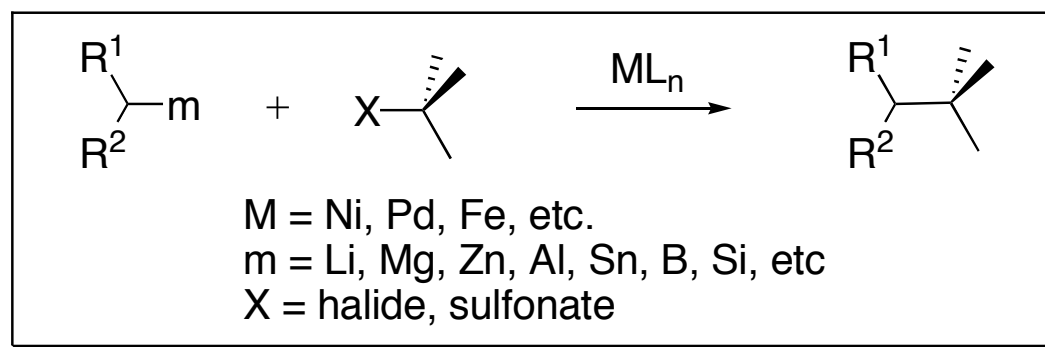


Rubén Martín, Alois Fürstner,
“Cross-Coupling of Alkyl Halides with Aryl
Grignard Reagents Catalyzed by a Low-
Valent Iron Complex,”
Angew. Chem. Int. Ed. **2004**, 43, 3955-3957.



Tyler E. Benedum
Current Literature
October 16, 2004

Topics

§ Background

§ Early examples of aliphatic halide cross-coupling

§ Kochi's work with iron catalyzed cross-coupling

§ Recent low valent iron-catalyzed cross-coupling

- ◆ E. Nakamura

- ◆ T. Hayashi

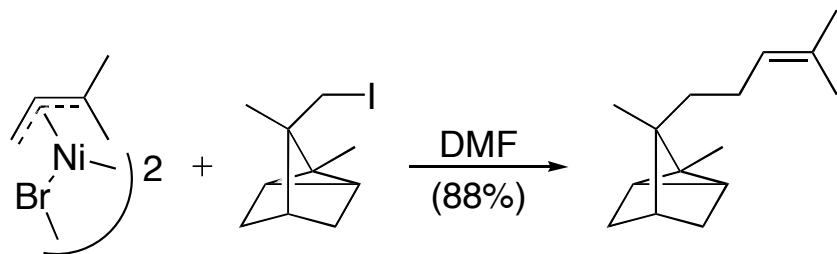
- ◆ A. Fürstner

§ Summary

Background

- § Numerous examples of palladium- and nickel-catalyzed cross-coupling reactions with aryl and vinyl halides in the literature
- § Alkyl halides have recently been included in the scope of this methodology
 - ◆ Predominance of literature *post-2000*
- § First reported transition metal complex reacting with sp^3 carbon-iodide bond in 1967

(Corey, E.J.; Semmelhack, M.F. *J. Am. Chem. Soc.* **1967**, *89*, 2755-2757.)



Kumada-Corriu Reaction

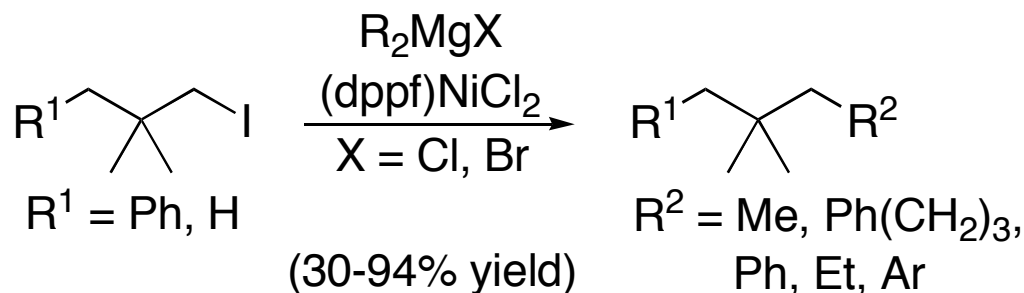
⌘ 1986 - First cross-coupling reaction employing Pd(0) and using simple aliphatic iodides with a variety of Grignard reagents

(Castle, P.L.; Widdowson, D.A. *Tetrahedron Lett.* **1986**, 27, 6013-6016.)

