

Direct and Facile Metalation of Functionalized Substrates

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Group Meeting – SED Group

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Organometallic Reagents: Groups I, II, and III

- The term 'metalation' coined by Gilman and Young¹
- Organomagnesium reagents²
 - Can exist in equilibrium between 2R-Mg-X and $\text{R}_2\text{Mg} + \text{MgX}_2$
 - Can be pre-made or used *in situ*
- Organolithiums³
 - Aggregate and solvate structures
 - Very reactive and low temperature required for functional group (FG) tolerance
 - Most commonly generated by deprotonation or halogen exchange with alkyllithiums
- Organozincs⁴
 - Often formed by transmetalation in the presence of zinc salts with organomagnesiums and organolithiums.
 - More FG tolerance

¹H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, 1934, **56**, 1415-1416

²B. J. Wakefield, "Compounds of Alkali and Alkaline Earth Metals in Organic Synthesis", in *Comprehensive Organometallic Chemistry*, Vol. 7, Chap. 44, 1-110

³Schlenk and Bergmann, *Ann.*, 1928, **463**, 192; H. Gilman and J. W. Morton Jr., *Org. Reactions*, 1954, **8**, 258-304

⁴P. Knochel, N. Millot, and A. L. Rodriguez, *Org. Reactions*, 2001, **58**, 417-731

Organometallic reagents: Uses

- Addition to electrophiles

carbonyls, organohalides, X_2 , epoxides, etc.

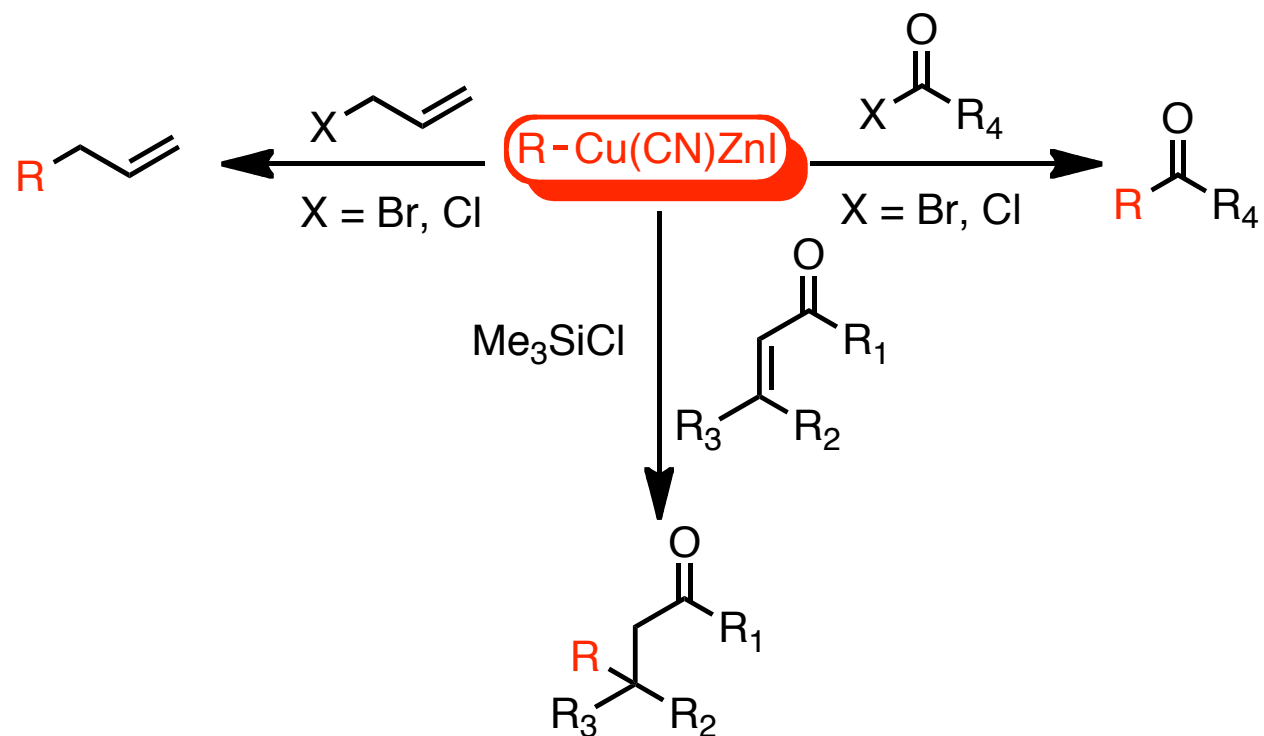
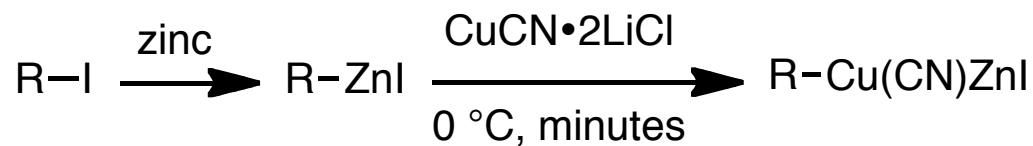
- Transmetalation with other metals

aluminum, zinc, copper, etc.

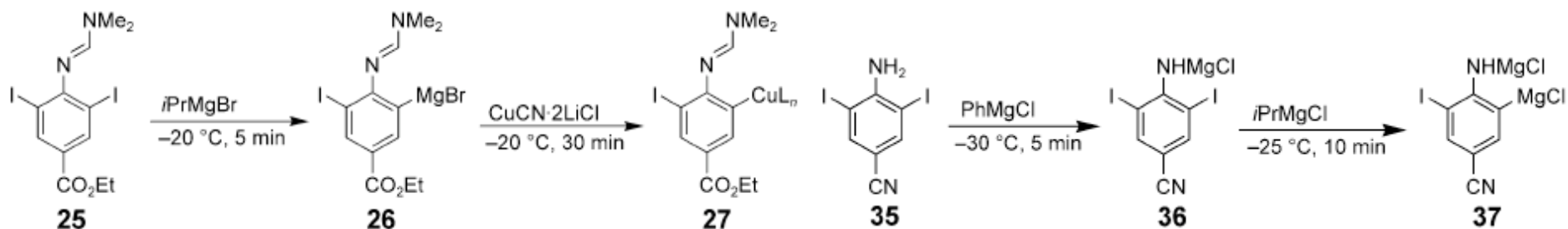
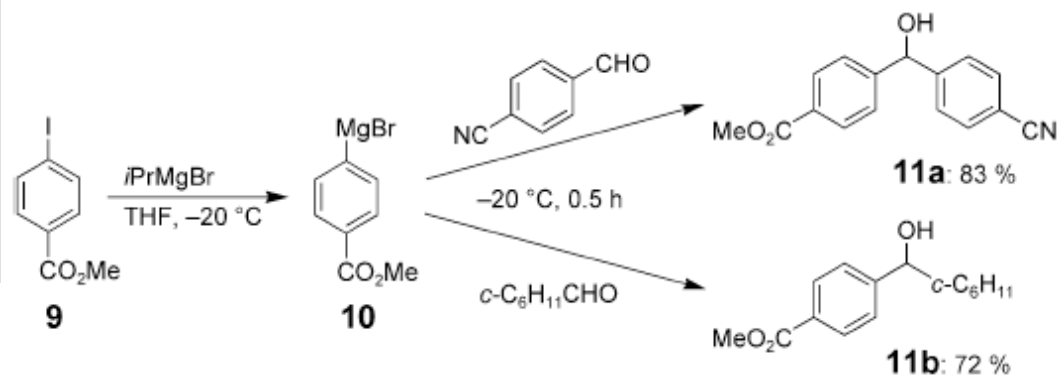
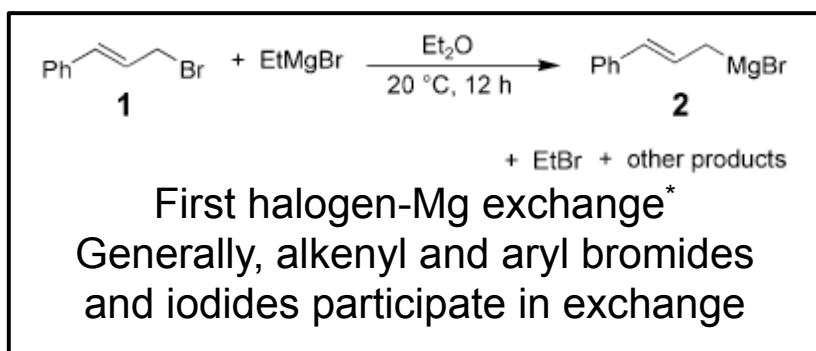
- High polarity of C-M bond affords a carbanion-like compound

- Cross-coupling with transition metal complexes

Zinc Transmetalation with Copper

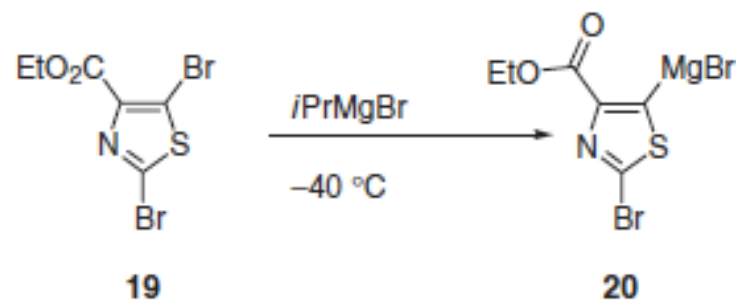
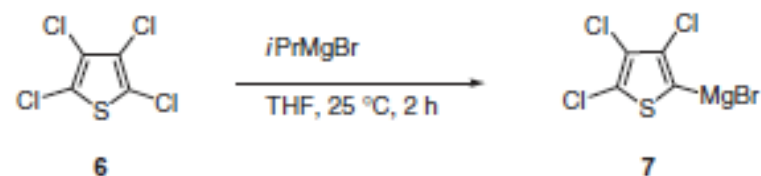
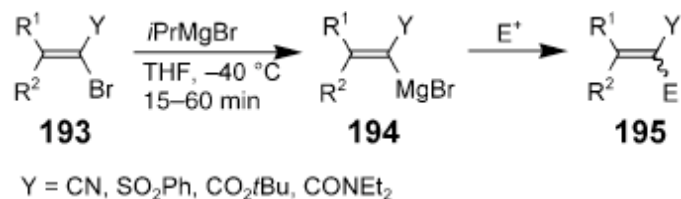
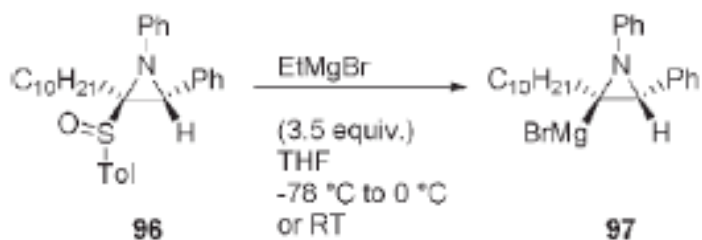
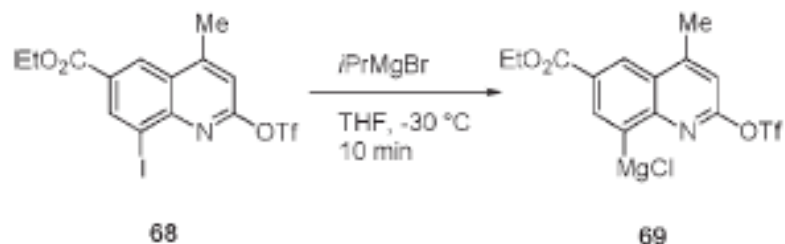
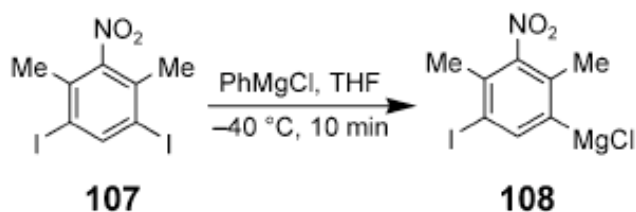
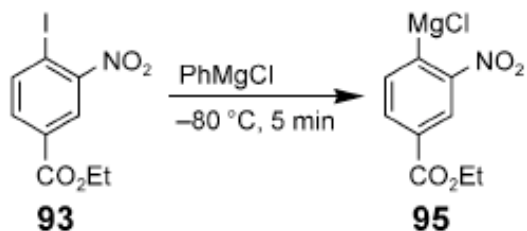


Halide-Magnesium Exchange Reactions



*C. Prévost, *Bull. Soc. Chim. Fr.*, 1931, **49**, 1372
 P. Knochel et. al., *Angew. Chem Int. Ed.*, 2003, **43**, 4302-4320

Halide-Magnesium Exchange Reactions



Magnesium-Halide exchange works but could it be more general?

