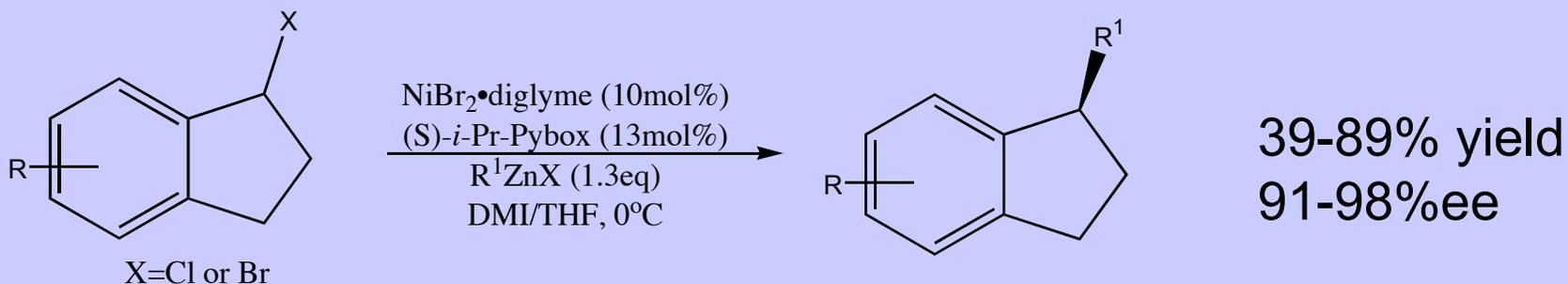
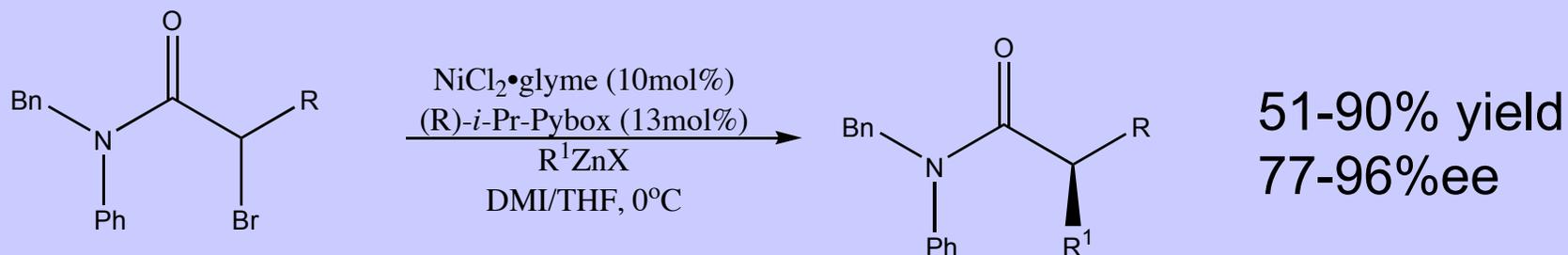
Alkyl grignards as the organometallic donor

# Initial Ligand Development

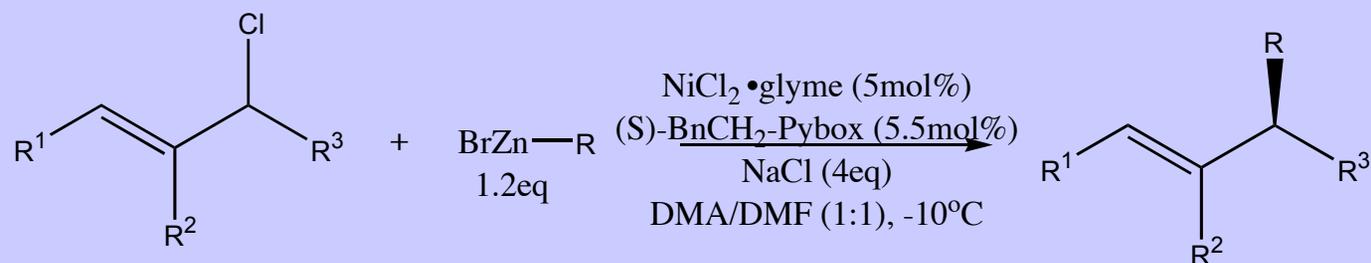


1<sup>o</sup> or 2<sup>o</sup> alkyl bromides or iodides  
Highly functional group tolerant  
62-78% yield