- ◆ However, disproportionation also occurs under these conditions

(Yuan, K.; Scott, W.J. *Tetrahedron Lett.* **1989**, 30, 4779-4782; *J. Org. Chem.* **1990**, 55, 6188-6194; *Tetrahedron Lett.* **1991**, 32, 189-192.)

⌘ Yuan conducted more detailed study with neopentyl substrates



Suzuki Reaction

⌘ Functional group tolerance

◆ Esters, ketals, cyano

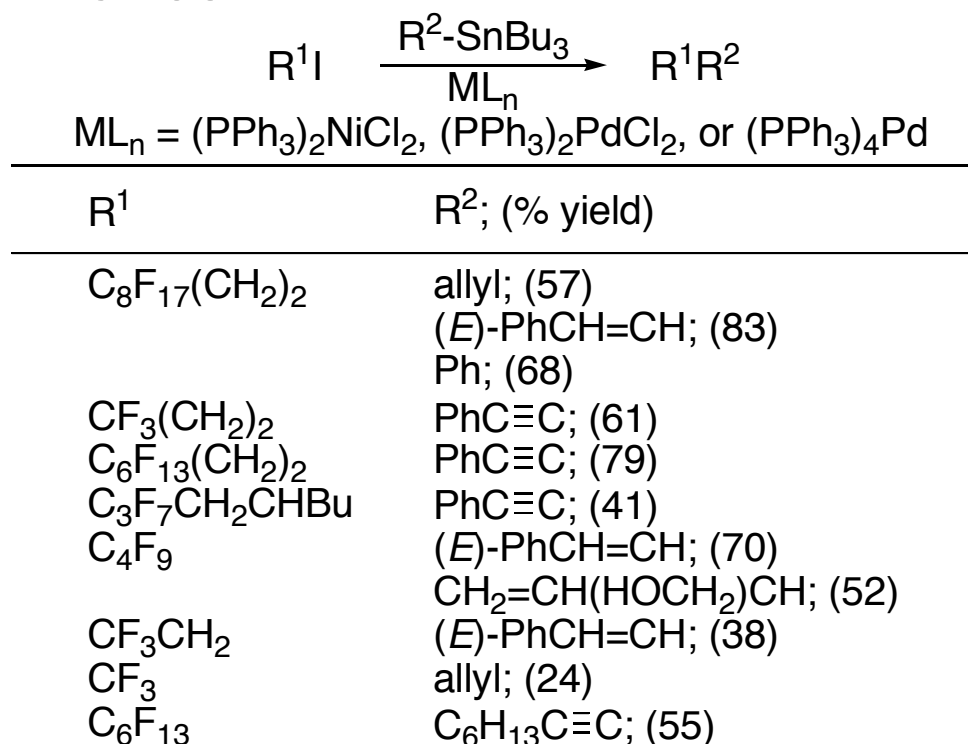
(Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691-694.)

R^1	$\xrightarrow[\text{(PPh}_3)_4\text{Pd}]{R^2\text{-9-BBN}}$	R^1R^2
R^1	R^2 ; (% yield)	
Me	MeO ₂ C(CH ₂) ₁₀ ; (71)	
C ₆ H ₁₃	C ₈ H ₁₇ ; (64)	
<i>t</i> -Bu	MeO ₂ C(CH ₂) ₁₀ ; (45)	
C ₆ H ₁₃	BnOCH ₂ CH ₂ CHMe; (58)	
NC(CH ₂) ₃	Me ₂ C=CH(CH ₂) ₂ CHMe(CH ₂) ₃ ; (61)	
C ₁₀ H ₂₁	Me(CH ₂) ₃ CH=CH; (64)	

⌘ Approach extended to iodocyclopropanes and their coupling to boronic acids and esters

Stille Reaction

⊘ Successful coupling of alkyl halides with various organostannanes



a) Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **1996**, *37*, 8405-8408.

b) Matsubara, S.; Mitani, M.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 5857-5860.

