

# $Sp^3-sp^3$ : The Final Challenge in Cross-Coupling

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Denmark Group

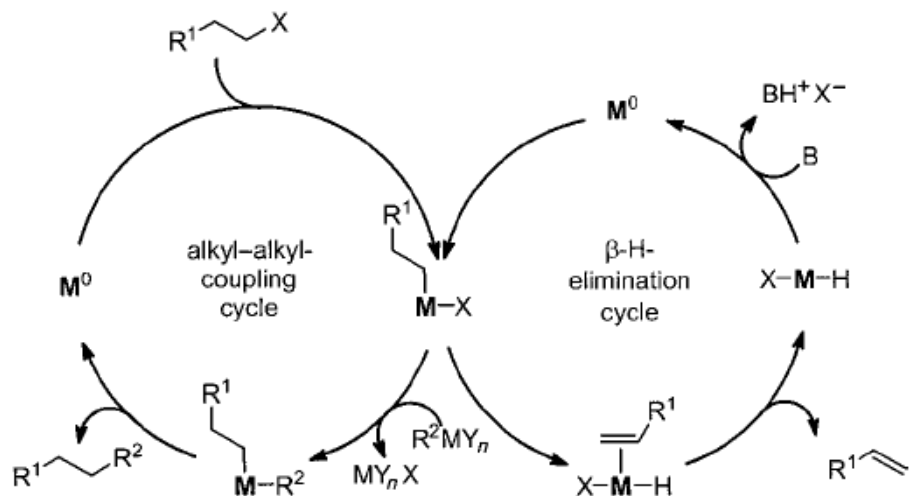
August 28, 2012

# Outline

- Background
- Preliminary  $sp^3$ - $sp^3$  couplings
- Kumada couplings
- Palladium-catalyzed couplings
- Nickel-catalyzed couplings
- Applications to Natural Product Synthesis
- Conclusions

# Why is $sp^3$ - $sp^3$ coupling difficult?

- Oxidative addition and reductive elimination are relatively slow
  - $C(sp^3)$ -X bond comparatively more electron-rich than  $C(sp^2)$ -X
- Alkyl halides can oxidize low-valent T. metals by SET mechanisms
- $\beta$ -hydride elimination is generally fast (relatively)

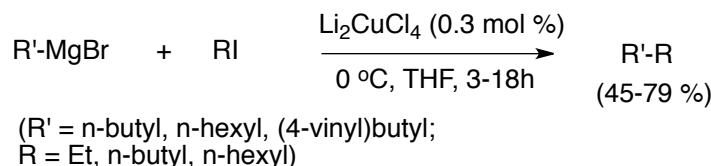


Beller, M., et. al. *Angew. Chem. Int. Ed.*, **2005**, 44, 674.

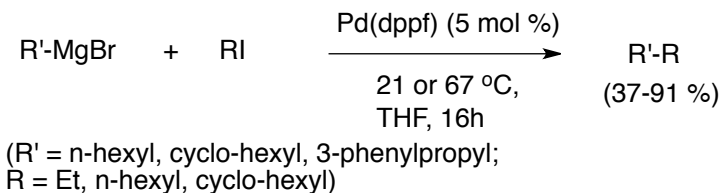
Vicic, et. al. *J. Am. Chem. Soc.*, **2006**, 128, 13175.

# Preliminary Findings: Kumada

- Cu(I)-catalyzed cross coupling of primary alkyl bromides (Kochi)



- Widdowson reports efficient coupling with Pd(0) cat formed in situ



- No  $\beta$ -hydride elim. products reported
- These results were questioned by Scott
  - Repetition: mostly reduction observed (hydrodehalogenation)

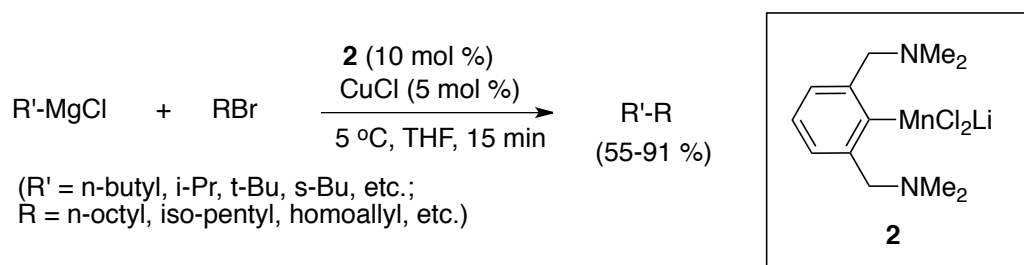
Kochi, J., et. al. *Synthesis*, **1971**, 303.

Widdowson, D.A., et. al. *Tet. Lett.*, **1986**, 27, 6013.

Scott, W.J., et. al. *Tet. Lett.*, **1989**, 30, 4779.