# Asymmetric Catalysis



# Asymmetric Catalysis (Part II)



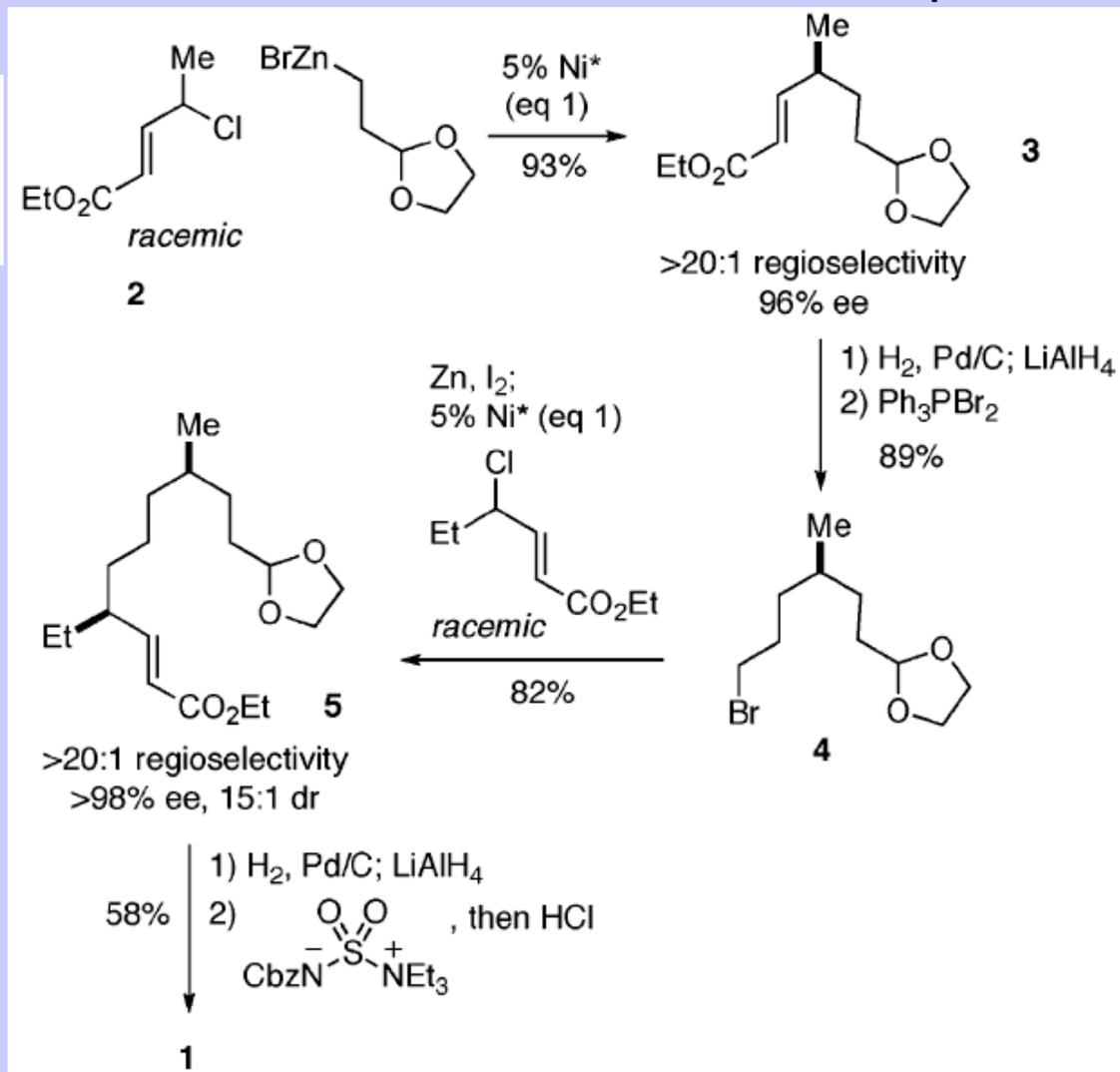
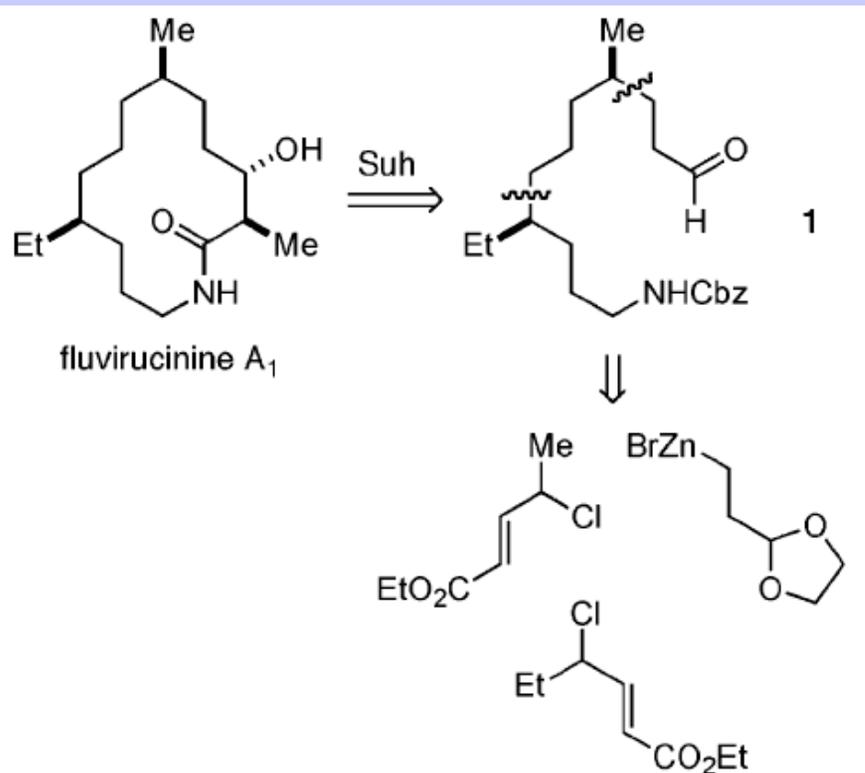
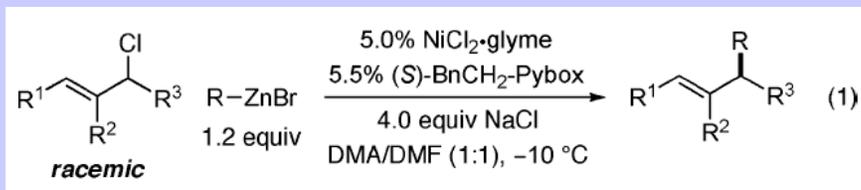
$\text{R}^1=\text{R}^3$  54-95%, 69-98%ee  
 $\text{R}^3=\text{Me}$  57-97%, 81-96%ee

