

Recent Advances in Nickel Catalyzed Cross Coupling Reactions with Alkyl Halides

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Literature Seminar
January 31, 2008

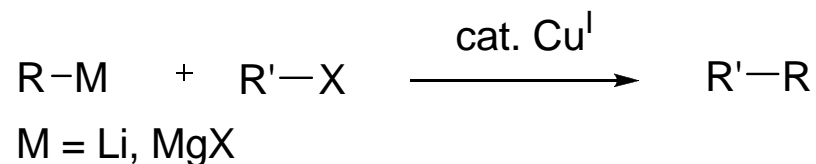
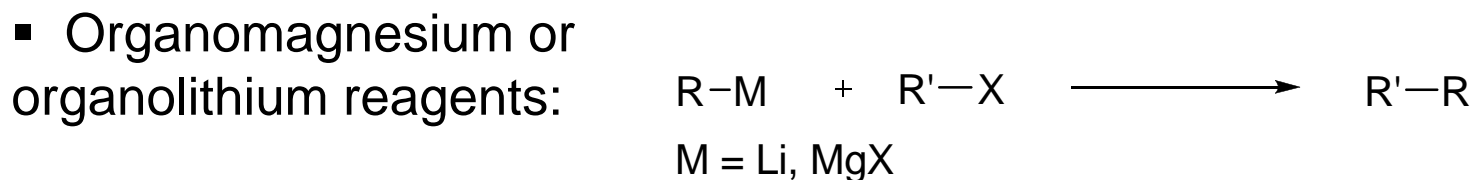
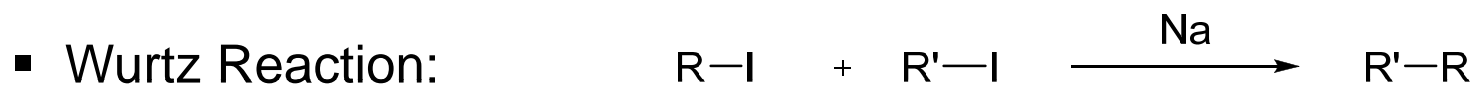
Transitions Metal Catalyzed Cross Coupling Reactions



	R-M	R'
Negishi	R-ZnX	aryl, alkenyl, alkynyl, acyl
Suzuki	R-BR ₂	alkyl, aryl, alkenyl
Stille	R-Sn(alkyl) ₃	aryl, alkenyl, acyl
Kumada	R-MgX or Li	alkyl, aryl, alkenyl
Hiyama	R-SiR ₃	alkyl, aryl, alkenyl

- Extensively used for aryl-aryl, aryl-alkenyl, alkenyl-alkenyl couplings
- High functional group compatibility
- Limited use of alkyl electrophiles

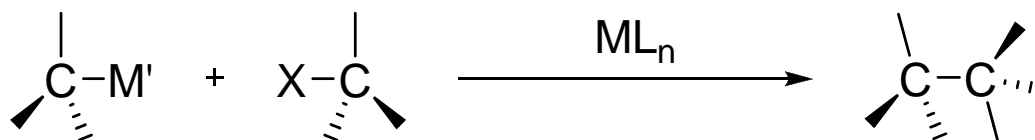
Cross Coupling Reactions between sp^3 Carbons



Transition Metal Catalysis for the Cross Coupling of sp^3 Carbons

“ The efficient formation of $C(sp^3)-C(sp^3)$ bonds from organic electrophiles and mild nucleophiles compatible with a wide range of functional groups represents one of the subjects remaining to be solved in transition metal catalyzed synthetic organometallic chemistry.”

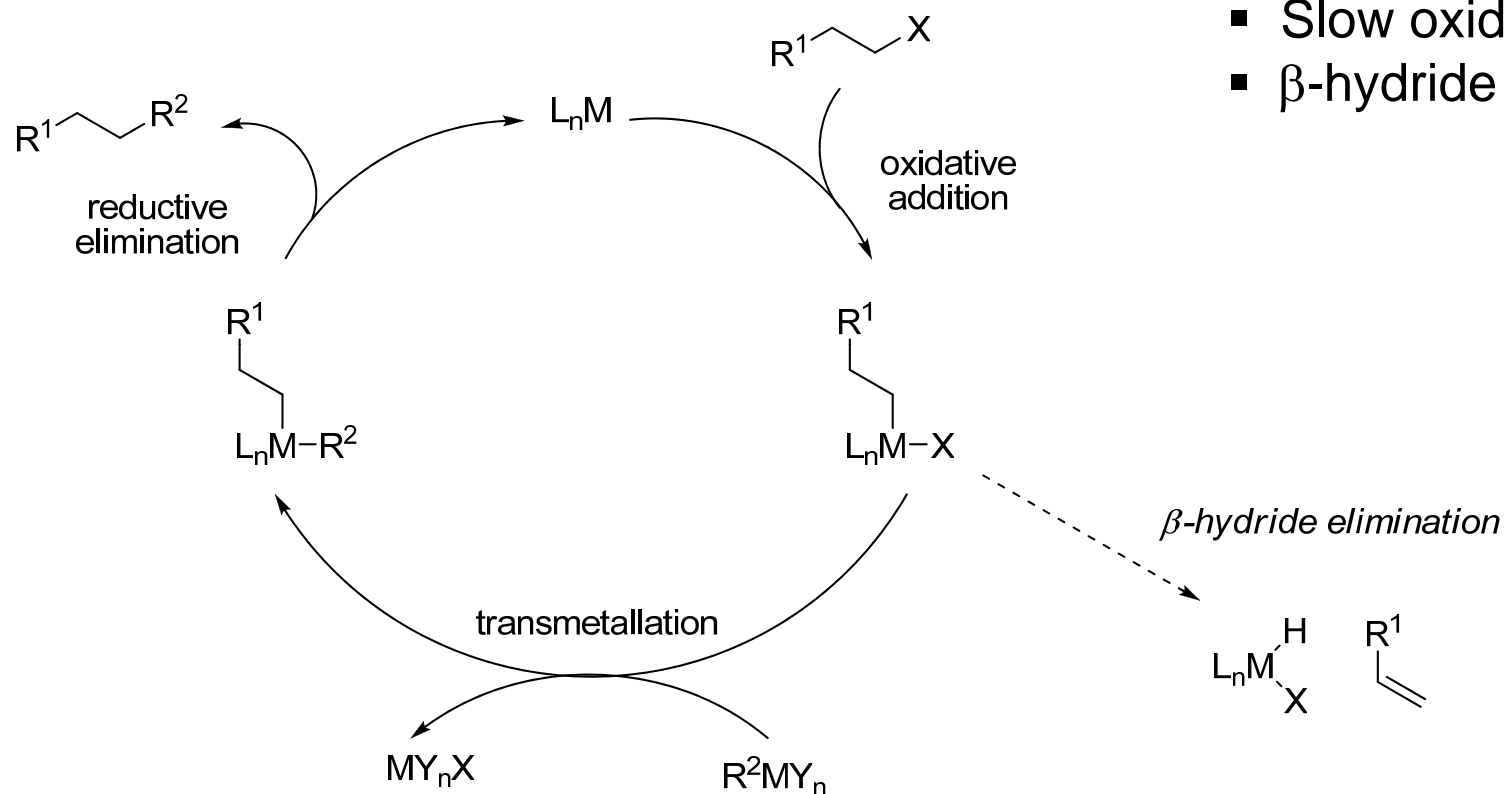
-Cardenas



X = halide, sulfonate; M' = Li, Mg, Zn, Al, Sn, B, Si; M = Ni, Pd, etc.

Mechanism of Transition Metal Catalyzed Cross Coupling Reactions

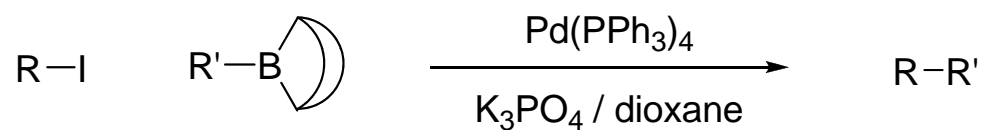
- Slow oxidative addition
- β -hydride elimination

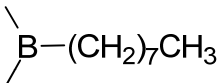
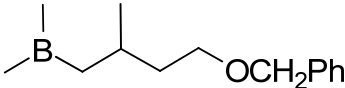
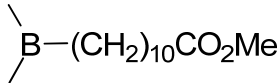
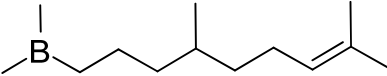
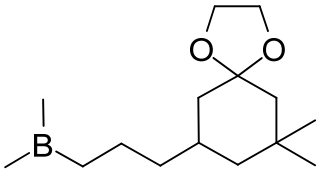


Outline

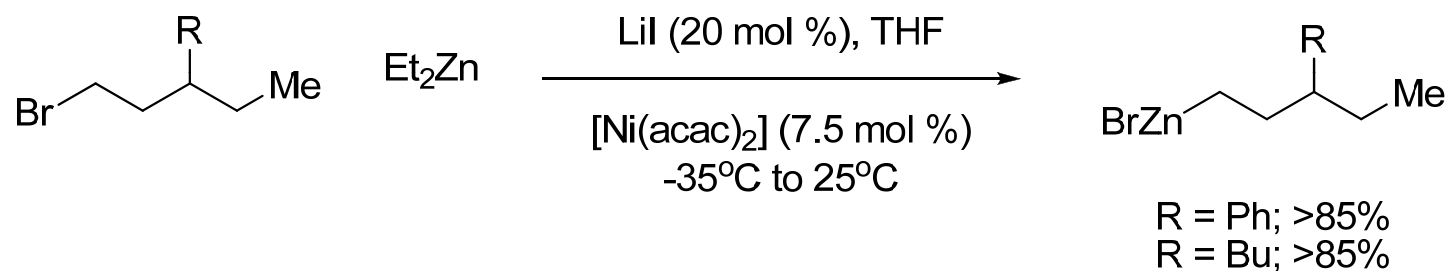
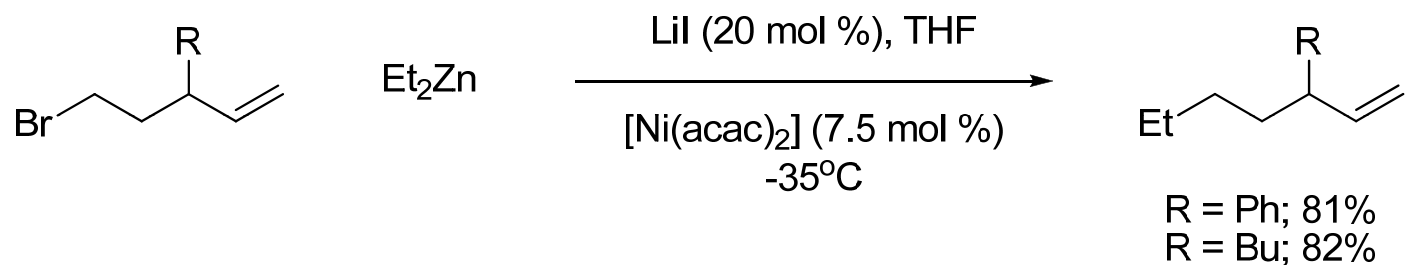
- Alkyl-alkyl/aryl cross couplings of alkyl halides
- Asymmetric cross coupling reactions
- Cascade reactions
- Conclusions

Pioneering Work by Suzuki

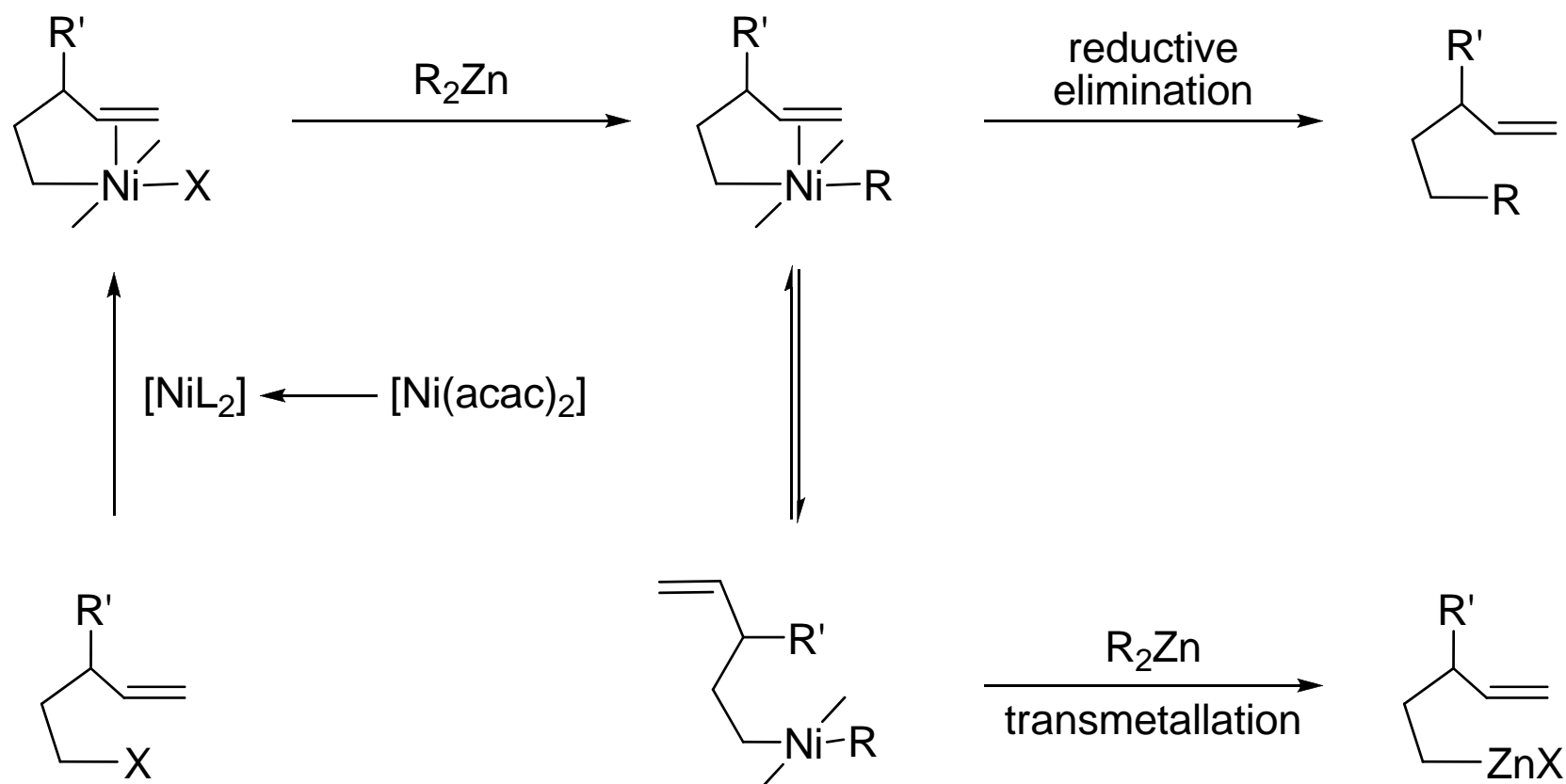


Entry	Halide	9-R-9-BBN	% Yield
1	CH ₃ (CH ₂) ₅ I		64
2	CH ₃ (CH ₂) ₅ I		58
3	CH ₃ (CH ₂) ₅ I		54
4	N≡C(CH ₂) ₃ I		61
5	MeO ₂ C(CH ₂) ₃ I		57

Knochel: Alkyl-Alkyl Negishi Couplings



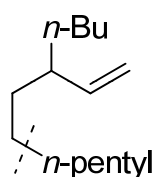
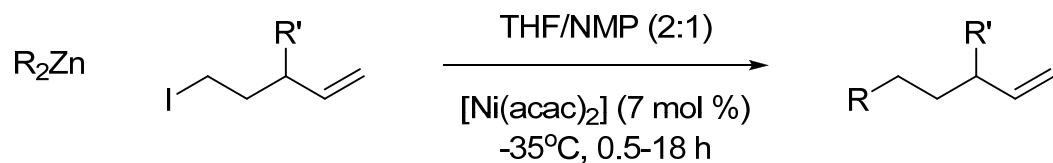
Proposed Mechanism of Ni-Catalyzed Alkyl-Alkyl Negishi Reactions



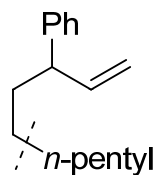
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Giovanninni, R.; Studemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544-3553.