# Kumada Couplings

- van Koten increases scope of Grignard reagent groups with an organomanganese(II) complex



- Grignard reagents limit substrate scope
  - Low functional group tolerance
  - Best to use alternative nucleophiles

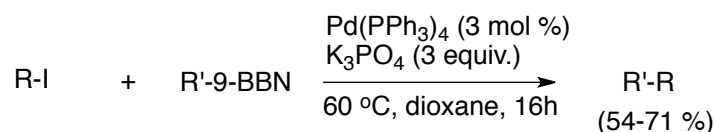
van Koten, G., et. al. *J. Organomet. Chem.*, **1998**, 558, 61.

# Pd-catalyzed couplings

- Suzuki-Miyaura couplings
  - Variation of Leaving Groups
  - Variation of Nucleophile
  - Variation of Ligand
- Negishi
  - Primary (pseudo)halides
  - Secondary (pseudo)halides

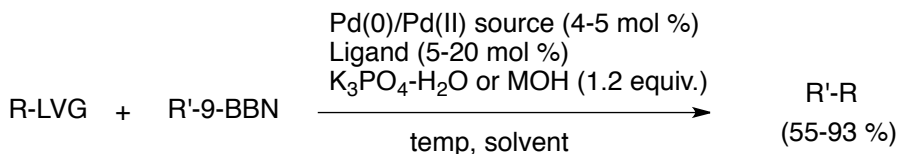
# Primary (Pseudo)halides with Alkyl 9-BBN Nucleophiles: Leaving Group

- Primary Iodides (Suzuki)



(R = Me, n-hexyl, alkyl-CN, alkyl-COOMe;  
R' = alkyl-COOMe, alkyl-acetal, etc.)

- Primary Bromides, Chlorides, and Tosylates (Fu)



– Broad substrate scope (tolerance of nitrile, ester, ketone, alcohol, amide)

Suzuki, A., et. al. *Chem Lett.*, **1992**, 691.

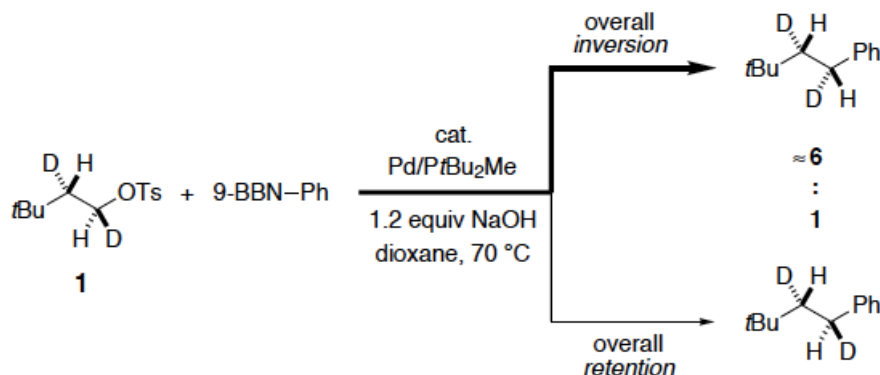
Fu, G.C., et. al. *J. Am. Chem. Soc.*, **2001**, 123, 10099.

Fu, G.C., et. al. *Angew. Chem. Int. Ed.*, **2002**, 41, 1945.

Fu, G.C., et. al. *Angew. Chem. Int. Ed.*, **2002**, 41, 3910.

# Stereochemical Studies: Palladium

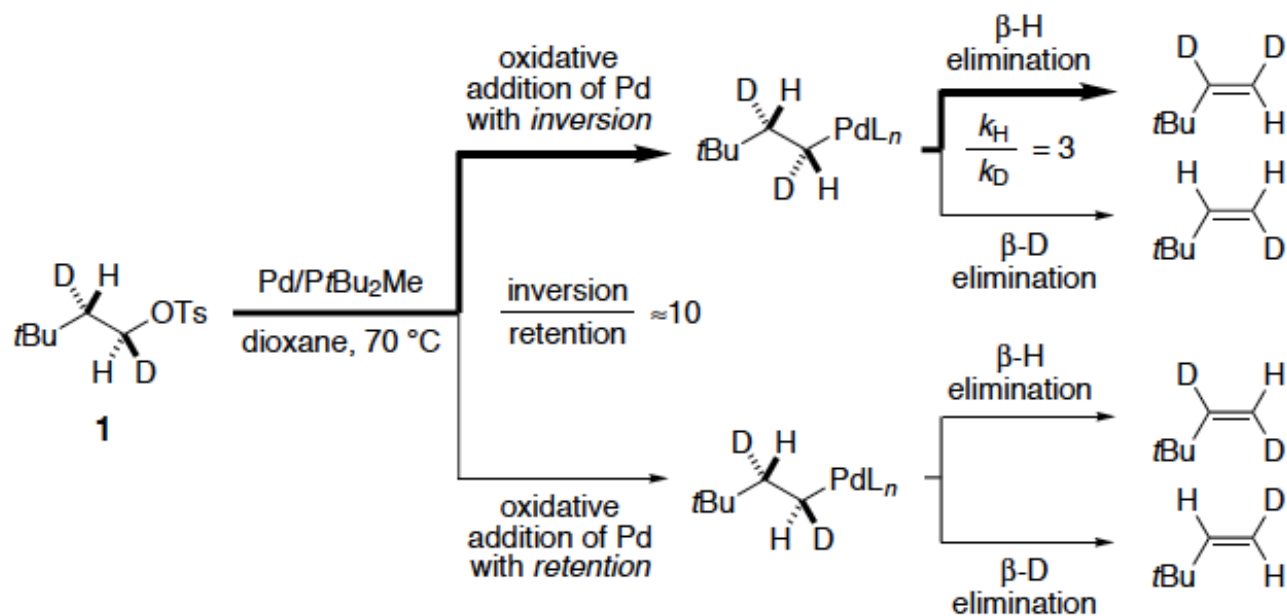
- Suzuki reactions with primary alkyl tosylates
  - Experiment 1: Determine the net stereochemical outcome





