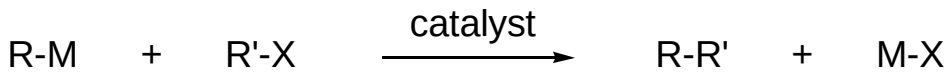
Transition Metal Catalyzed Cross Coupling Reactions of Unactivated Alkyl Halides

Jung Min Joo

8/2/2006

Transition Metal-Catalyzed Cross Coupling Reactions

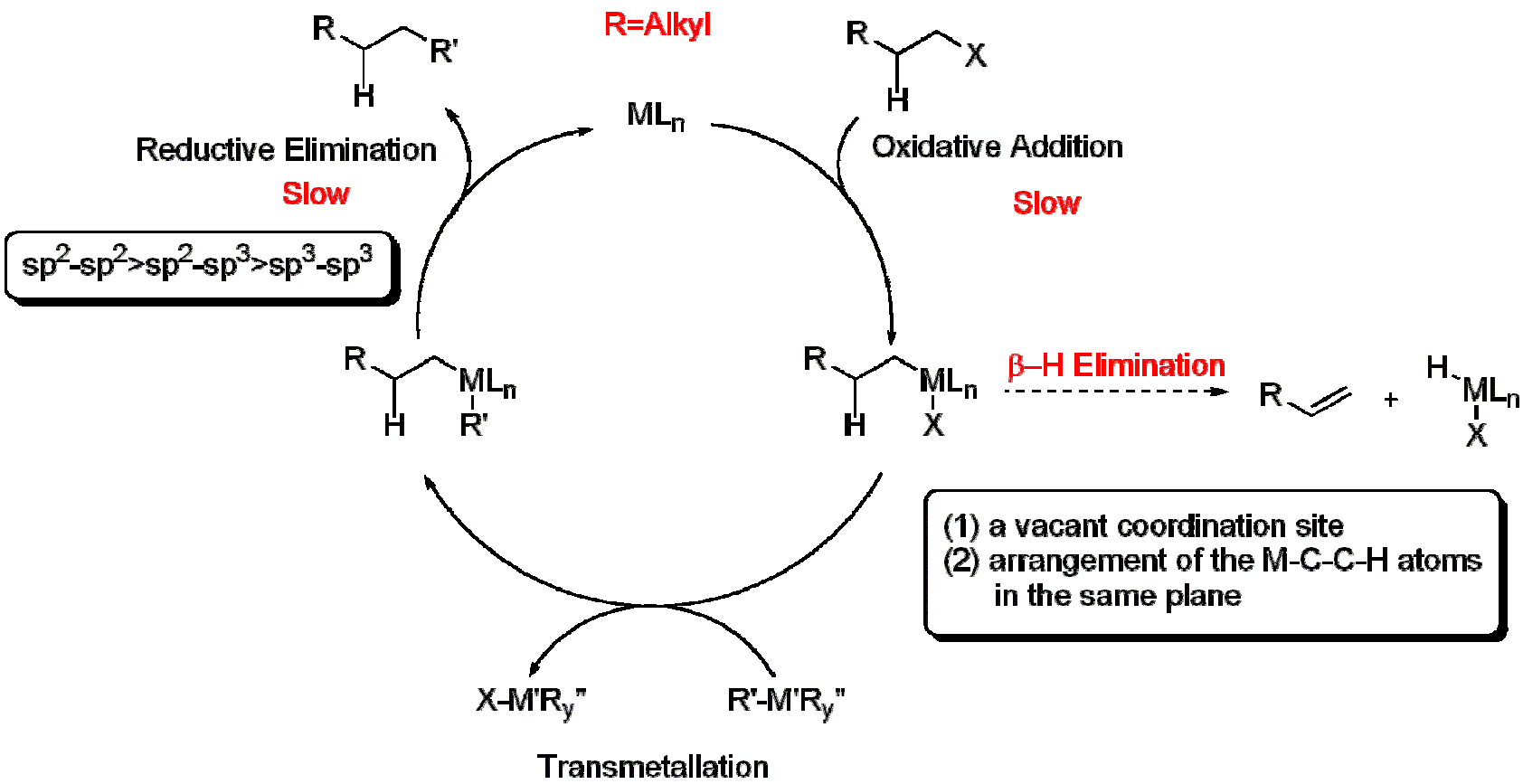


Named Reaction	R-M	R'-X
Kumada-Corriu	R-MgX or R-Li	aryl, alkenyl
Suzuki-Miyaura	R-BR'_2	aryl, alkenyl, alkyl
Negishi	R-ZnX	aryl, alkenyl, alkynyl, acyl
Stille	R-$Sn(alkyl)_3$	aryl, alkynyl, acyl
Heck	alkene	aryl, alkenyl, alkyl (no β hydrogen)

Unactivated alkyl halides: that are not functionalized with activating groups in the α position.
Activated alkyl halides: benzyl, allyl, propargyl, cyclopropyl, α-alkoxy, α-carbonyl alkyl halides

Strategic Applications of Named Reactions in Organic Synthesis,
(Eds.: L. Kurti, B. Czako), Elsevier Academic Press, **2005**.

General Mechanism

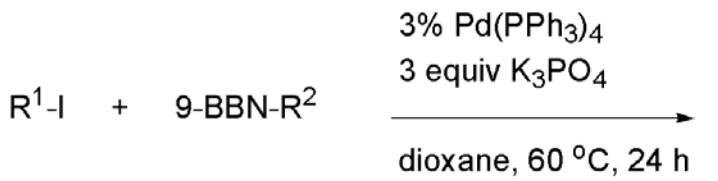


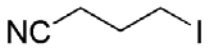
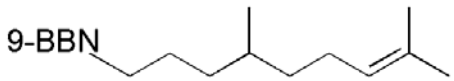
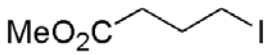
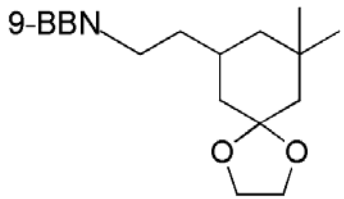
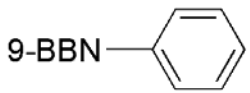
Transition Metal Catalyzed Cross Couplings of Unactivated Alkyl Halides