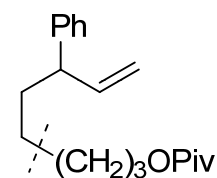
Substrate Scope for Alkyl-Alkyl Negishi Reactions



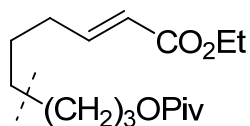
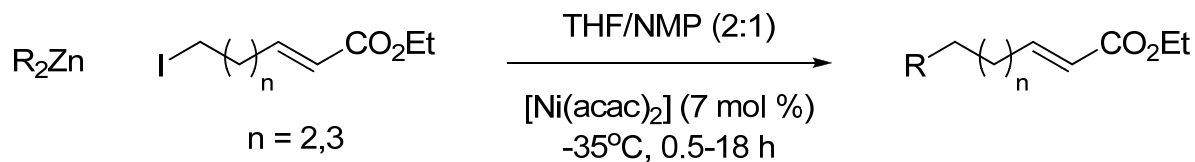
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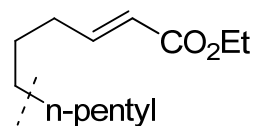
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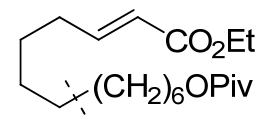
90%



79%



83%

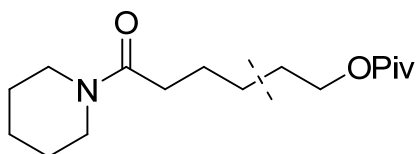
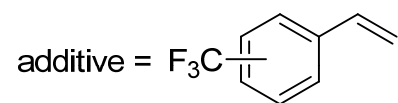
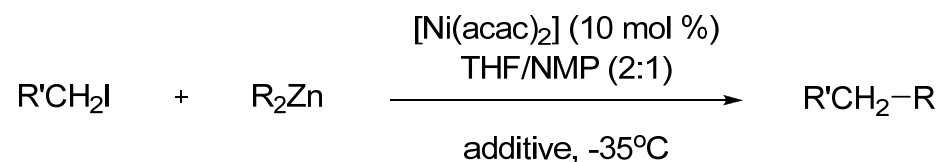


73%

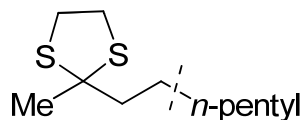
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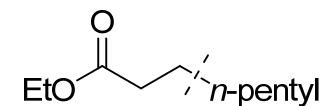
Extension of Knochel's Methodology



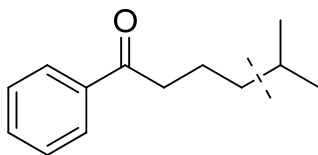
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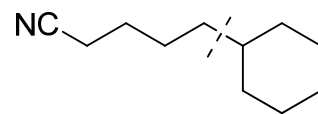
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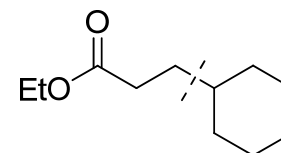
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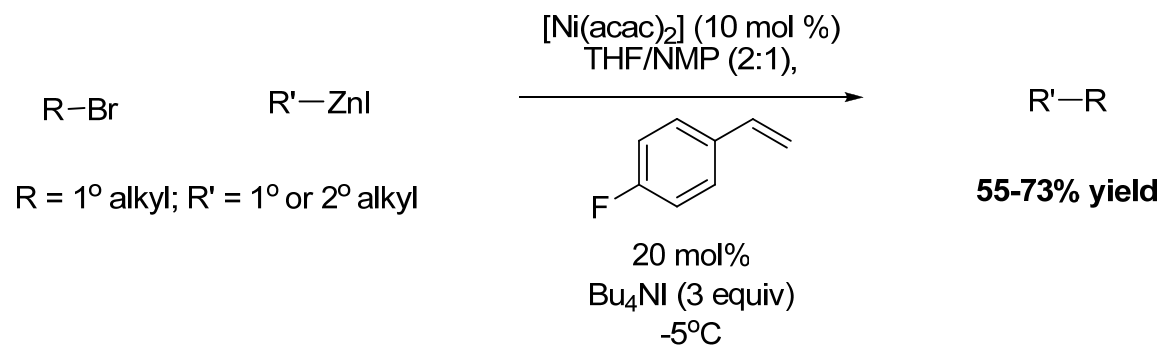
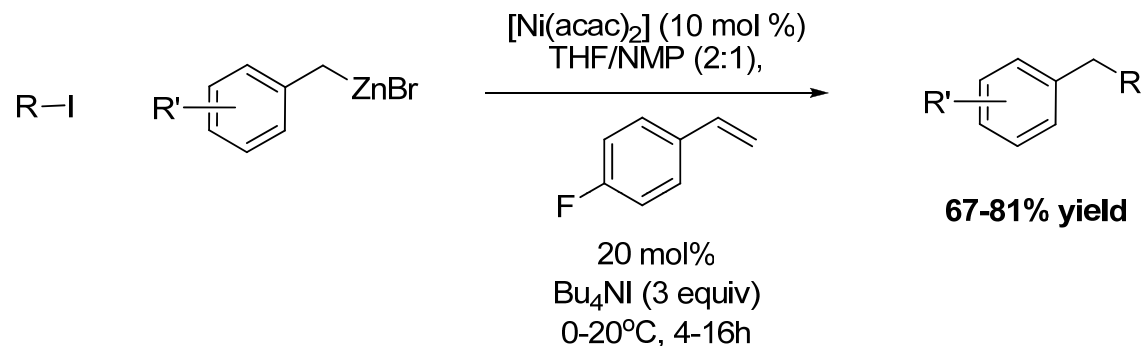
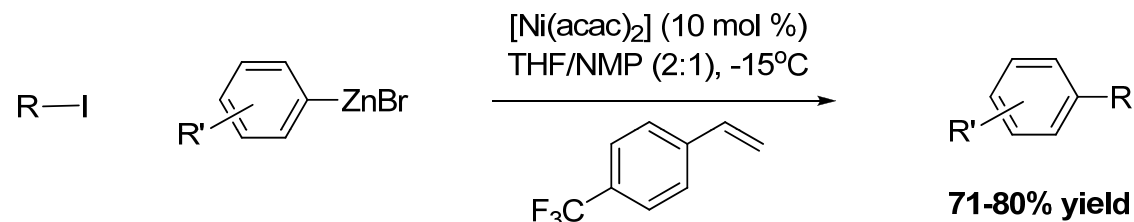


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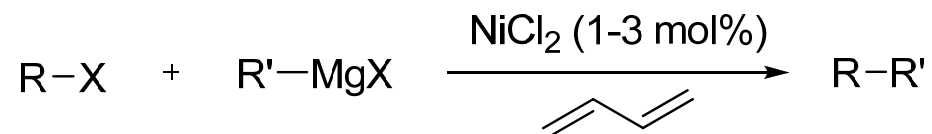
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Extension of Knochel's Methodology

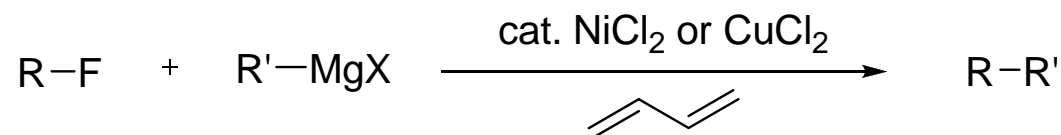


Kambe: Alkyl-Alkyl Kumada Coupling Reactions

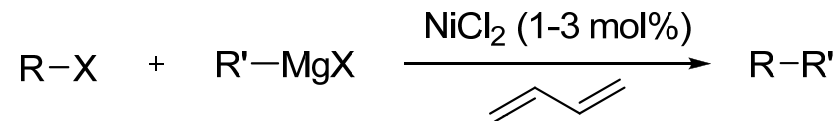
- Cross coupling of primary alkyl halides and grignard reagents



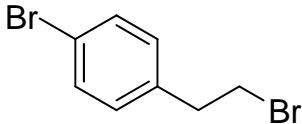
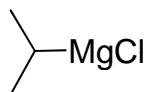
- Alkyl fluorides can also be used as coupling partners



Substrate Scope for Alkyl-Alkyl Kumada Reactions



R = alkyl; X = Cl, Br, OTs, F; R' = alkyl, aryl

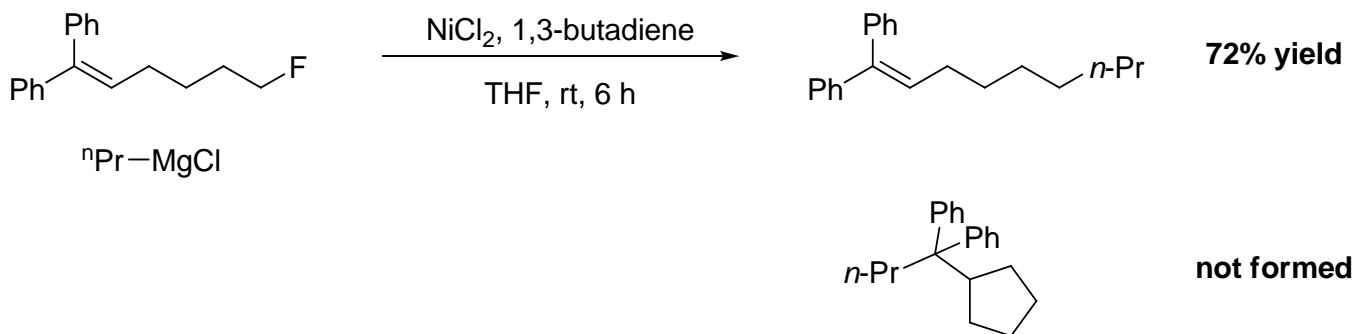
Entry	R-X	R'-MgX	1,3-butadiene (mol %)	% Yield
1	${}^n\text{C}_{10}\text{H}_{21}\text{Br}$	${}^n\text{Bu-MgCl}$	10	100
2		${}^n\text{Bu-MgCl}$	10	100
3	$\text{Ph-CH}_2\text{-CH}_2\text{-OTs}$	Et-MgCl	30	87
4	${}^n\text{Oct-Br}$		30	72
5	${}^n\text{Oct-Cl}$	${}^n\text{Bu-MgCl}$	50	96
6	${}^n\text{Oct-F}$	${}^n\text{Pr-MgCl}$	200	67

Mechanistic Studies

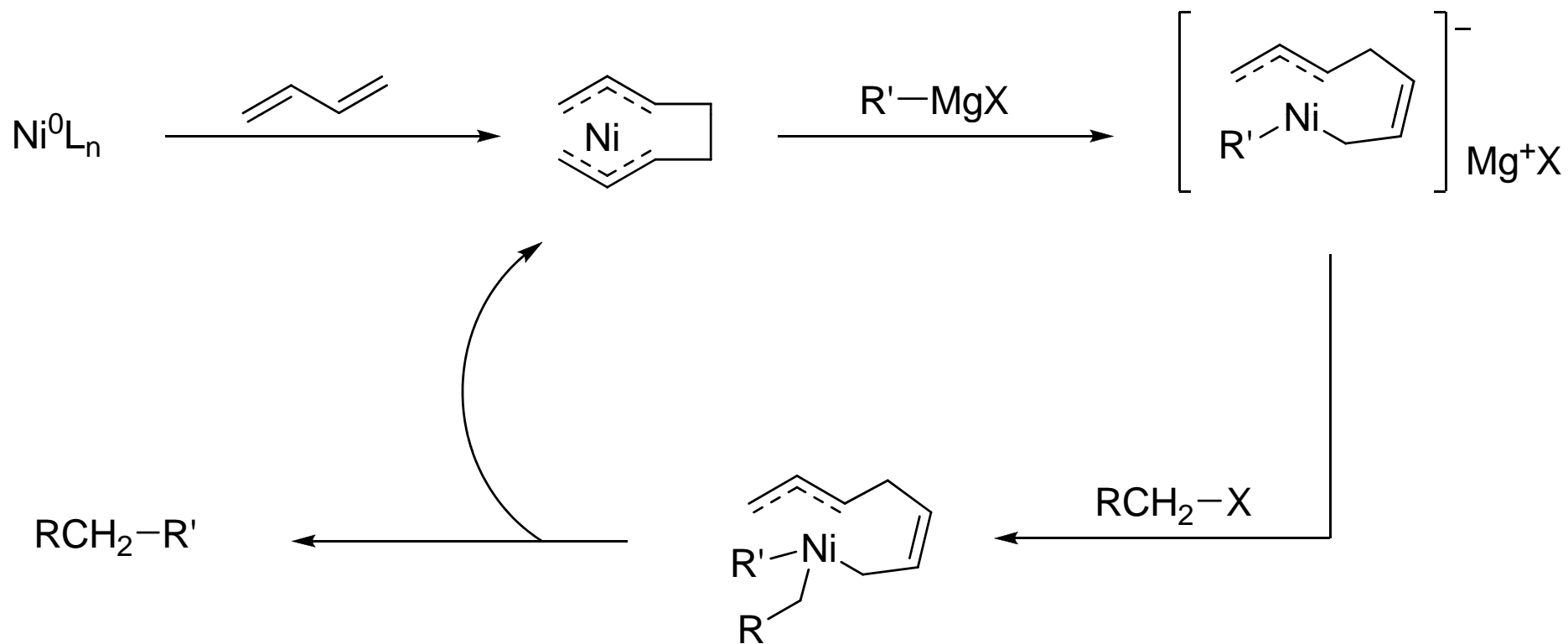
- Rate of reactivity: Br > F > Cl

				NiCl ₂	CuCl ₂
	<i>n</i> -C ₈ H ₁₇ -Cl	1.5 equiv		0%	0%
<i>n</i> -C ₅ H ₁₁ -MgBr 1.0 equiv	<i>n</i> -C ₉ H ₁₉ -F	1.5 equiv	NiCl ₂ or CuCl ₂ (3 mol %), 1,3-butadiene THF, rt, 30 min	8%	16%
	<i>n</i> -C ₁₀ H ₂₁ -Br	1.5 equiv		39%	40%