# Pd (cont.)

- Experiment 2

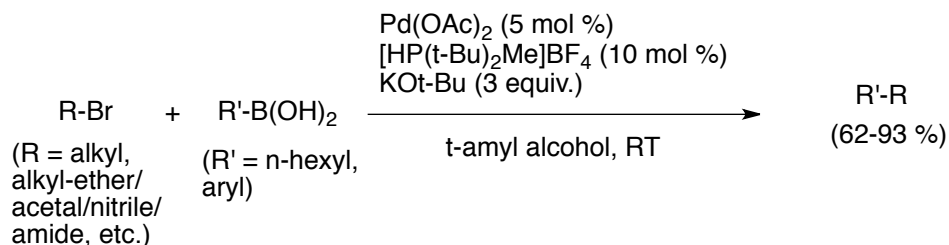


# Group Problem #1

- Using the results of the previous 2 experiments to determine the stereochemical course of both oxidative addition and reductive elimination.

# Boronic acids as nucleophiles

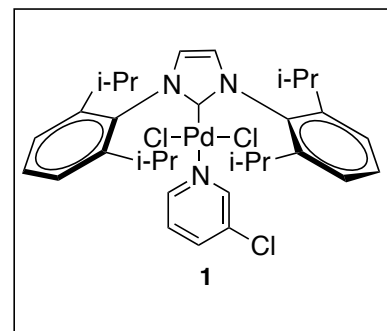
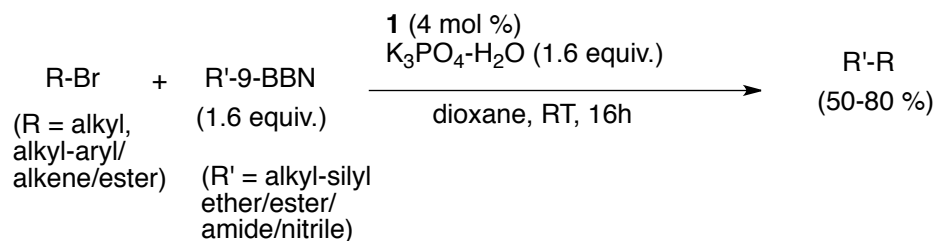
- Mostly aryl boronic acids utilized
  - Ease of handling: boronic acid, phosphonium salt



Fu, G.C., et. al. *J. Am. Chem. Soc.*, **2002**, 124, 13662.

# Alternative Ligands

- Use of NHC ligands
  - Desirable due to low air and moisture-sensitivity
  - Essentially no improvement in yield, substrate scope

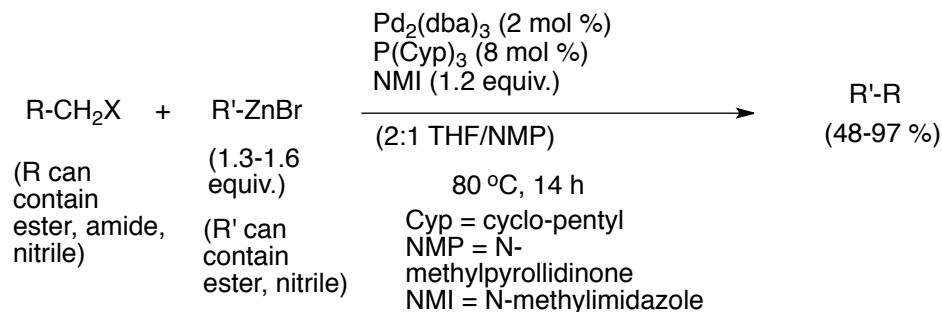


Caddick, S., et. al. *Tet. Lett.*, **2004**, 3511.