- Suppress β-hydride elimination
- Facilitate oxidative addition
- Facilitate reductive elimination
- Utilize new mechanisms

➔ Transition Metal / Ligand / Solvent / Base / Additive

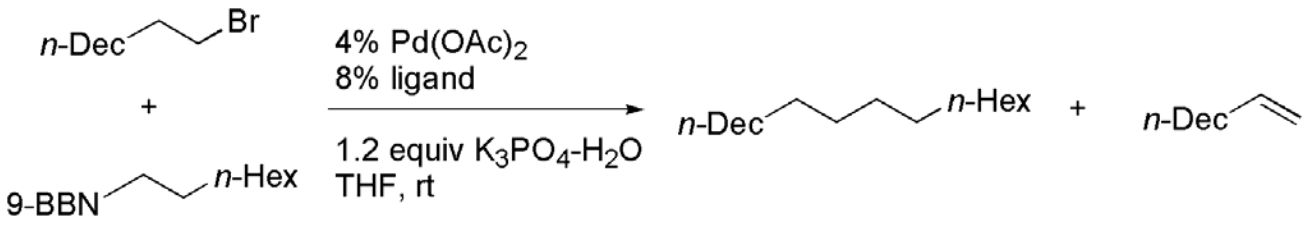
Suzuki Coupling



entry	alkyl halide	9-BBN-R^2	yield
1			61%
2			57%
3	$CH_3(CH_2)_9$-I		55%

Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A.* *Chem. Lett.* **1992**, 691.

Suzuki Coupling-Alkyl Bromides

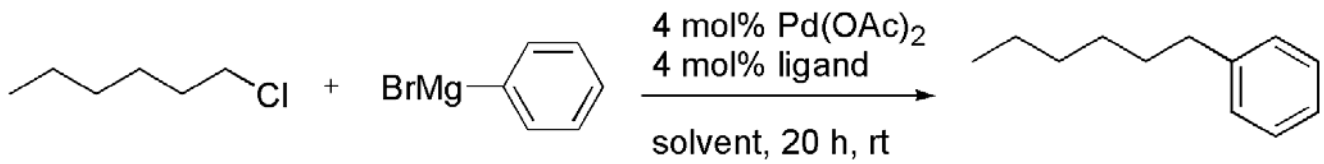


entry	ligand	cone angle (°)	product yield (%)	alkene yield (%)
1	PCy_3	170	85	<2
2	$P(i\text{-}Pr)_3$	160	68	6
3	$P(t\text{-}Bu)_3$	182	<2	21
4	$P(n\text{-}Bu)_3$	132	9	27
5	dcpe		<2	21
6	PPh_3		<2	<2

dcpe: 1,2-bis(dicyclohexylphosphino)ethane

Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C.* *J. Am. Chem. Soc.* **2001**, *123*, 10099.

Kumada Coupling (Alkyl Chlorides)