H. Ila, O. Baron, A. J. Wagner, and P. Knochel, *Chem. Commun.*, 2006, 583-593

H. Ila, O. Baron, A. J. Wagner, and P. Knochel, *Chem. Lett.*, 2006, **35**, 2-7

P. Knochel et. al., *Angew. Chem Int. Ed.*, 2003, **43**, 4302-4320

The Importance of Lithium Additives

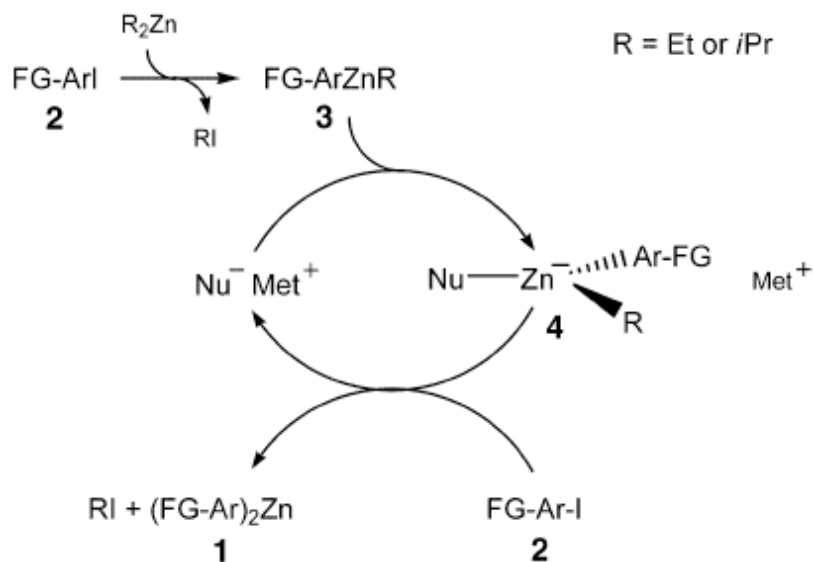
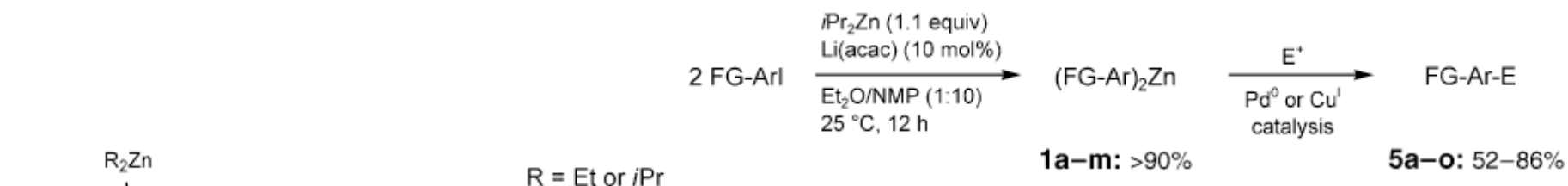
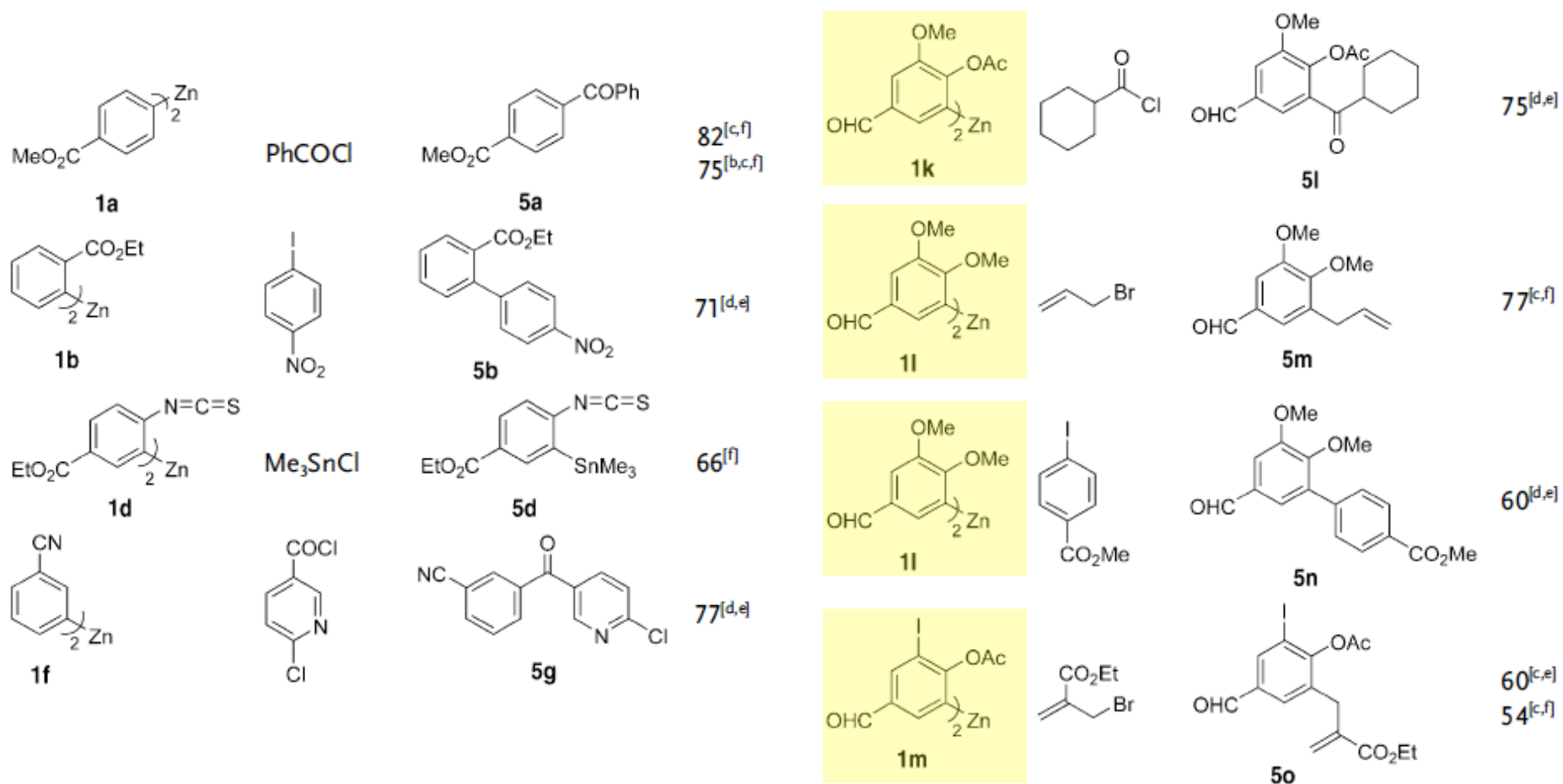


Table 1: The influence of metallic salts on the rate of the iodine–zinc exchange of **2a** with $i\text{Pr}_2\text{Zn}$ in $\text{Et}_2\text{O/NMP}$ (1:10) at 25°C .

Entry	Additive ^[a]	Conversion [%] ^[b]
1	MgCl_2	30
2	MgBr_2	15
3	MgI_2	2
4	Bu_4NI	10
5	LiCl	0
6	LiBF_4	2
7	LiClO_4	2
8	Li(acac)	87
9	Mg(acac)_2	33
10	Cs(acac)	84
11	Zn(acac)_2	2

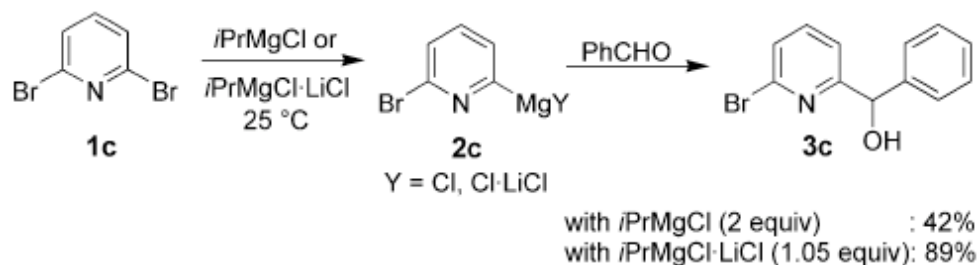
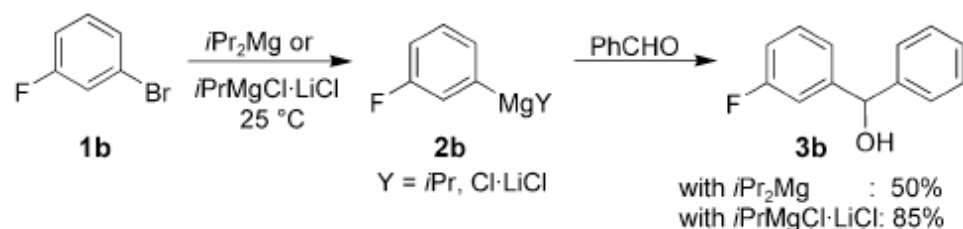
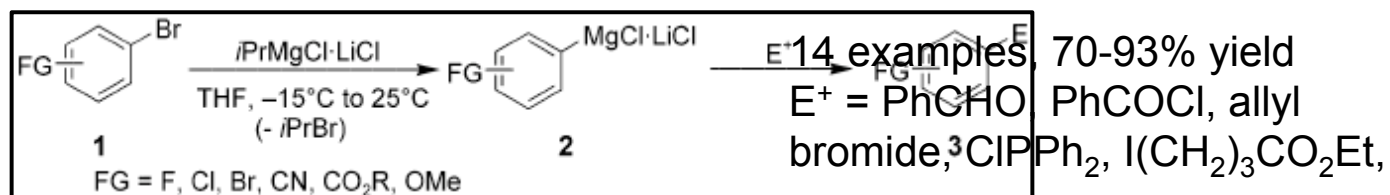
[a] Metal salt: 10 mol%. [b] The conversion was determined after a reaction time of 15 min by analysis of reaction aliquots by GC with tetradecane as an internal standard; accuracy: $\pm 2\%$.

Functional Group Tolerance

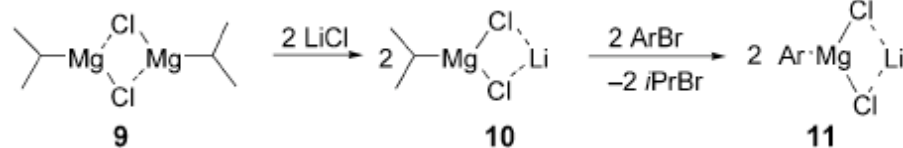
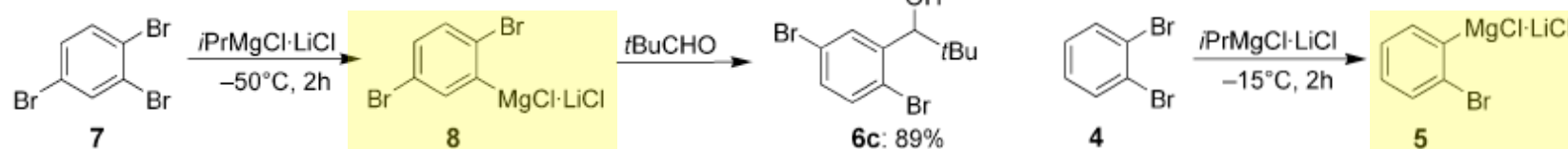


[a] Yields of analytically pure products. [b] Yield of the reaction on a 25-mmol scale. [c] In the presence of CuCN·2LiCl (20 mol %). [d] In the presence of [Pd(dba)₂] (2.5 mol %) and tfp (5.0 mol %). [e] With *i*Pr₂Zn as the reagent for the exchange. [f] With *s*Bu₂Zn, generated in situ by transmetalation of *s*BuLi, as the reagent for the exchange.

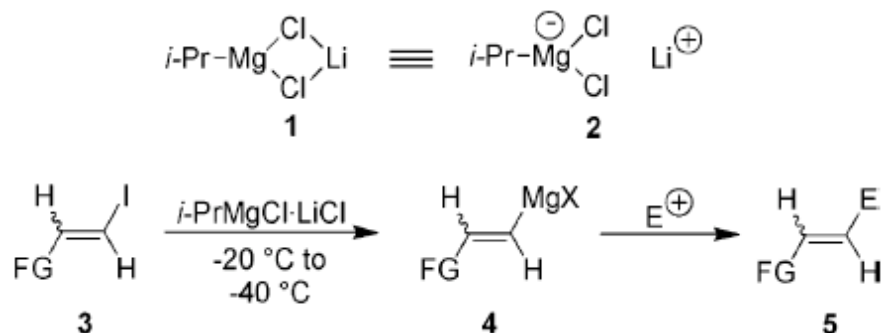
LiCl Catalyzed Aryl-Br/Mg Exchange



8 & 5 unstable even at
 -10 °C (*t*_{1/2} 12 & 24 h,
 respectively)

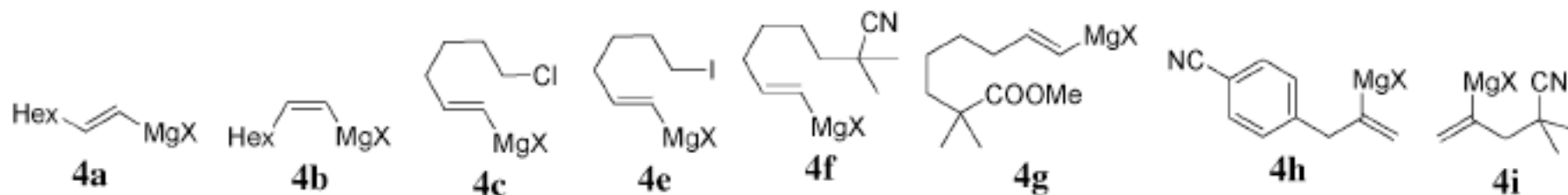


Stereoselective Alkenyl-I/Mg Exchange



- Much faster X/Mg exchange than with standard Mg reagents, *i*-PrMgCl and *i*-Pr₂Mg
- Exchange can now be performed at low temp. avoiding side reactions associated with higher temp. exchanges
- Likely due to increased electron density at Mg

Substrates Tested



EtCHO, DMF, (PhS)₂,
 allyl bromide, TsCN,
 2-iodo-benzaldehyde

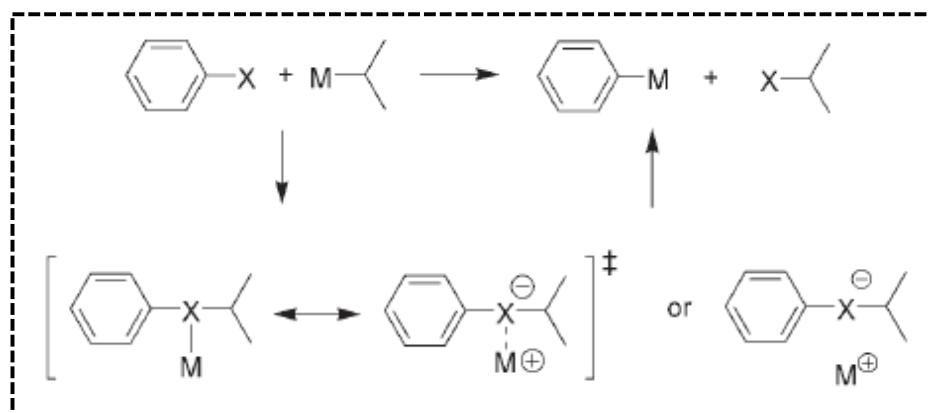
71-91% yield, complete stereoretention

Alkenyl-I/Mg exchange has been demonstrated with cyclic substrates, more electrophiles, and [Zn]-transmetallation/Negishi coupling*

H. Ren, A. Krasovskiy, and P. Knochehl, *Org. Lett.*, 2004, **6**, 4215-4217

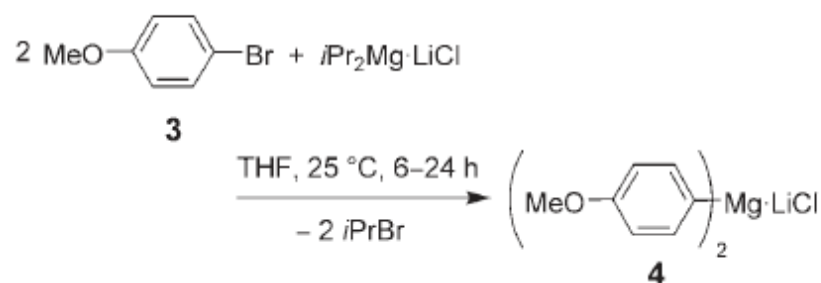
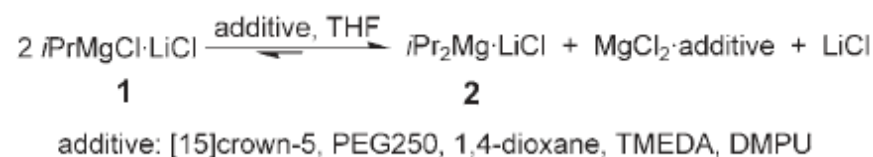
*H. Ren, A. Krasovskiy, and P. Knochehl, *Chem. Commun.*, 2005, 543-545

Active Exchange Reagent?



One-step exchange vs. Two-Step
Ate-Complex Intermediate

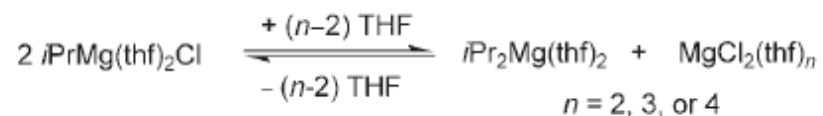
Sequestration of M^+ should
afford a greater electron density
at Mg (faster Br/Mg exchange)



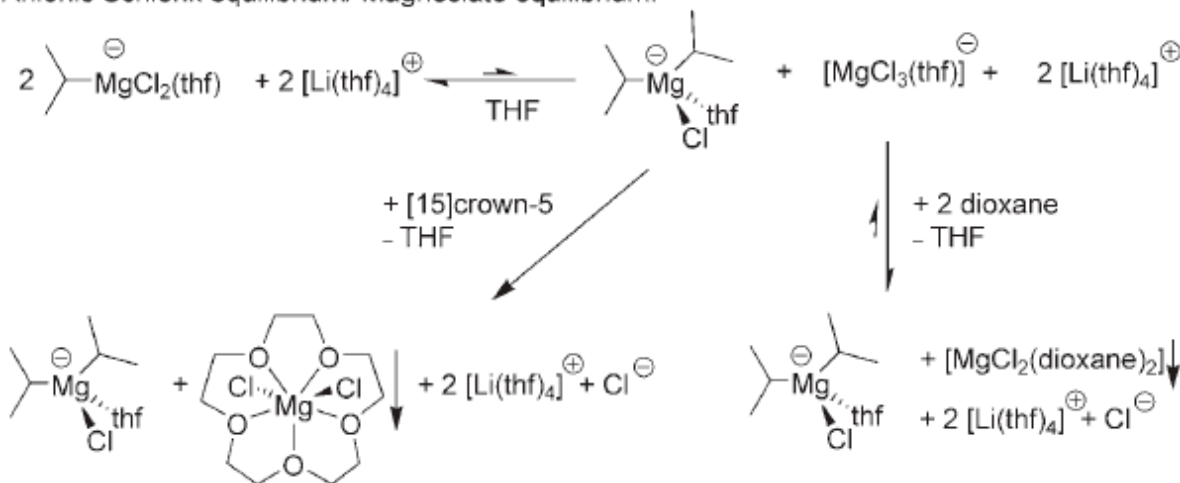
Entry	Additive	Amount	Conversion [%] ^[b]
1	–	–	31
2	[15]crown-5	1.0 equiv	100 ^[c] (6 h)
3	[18]crown-6	1.0 equiv	77
4	PEG250	10 vol %	55
5	Me(OCH ₂ CH ₂) ₄ OMe	10 vol %	60
6	DME	10 vol %	70
7	1,4-dioxane	10 vol %	100 ^[d] (10 h)
8	DMPU	10 vol %	60
9	TMEDA	10 vol %	77