Organ, M.G. et. al. *Chem. Commun.*, **2008**, 735.

# Pd-catalyzed Negishi couplings: primary (Pseudo)halides

- Versatility
  - One catalyst system for all 4 leaving groups
  - NMI is essential to increase yield
    - Possibly activates R'ZnBr toward transmetallation



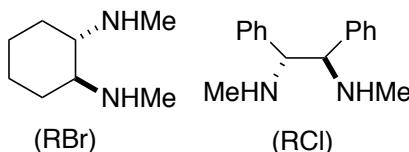
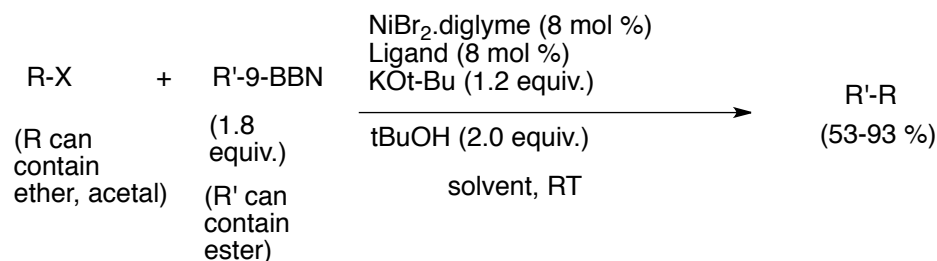
Fu, G.C., et. al. *J. Am. Chem. Soc.*, **2003**, 125, 12527.

# Ni-catalyzed couplings

- Initial Suzuki-Miyaura couplings
- Asymmetric Suzuki-Miyaura couplings
- Negishi couplings of Primary (Pseudo)halides
- Negishi couplings of Secondary (Pseudo)halides
- Asymmetric Negishi couplings

# Initial Ni-catalyzed Suzuki-Miyaura Couplings

- Fu: Unactivated, secondary halides



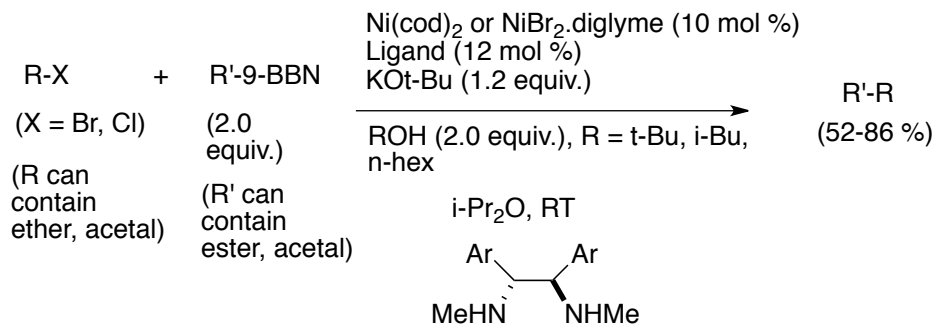
- Previously, these electrophiles could only be cross-coupled with organozinc reagents

Fu, G.C., et. al. *J. Am. Chem. Soc.*, **2007**, 129, 9602.

Fu, G.C., et. al. *Angew. Chem. Int. Ed.*, **2010**, 49, 6676.

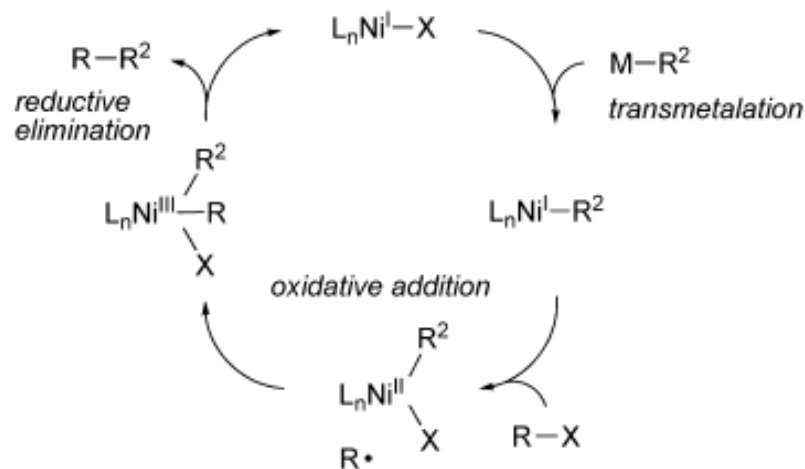
# Asymmetric Ni-catalyzed Suzuki-Miyaura Couplings