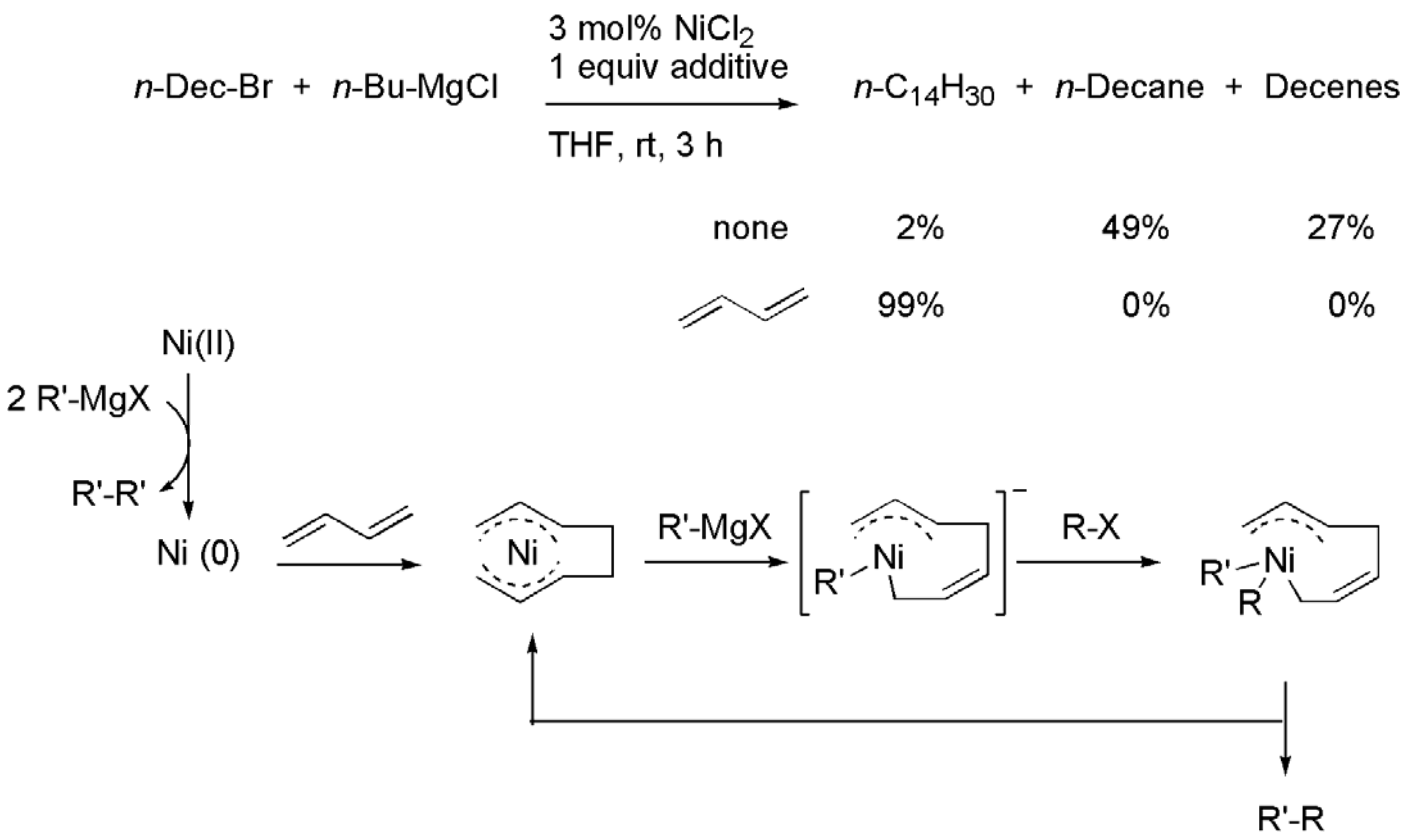


entry	solvent	Ph-MgBr (eq)	Ligand	conversion (%)	yield (%)
1	THF	1.2	PCy_3	1	1
2	dioxane	1.2	PCy_3	1	2
3	DMF	1.2	PCy_3	70	3
4	DMAc	1.5	PCy_3	95	84
5	**NMP**	**1.5**	**PCy_3**	**99**	**96**
6	NMP	1.2	PPh_3	88	9
7	NMP	1.2	$P(o\text{-tol})_3$	92	11
8	NMP	1.2	$PtBu_3$	70	27

DMAc: *N*,*N*-Dimethylacetamide; NMP: *N*-methylpyrrolidinone

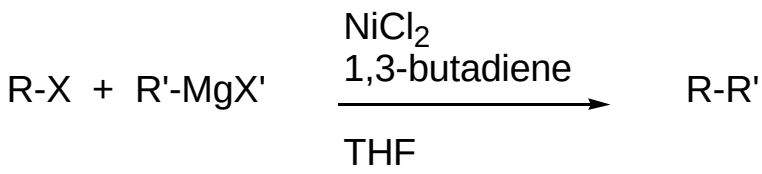
Frisch, A. C.; Shaikh, N.; Zaph, A.; Beller, M.* *Angew. Chem. Int. Ed.* **2002**, *41*, 4056.

Kumada Coupling (sp^3-sp^3)



Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N.* *J. Am. Chem. Soc.* **2002**, *124*, 4222.

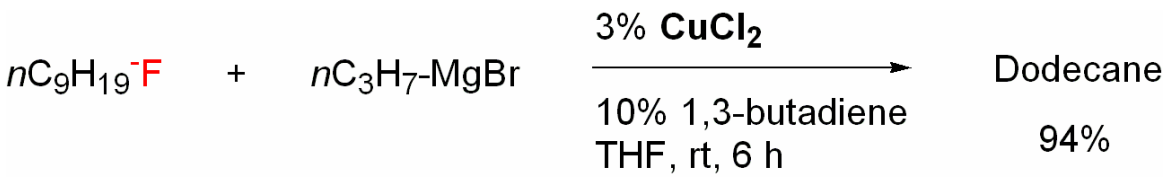
Kumada Coupling (sp^3-sp^3)

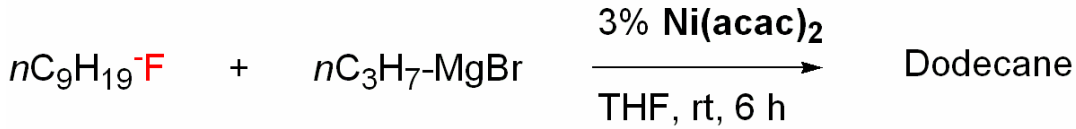


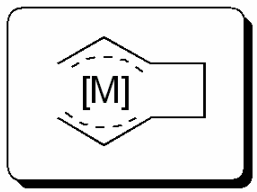
entry	R-X	R'-MgX'	Yield (%)
1	*n*$C_{10}H_{21}$-Br	*n*Bu-MgCl	100
2	(4-Br-C_6H_4)CH_2CH_2Br	*n*Bu-MgCl	100
3	PhCH_2CH_2OTs	Et-MgBr	87
4	*n*Bu-OTs	*n*Bu-MgCl	100
5	Et-OTs	Ph-MgBr	56
6	*n*Oct-Br	Ph-MgBr	90
7	*n*Oct-Br	*i*Pr-MgCl	72
8	*n*Oct-Cl	*n*Bu-MgCl	96

Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N.* *J. Am. Chem. Soc.* **2002**, *124*, 4222.

Kumada Coupling (Alkyl Fluorides)

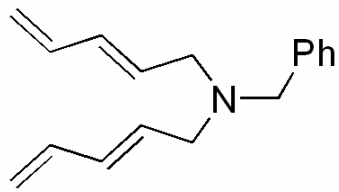






additive:	Yield
30% 1,3-butadiene	11%
100% 1,3-butadiene	58%
200% 1,3-butadiene	65%