[15]crown-5 & 1,4-dioxane superior additives
[12]crown-4 (Li⁺ selective) gave no rate enhancement

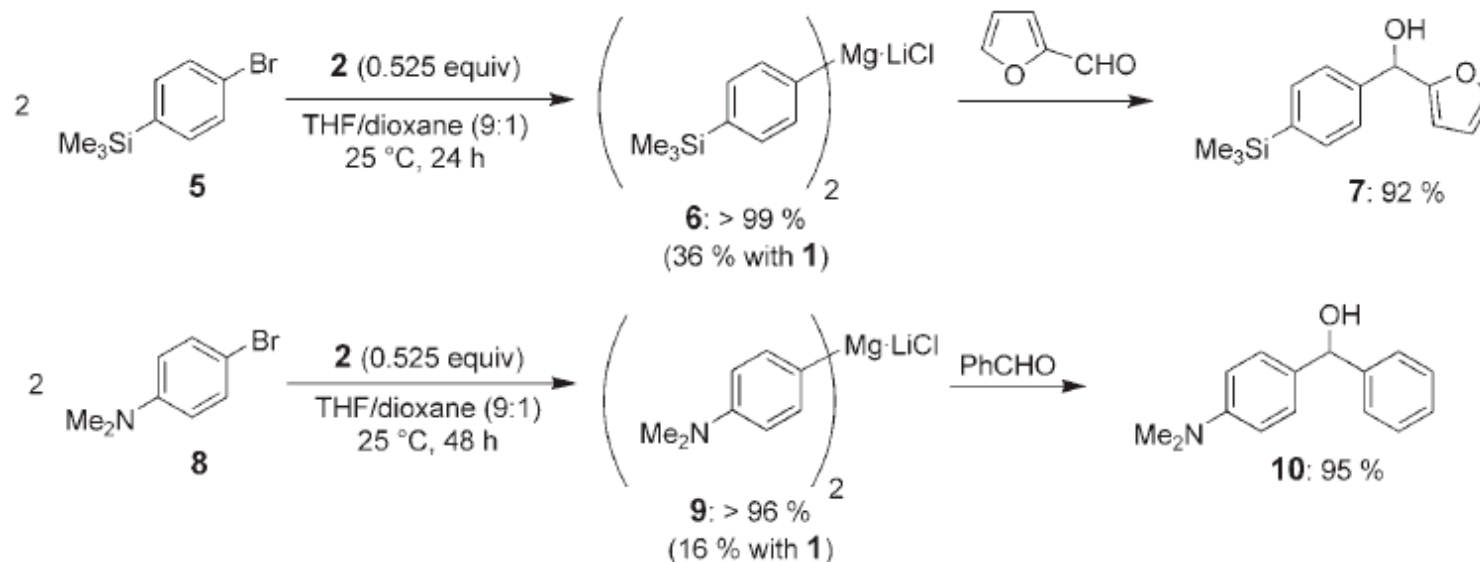
Schlenk equilibrium:



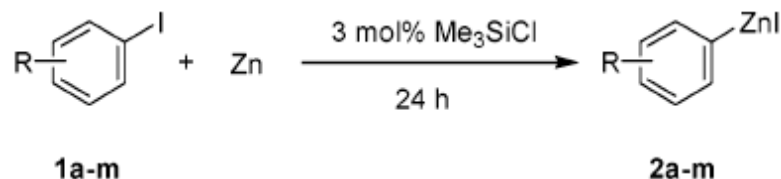
Anionic Schlenk equilibrium/ Magnesiate equilibrium:



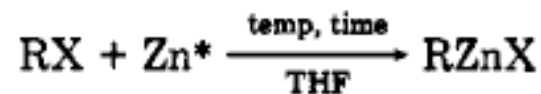
Can additives promote exchange with electron rich aryl halides (typically slow)?



Organozinc Reagents From Organobromides & Iodides

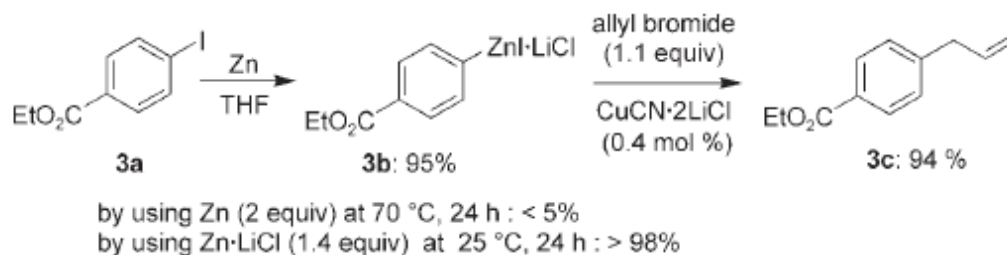
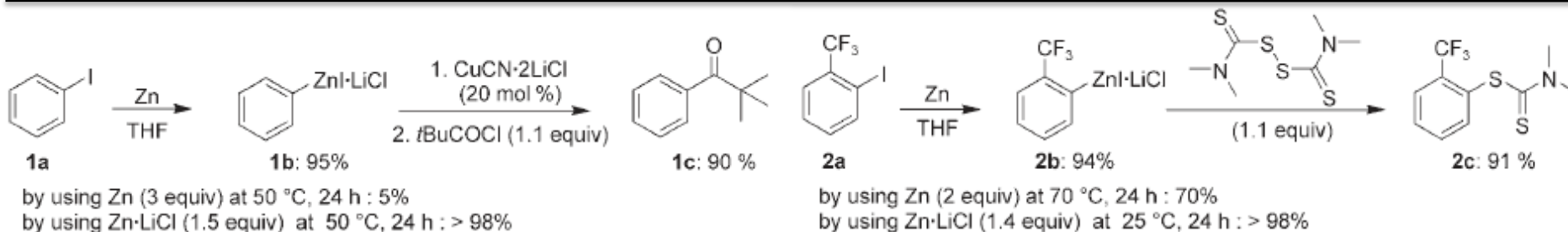


in THF, R = 2-EWG, 70 °C
Not general, relatively
harsh conditons¹



Rieke zinc (nanoparticles), 1-3
equivalents, not shelf stable²

Can direct zinc metallation be general with readily available zinc sources?

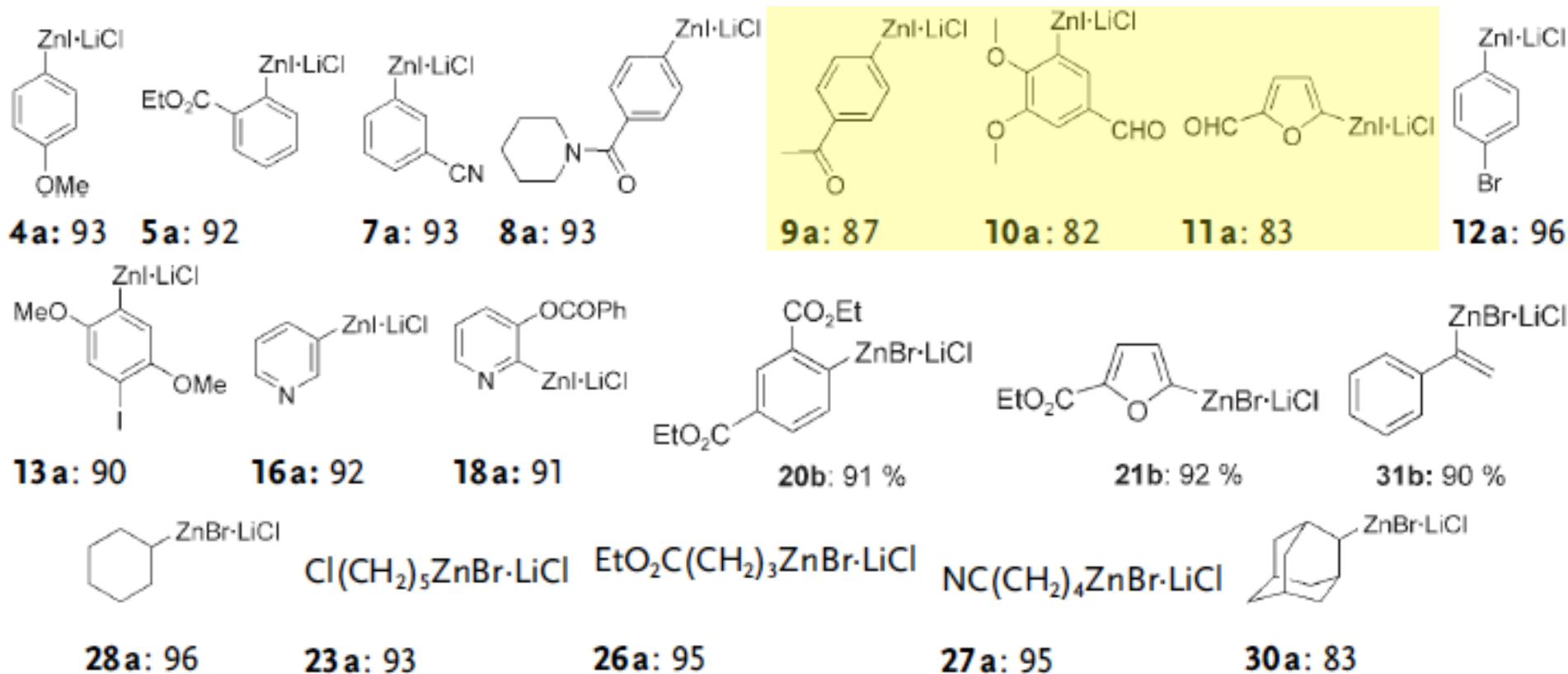


¹R. Ikegami, A. Koresawa, T. Shibata, K. Takagi, *J. Org. Chem.*, 2003, **68**, 2195-2199

²L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.*, 1991, **56**, 1445-1453

A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 6040-6044

Substrate Scope

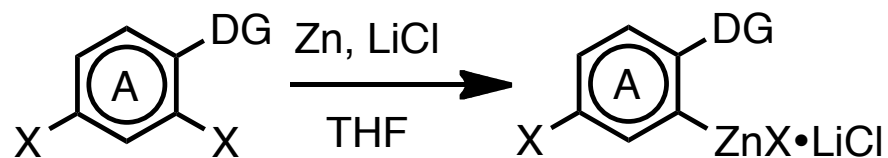


Wide functional group tolerance

Subsequent electrophile trapping or Negishi coupling afforded good to excellent yields

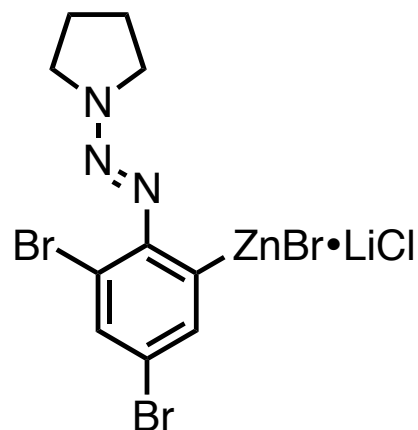
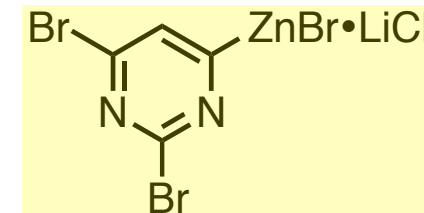
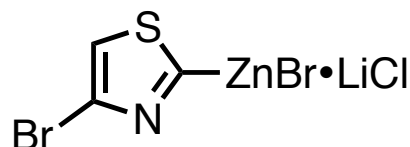
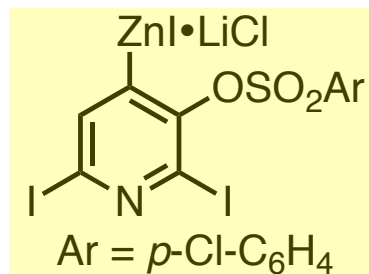
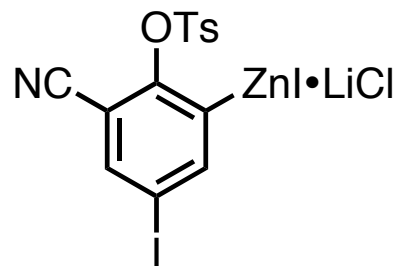
Hypothesis: LiCl complexes with R-ZnX *in situ*, more soluble, and more available surface area

Directed Ortho Insertion (DOI) with Zinc and LiCl



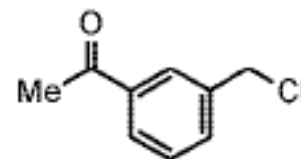
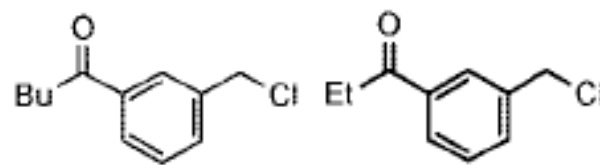
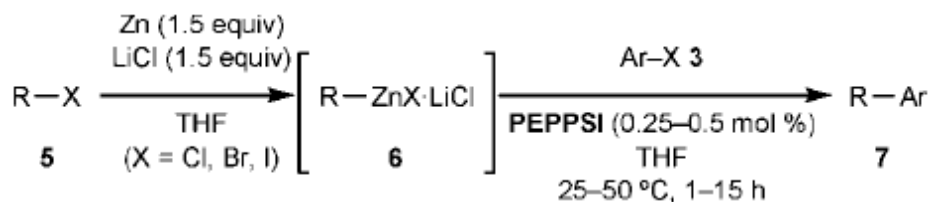
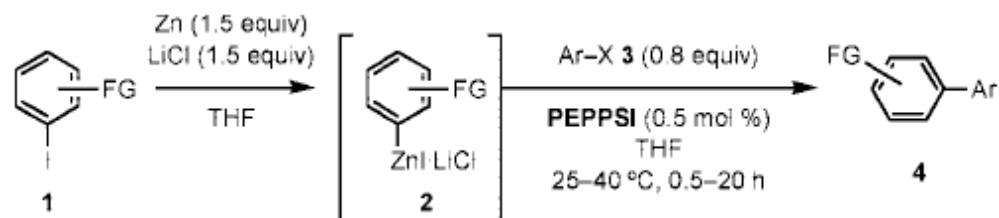
A = Aryl or Heteroaryl

X = I, Br ; DG = $-\text{CO}_2\text{R}$, $-\text{COR}$, $-\text{OAc}$, $-\text{N}=\text{N}-\text{NR}_2$, $-\text{OCON}(i\text{-Pr})_2$, $-\text{OSO}_2\text{Ar}$



Generally, higher temps. required for bromide insertion.
Arylzinc compounds were subsequently trapped with acyl or allyl electrophiles via Cu^I catalysis or Negishi cross-coupled with aryl iodides in good yields

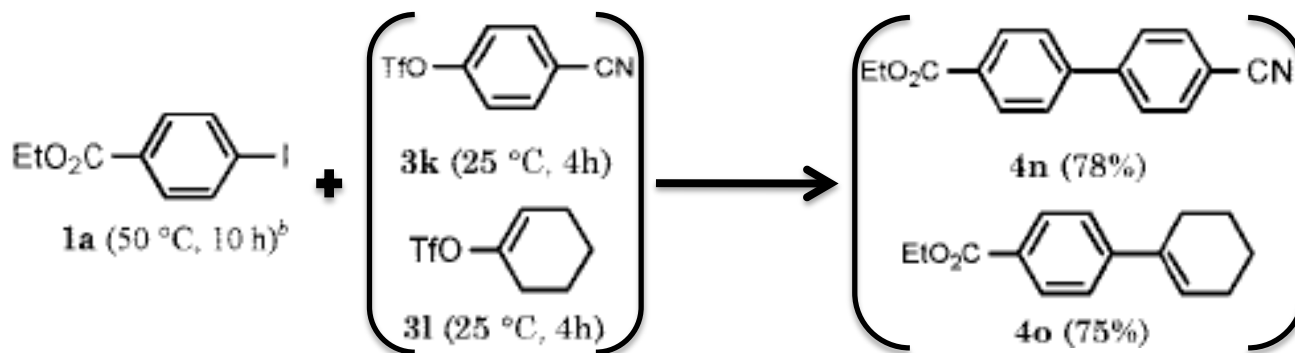
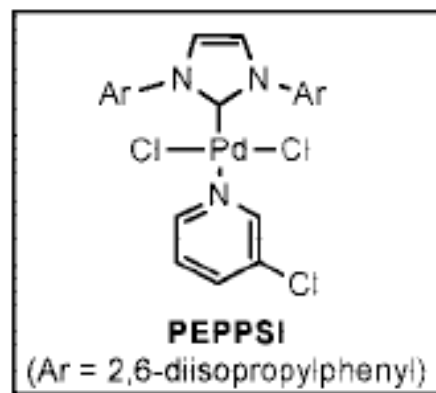
One-Pot Negishi Coupling with Aryl Chlorides, Bromides, and Triflates