- General scheme



- Proposed Mechanism

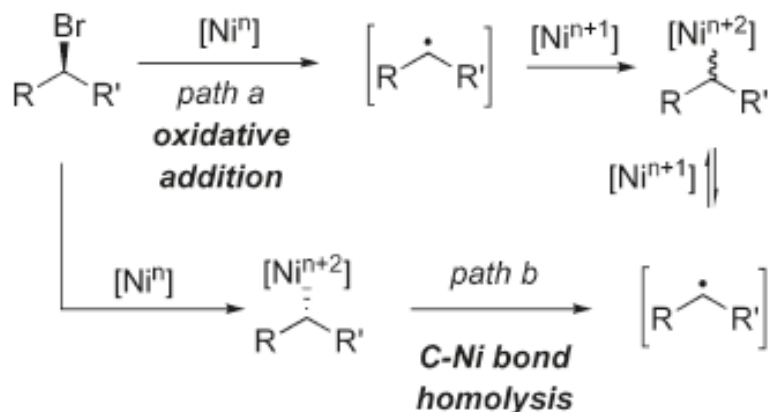
- Supported by rate law
- Rate =  $k[\text{cat}][\text{Nuc}][\text{RX}]^0$





# Stereochemical Studies: Nickel

- Stille envisioned two possible mechanistic extremes
  - Radical oxidative addition (path a)
  - Reversible C-Ni bond homolysis (path b)

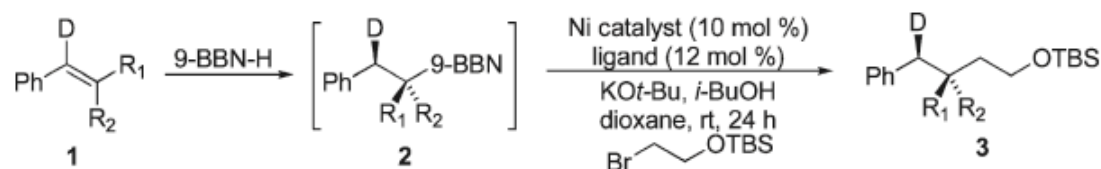


Stille, J.K. et. al. *J.Organomet. Chem.* **1977**, 124, 253.

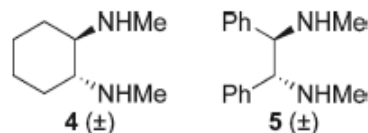
Jarvo, E.R. et. al. *J. Org. Chem.* **2011**, 76, 7573.

# Stereochemical studies (cont.)

- Experiments



entry	styrene	R <sub>1</sub>	R <sub>2</sub>	catalyst	ligand	product
1	1a	D	H	NiCl <sub>2</sub> ·DME	4	3a
2	1b	H	D	NiCl <sub>2</sub> ·DME	4	3b
3	1b	H	D	Ni(cod) <sub>2</sub>	5	3b

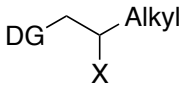
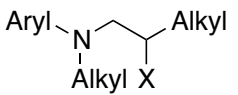
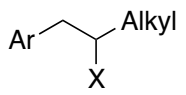
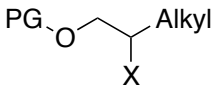
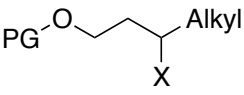


- Stereospecificity: path a most likely
- Transmetalation (the turnover-limiting step) is retentive

# Enantioselectivity vs. Substrate Scope

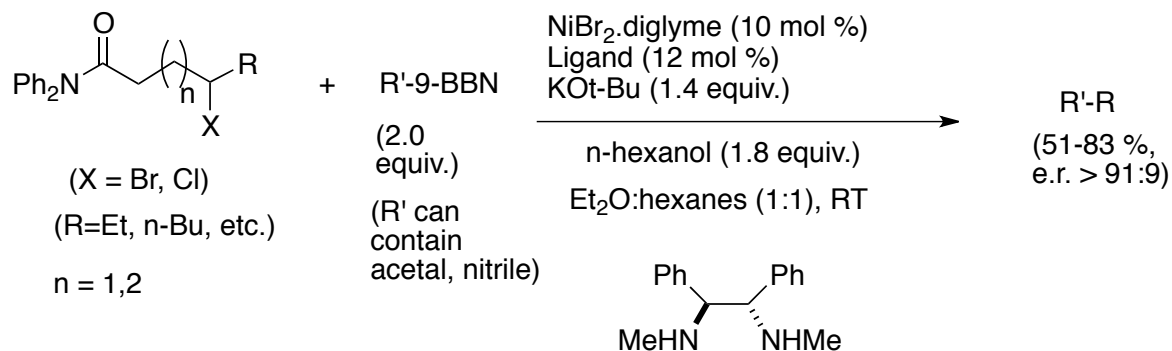
- Directing group typically needed

Enantioselectivity Trends

Substrate	DG (PG)	e.r.	Comments
	carbamate, sulfonamide, sulfone	> 86:10	
	N/A	> 91:9 (mostly)	
	N/A	54:46 to 97:3	Some dependence of e.r. on R'
	(N-benzyl, N-phenylamide)	> 95:5	
	(N-benzyl, N-phenylamide)	95:5	R' = 3-phenylpropyl (Ligand group Ar = meta-CF <sub>3</sub> )