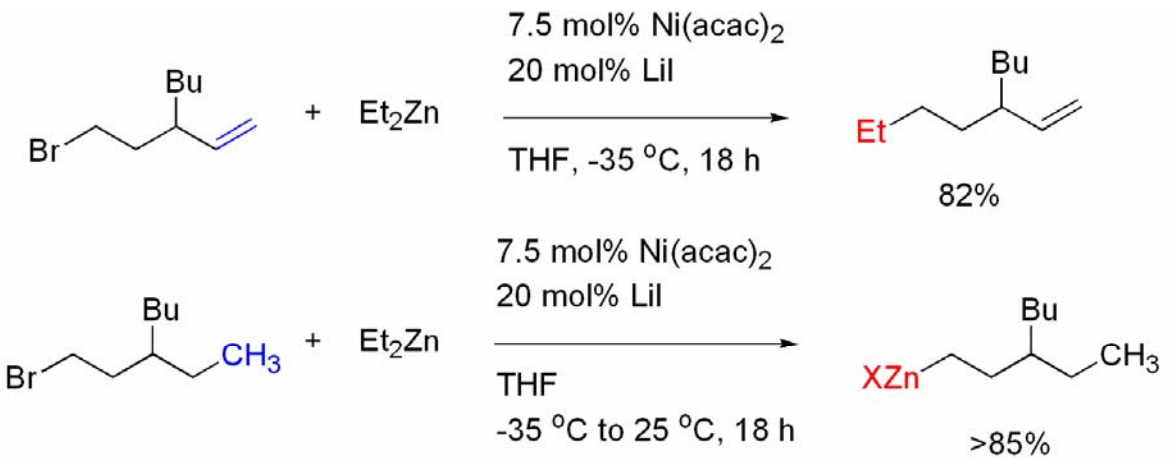
15%

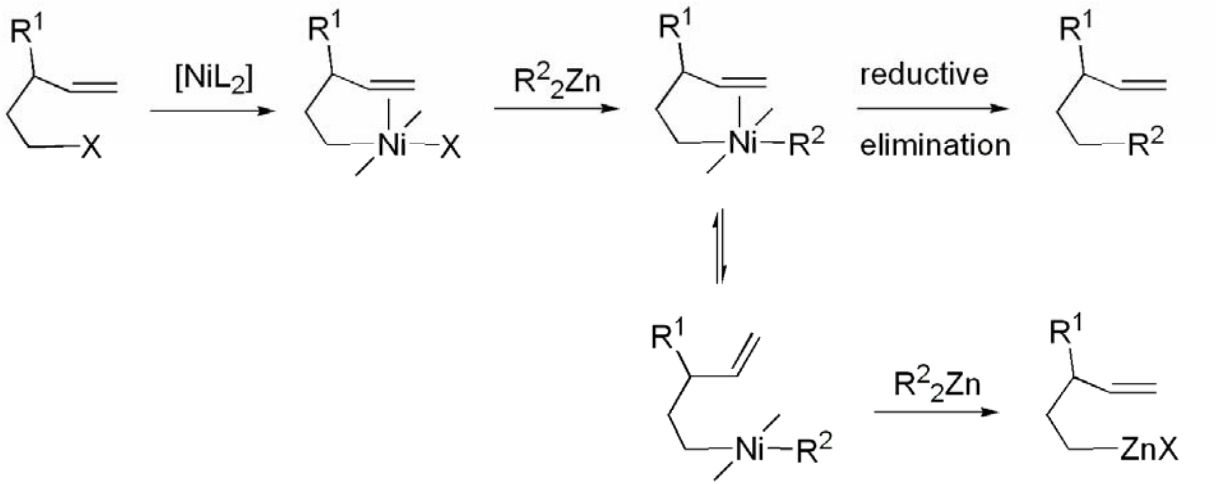


94%

Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N.* *J. Am. Chem. Soc.* **2003**, *125*, 5646.
Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N.* *Angew. Chem. Int. Ed.* **2004**, *43*, 6180.

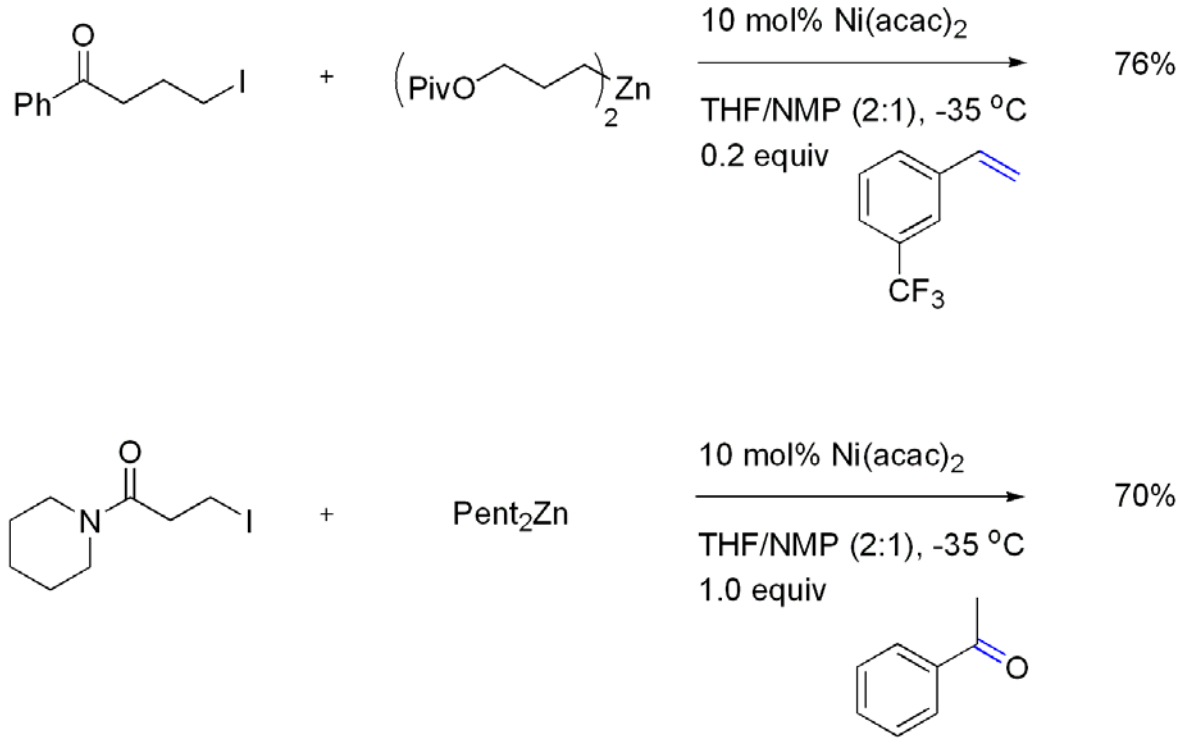
Negishi Coupling





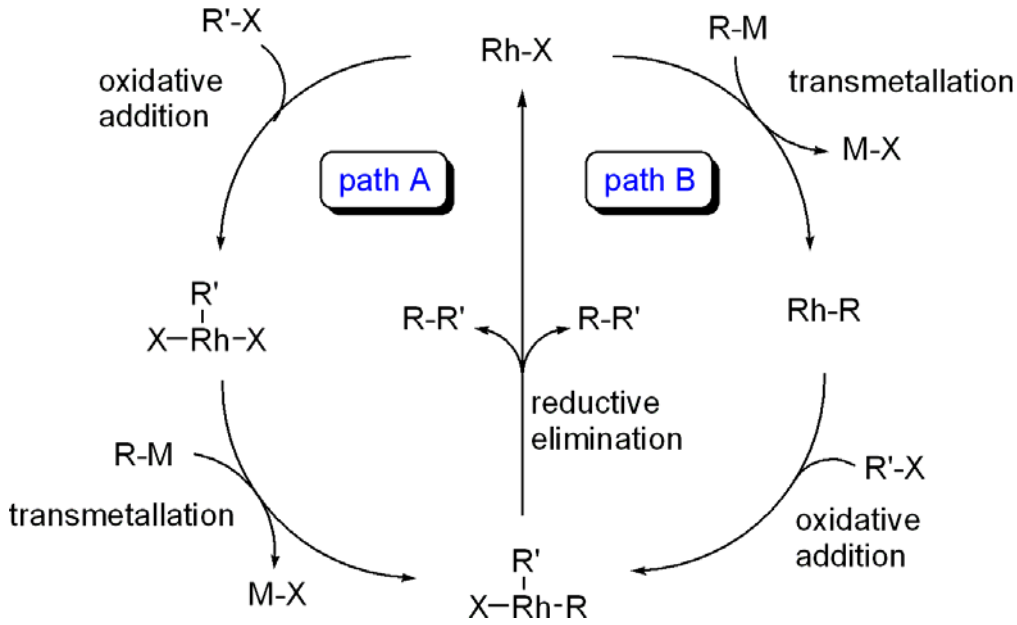
P.Knochel et al. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723.