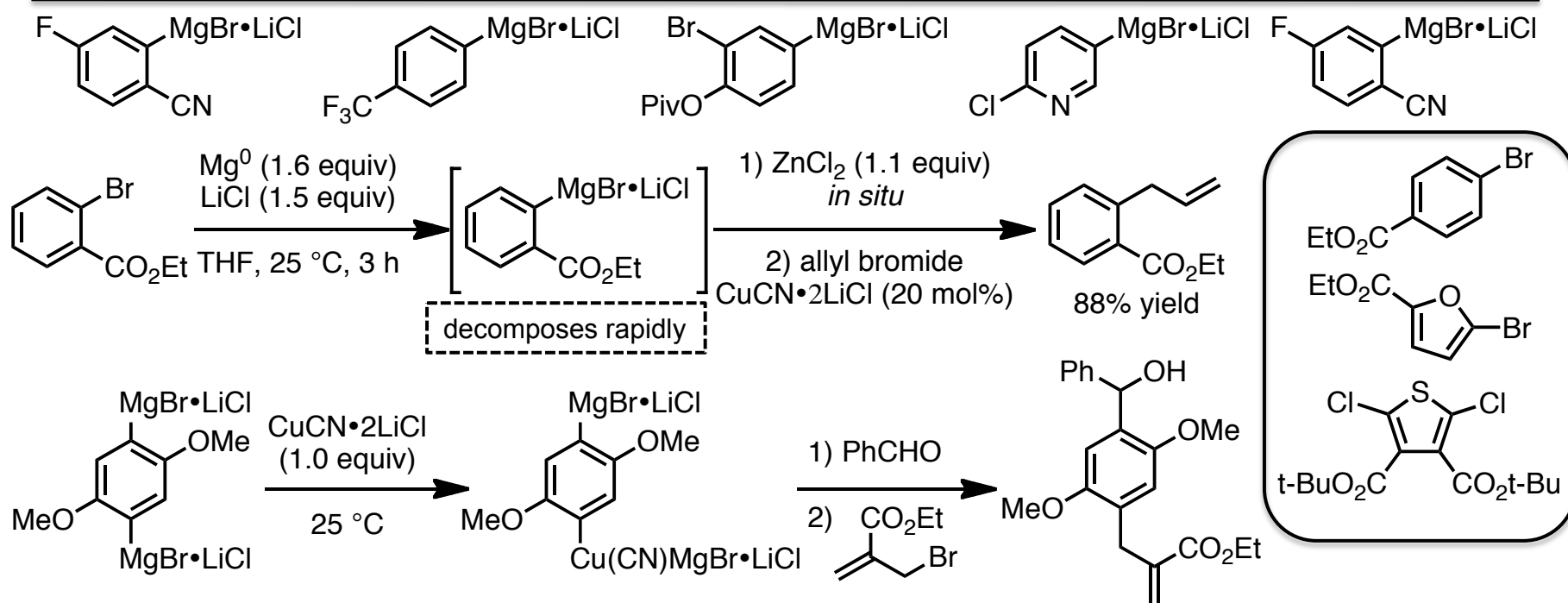
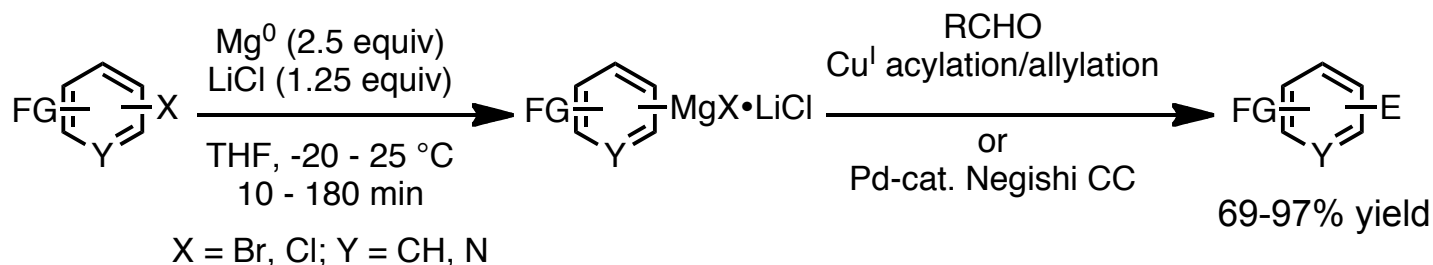
5e (25 °C, 3 h)^c

Good to excellent yields, EDG & EWG tolerated along with heteroaryl substrates & coupling partners

Can be generated *in situ* and then cross-coupled

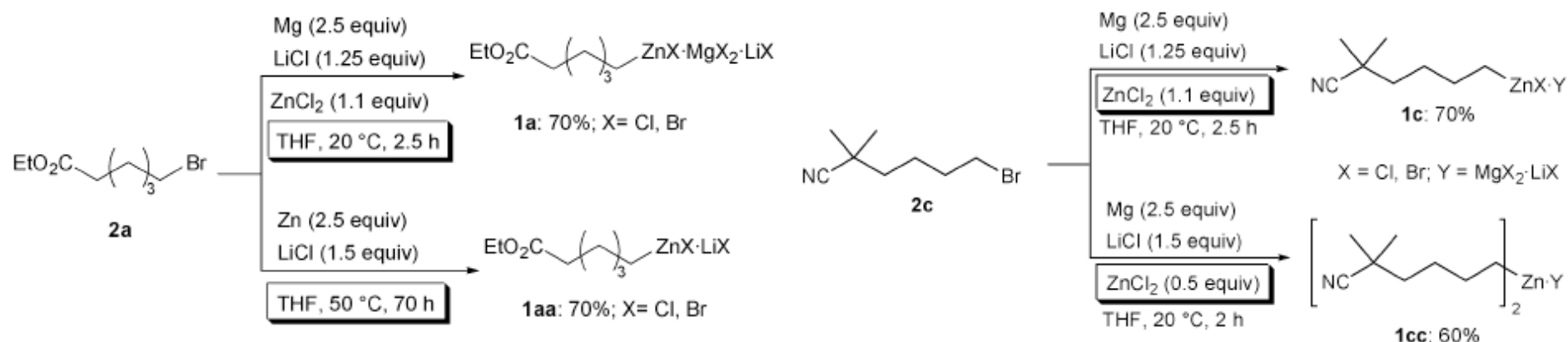


Direct Magnesiation from Functionalized Aryl Halides

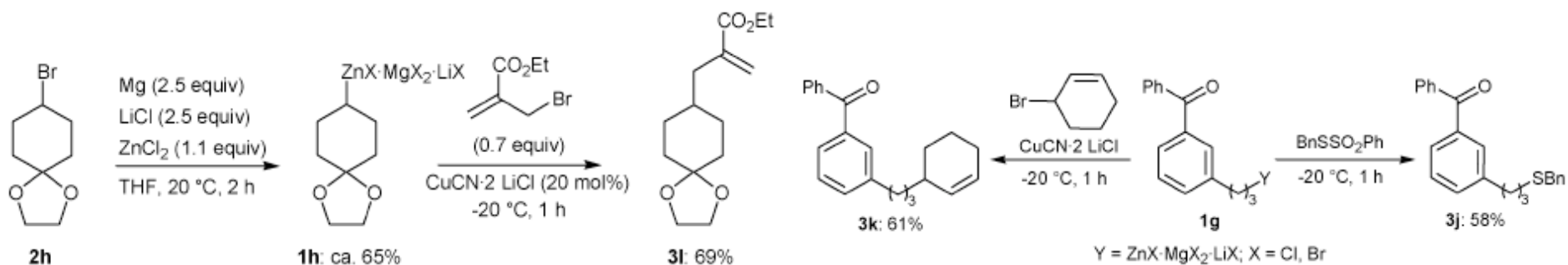


Magnesium exchange with sacrificial Grignard reagent no longer required
In situ zinc transmetalation is necessary for sensitive substrates

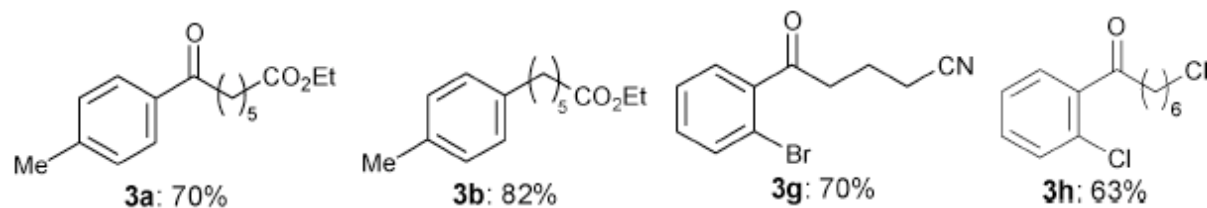
Alkylzinc Halides from Alkyl Bromides



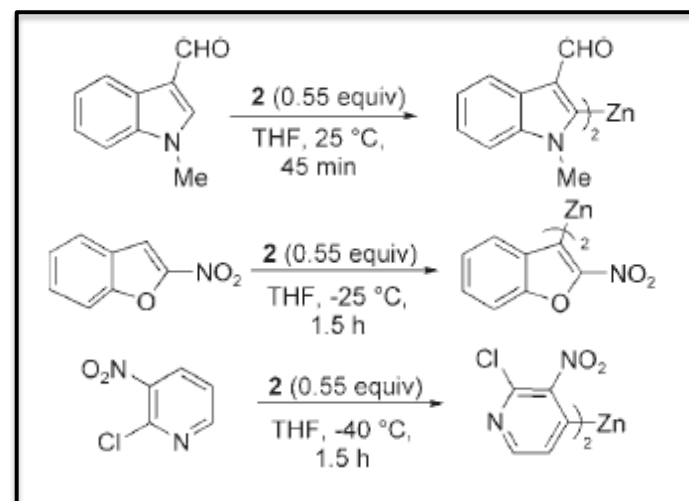
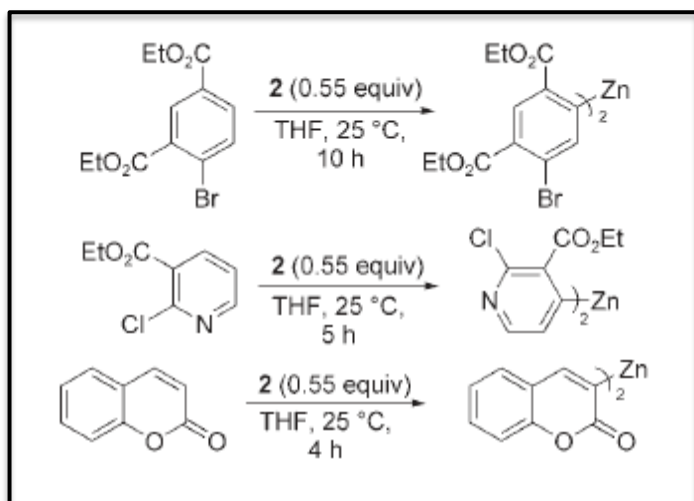
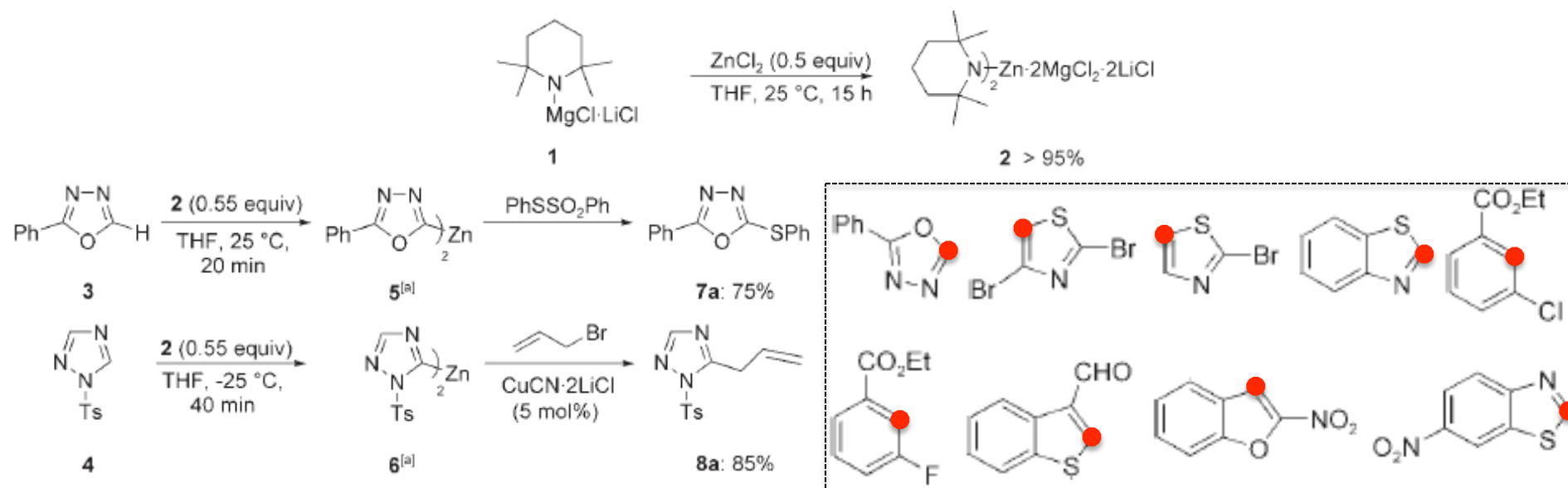
**Organomagnesium intermediate can be trapped *in situ* with ZnCl₂
Mg⁰ provides significant rate enhancement**