When  $\text{R}^1 \neq \text{R}^3$ : If  $\text{R}^1$  is smaller, the constitutional isomer is formed.

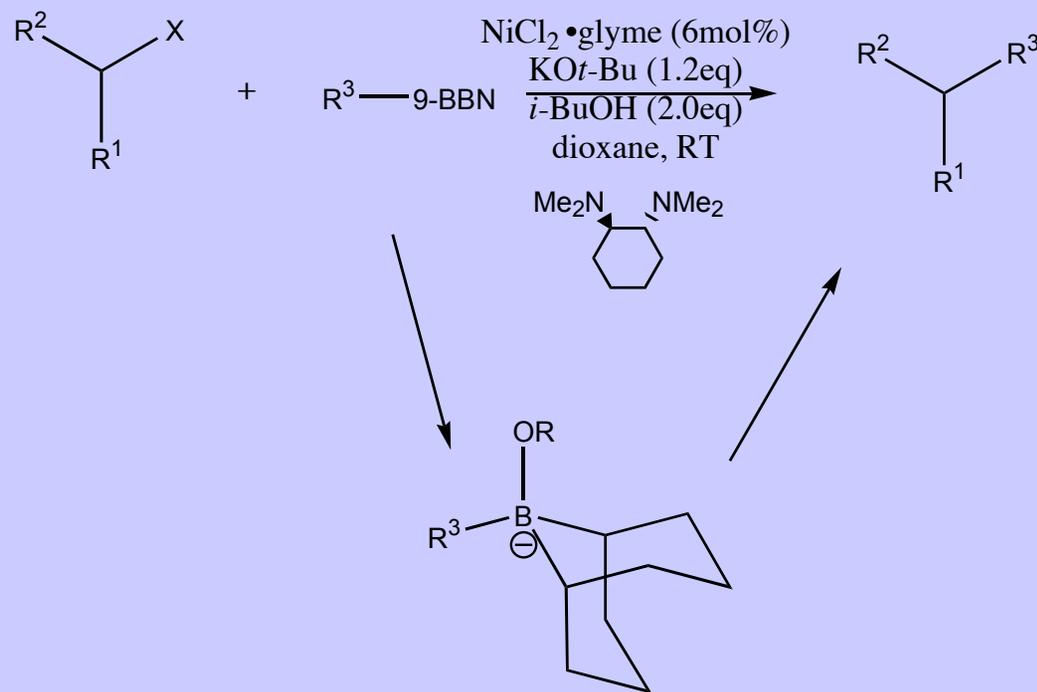
If  $\text{R}^1$  is  $e^-$  withdrawing, substitution is always at the  $\gamma$  position.

Substrate scope is excellent: esters, amides, silyl ethers, acetals, alkenes, phosphonate ester, and weinreb amide.

# Formal Total Synthesis of Fluvirucinine A<sub>1</sub>



# Boranes as the Organometallic Source



Tolerant of protected alcohols (TBS) and amines (Cbz)

Rate: X = I > Br >> Cl

2° > 1° >> 3° (very low yielding)