Negishi Coupling



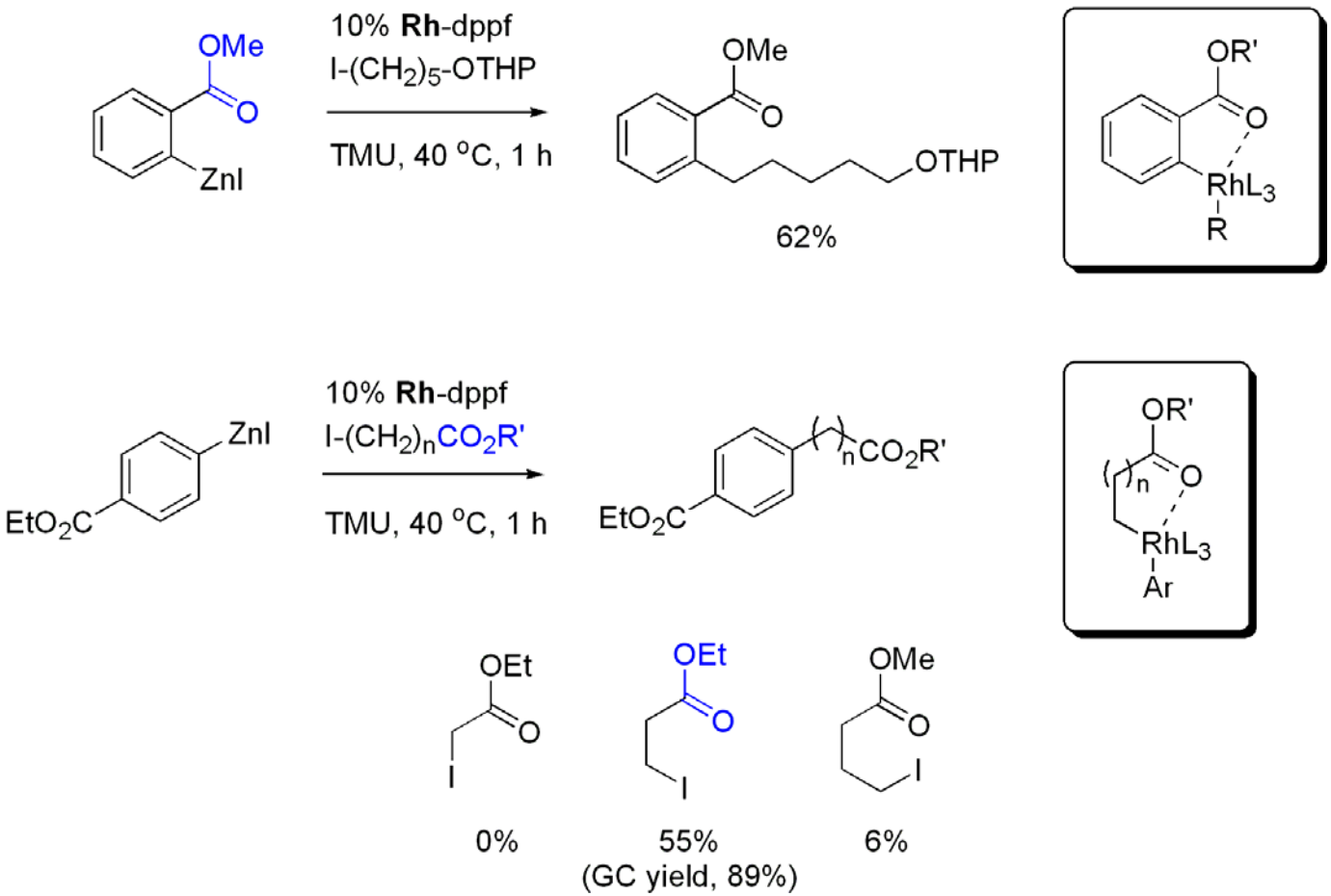
Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P.* *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2387.

Rh in Negishi-Type Coupling



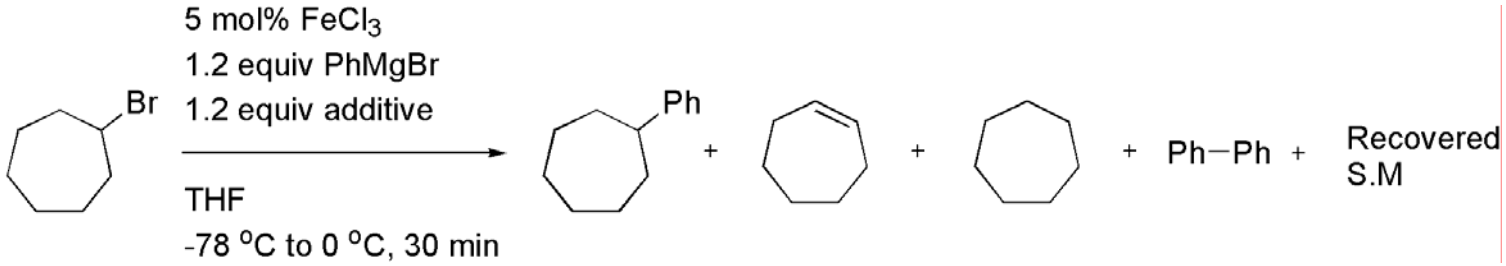
Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K.*
Org. Lett. **2006**, *8*, 3037.