- Investigation of radical pathway

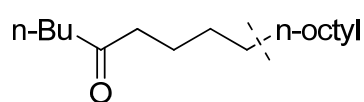
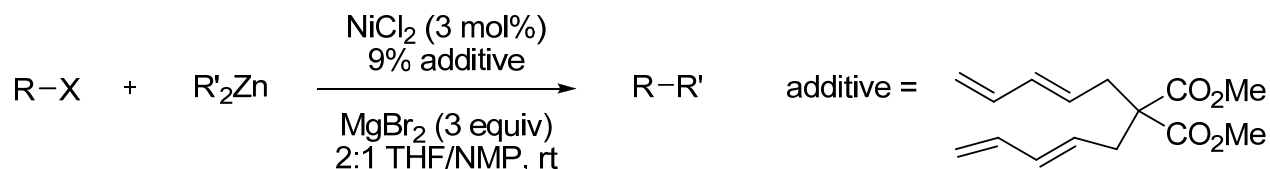


Proposed Mechanism of Ni-Catalyzed Alkyl-Alkyl Kumada Reactions

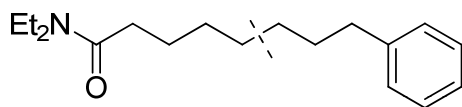


Extension of Kambe's Methodology

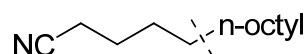
- Changing additive allows dialkyl zincs to be used in reaction



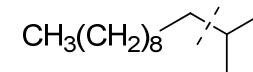
87%



91%

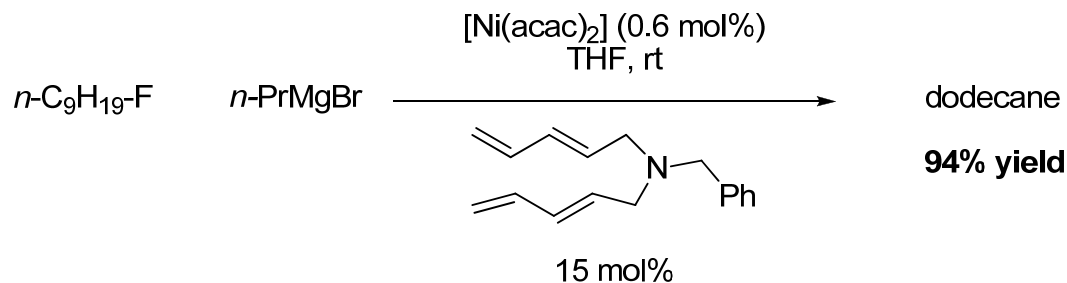


96%



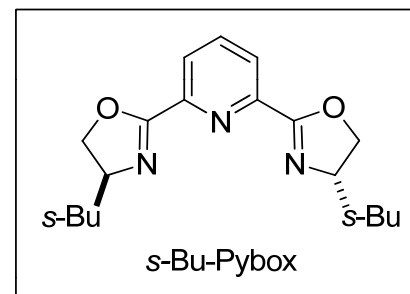
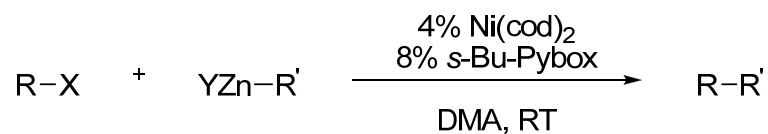
79%

- Higher yields with alkyl fluorides



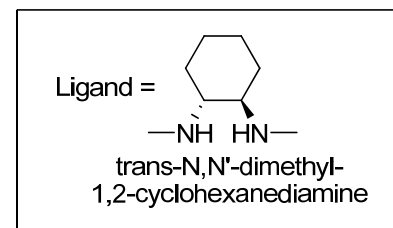
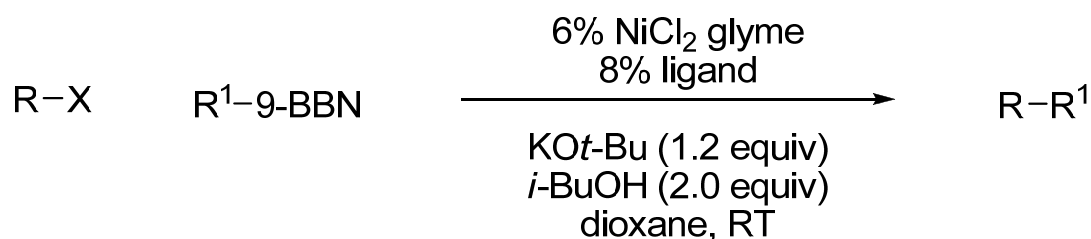
with NiCl_2 , n-octyl-F, **67% yield**

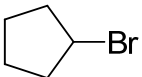
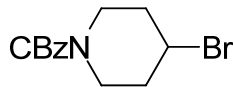
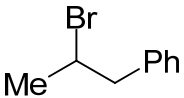
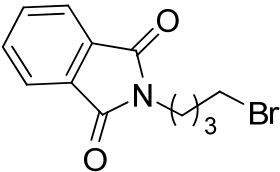
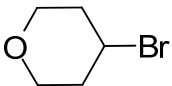
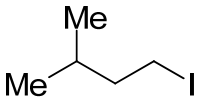
Fu: Negishi Cross Couplings with Secondary Alkyl Halides



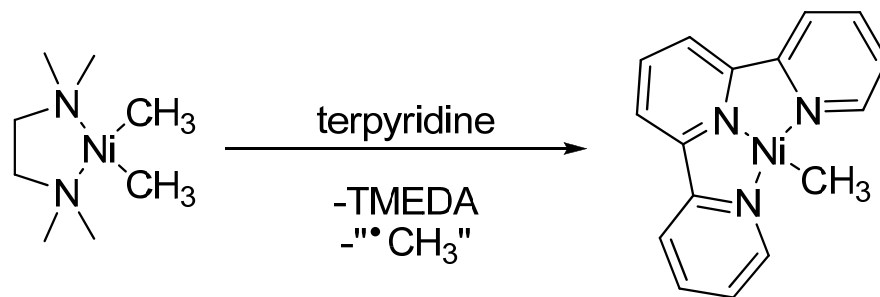
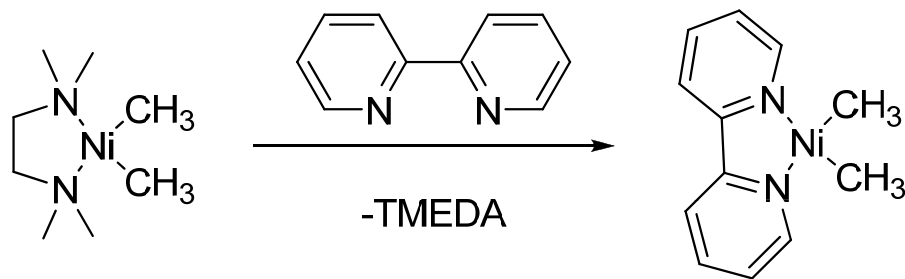
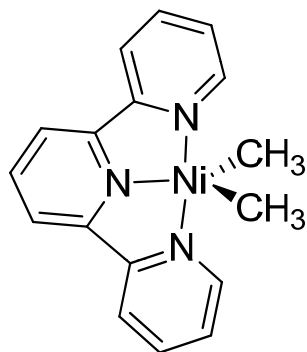
entry	R-X	YZn-R'	% yield
1			66
2			62
3			62
4			74
5			65

Fu: Suzuki Cross Couplings with Secondary Alkyl Halides

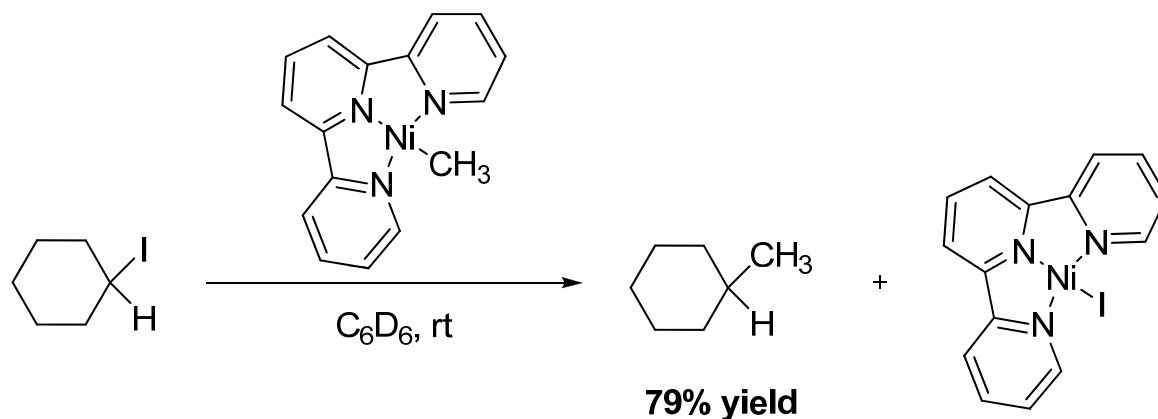


entry	R-X	R ¹ -9-BBN	% yield	entry	R-X	R ¹ -9-BBN	% yield
1		Ph-CH ₂ -CH ₂ -CH ₂ -9-BBN	77	4		MeO-C(=O)-CH ₂ -C(Me) ₂ -CH ₂ -9-BBN	64
2		Ph-CH ₂ -CH ₂ -CH ₂ -9-BBN	82	5		Ph-CH ₂ -CH ₂ -CH ₂ -9-BBN	77
3		TBSO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -9-BBN	87	6		TBSO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -9-BBN	94

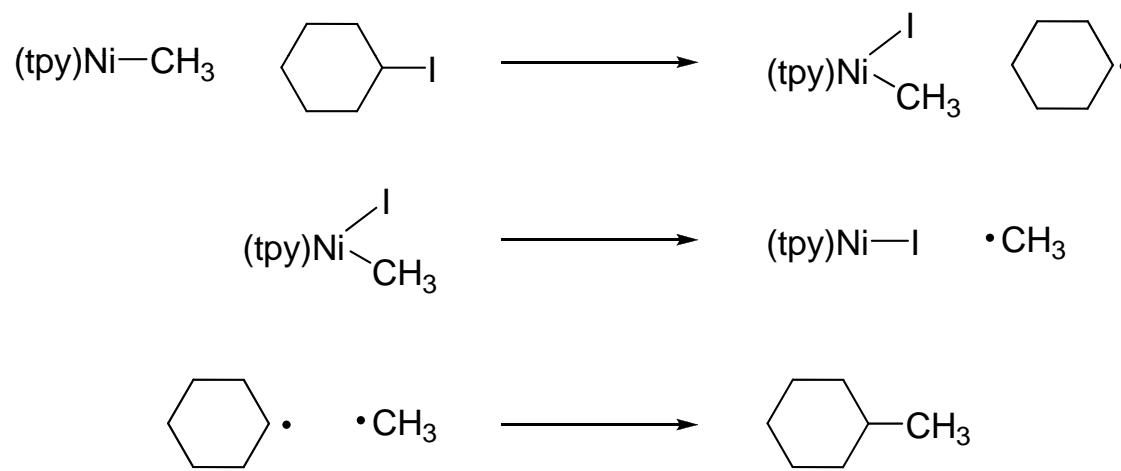
Vicic: Mechanistic Studies on Alkyl-Alkyl Cross Coupling Reactions



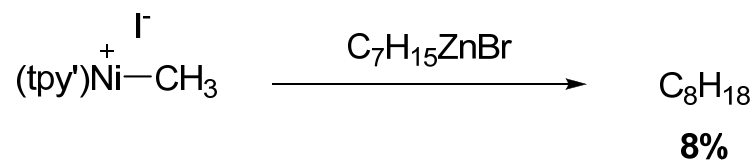
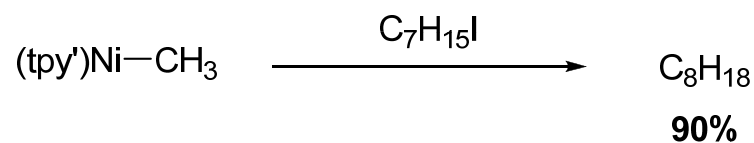
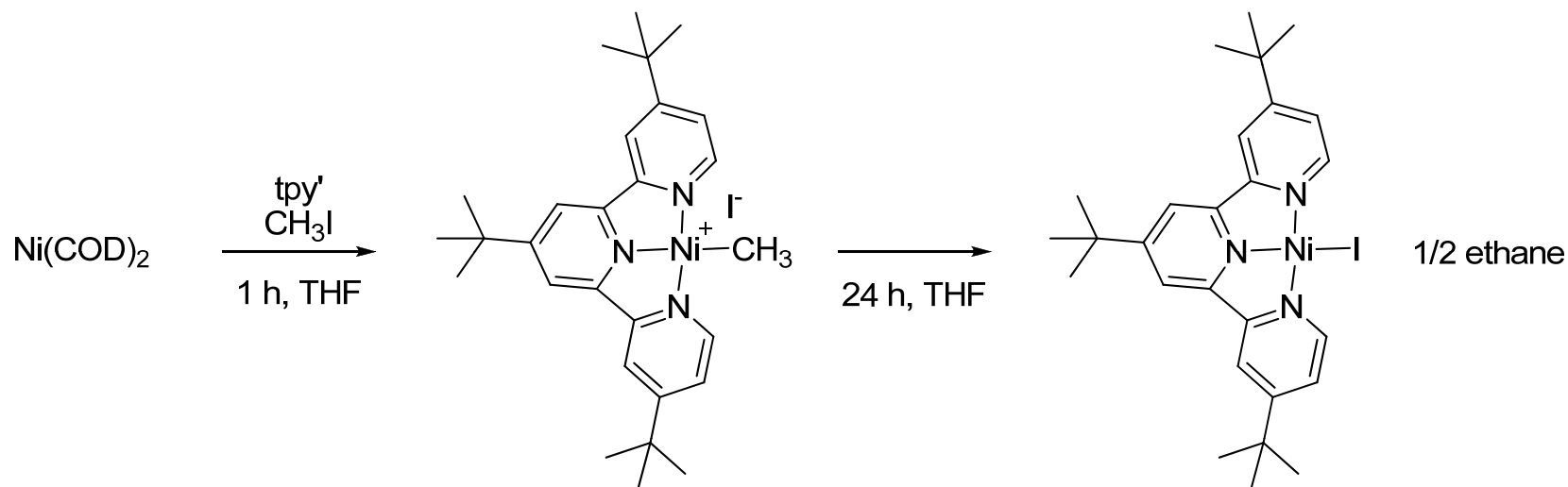
Mechanistic Studies on Alkyl-Alkyl Cross Coupling Reactions