# Remote Directing Groups

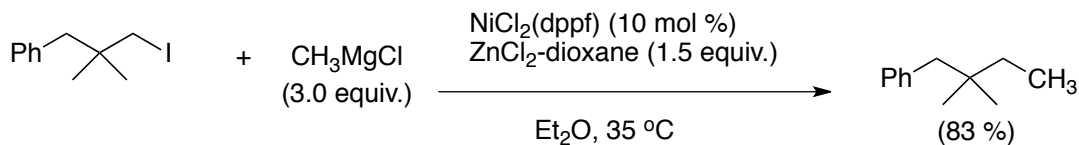
- $\gamma$ -alkylation of N,N-diphenylamides
  - No apparent dependence of e.r. on tether length



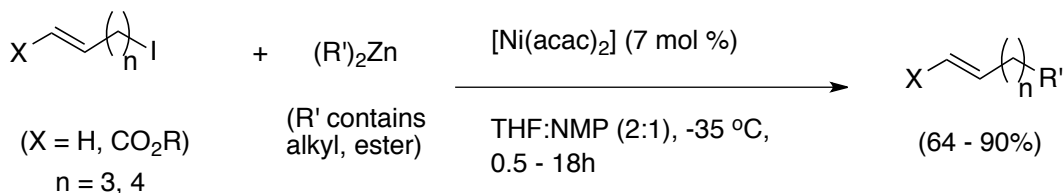
Fu, G.C., et. al. *J. Am. Chem. Soc.*, **2011**, *133*, 15362.

# Ni-catalyzed Negishi couplings of Primary Halides

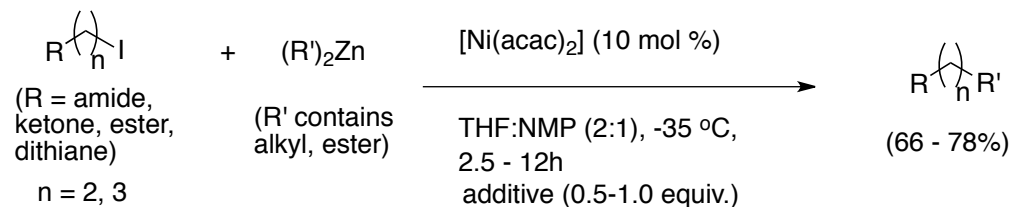
- Unactivated Neopentyl Iodides (Scott)



- Knochel: Tethered olefin



- External olefin



(additive = acetophenone or (meta-trifluoromethyl)styrene)

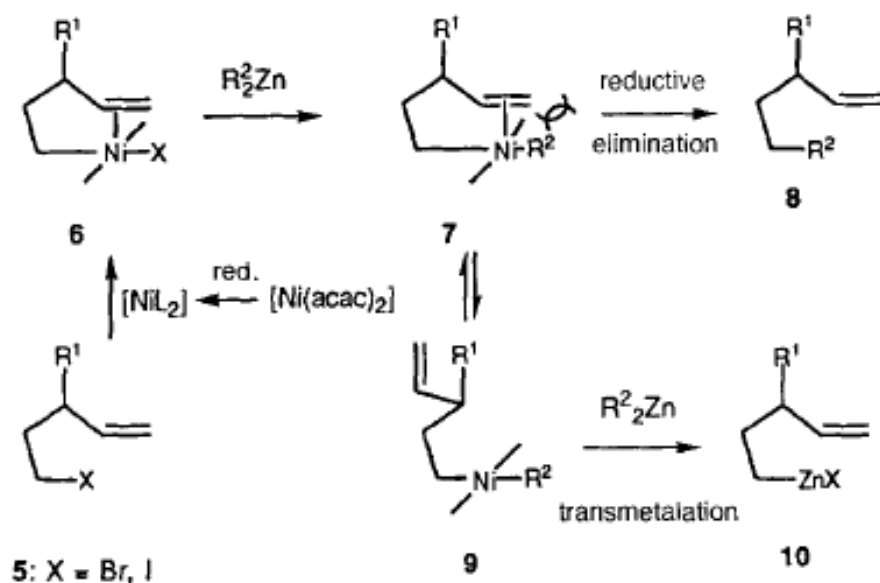
Scott, W.J. et. al. *J. Org. Chem.* **1993**, *58*, 4866.

Knochel, P. et. al. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723.

Knochel, P. et. al. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387.