Rh in Negishi-Type Coupling



Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K.*
Org. Lett. **2006**, *8*, 3037.

Fe in Kumada-Type Coupling

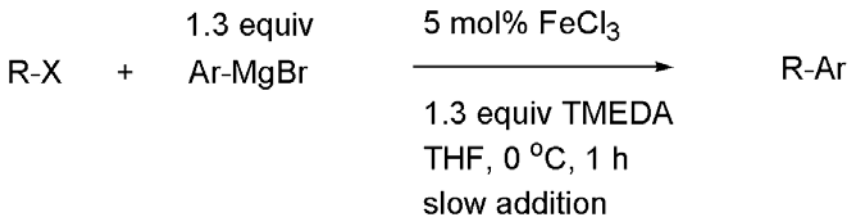


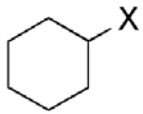
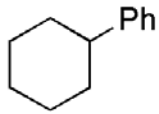
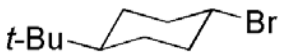
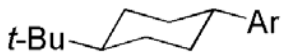
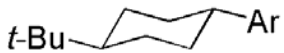
entry	additive					
1	none	5	79	0	6	4
2	Et_3N	3	78	0	5	11
3	*N*-methyl morpholine	8	72	0	5	4
4	DABCO	20	2	0	3	75
5	TMEDA	71	19	3	10	trace

TMEDA: *N,N,N',N'*-tetramethylethylenediamine

Nakamura, M.*; Matsuo, K.; Ito, S.; Nakamura, E.* *J. Am. Chem. Soc.* **2004**, *126*, 3686.

Fe in Kumada-Type Coupling

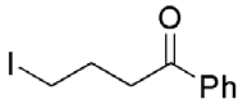
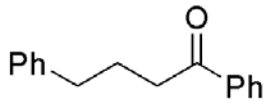
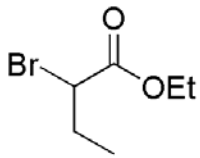
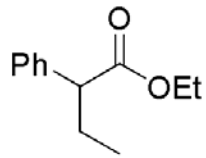
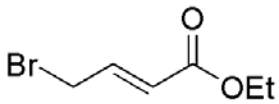
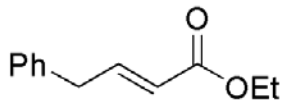
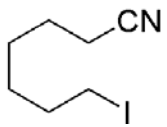
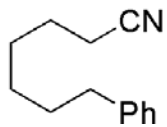


entry	alkyl halide	Ar-MgBr	Product	yield
1		Ph-MgBr		99% (X=I) 99% (X=Br) 99% (X=Cl)
2	nC_8H_{17}-X	Ph-MgBr	nC_8H_{17}-X	97% (X=I) 91% (X=Br) 45% (X=Cl)
3		4-$MeOC_6H_4$-MgBr		96%
4		4-$MeOC_6H_4$-MgBr		98%

Nakamura, M.*; Matsuo, K.; Ito, S.; Nakamura, E.* *J. Am. Chem. Soc.* **2004**, *126*, 3686.

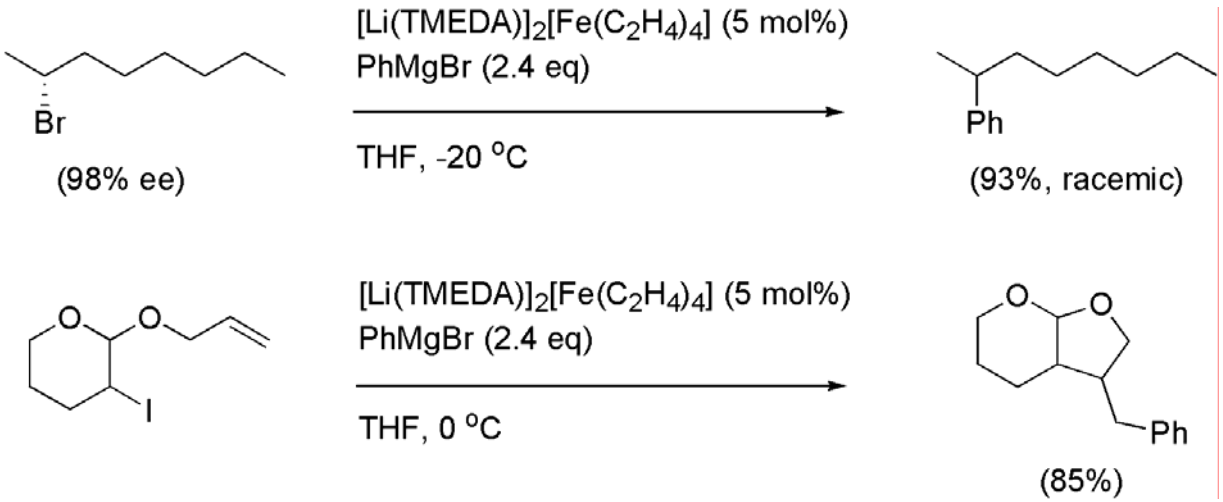
Fe in Kumada-Type Coupling

- Cross coupling reactions catalyzed by $[Li(TMEDA)]_2[Fe(C_2H_4)_4]$

entry	substrate	RMgX	product	yield (%)
1		PhMgBr		91%
2		PhMgBr		87%
3		PhMgBr		94%
4		PhMgBr		83%