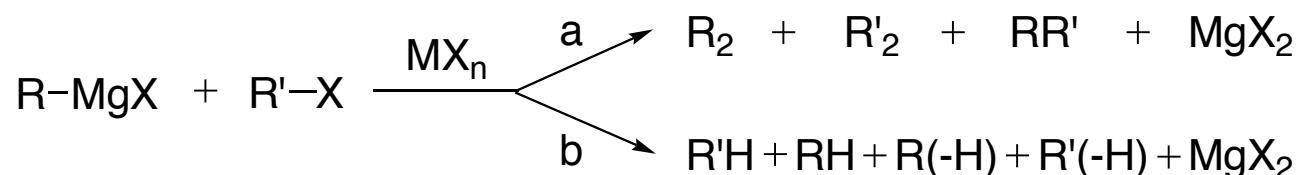
Kochi's Early Work with Iron

- ⌘ Electron transfer mechanisms for organometallic intermediates in catalytic reactions
 - ◆ Specifically, studied the reduction of ferrous and ferric chloride
- ⌘ Applied his findings to metal-catalyzed alkyl transfer reactions of Grignard reagents
 - ◆ Known generally as the Kharasch (Kumada) reaction

Kochi, J.K. *Acc. Chem. Res.* **1974**, *7*, 351-370.

Kochi, *et al.* and the Kharasch Reaction

⌘ Reaction between organometals and alkyl halides using catalytic transition metal complexes



a. Coupling; b. Disproportionation

⌘ Silver (I) and copper (I) are effective catalysts for pathway a

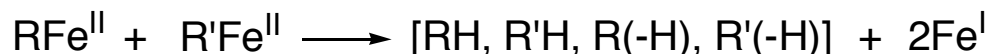
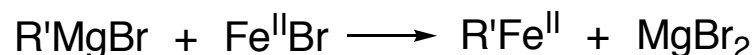
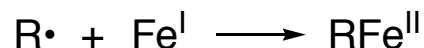
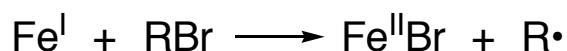
⌘ Iron, however, causes the reaction to proceed via pathway b

- ◆ Except with aryl and vinyl halides and substrates lacking β -hydrogens (methyl, neopentyl, and benzyl)

Tamura, M.; Kochi, J. K. *J. Organometal. Chem.* **1971**, *31*, 289-309

Mechanistic Viewpoint

⌘ Kochi proposes:



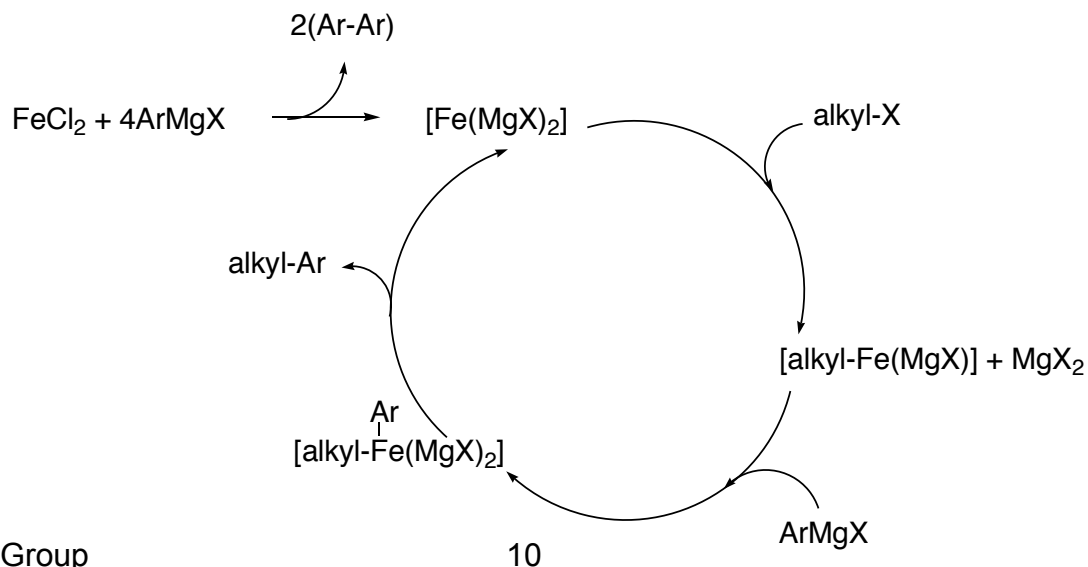
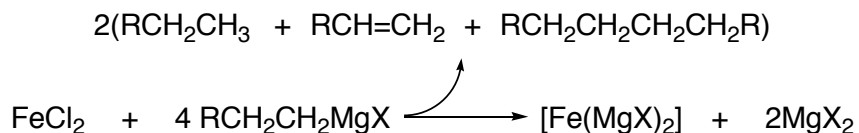
⌘ The unstability of the alkyliron intermediate, compared to other alkylmetal intermediates, possibly results in disproportionation versus coupling

- ◆ Iron intermediate suffers from fast β -hydride elimination

A Low Valent Iron?