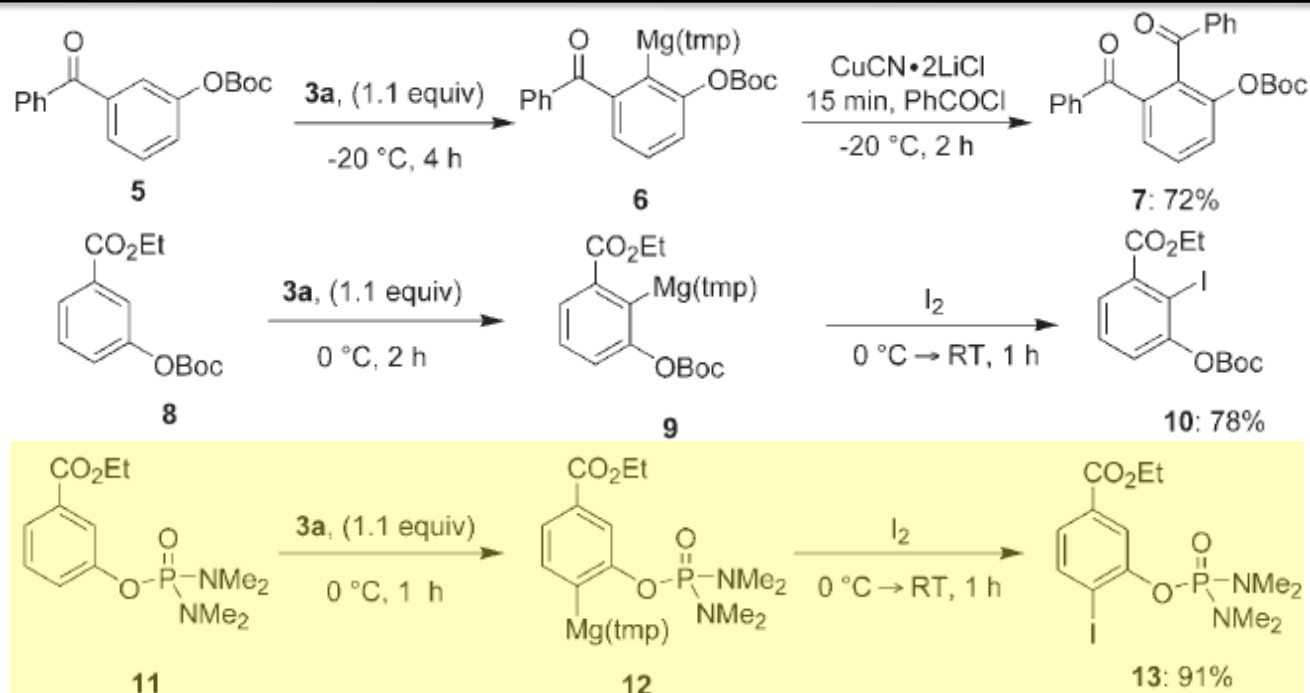
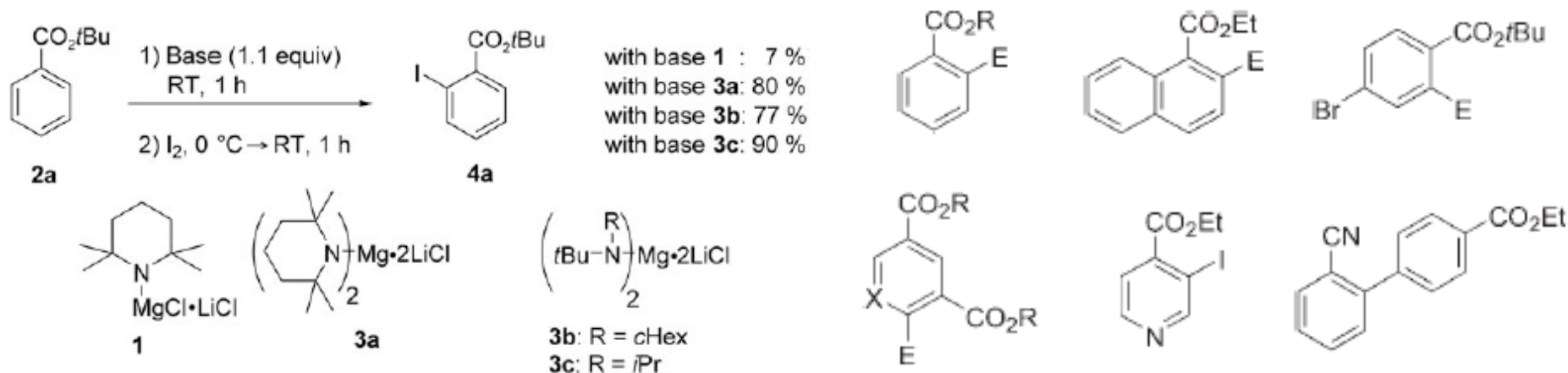
After transmetalation with CuCN·2LiCl (1.0 equiv, -30 °C) or Pd^{II} a variety of cross-coupling products are obtained



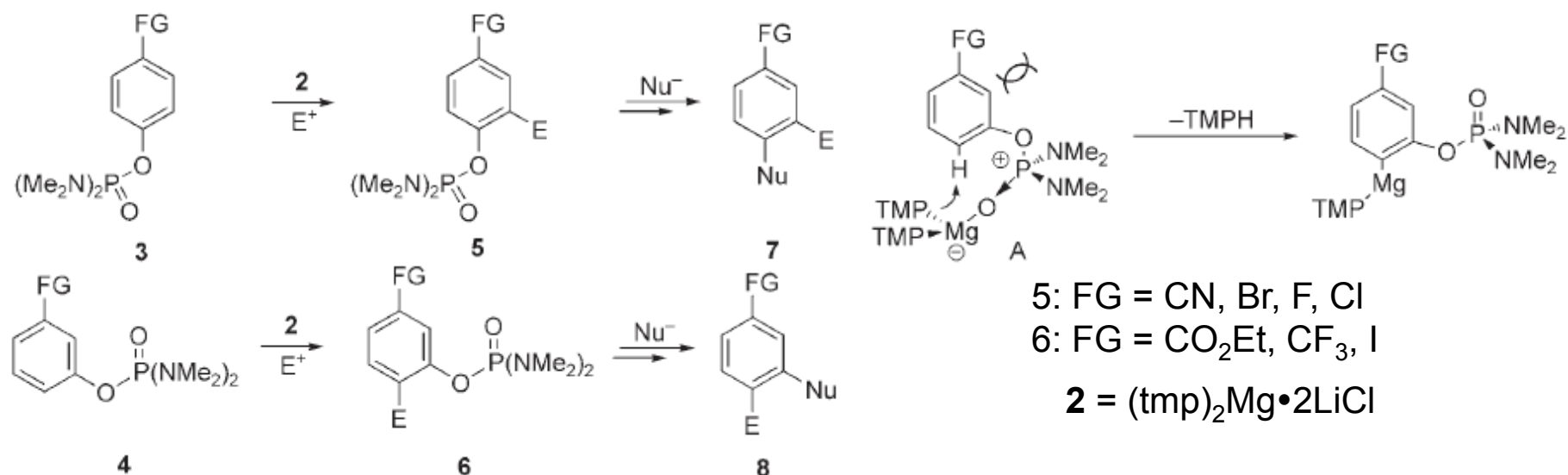
Reactive Arene and Heteroarene Zincation



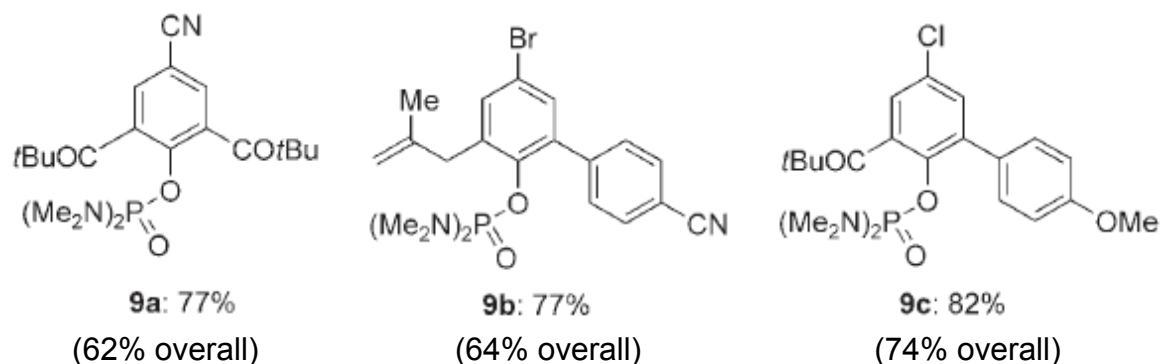
Directed Aryl Magnesyation with $(\text{tmp})_2\text{Mg}\cdot 2\text{LiCl}$



Directed *Meta* and *Para* Magnesylation with Aryl Phosphoramidates



Synthesis of **5** & **6** analogs proceeded well (72-90% yield)



Phosphoramidate directing group could subsequently be manipulated to nonaflates for nickel-catalyzed cross-coupling or palladium catalyzed reduction

Directed Magnesium and Zincation with N-Heterocycles

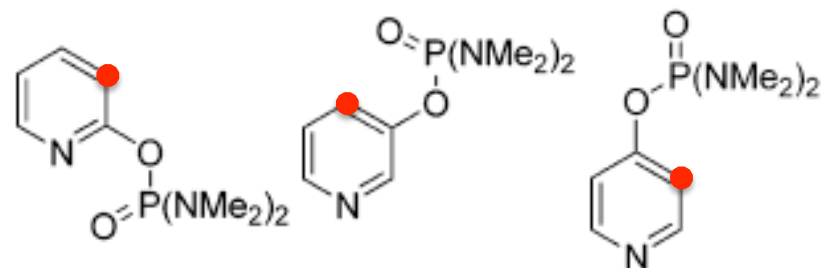
Reagents used

4a = (tmp)MgCl•LiCl

4b = (tmp)₂Mg•2LiCl

4c = (tmp)₂Zn•2MgCl₂•2LiCl

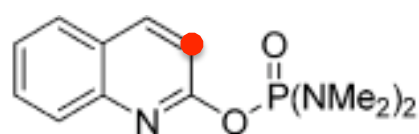
Subsequent electrophile trapping, Cu^I (cat.) additions, and Negishi cross-coupling



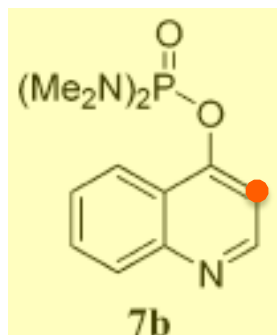
5a

5b

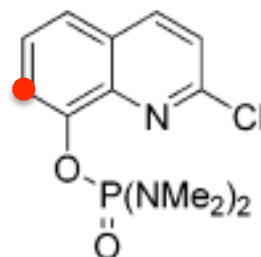
5c



7a



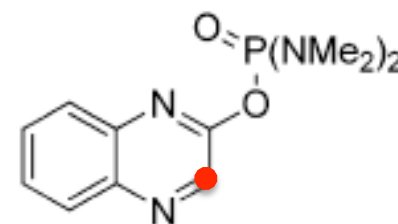
7b



7c



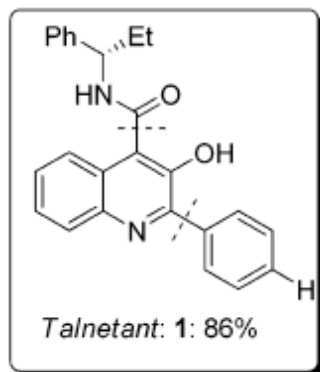
7d



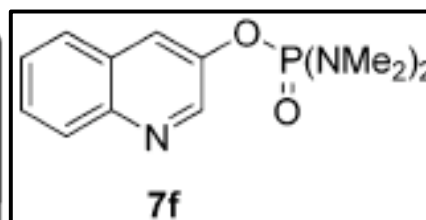
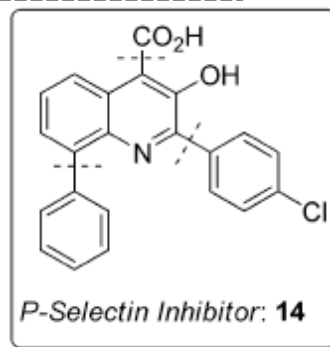
7e

DMG site-selective over kinetic site preference

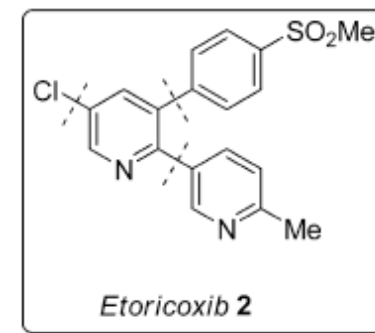
• = Site of metalation



55% overall from **7f**

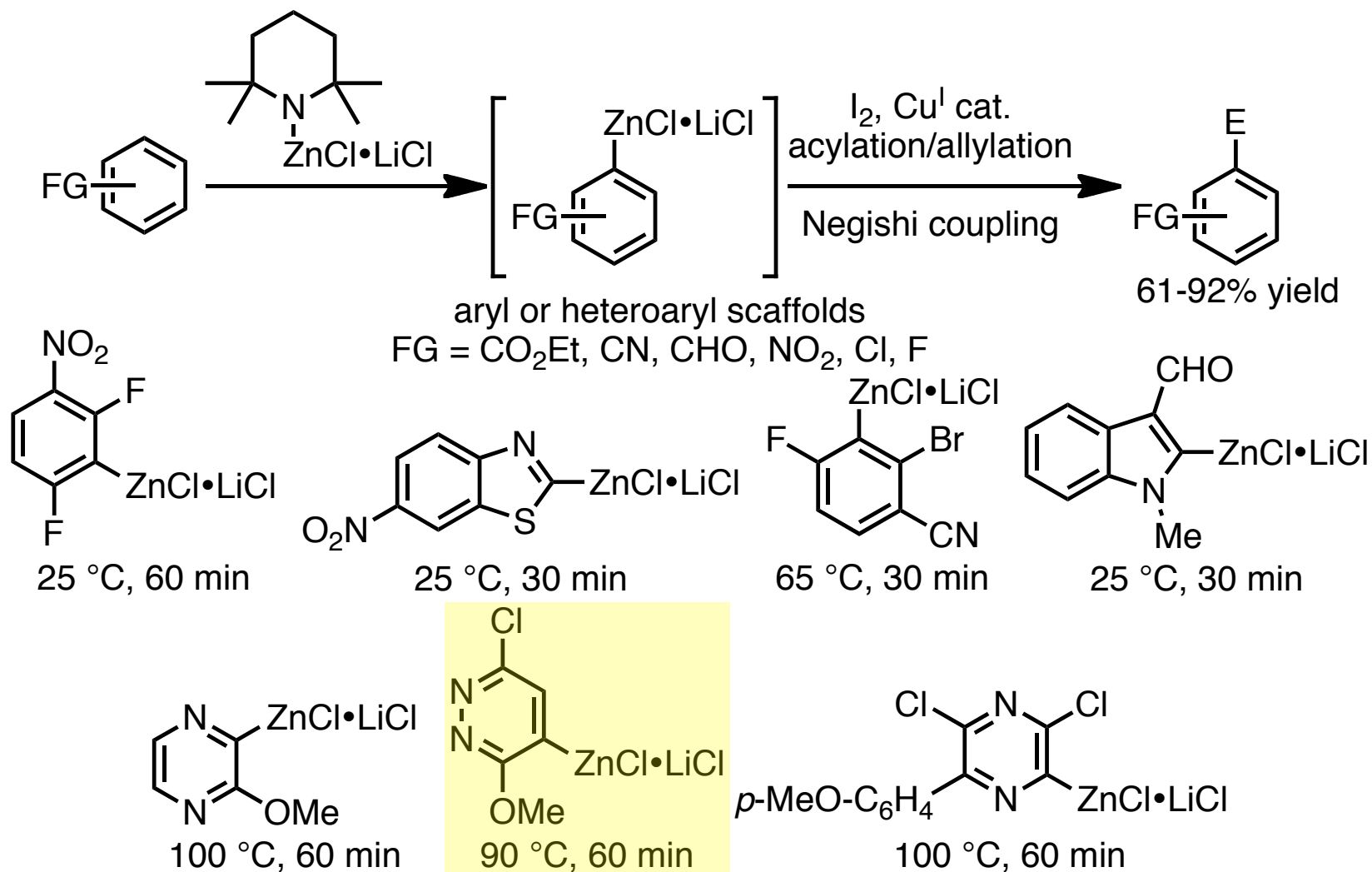


46% overall from **7f**



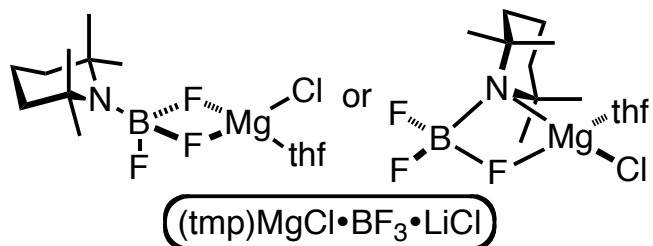
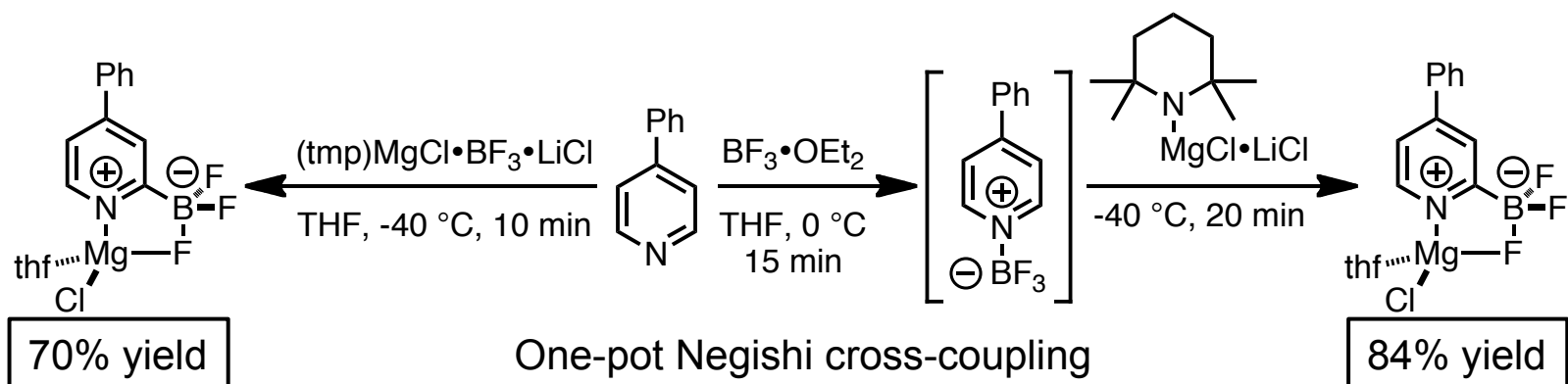
From **5a**