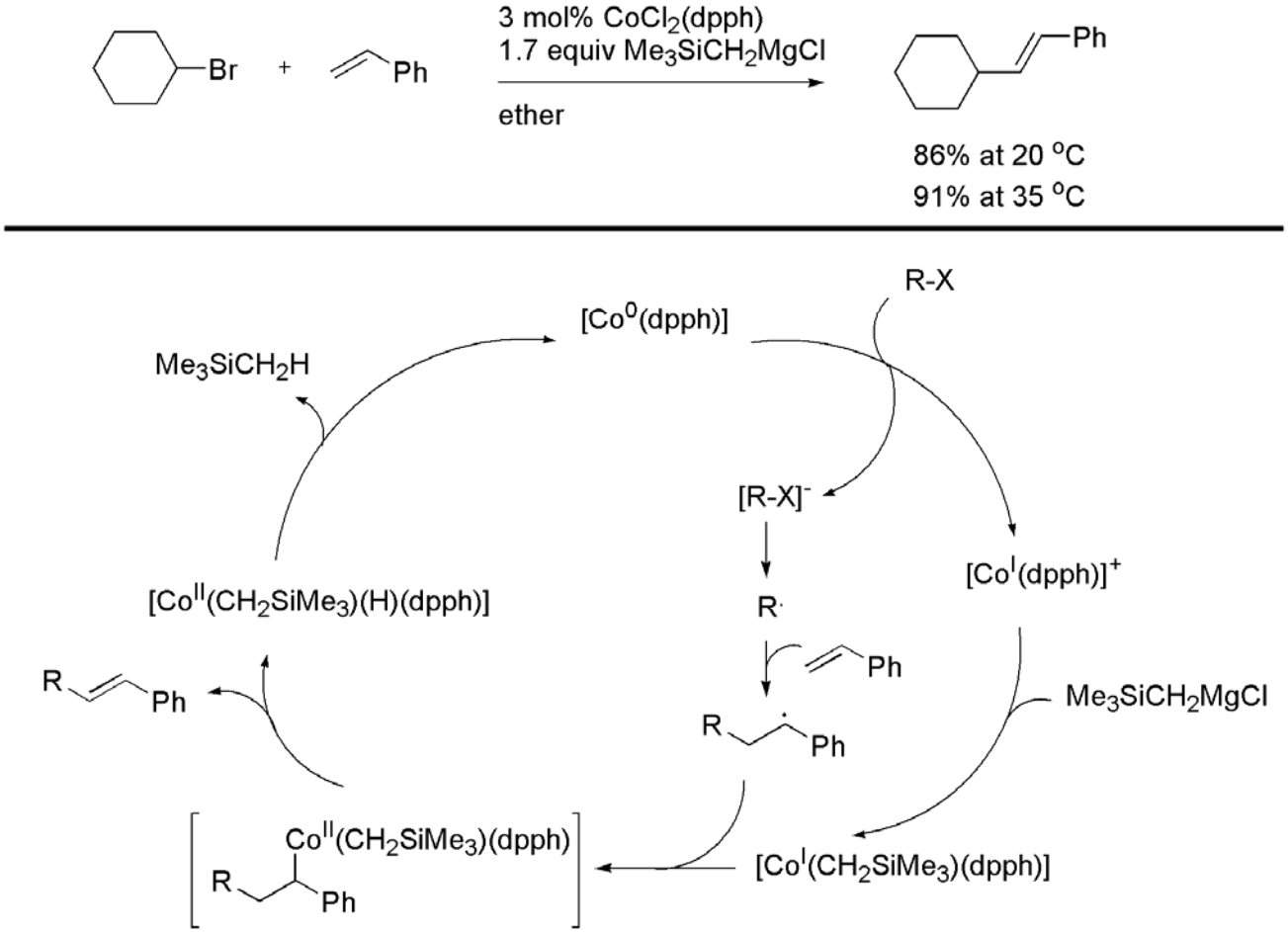
Martin, R.; Fürstner, A.* *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

Fe in Kumada-Type Coupling



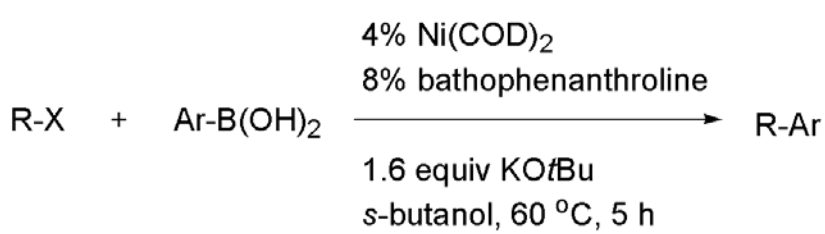
Martin, R.; Fürstner, A.* *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

Heck-Type Reaction

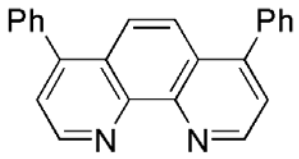


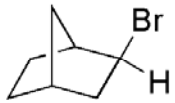
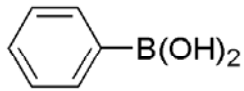
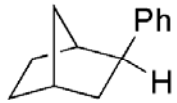
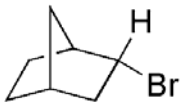
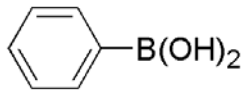
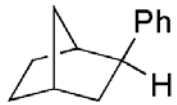
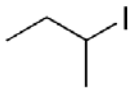
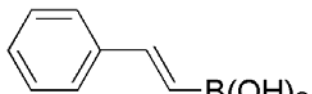
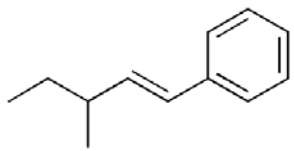
Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514.
Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.*; Oshima, K.*; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.