- Proposed radical mechanism:



Mechanistic Studies on Alkyl-Alkyl Cross Coupling Reactions

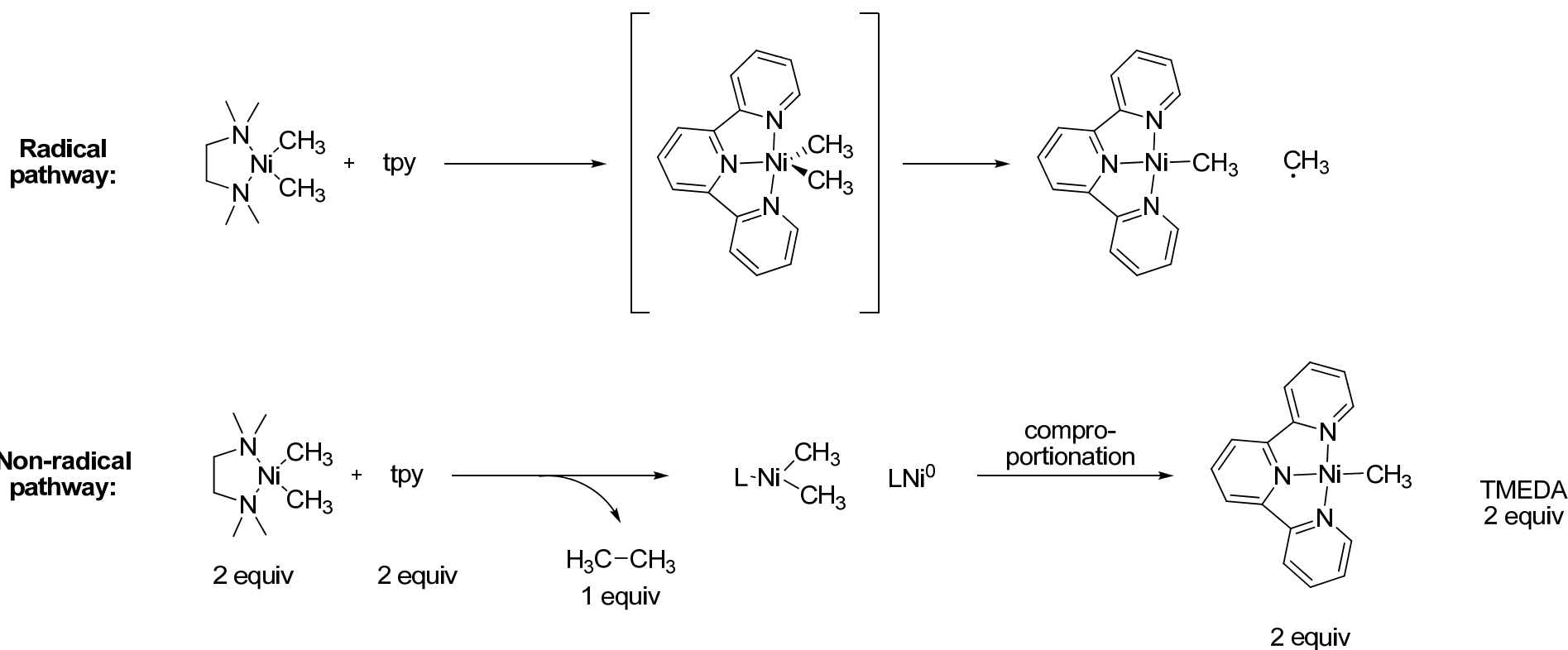


Jones, G. D. et. al. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A.; *Chem. Commun.* **2005**, 4211-4213.

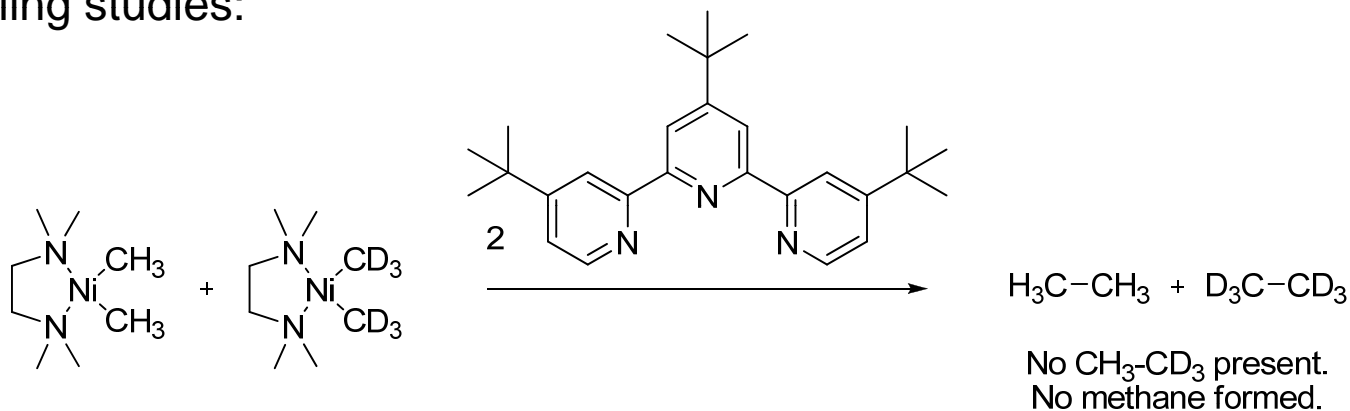
Mechanistic Studies on Alkyl-Alkyl Cross Coupling Reactions

- Investigation of (tpy)Ni-CH₃ formation:

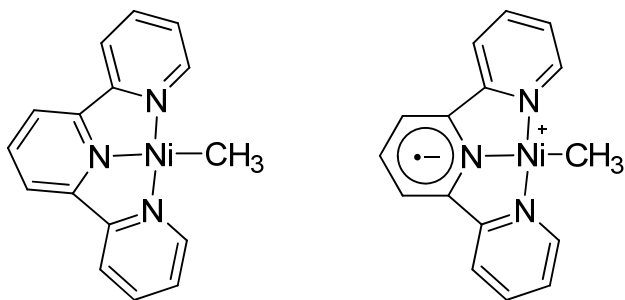


Mechanistic Studies on Alkyl-Alkyl Cross Coupling Reactions

- Labeling studies:



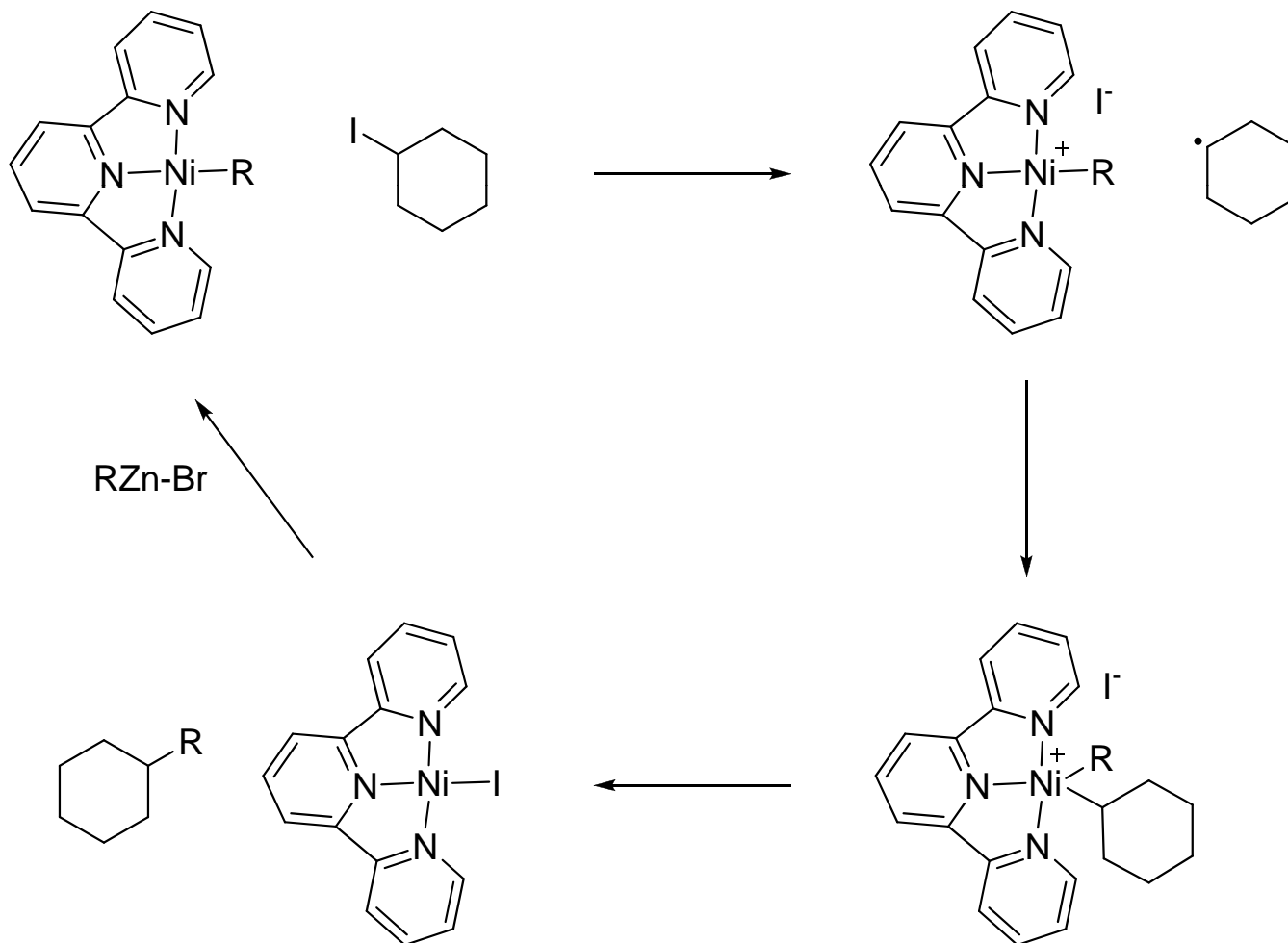
- Organic based radical by EPR and DFT studies



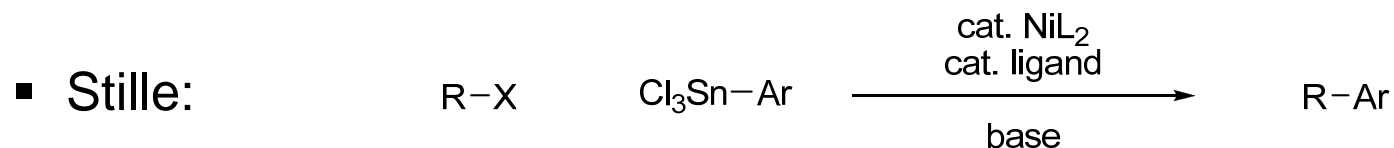
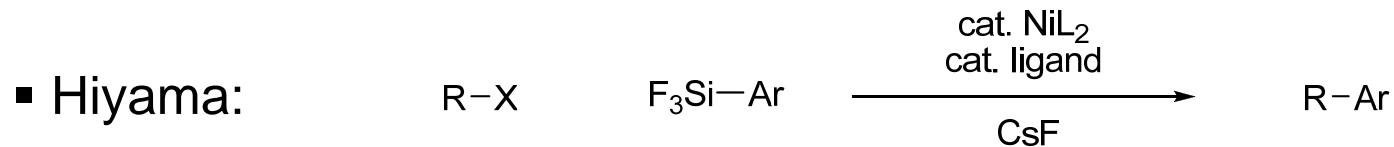
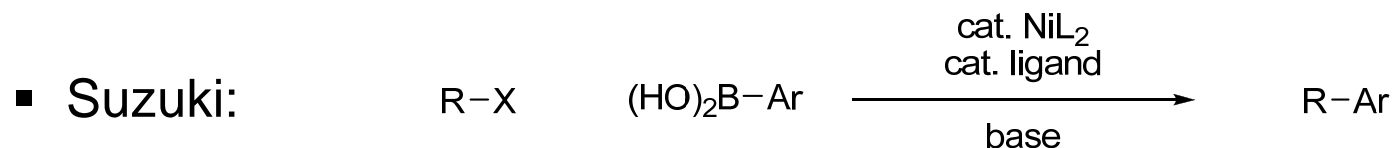
Jones, G. D. et. al. *J. Am. Chem. Soc.* **2006**, 128, 13175-13183.

Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A.; *Chem. Commun.* **2005**, 4211-4213.