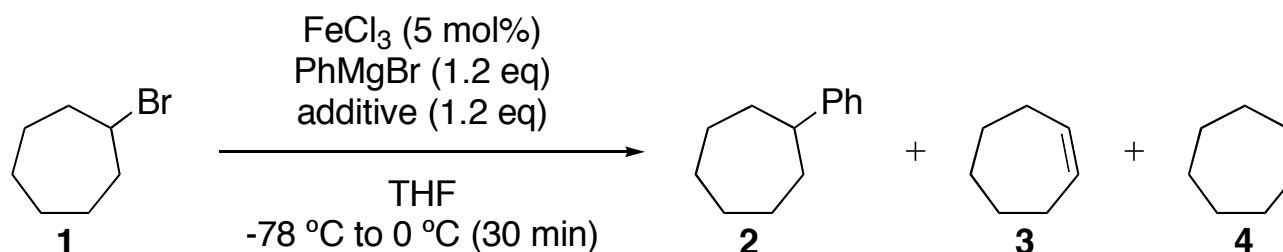
§ New, Generally “Accepted” Catalytic Cycle

- ◆ “...speculated that highly reduced iron-magnesium clusters of the formal composition $[\text{Fe}(\text{MgX})_2]_n$ generated *in situ* may play a decisive role in the catalytic cycle.” (Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955-3957.)



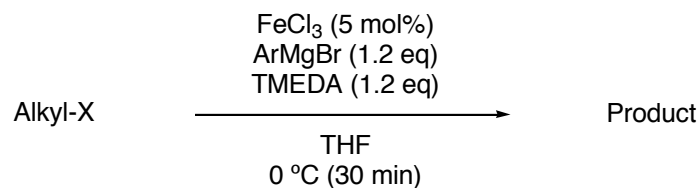
E. Nakamura's Research

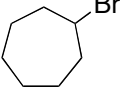
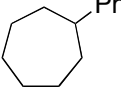
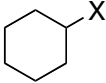
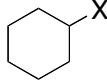
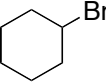
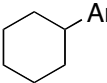
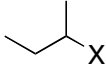
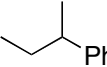
Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686-3687.



Entry	additive	% yield				
		2	3	4	1	Ph-Ph
1	none	5	79	0	4	6
2	TEA	3	78	0	11	5
3	<i>N</i> -methyl morpholine	8	72	0	4	5
4	DABCO	20	2	0	75	3
5	NMP	15	3	trace	79	4
6	TMEDA	71	19	3	trace	10

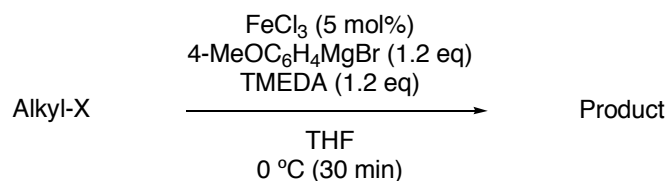
E. Nakamura's Research

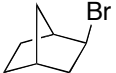





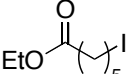
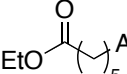
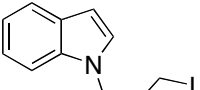
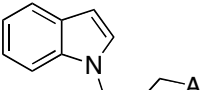


Alkyl halide	ArMgBr, Ar =	Product	% yield
	Ph-		96
	Ph-		99 (X = I) 99 (X = Br) 99 (X = Cl)*
	4-MeOC ₆ H ₄ - 4-MeC ₆ H ₄ - 4-CF ₃ C ₆ H ₄ - 2-naphthyl- 1-naphthyl- 2-MeC ₆ H ₄ -		99 96 67 96 97 98
	Ph-		95 (X = I) 94 (X = Br) 84 (X = Cl)*
$n\text{-C}_8\text{H}_{17}\text{-X}$	Ph-	$n\text{-C}_8\text{H}_{17}\text{-Ph}$	97 (X = I) 91 (X = Br) 45 (X = Cl)*

*Reaction temperature was 40 °C.