Direct and Selective Zincation with $\text{TMPZnCl}\cdot\text{LiCl}$

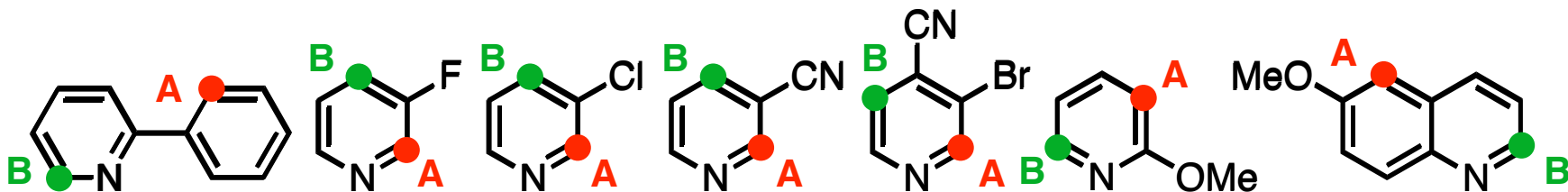


When $(\text{tmp})_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ was used poor site selectivity was observed

BF₃-Assisted, Direct Metalation of Unactivated Heteroaryl Compounds

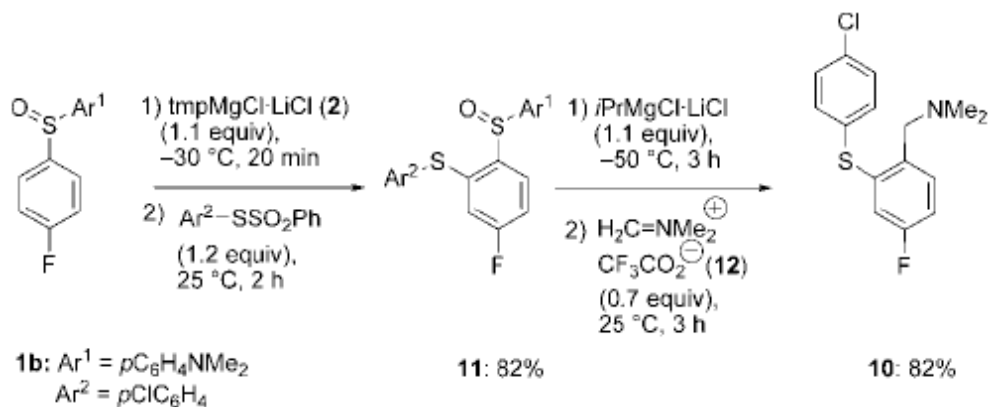
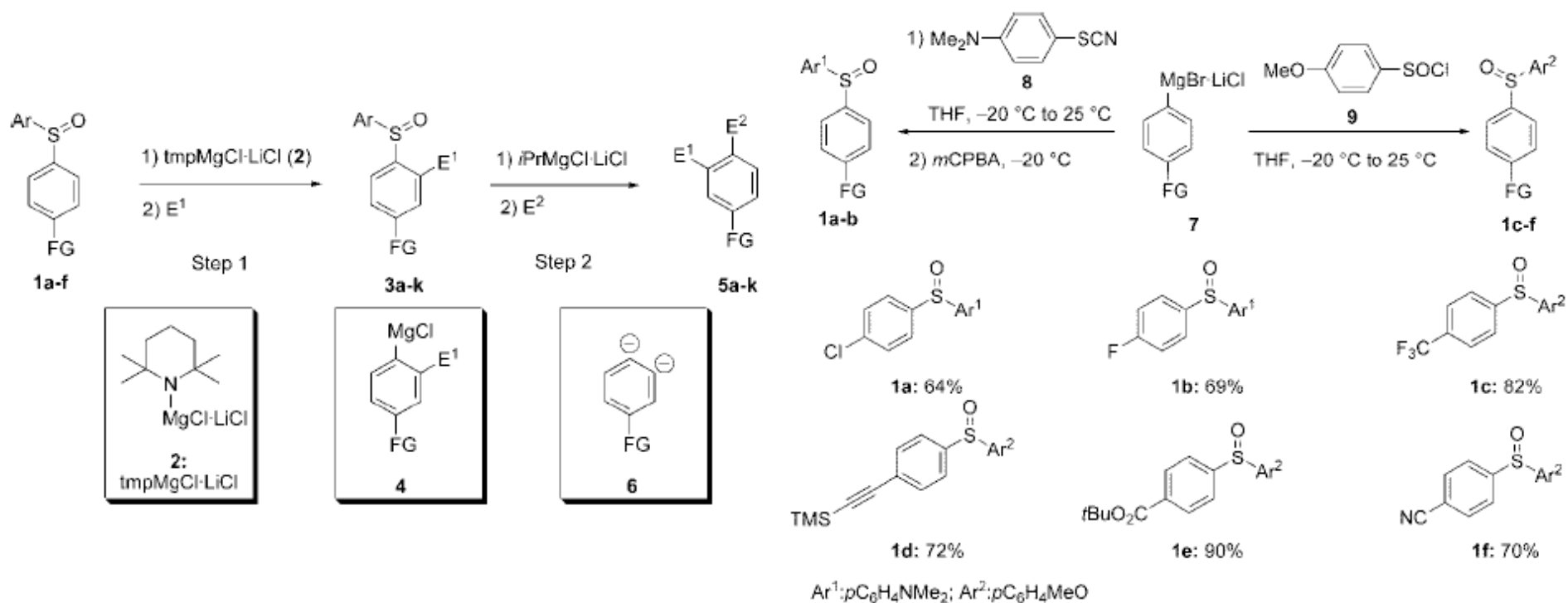


Procedure A: No BF₃, (tmp)MgCl·LiCl, (tmp)ZnCl·LiCl, (tmp)₂Zn·2MgCl₂·2LiCl, or (tmp)₃Al·3LiCl
Procedure B: BF₃ precomplex, (tmp)MgCl·LiCl or (tmp)₂Zn·2MgCl₂·2LiCl



Possible steric influence of the BF₃-complex on site-selectivity of metalation

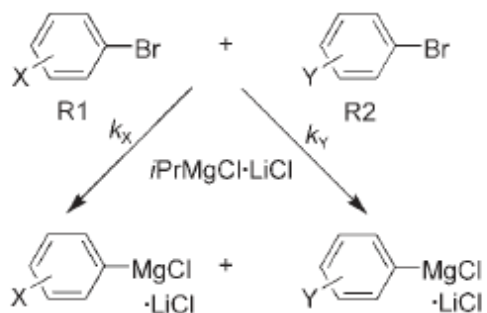
Sulfoxide-Magnesium Exchange



Regioselectivity of SO(Ar)₂/Mg exchange is determined by the electron density of the aryl substituents

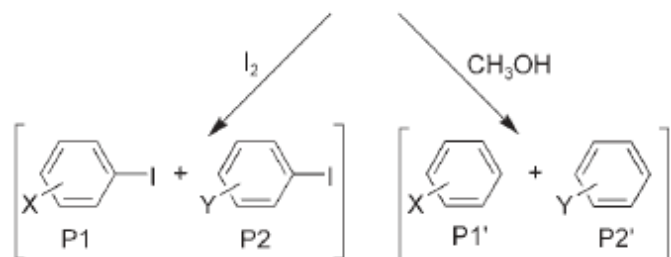
The most stable organomagnesium intermediates contains the EWG-aryl group

Bromine-Magnesium Exchange Rate via Competition Studies



$$\kappa = \frac{k_x}{k_y} = \frac{\lg(1 + [P1]_t/[R1]_t)}{\lg(1 + [P2]_t/[R2]_t)}$$

Quenching method did not affect results

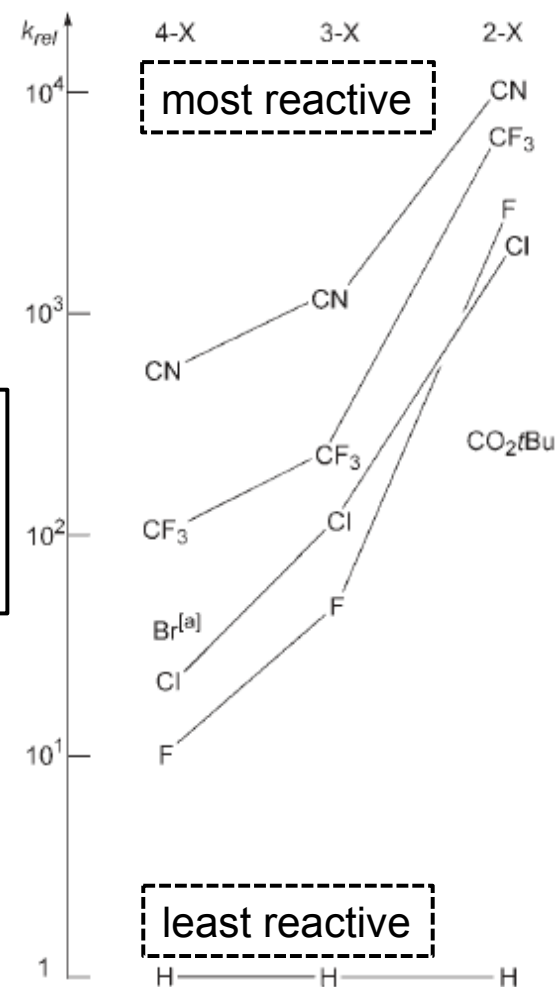


X, Y = H, F, Cl, Br, CF₃, CO₂t-Bu, CN
22 competition constant total

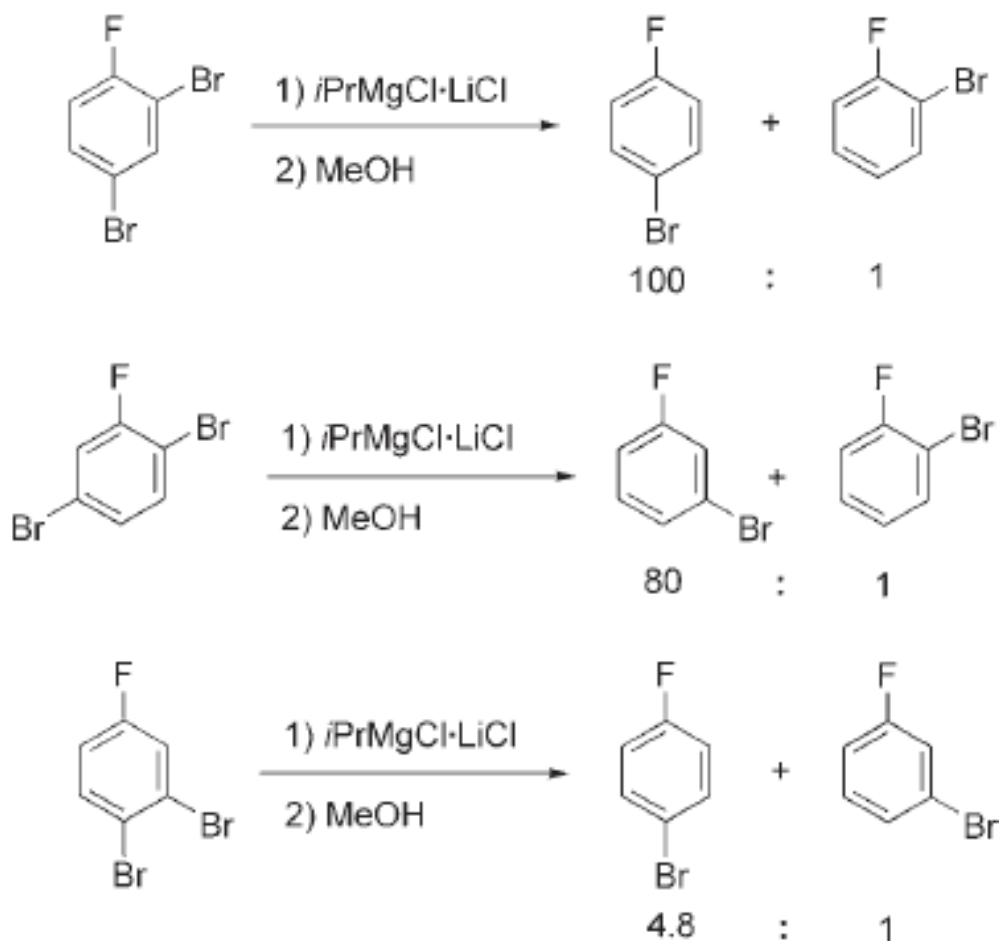
The substituent effects do not correlate with any Hammett substituent constants!



No exchange product observed via GC, competition constants, κ , are independent of reactant concentrations



Bromine-Magnesium Exchange Rate via Competition Studies

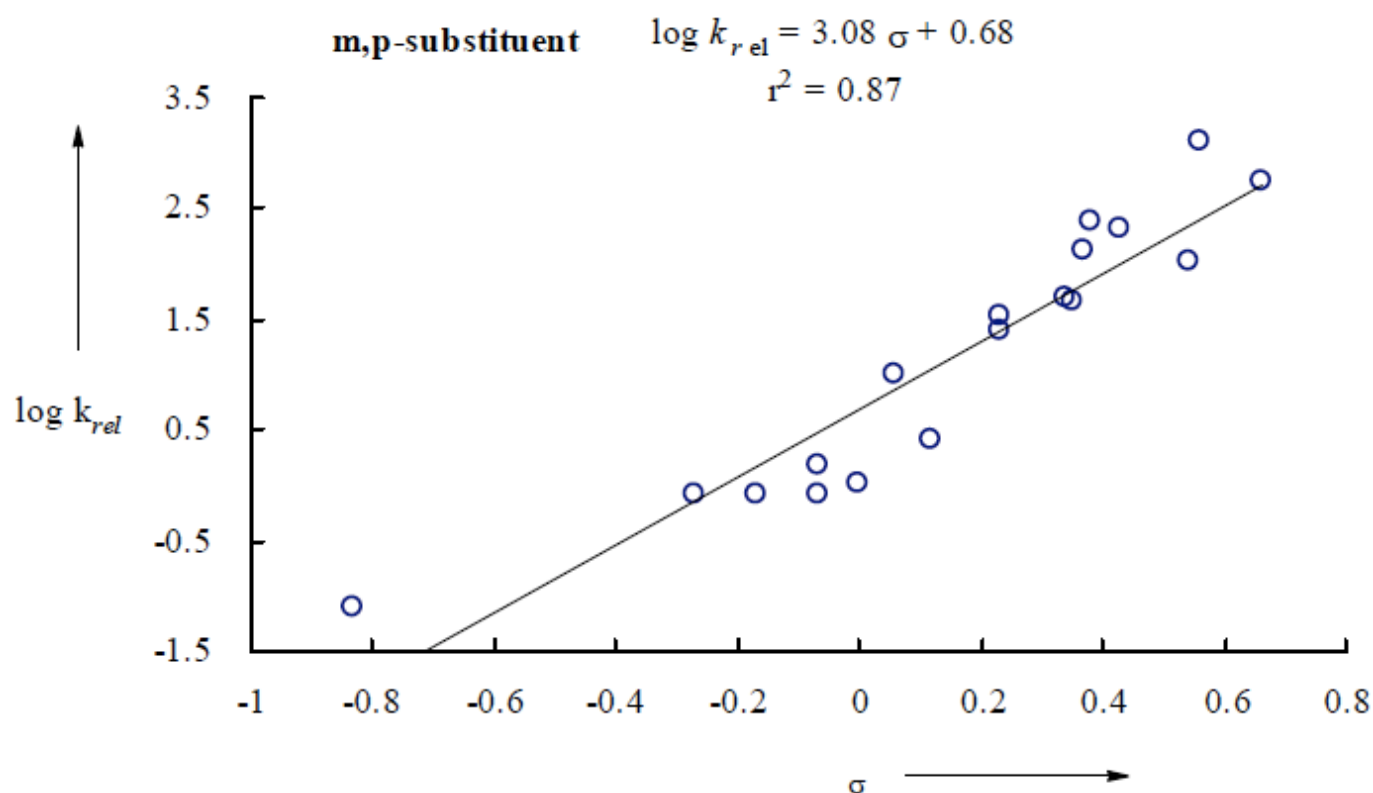


Can a model for site-selectivity in polyfunctional aromatic compounds be made?