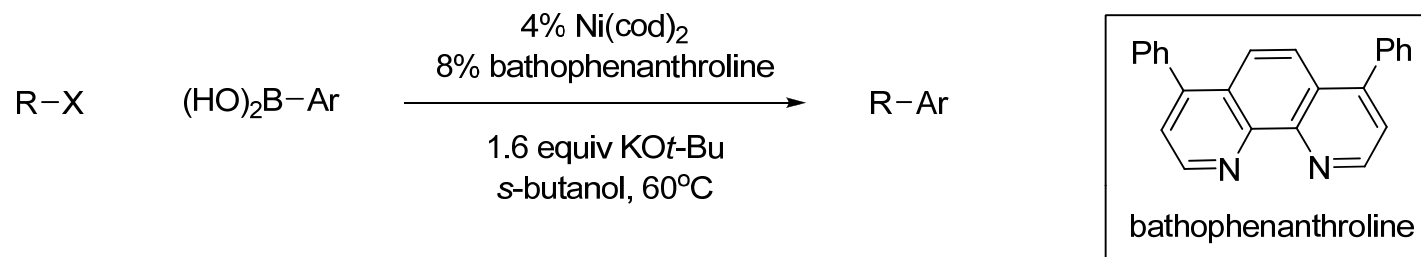
Revised Mechanism for Ni-Catalyzed Alkyl-Alkyl Cross Coupling Reactions

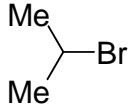
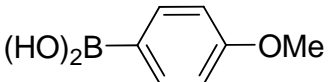
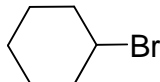
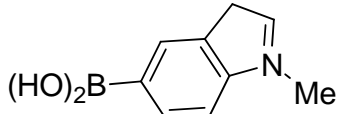
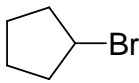
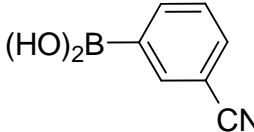
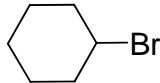
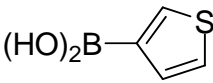
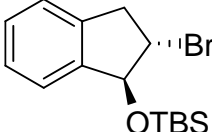
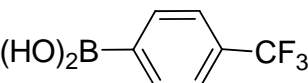
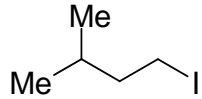
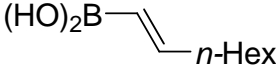


Fu: Ni-catalyzed Alkyl-Aryl Cross Coupling Reactions with Secondary Alkyl Halides

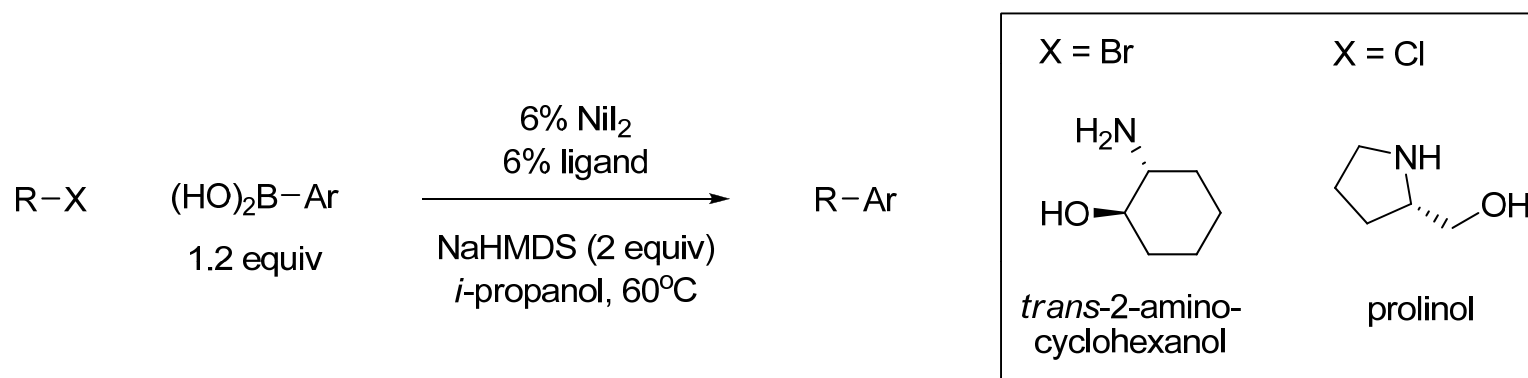


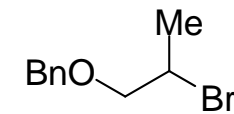
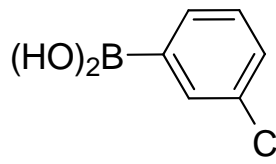
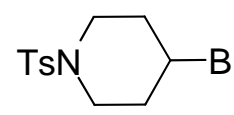
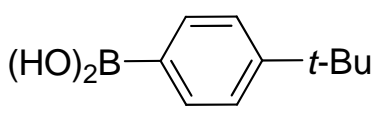
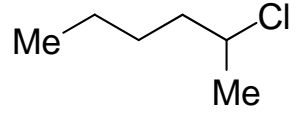
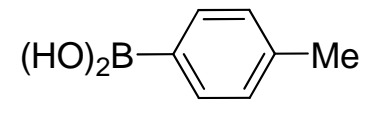
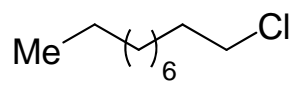
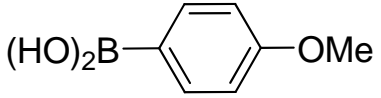
Suzuki Cross Couplings of Unactivated Secondary Alkyl Halides



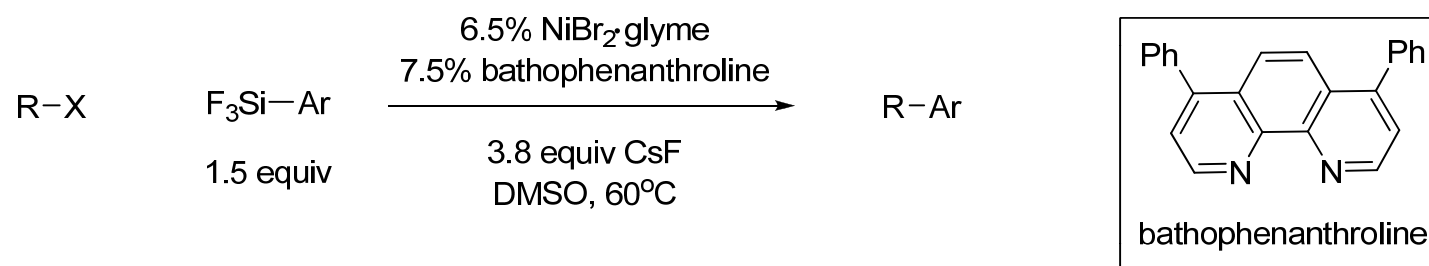
entry	R-X	(HO) ₂ B-Ar	% yield	entry	R-X	(HO) ₂ B-Ar	% yield
1			68	4			67
2			44	5			63
3			63	6			63

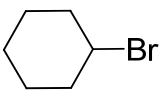
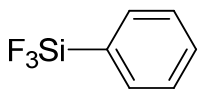
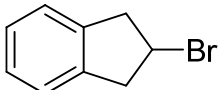
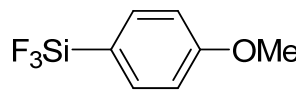
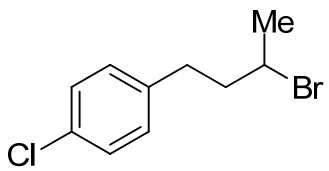
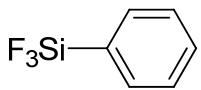
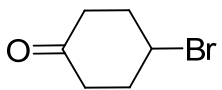
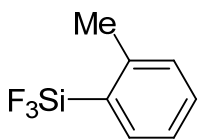
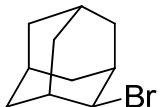
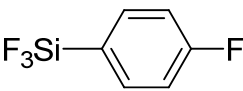
Suzuki Cross Couplings of Unactivated Secondary Alkyl Halides Revisited



entry	R-X	(HO) ₂ B-Ar	% yield
1			85
2			66
3			74
4			82

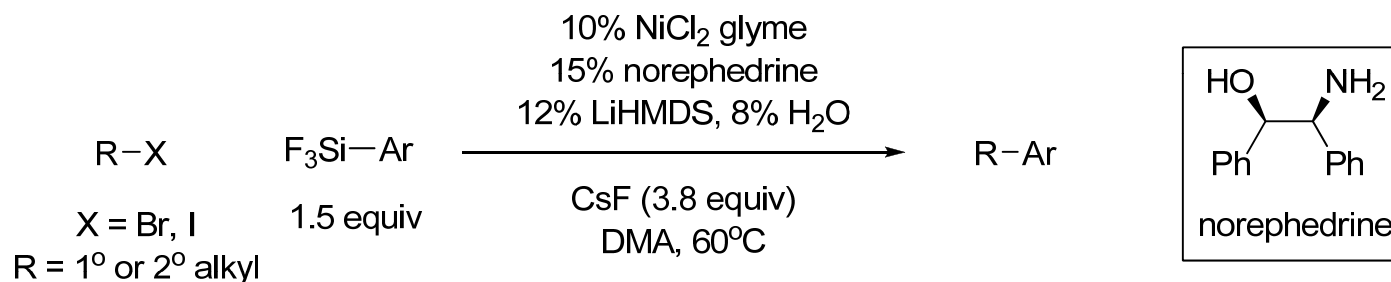
Hiyama Cross Couplings of Unactivated Secondary Alkyl Halides



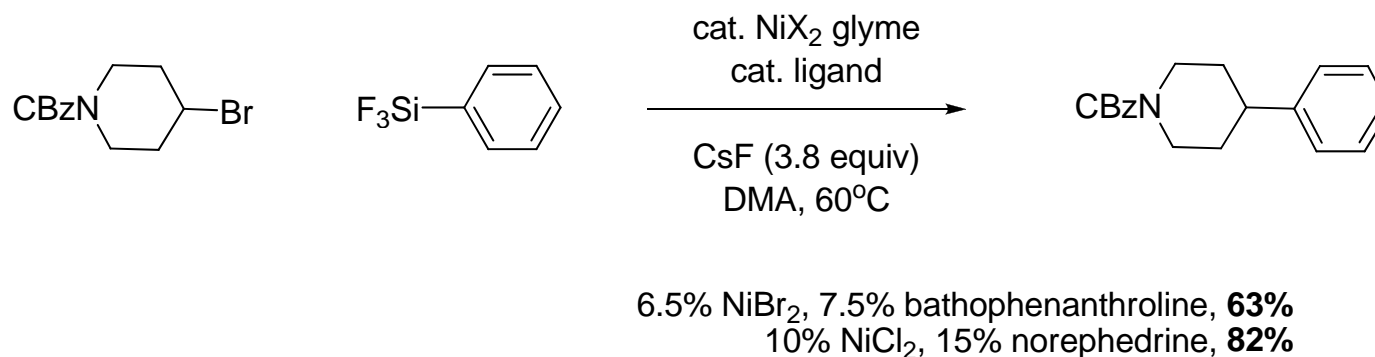
entry	R-X	F ₃ Si-Ar	yield
1			80
2			71
3			72
4			82
5			68

Hiyama Cross Couplings of Unactivated Secondary Alkyl Halides Revisited

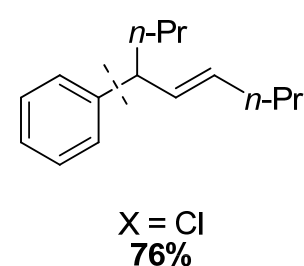
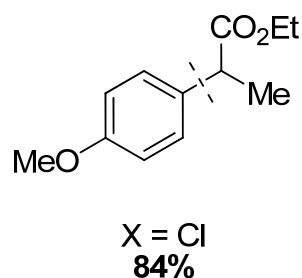
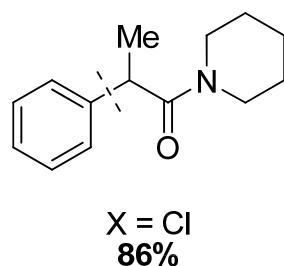
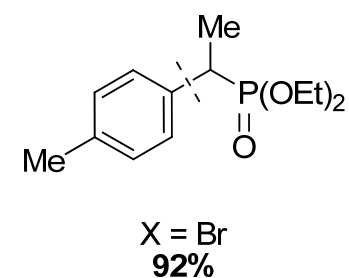
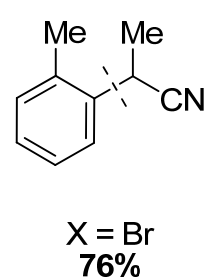
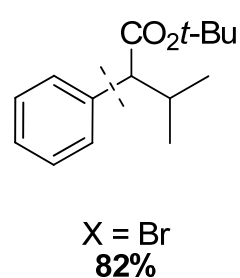
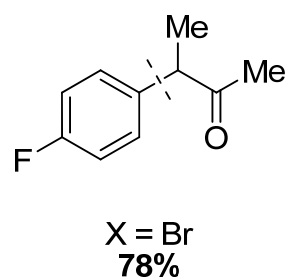
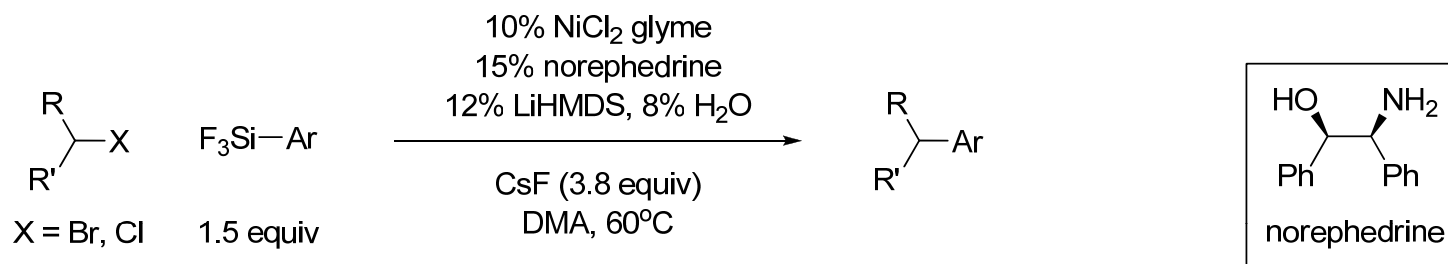
- Potential for asymmetric Hiyama reactions



- Higher yields

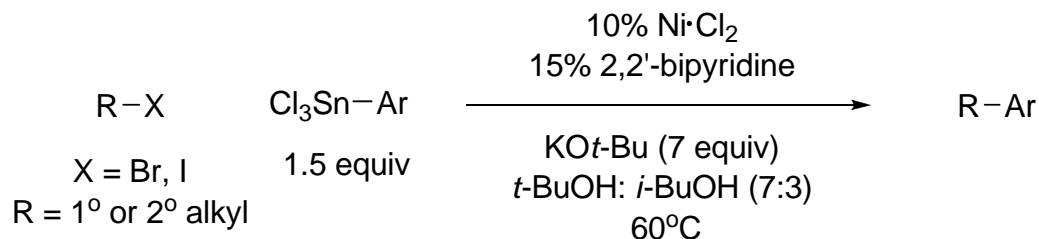


Substrate Scope for Hiyama Cross Couplings of Secondary Alkyl Halides

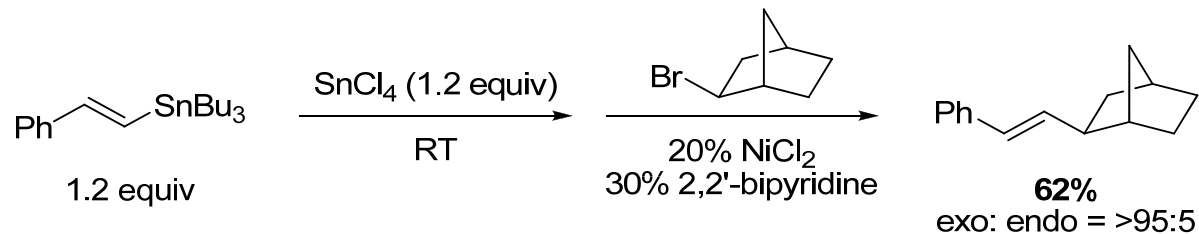
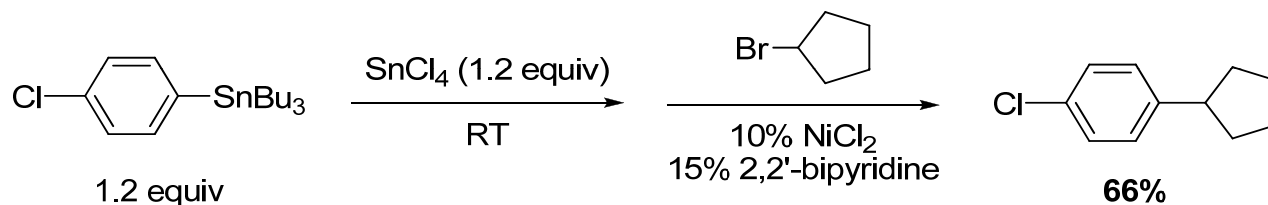