Suzuki Coupling
Secondary Alkyl Bromides and Iodides



bathophenanthroline



entry	alkyl halide	boronic acid	product	yield
1				74%
2				71%
3				65%

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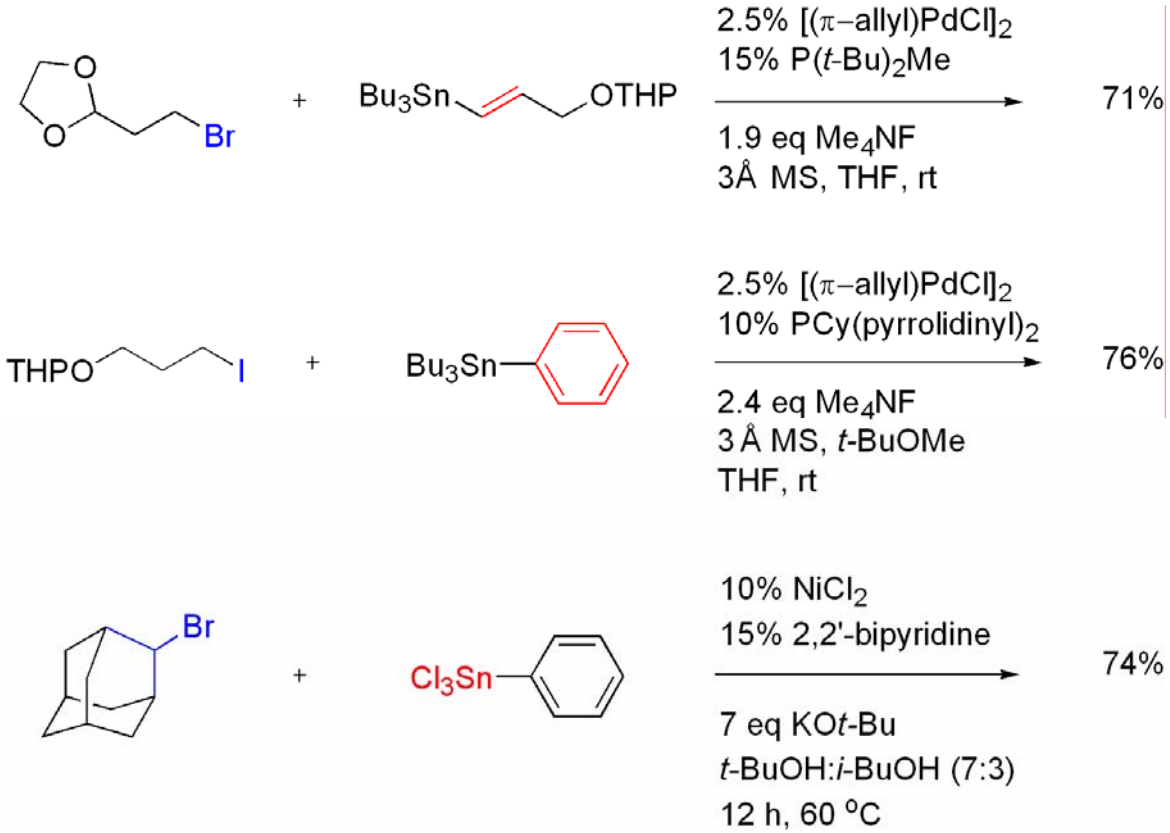
Stille Coupling



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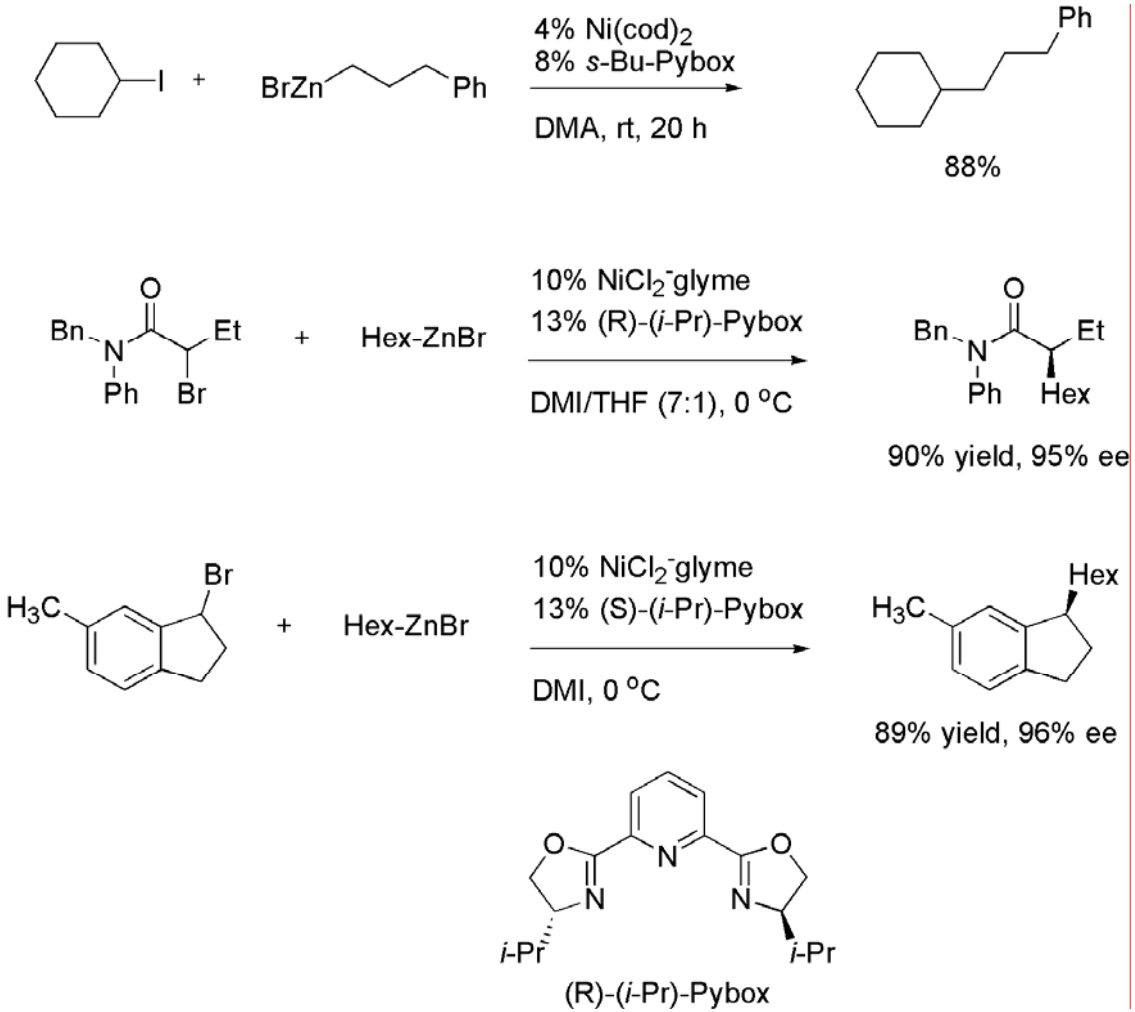
Asymmetric Negishi Coupling
Secondary Alkyl Bromides and Iodides



DMI: 1,3-dimethyl-2-imidazolidinone; DMA: *N,N*-dimethylacetamide

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Conclusions

- Cross Coupling reactions of unactivated alkyl halides have been successfully demonstrated.
- Expanding the scope of these processes
- Developing asymmetric reactions
- Understanding the mechanisms

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