Progress Towards a General Model

- More substrates were screened with 58 competition constants total
- EDG substituents also examined
- 1 & 2-Bromonaphthalene and 9-bromoanthracene analogs also examined

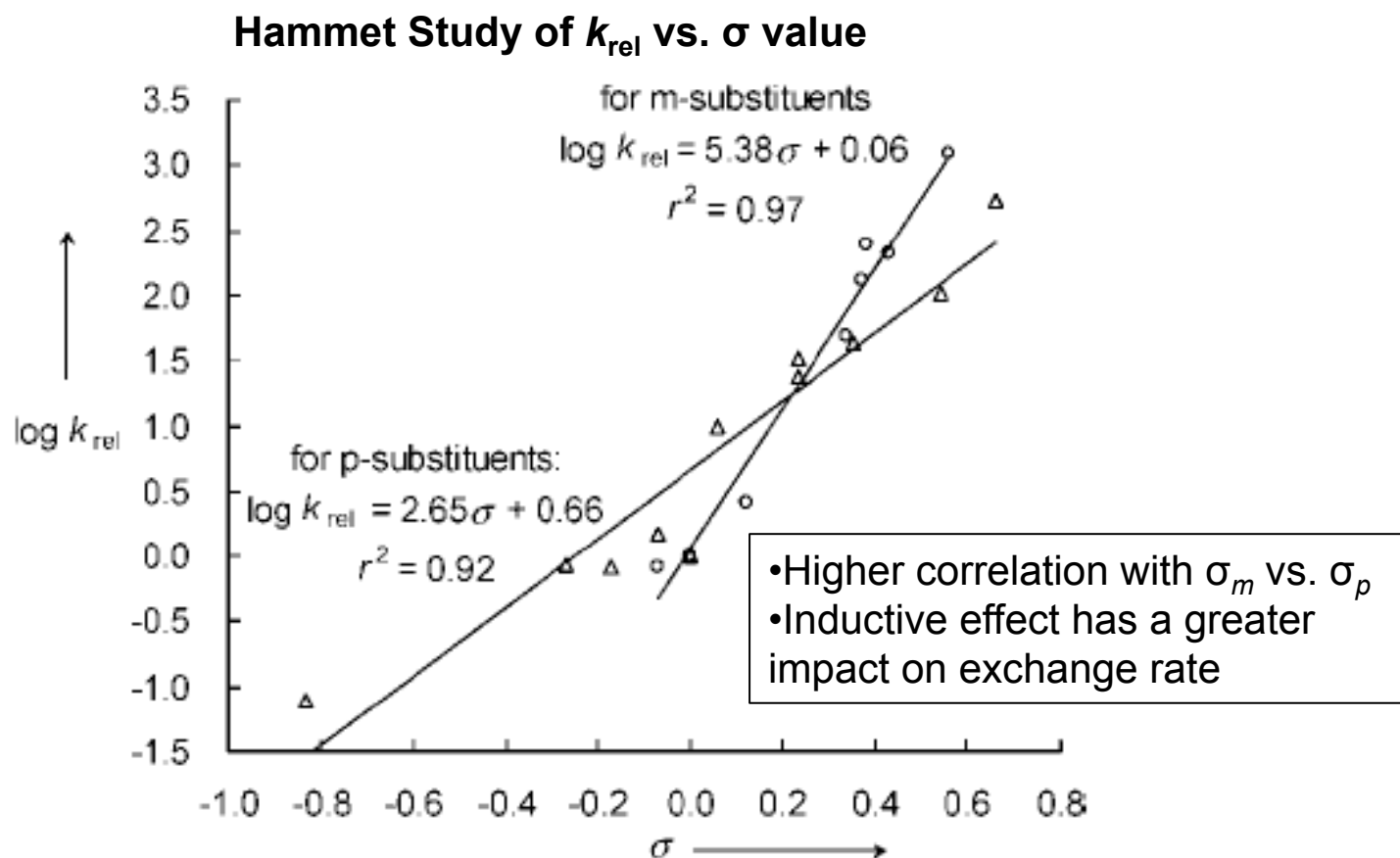
Hammett Study of k_{rel} vs. σ value



Initially σ_m and σ_p were plotted together, but separately...

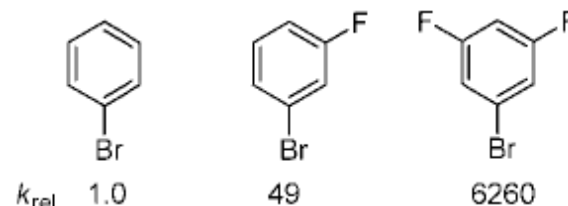
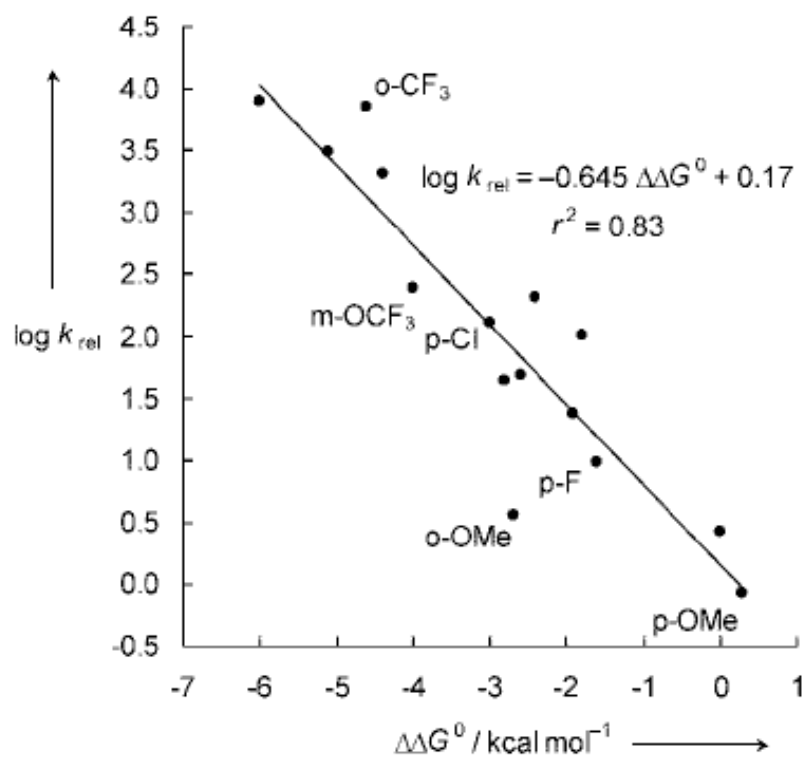
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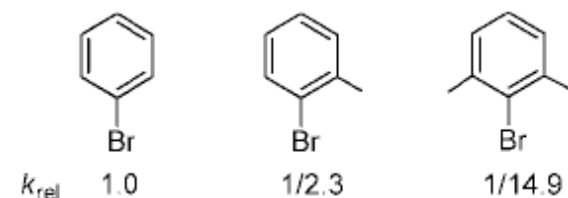


Progress Towards a General Model: Additional Correlations and Influences

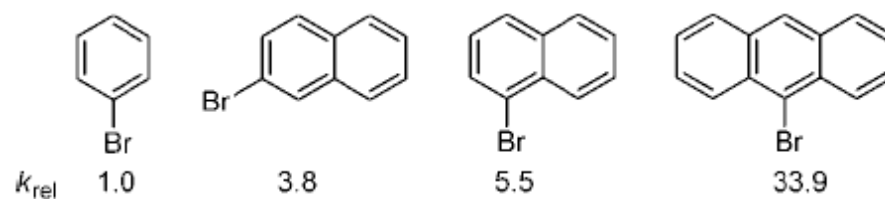
k_{rel} vs. Aryllithium Basicity*



Additional fluorine affords a synergistic rate enhancement



Steric shielding impacts rate in addition to inductive effects

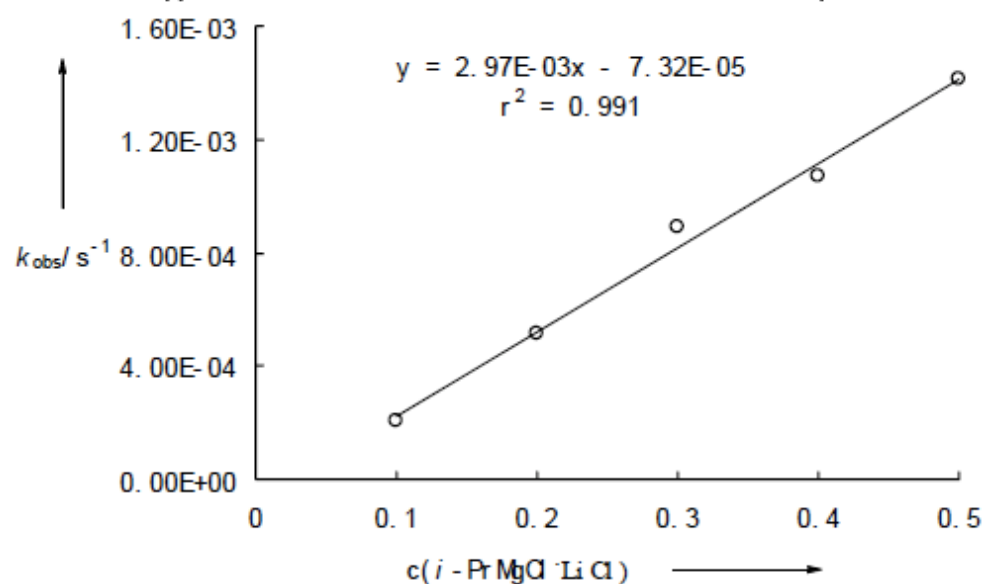
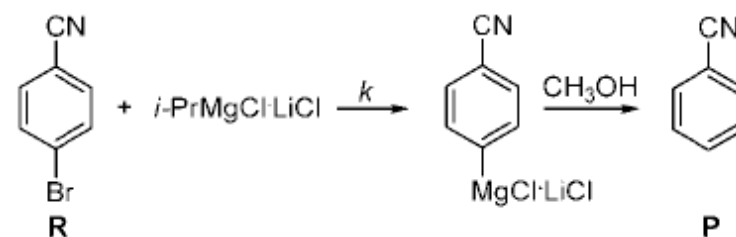
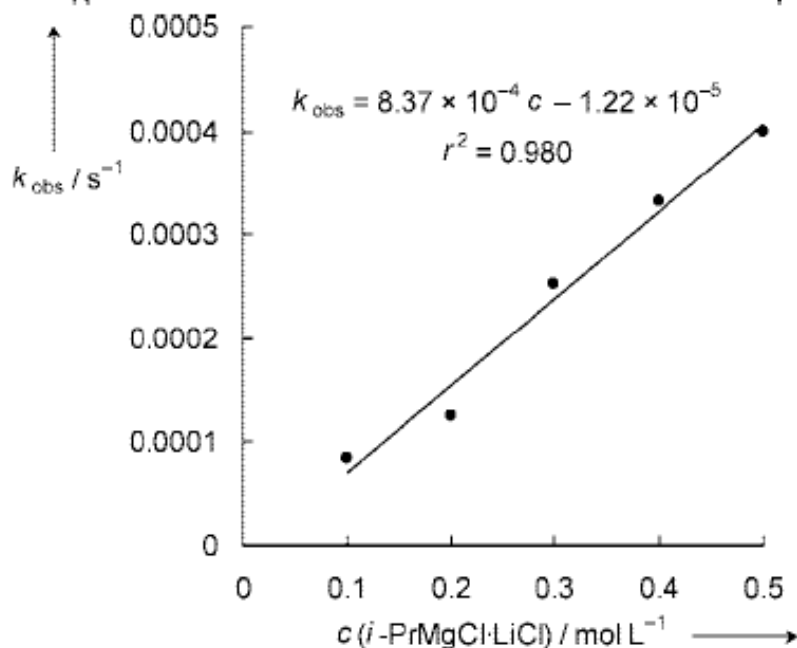
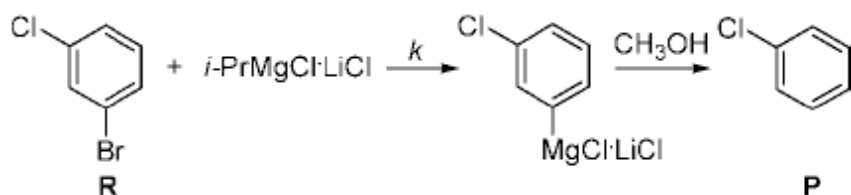


Consistent with the reactivity in electrophilic aromatic substitution



*J. Gorecka-Kobylinska and M. J. Schlosser, *J. Org. Chem.*, 2009, **74**, 222-229
L. Shi, Y. Chu, P. Knochel, and H. Mayr, *J. Org. Chem.*, 2009, **74**, 2760-2764

Progress Towards a General Model: Determining the Absolute Rate Constant

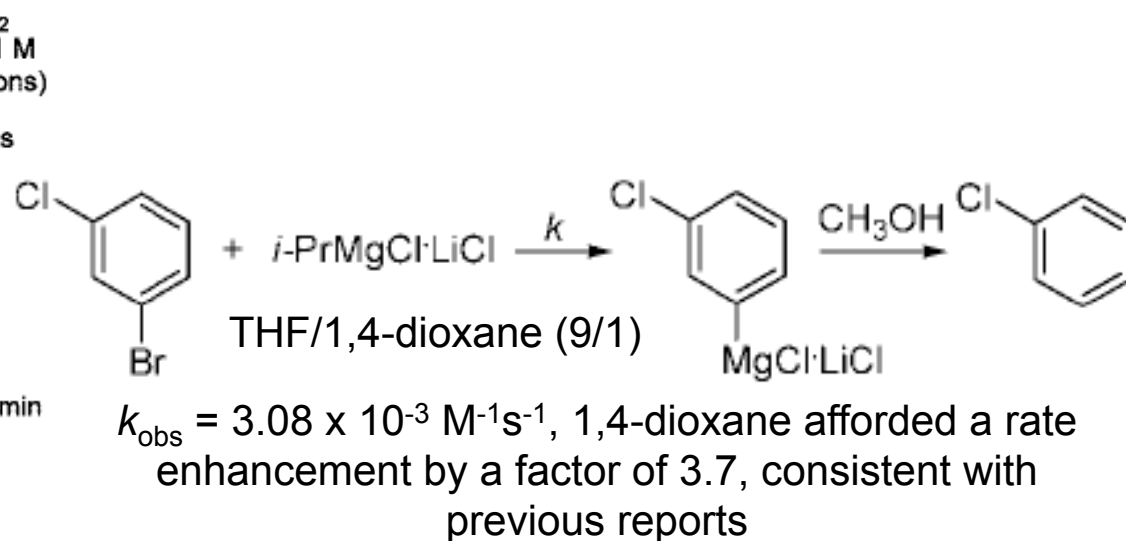
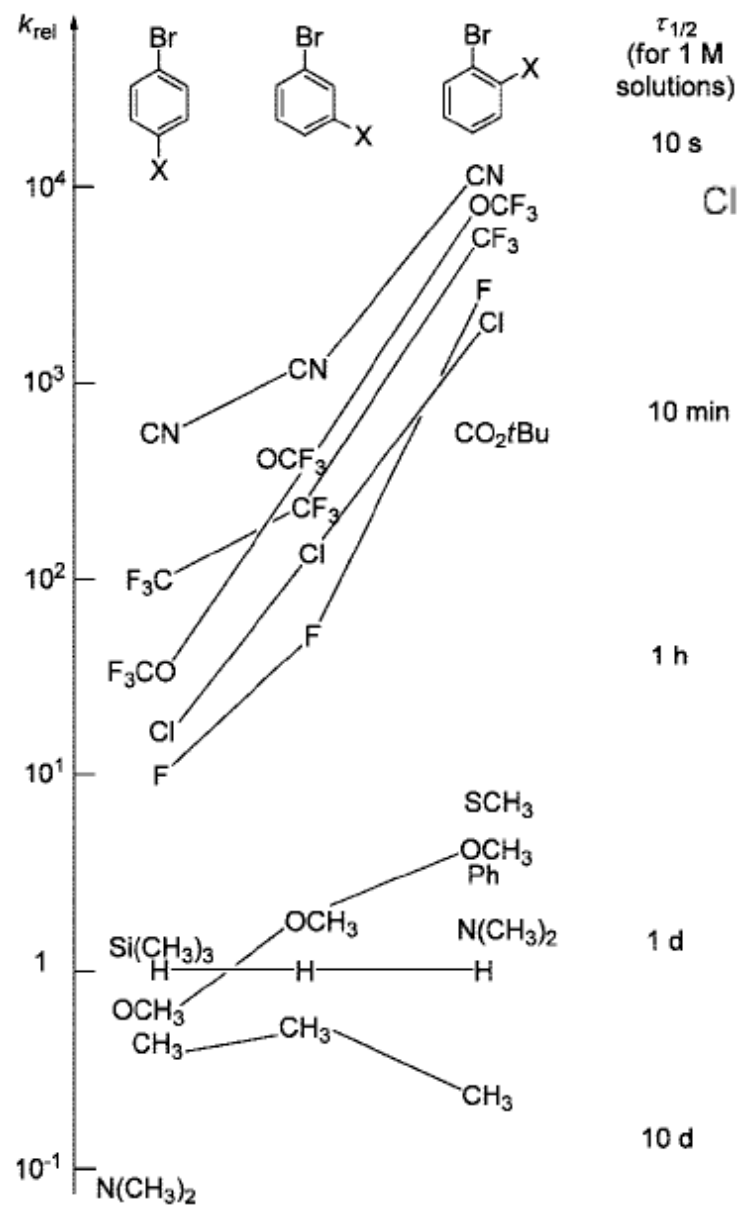


$$[\text{R}] = 0.01 \text{ M} \quad \frac{-d[\text{R}]}{dt} = k[\text{R}]^n [i\text{PrMgCl}\cdot\text{LiCl}]^1$$