Stille Cross Couplings with Unactivated Secondary Alkyl Halides

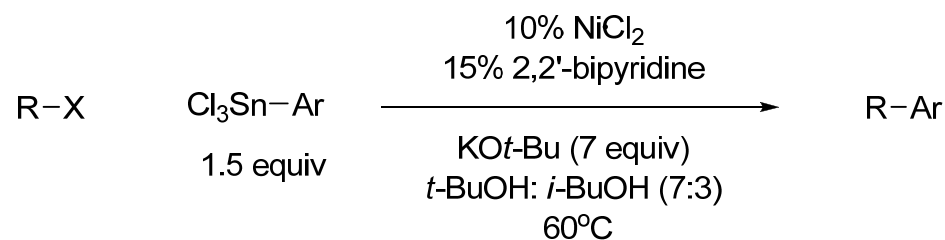
- Uses monoorganotin reagents ($R-SnX_3$)

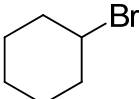
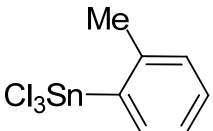
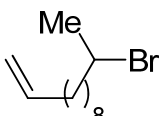
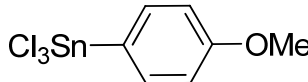
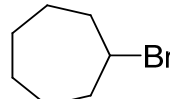
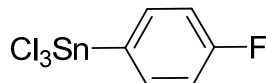
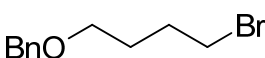
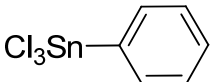
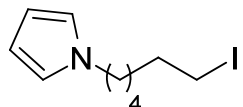
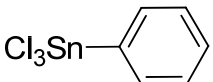


- Can convert readily available triorganotin compounds into trichlorotin reagents



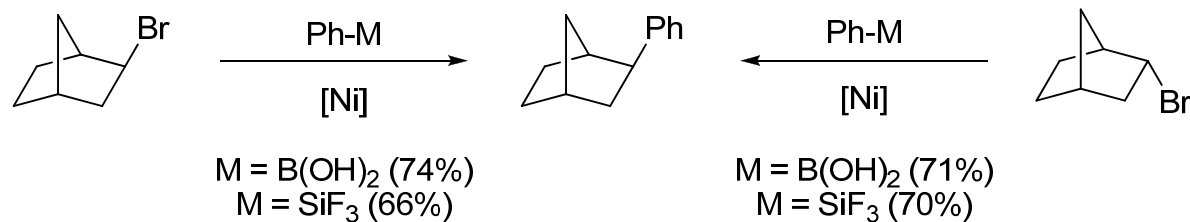
Substrate Scope of Stille Cross Couplings with Unactivated Secondary Alkyl Halides



entry	R-X	Cl ₃ Sn-Ar	% yield
1			47
2			68
3			67
4			61
5			62

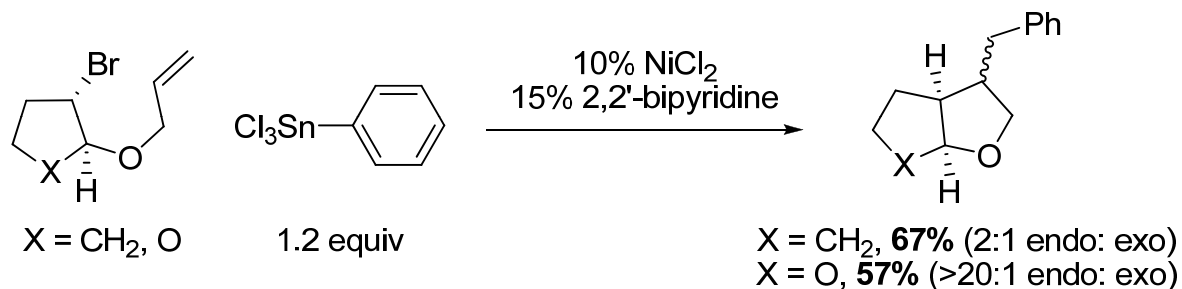
Mechanistic Studies on Alkyl-Aryl Cross Coupling Reactions

Hiyama and Suzuki:



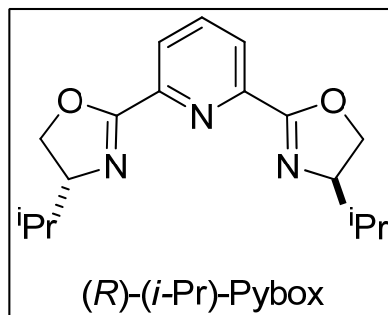
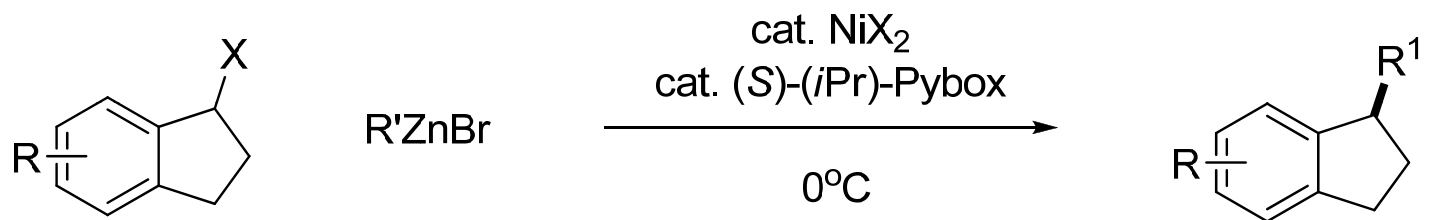
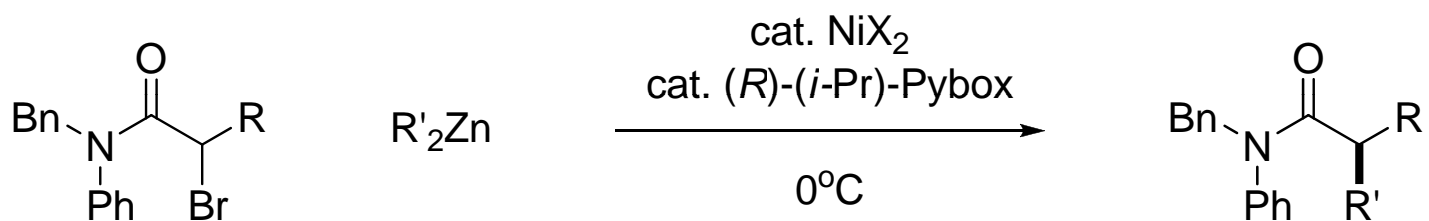
- *Exo* product formed exclusively

Stille:



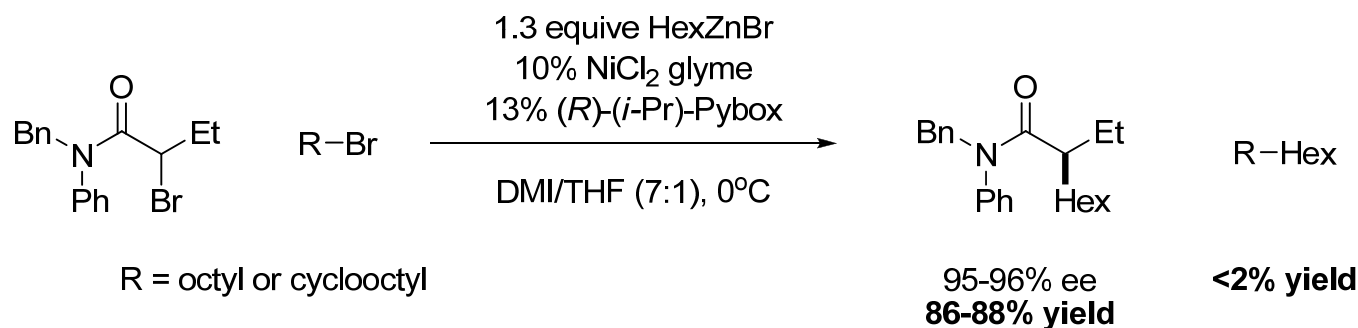
- Diastereoselectivity independent of ligand
- Same diastereomeric ratios observed in radical cyclizations

Asymmetric Examples of Cross Couplings with Secondary Alkyl Halides

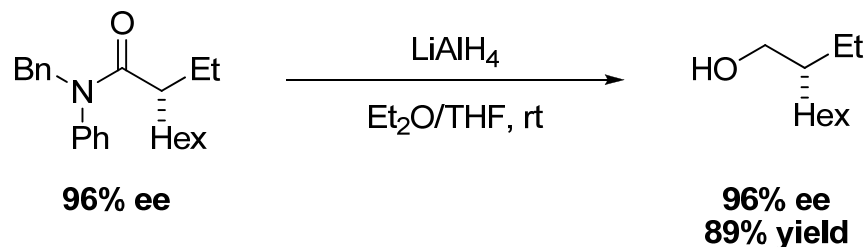


Cross Couplings of Secondary α -Bromo Amides

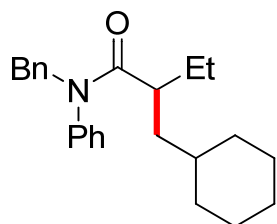
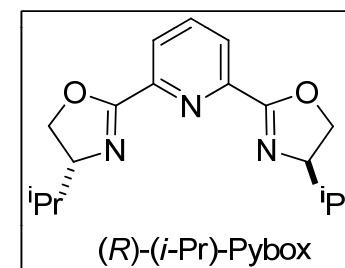
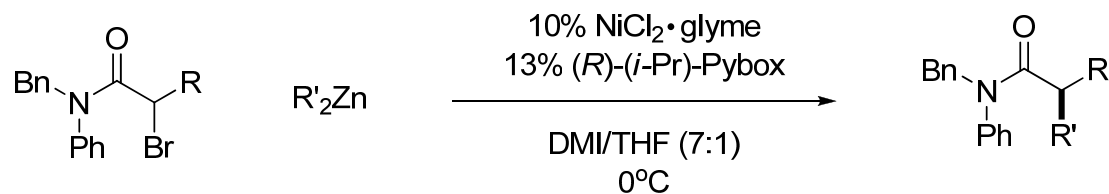
- Racemic starting material
- Selective for coupling of α -bromo amide in the presence of other unactivated halides



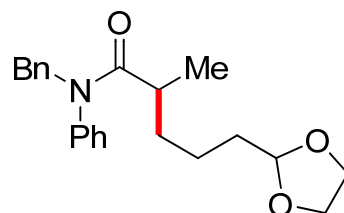
- Amide is easily converted to other useful functional groups:



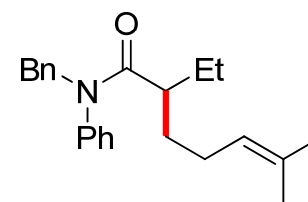
Substrate Scope for Cross Couplings of Secondary α -Bromo Amides



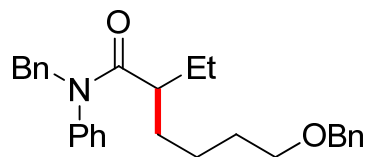
56% yield
92% ee



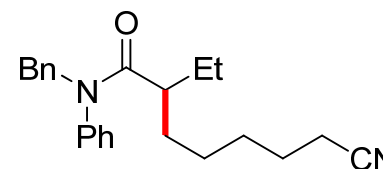
60% yield
>98% ee



78% yield
95% ee



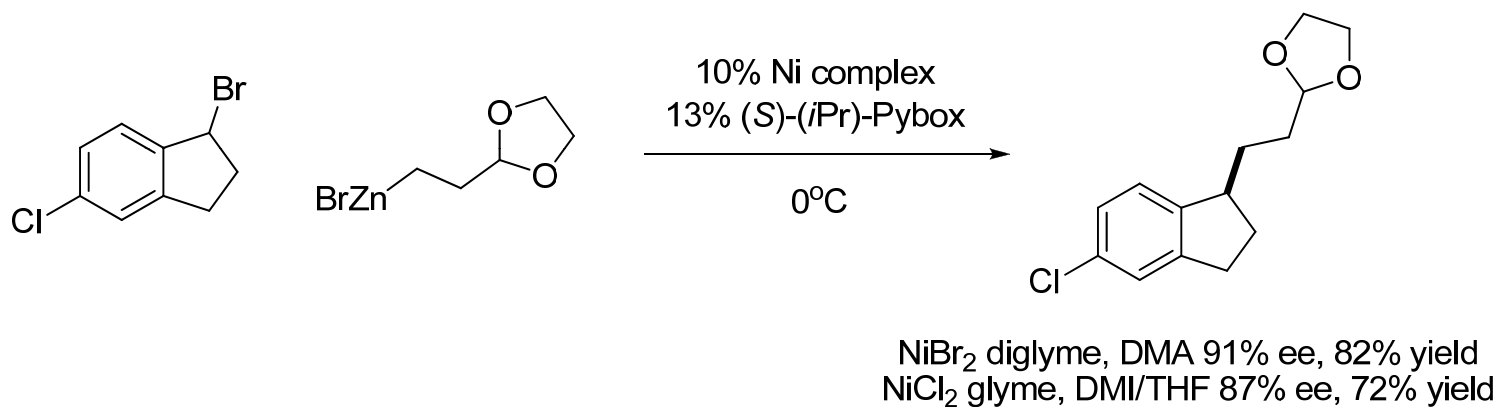
77% yield
96% ee



70% yield
93% ee

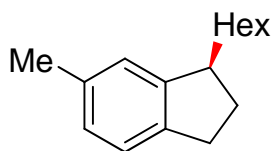
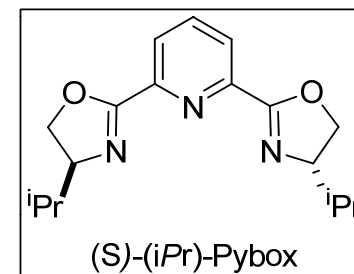
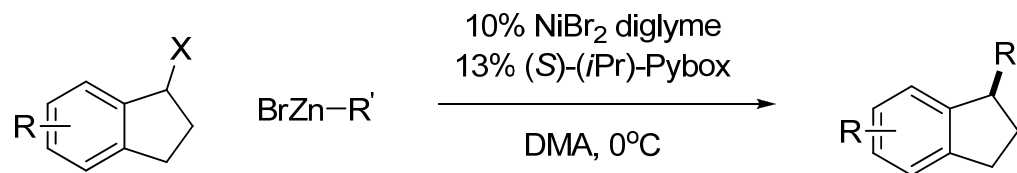
Cross Coupling of Secondary Benzylic Halides