E. Nakamura's Research



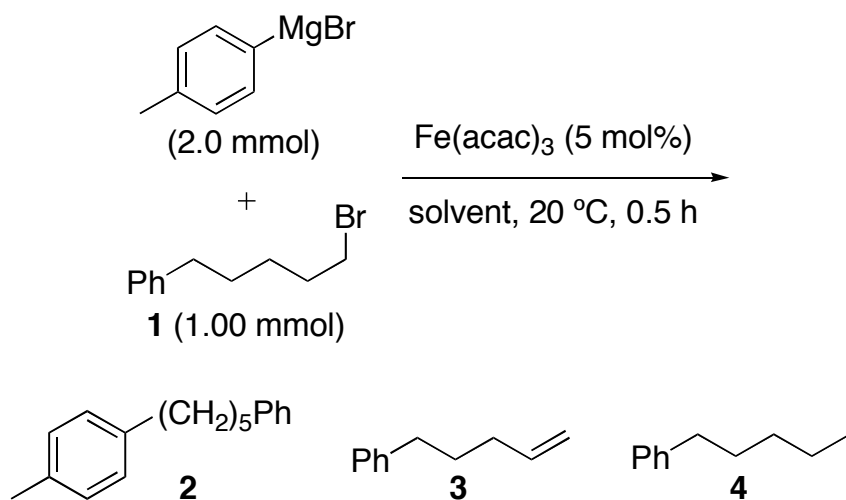
Alkyl-X	Product (Ar = 4-MeOC ₆ H ₄)	% yield
	 (<i>exo:endo</i> = 95:5)	91
	 (<i>trans:cis</i> = 96:4)	96
	 (<i>trans:cis</i> = 95:5)	98
		88
		87

Methodology allows for variety of functional groups

- ◆ Alkoxy carbonyl
- ◆ Alkenyl
- ◆ Alkynyl
- ◆ *N*-indolyl

Hayashi's Studies

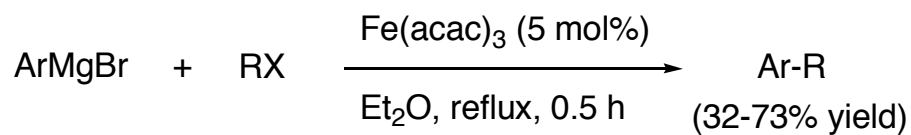
Nagano, T.; Hayashi, T. "Iron-Catalyzed Grignard Cross-Coupling with Alkyl Halides Possessing β -Hydrogens," *Org. Lett.* **2004**, 6, 1297-1299.



Entry	solvent	product (mmol)				Ar-Ar
		2	3	4	1	
1	THF/NMP	0.25	0.25	0.24	0.15	0.26
2	THF	0.27	0.37	0.20	0	0.25
3	diethyl ether	0.60	0.19	0.12	0	0.12
4*	diethyl ether	0.69	0.18	0.09	0	0.08

*Reaction was carried out in refluxing diethyl ether.