# Knochel's Mechanistic Hypothesis

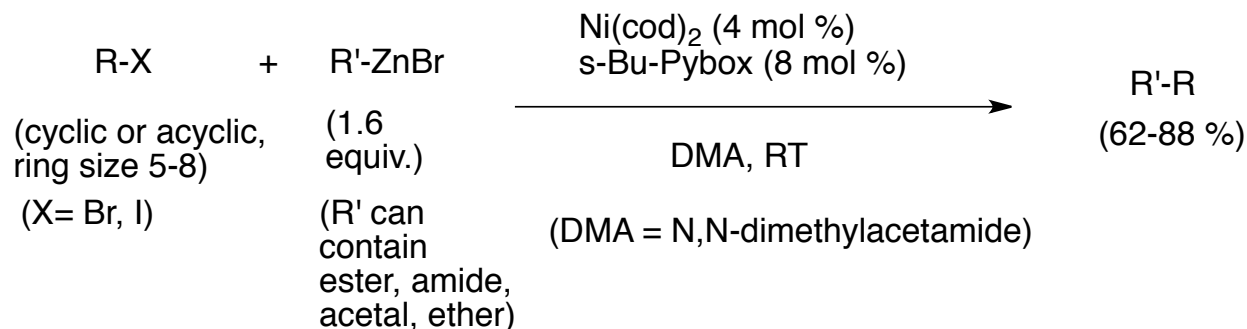
- In situ reduction of Ni(II)
- The olefin stabilizes oxidative addition intermediate (7), provided that R is not overly large



Knochel, P. et. al. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2723.

# Ni-catalyzed couplings of Secondary Halides

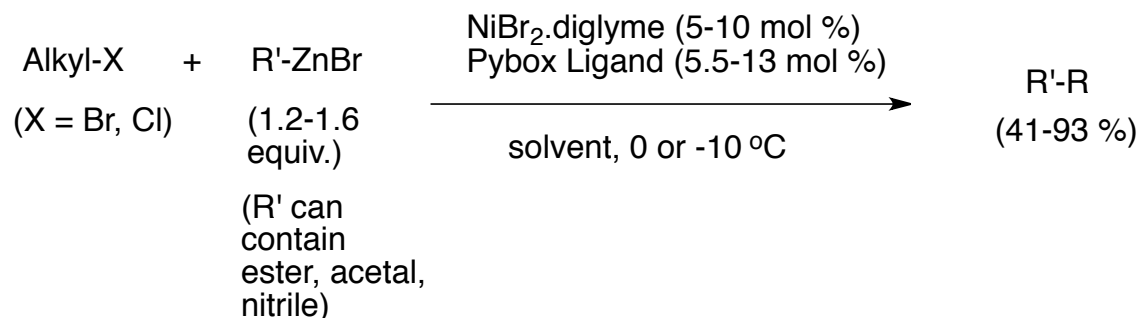
- Unactivated Halides



Fu, G.C. et. al. *J. Am. Chem. Soc.* **2003**, *125*, 14726.

# Asymmetric Ni-catalyzed Negishi Couplings

- Requires Activated Electrophiles



- Solvents

– DMA, DMI (1,3-dimethyl-2-imidazolidinone), THF

Fu, G.C. et. al. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

Fu, G.C. et. al. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

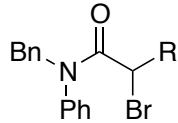
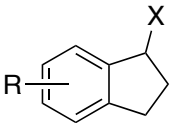
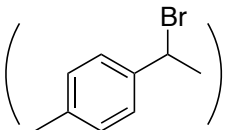
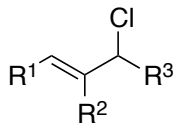
Fu, G.C. et. al. *J. Am. Chem. Soc.* **2008**, *130*, 2756.



# Substrate Scope

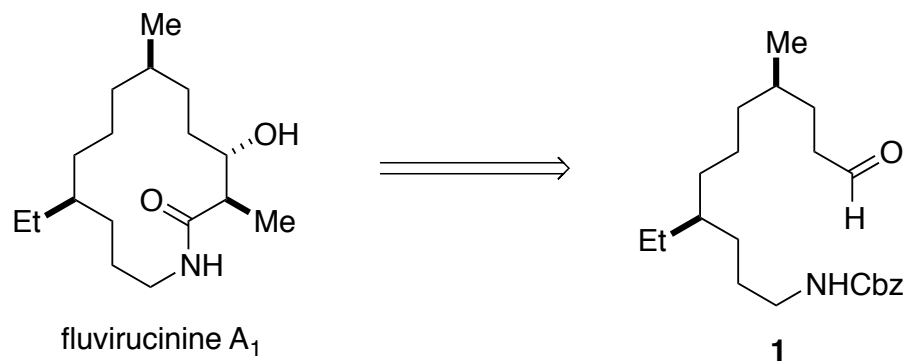
- Observed Enantioselectivity

Reactivity and Enantioselectivity Trends

Substrate	R	e.r.	Comments
	Et, n-Bu, etc.	> 89:11	
	Me, Cl, CN	> 91:9 (mostly)	e.r. > 95.5:4.5 (All indanes)
	N/A	87.5:12.5	
	Alkyl, ester, phosphonate, etc.	85:15 to 97.5:2.5	e.r. has dramatic dependence on substitution of electrophile and on Zn center