- Racemic starting material
- Selective for benzylic halide in the presence of an aryl halide

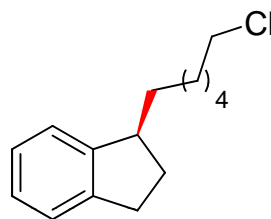


- Chiral indane products are useful intermediates in total synthesis

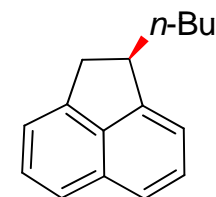
Substrate Scope for Cross Couplings of Secondary Benzylic Halides



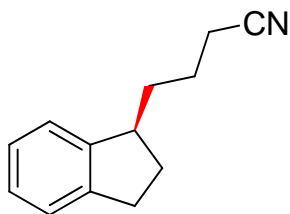
89% yield
96% ee



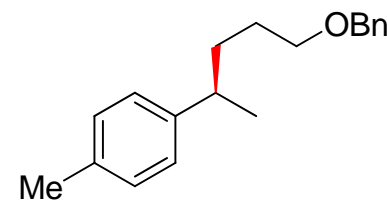
69% yield
94% ee



72% yield
98% ee

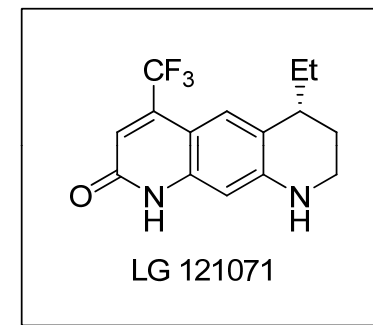


X = Br, **64% yield**, 91% ee
X = Cl, **56% yield**, 91% ee

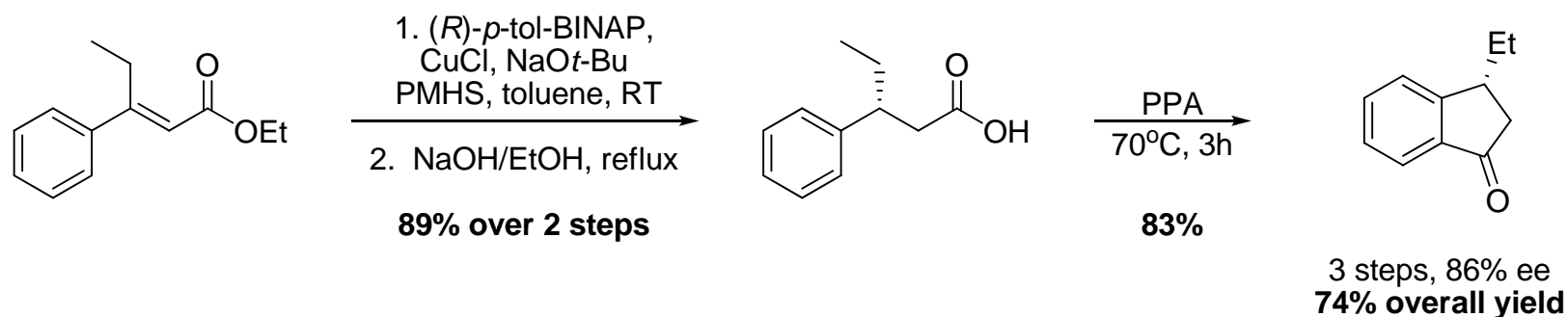


63% yield
75% ee

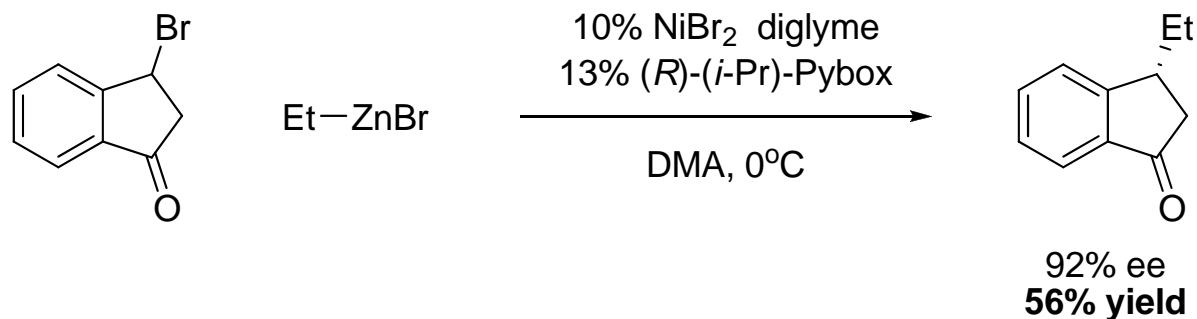
Application to Total Synthesis



- (*R*)-3-ethyl indanone was used as an intermediate in the synthesis of LG 121071.

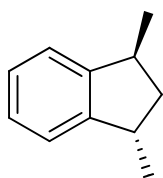
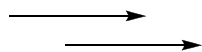
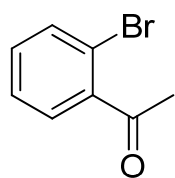


- Can be prepared via asymmetric cross coupling reactions in higher enantiomeric excess.

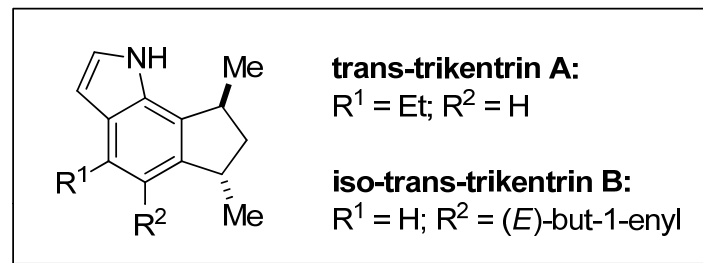


Application to Total Synthesis

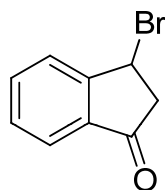
- Racemic *trans*-1,3-dimethyl indane was used as an intermediate in total synthesis of *trans*-trikentrin A and *iso-trans*-trikentrin B.



3 steps, **24% overall yield**
>9:1 *trans:cis*

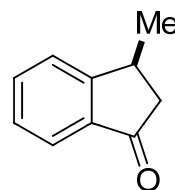


- Can be prepared enantioselectively using asymmetric cross coupling reactions.



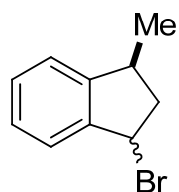
MeZnI
1.6 equiv

10% NiBr₂ diglyme
13% (*S*)-(*i*Pr)-Pybox
DMA, -15°C



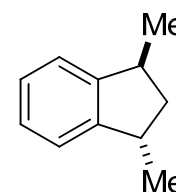
1. NaBH₄
2. PBr₃
92% over 2 steps

90% ee; 67% yield



MeZnI
1.6 equiv

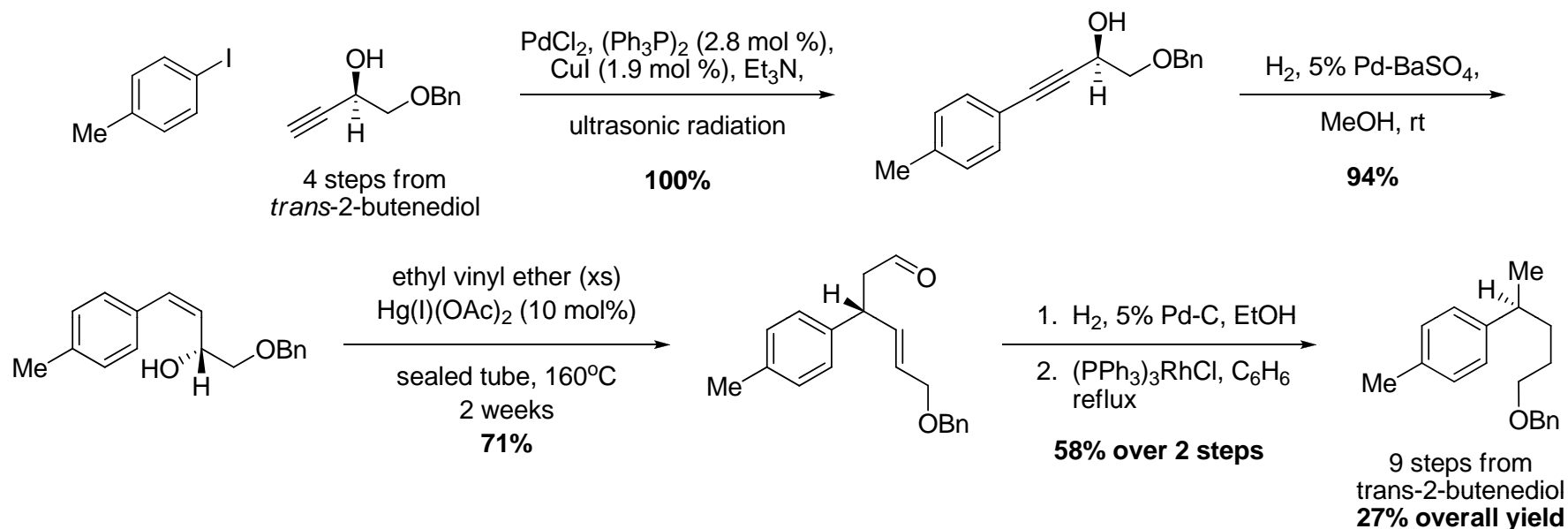
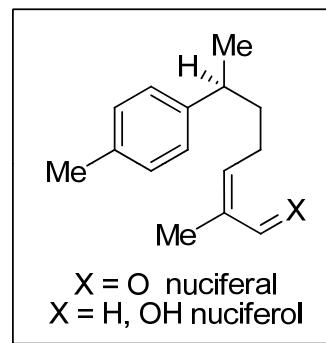
10% NiBr₂ diglyme
13% (*S*)-(*i*Pr)-Pybox
DMA, -15°C



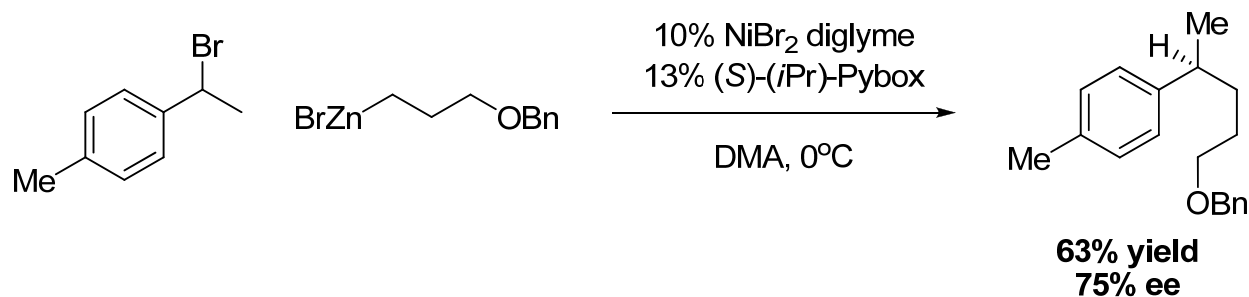
94% ee; 85% yield
>30:1 *trans:cis*

Application to Total Synthesis

- Previous synthesis for intermediate in the total synthesis of (+)-nuciferol and (+)-nuciferol



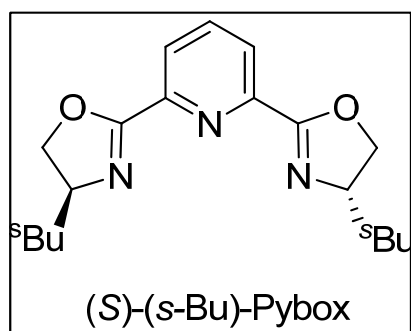
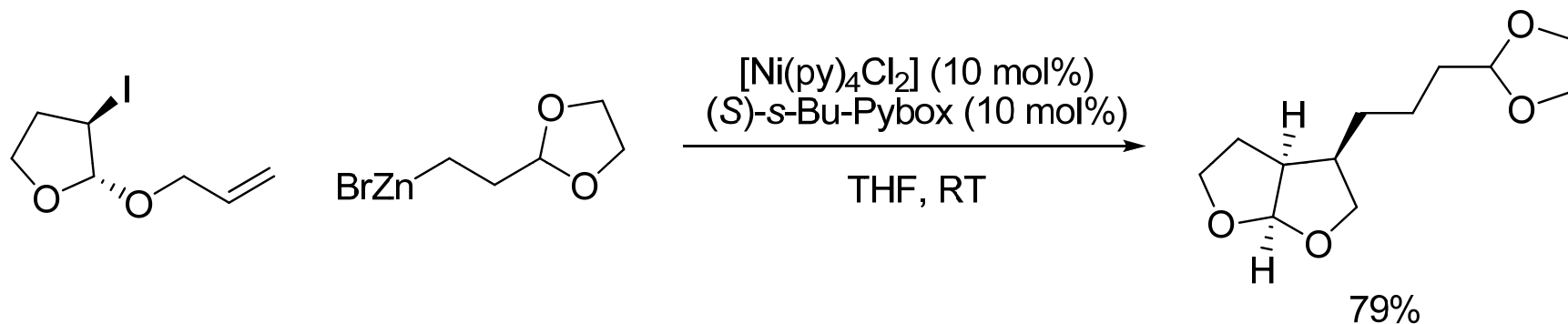
- Preparation via asymmetric cross coupling reactions:



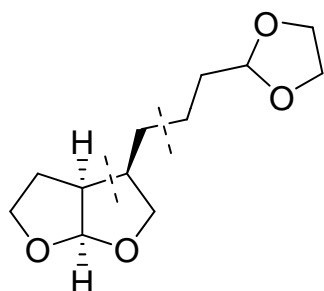
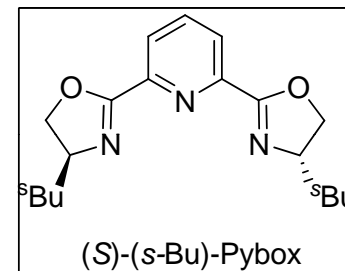
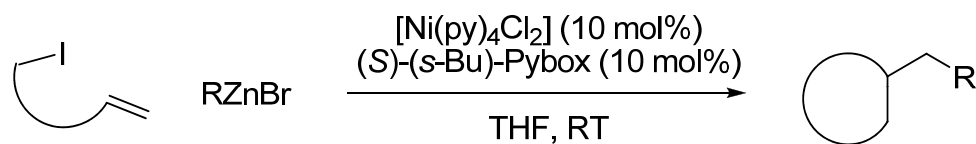
Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 127, 10482-10483.;

Takano, S.; Goto, E.; Ogasawara, K. *Tet. Lett.* **1982**, 23, 5567-5570.; Takano, S et. al. *Chem. Lett.* **1989**, 1781-1784.