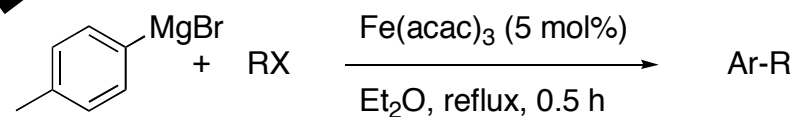
Hayashi's Studies



Ar = 4-MeC₆H₄, 4-MeOC₆H₄, 4-FC₆H₄,
2-MeC₆H₄, or 2,4,6-Me₃C₆H₂

R = *n*-C₆H₄

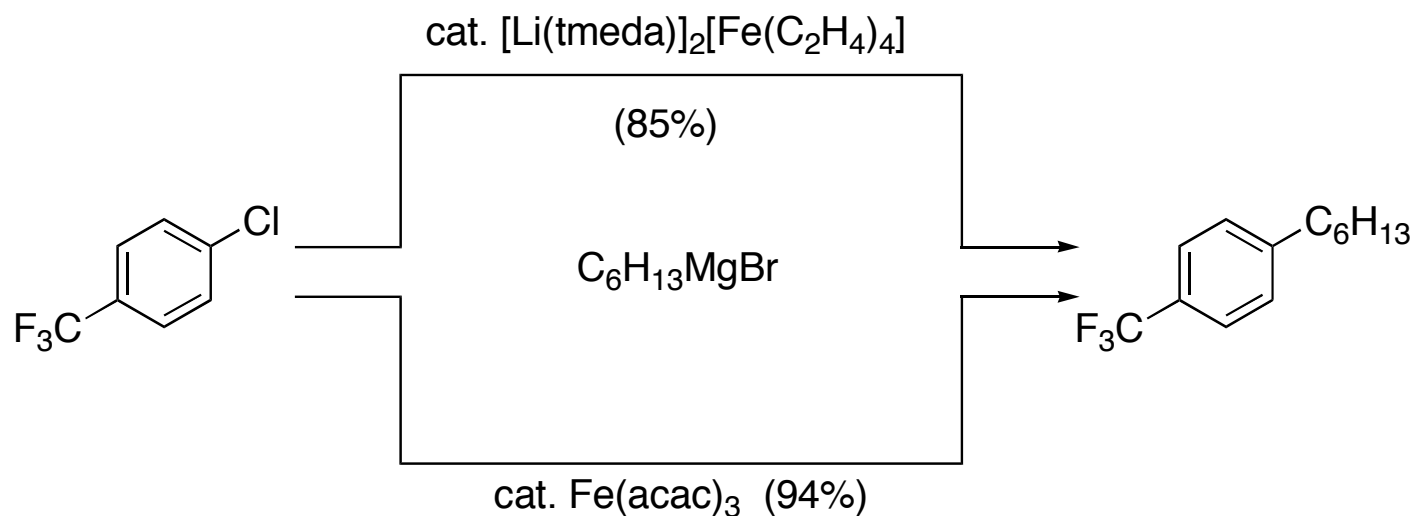
X = Br, Cl, I, or OTs



RX =	Product (% yield)
PhO(CH ₂) ₄ Br	(CH ₂) ₄ OPh (65%)
(CH ₂) ₅ Me Br	(CH ₂) ₅ Me (73%)
	(69%)

Fürstner

Initial studies



Low-valent catalyst described by Jonas

(Jonas, K.; Schieferstein, C.; Krüger, C.; Tsay, Y.-H. *Angew. Chem. Int. Ed.* **1979**, *18*, 549-550.)

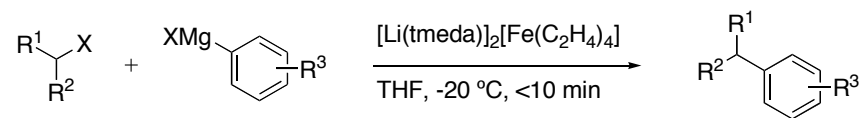
Fürstner

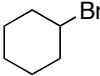
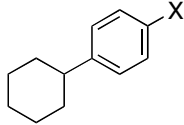
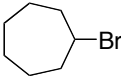
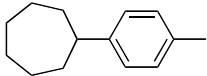
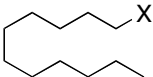
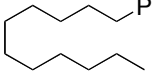
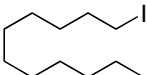
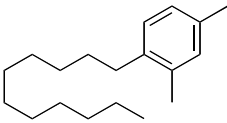

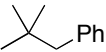
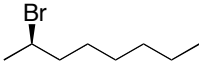
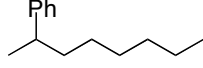
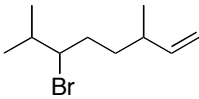
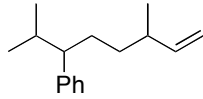
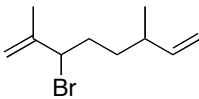
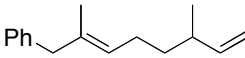
Scope

- Alkyl halides with aryl Grignard reagents and phenyllithium
- Primary alkyl iodides
- Secondary alkyl bromides
- Propargyl and allyl halides