# Applications to Natural Product Synthesis

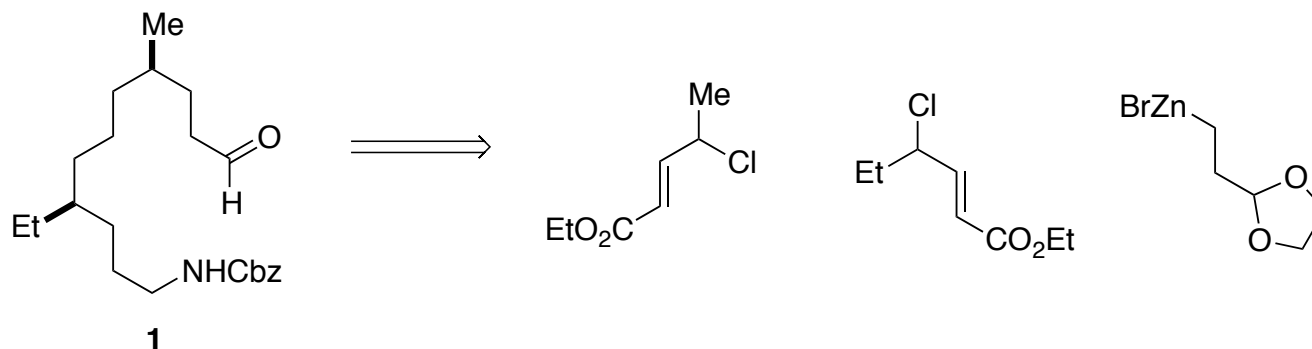
- Formal total synthesis of Fluvirucinine A<sub>1</sub>



Fu, G.C. et. al. *J. Am. Chem. Soc.* **2008**, *130*, 2756.

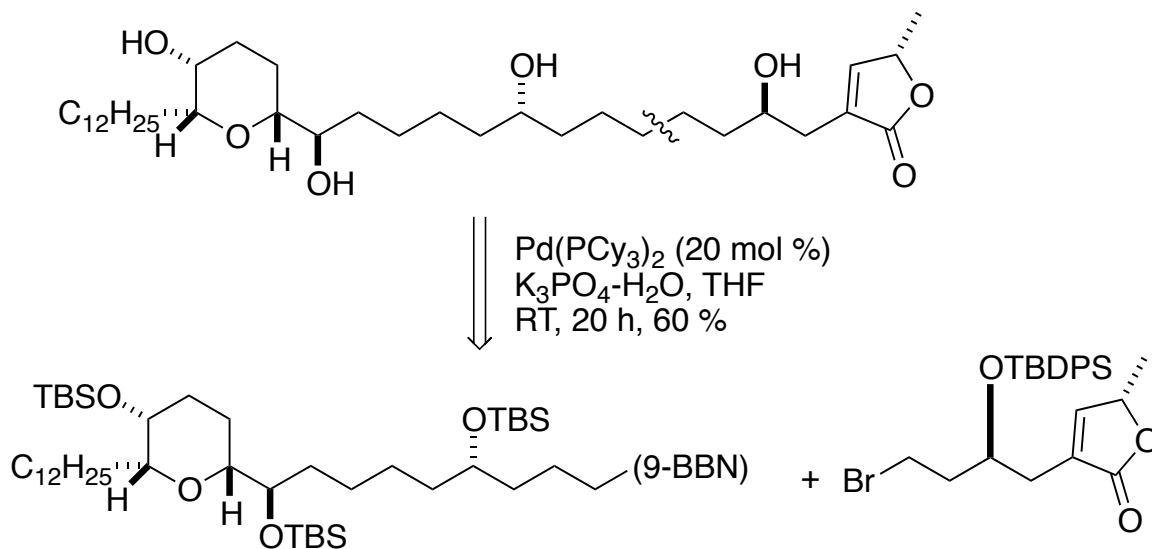
# Group Problem #2

- Devise synthetic steps to construct **1** from the three building blocks (you don't have to worry about controlling the configurations at the two stereocenters).



# Pyranicin

- An unexpected disconnection



Phillips, A.J. et. al. *Org. Lett.* **2008**, *10*, 4955.

# Conclusions

- Clearly, the potential of this methodology is tremendous
- However, there is still room for improvement
  - Further applications to Natural Product synthesis
  - Additional mechanistic studies
- A potential new frontier in Asymmetric Synthesis