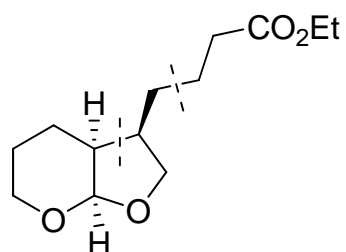
Cárdenas: Ni-Catalyzed Cascade Reactions with Secondary Alkyl Halides



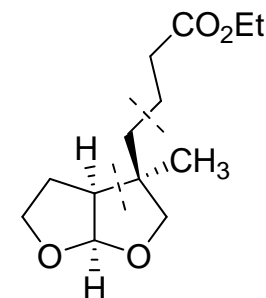
Substrate Scope for Cascade Reactions



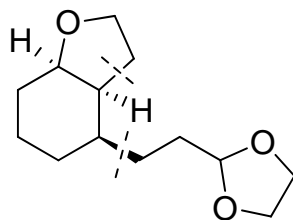
65%



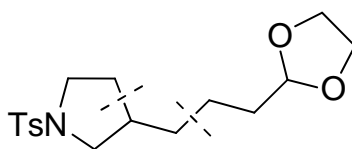
94% (97:3)



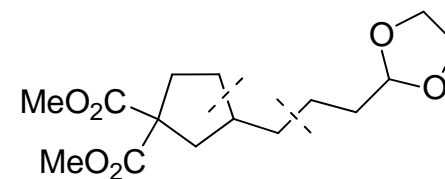
68%



46%

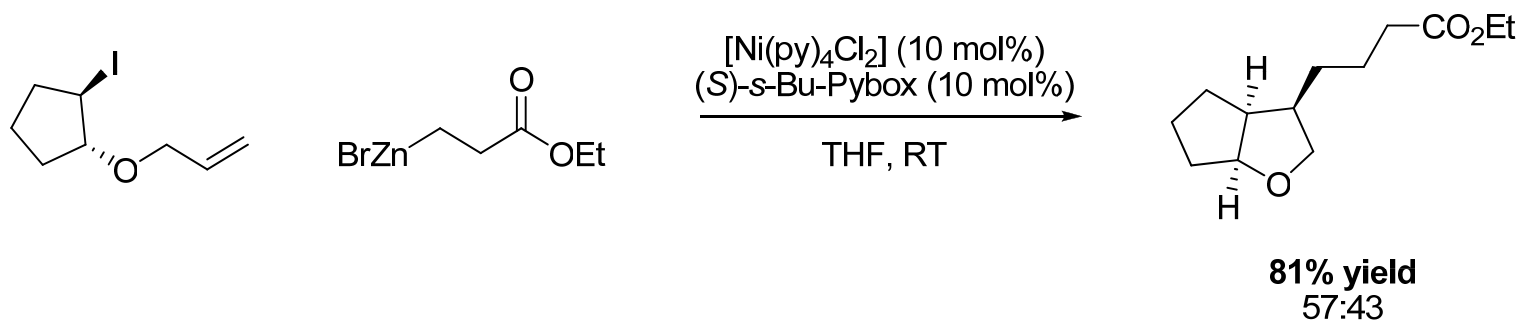
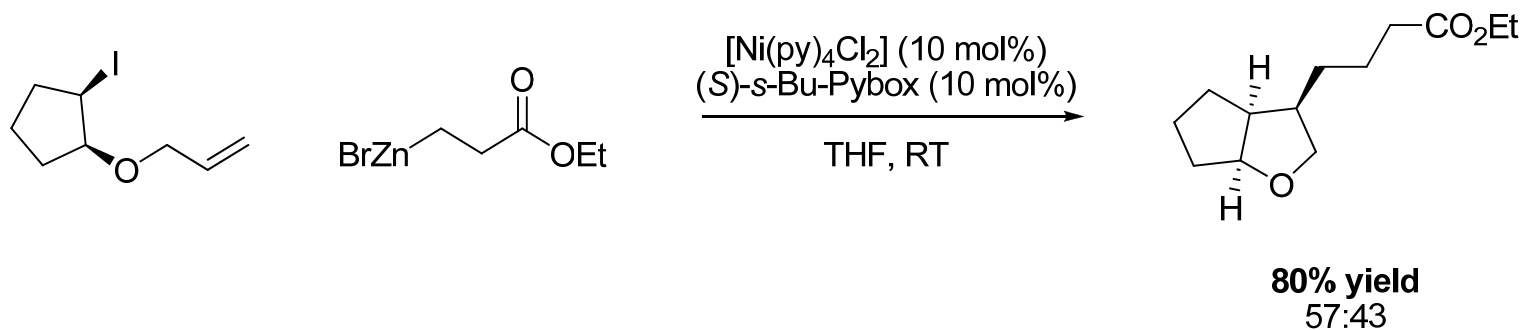


83%

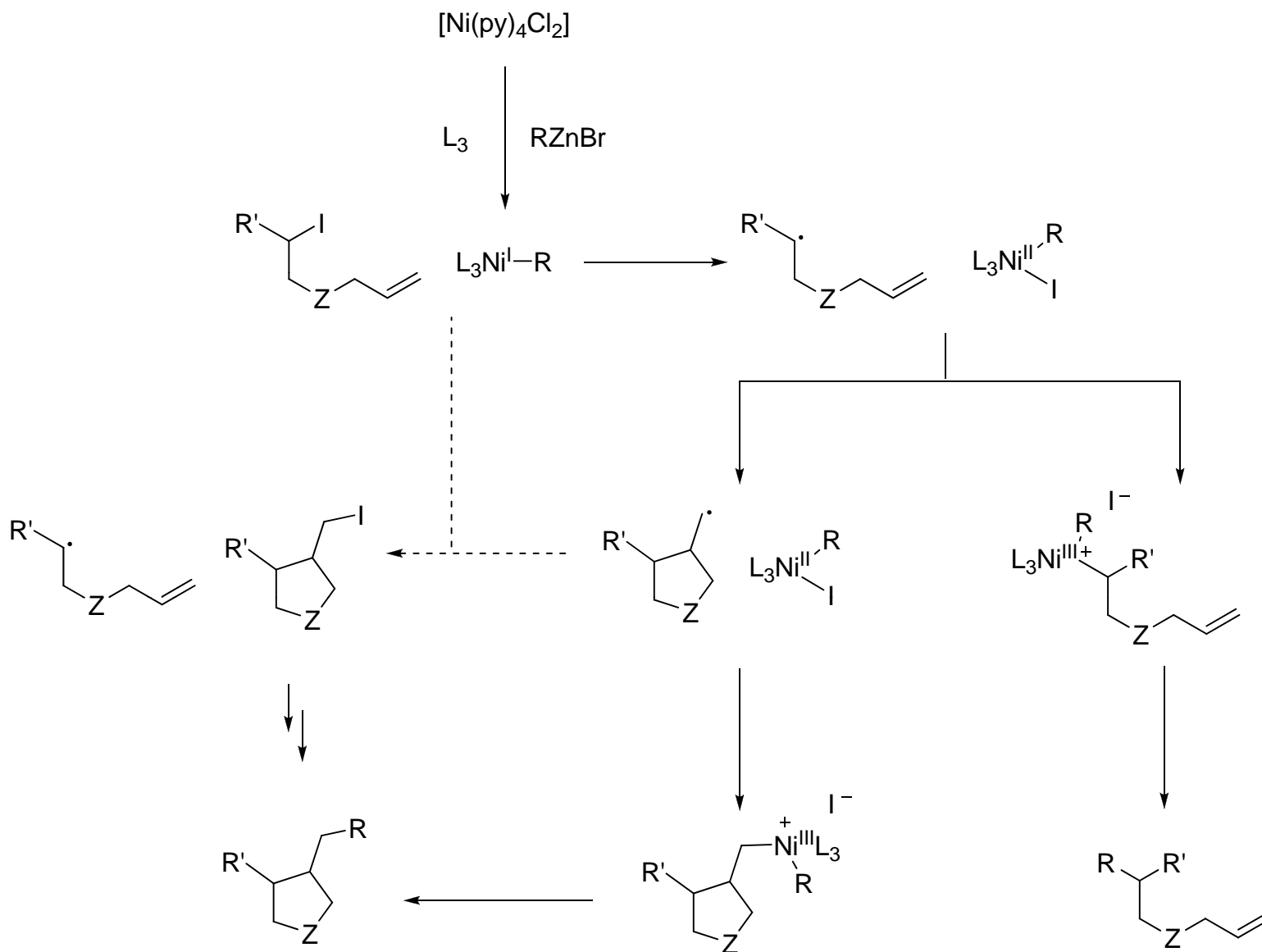


63%

Evidence for a Radical Mechanism



Proposed Mechanism for Cascade Reactions



Conclusions

- Primary and secondary alkyl halides can be utilized in Ni-catalyzed cross coupling reactions
- Fu and coworkers have shown that asymmetric cross couplings can be performed with *activated* alkyl halides
- Future directions:
 - Expanded scope and functional group tolerance
 - Asymmetric cross coupling reactions with unactivated alkyl halides
 - Cross coupling reactions with tertiary alkyl halides

Acknowledgements

Prof. Michael T. Crimmins



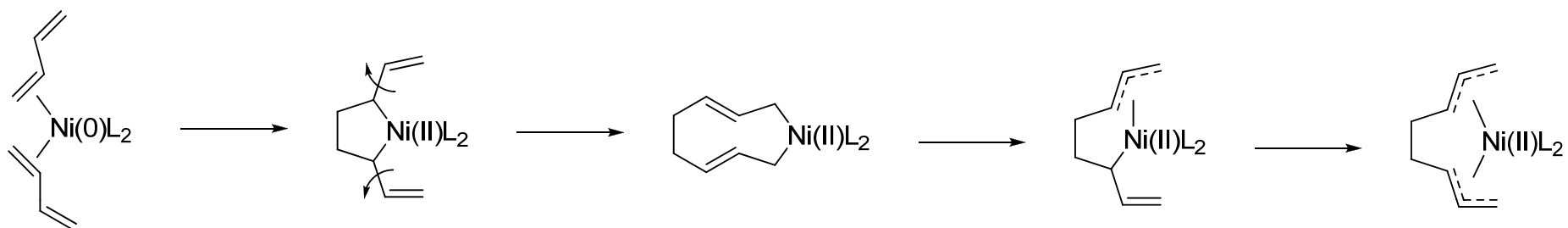
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Tim Martin

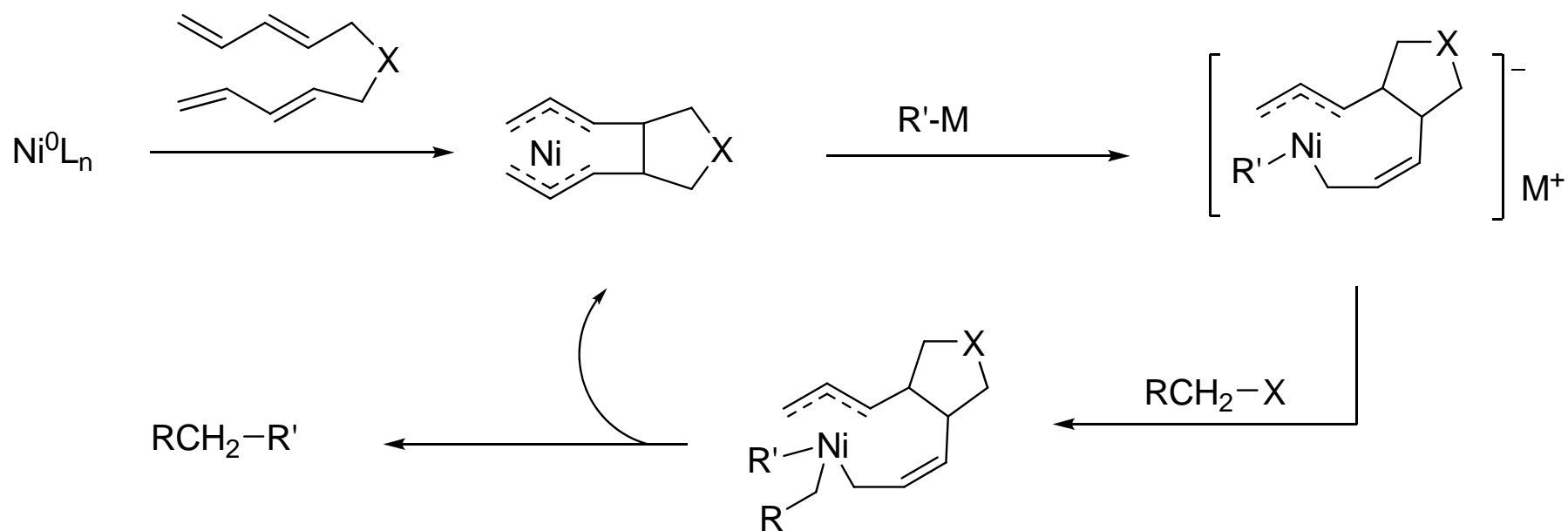
Dr. Christie Stauffer
Matt Haley
Anne-Marie Dechert
Colin Hughes

Dee Jacobs
Jay Stevens
Mark Mans
Phil Williams

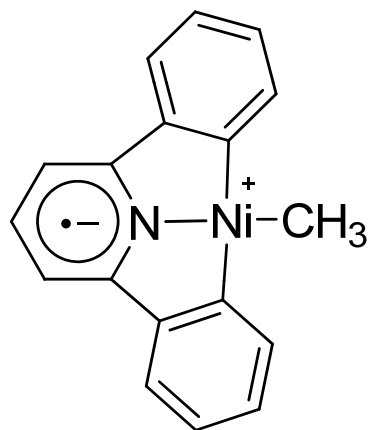
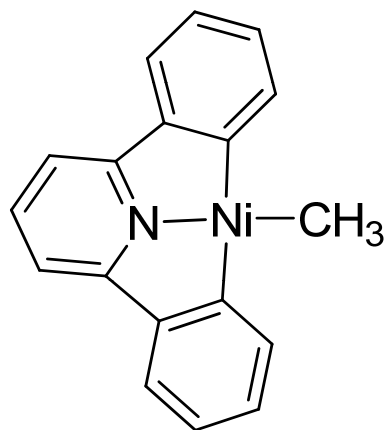
Formation of Bis(π -allyl)Ni complex



Mechanism of Kumada Reactions with 1,3,8,10 Tetraene Derivatives



EPR Results



A: EPR of monomethyl complex at RT

B: EPR of monomethyl complex at 77K