Limitations

- Tertiary halides
- Alkyl chlorides

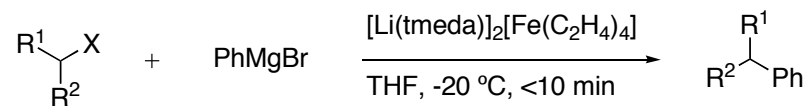


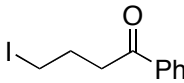
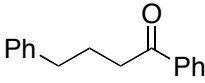
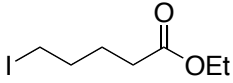
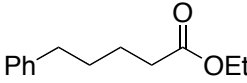
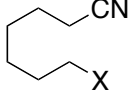
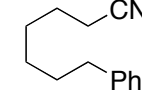
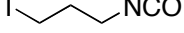
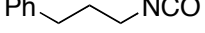
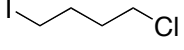
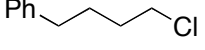
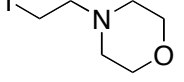
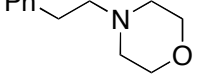
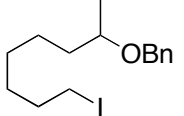
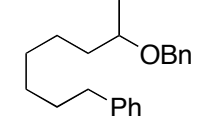
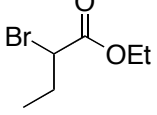
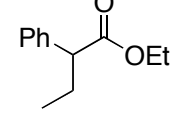
Substrate	RMgX/RLi	Product	Yield (%)
	PhMgBr PhLi 4-MeOC ₆ H ₄ MgBr 4-ClC ₆ H ₄ 4-PhC ₆ H ₄ MgBr 3-(TMS) ₂ NC ₆ H ₄ MgBr		94 (X = H) 92 (X = H) 95 (X = OMe) 67 (X = Cl) 93 (X = Ph) 88 (X = NH ₂)
	4-MeC ₆ H ₄ MgBr		95
	PhMgBr PhMgBr		96 (X = I) 61 (X = Br)
	2,4-(CH ₃) ₂ C ₆ H ₃ MgBr		94
	PhMgBr		74
	PhMgBr		93
	PhMgBr		89
	PhMgBr		84

Fürstner

Activation of the alkyl halide significantly faster than the attack of Grignard reagent to functional groups

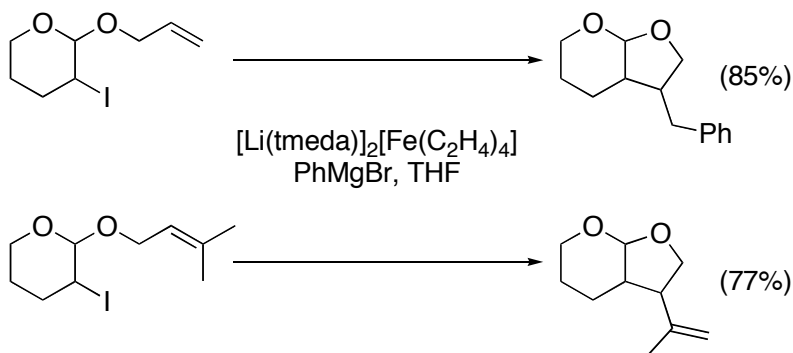
- ◆ Ketones
- ◆ Esters
- ◆ Enoates
- ◆ Chlorides
- ◆ Nitriles
- ◆ Isocyanates
- ◆ Ethers
- ◆ Acetals



Substrate	Product	Yield (%)
		91
		88
		83
		90
		86
		87
		95
		87

Fürstner

First effective example of iron-catalyzed cross-coupling of allylic halides



Substrate	Product	Yield (%)
		94
		93
		96
		87
		97
		98
		93
		96
		87

Highlights of Iron-Catalysis

- ⌘ Low Cost
- ⌘ Readily-available
- ⌘ Practical and “Green”
- ⌘ Scalability
- ⌘ Catalytic (compared to organocopper reagents)
- ⌘ Little optimization required
- ⌘ No requirements for special ligands
- ⌘ Relatively unreactive 2° bromides and chlorides undergo coupling
- ⌘ High reaction rates (rxns proceed within 20 min)
- ⌘ Mild conditions (-20 °C to 40 °C)

Summary

§ Conclusion

- ◆ Ability to couple various aryl Grignard reagents with a variety of alkyl halides in high yields
- ◆ Extension of sp^3 coupling methodology
- ◆ Further insight into the mechanism of iron-catalyzed couplings

§ Future Work

- ◆ Apply methodology to sp^3 - sp^3 coupling reactions
- ◆ Continue to elucidate the reaction mechanism