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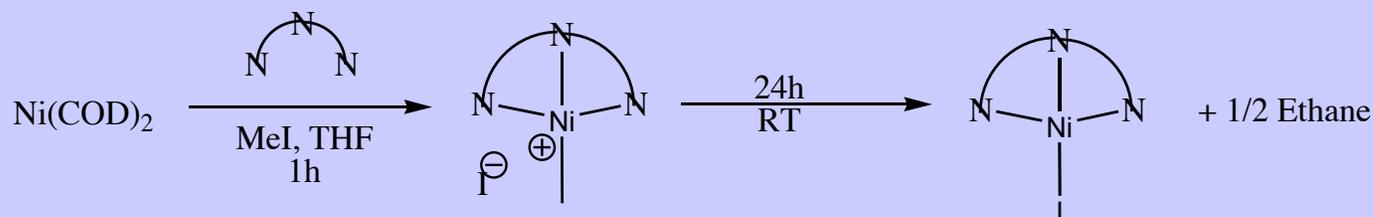
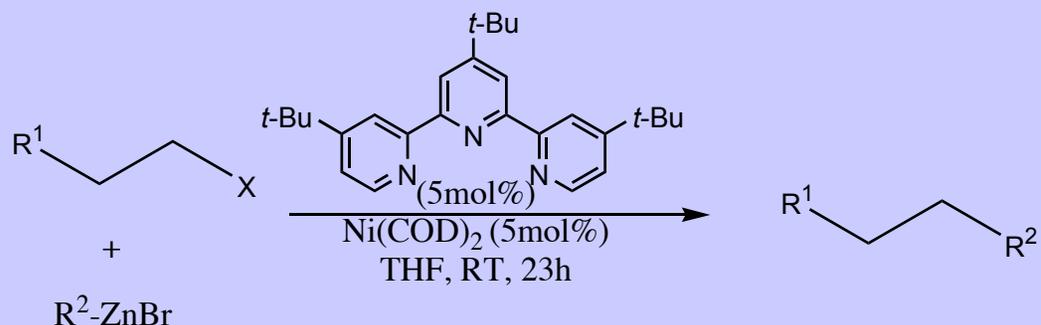
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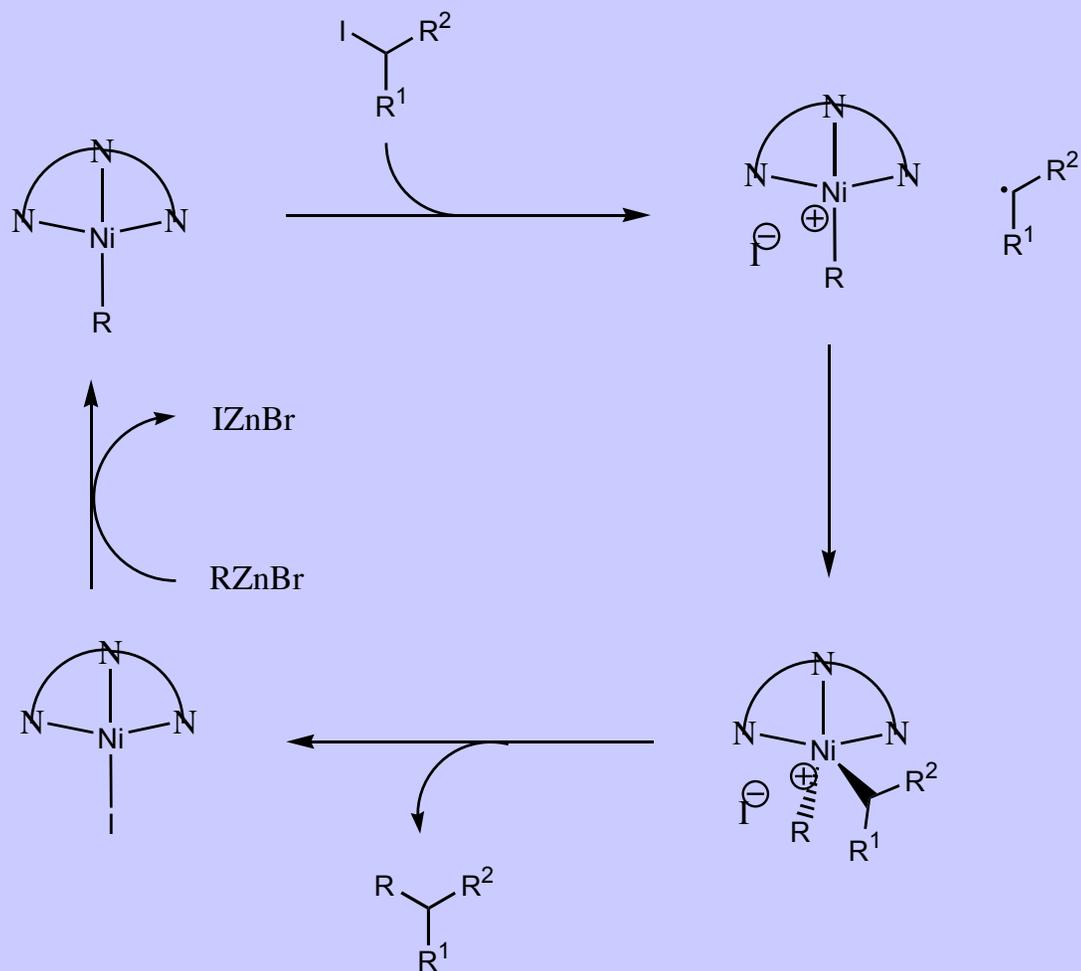
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# Some Mechanistic Insights



Both species shown above are catalytically active.  
Propose a mechanism for the coupling reaction

# Proposed Mechanism



The Ni(I) alkyl complex was independently synthesized and also shows catalytic competence.

Agrees with Knochel's observation that 1,4-dinitrobenzene inhibited the reaction.

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# Grignards as the Organometallic Source



1eq RX

R = alkyl

X = F, Cl, Br, OTs

1.3eq R'MgX

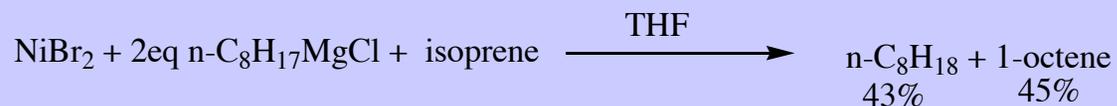
R'=aryl or alkyl

X'=Cl or Br

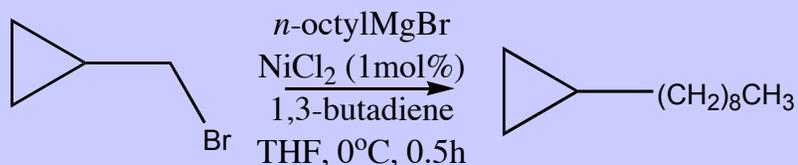
Substrate scope is diminished, tolerant of alkenes and arylbromides.

Capable of coupling with alkyl fluorides.

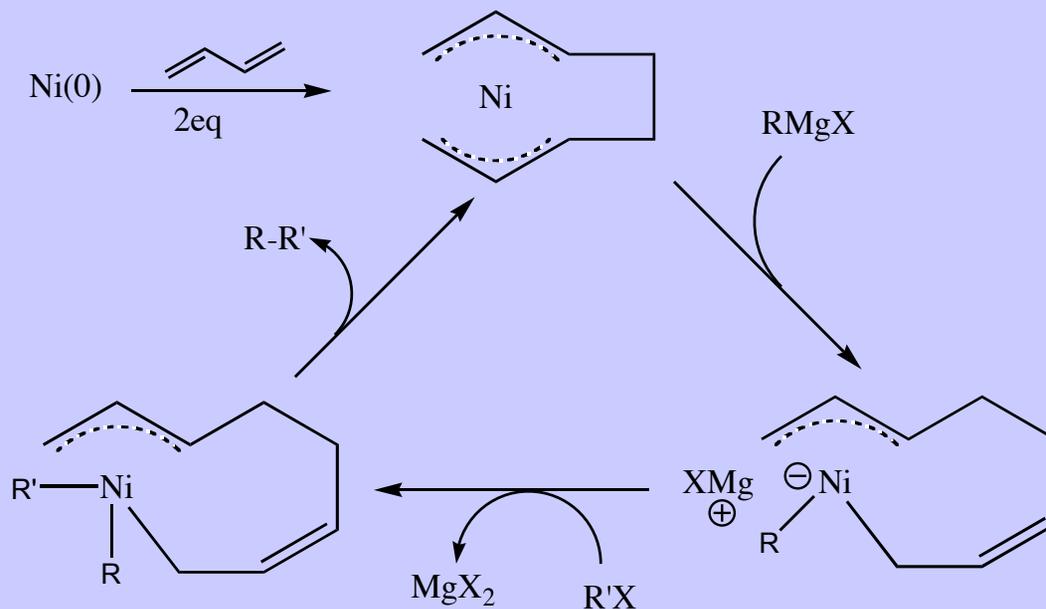
# Mechanism



To rule out a radical mechanism:



According to Kambe:  
 “This result would rule out a radical mechanism.”



# Conclusions

- Ni catalyst systems are robust and efficient
- Cross coupling of  $sp^3$ - $sp^3$  centers can be used in total synthesis
- Cross coupling can be used to set  $2^\circ$  stereo-centers

# For Reviews of Alkyl-Alkyl Couplings

- Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.
- Netherton, M. R.; Fu, G. C.; *Adv. Synth. Catal.* **2004**, *346*, 1525-1532.
- Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663-672.