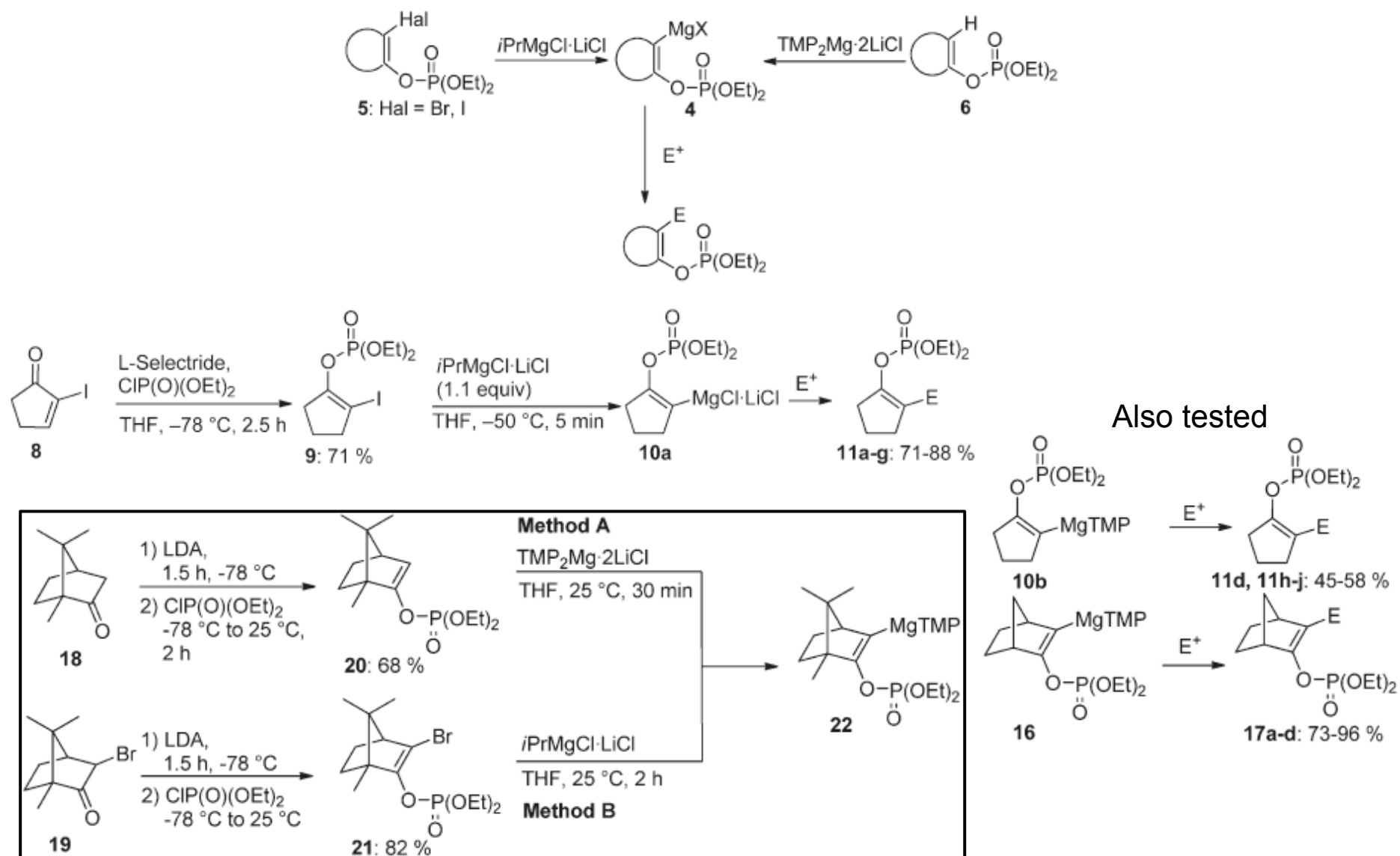
First-order rate dependence on Grignard reagent

$k_m/k_p = 3.55$ (vs. 4.14 from competition studies)
 Average value used to calculate $t_{1/2}$ values for k_{rel} values (not shown)

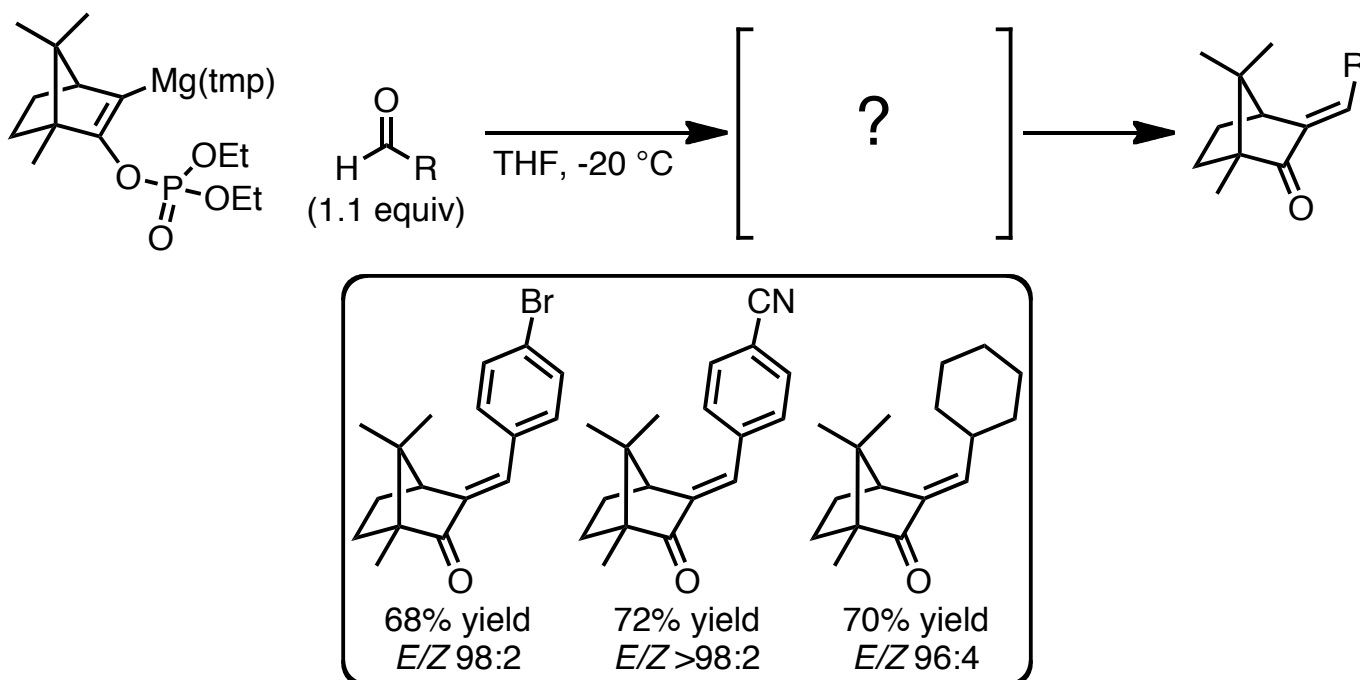
Progress Towards a General Model: Calculated Half-Lives



Magnesium-Halide Exchange with Enol Phosphates

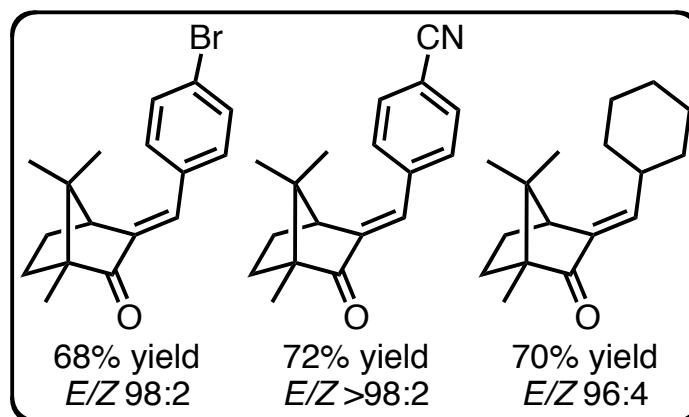
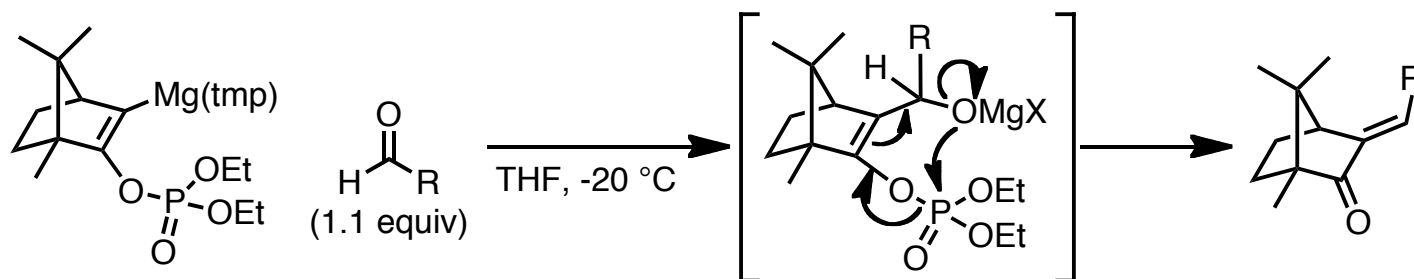


Group Question: Enol Phosphates



- 1) Provide intermediate and mechanism which accounts for the observed product
- 2) Rationalize the observed diastereoselectivity

Group Question: Enol Phosphates

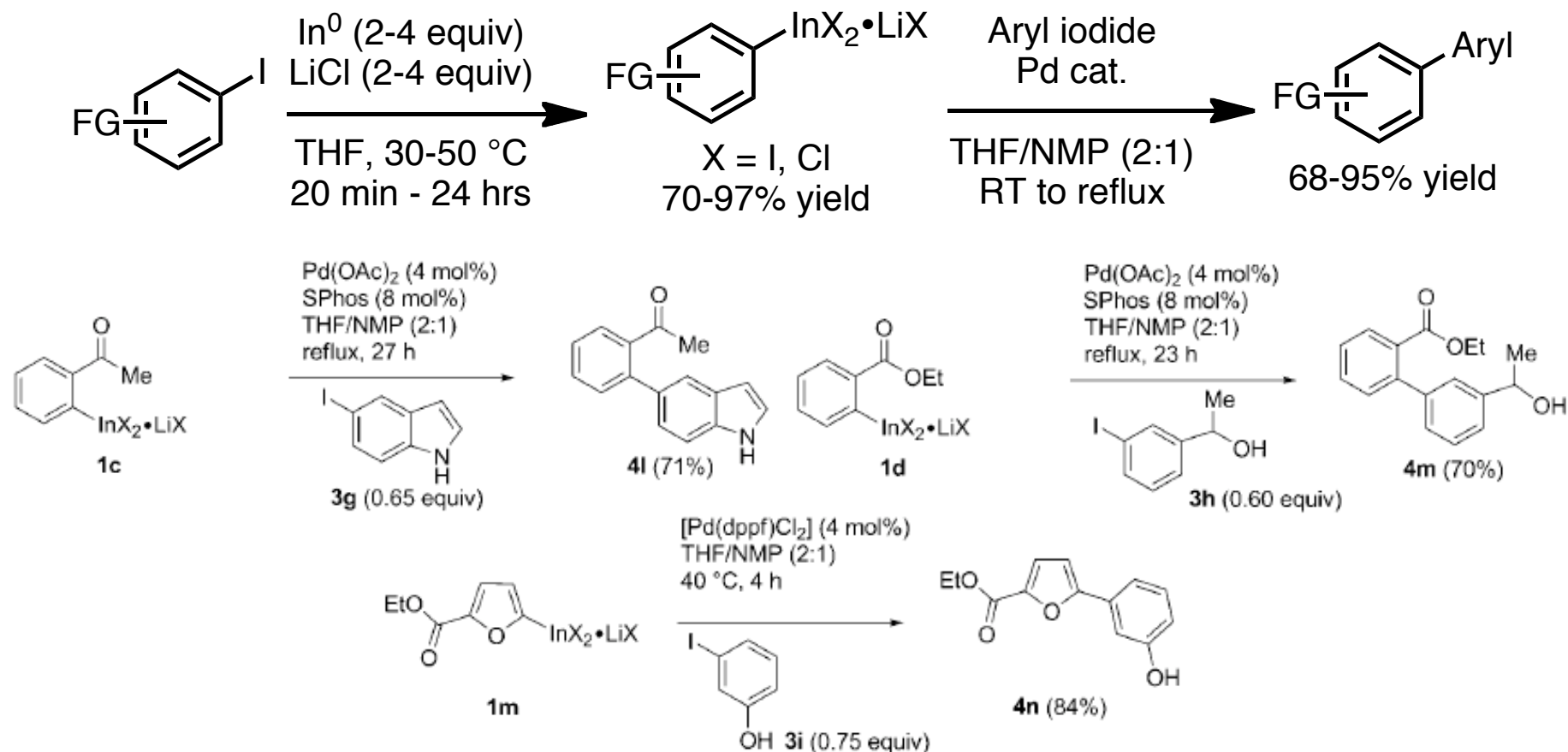


- 1) Provide intermediate and mechanism which accounts for the observed product
- 2) Rationalize the observed diastereoselectivity

6-membered transition state, R group oriented away as to avoid steric interaction

Direct Insertion of In^0 in Aryl and Heteroaryl Systems

Organoindium reagents can be compatible with aqueous systems, an advantage over traditional organometallics*



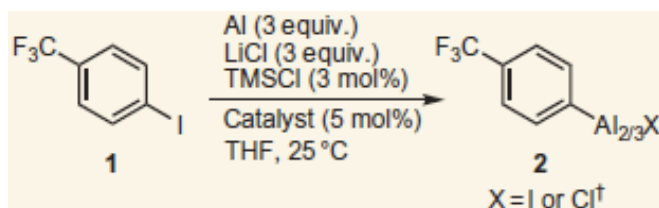
Exceptional functional group compatibility, aldehydes, ketones, esters, nitriles, and alcohols

Organoaluminum Synthesis from Aryl Halides

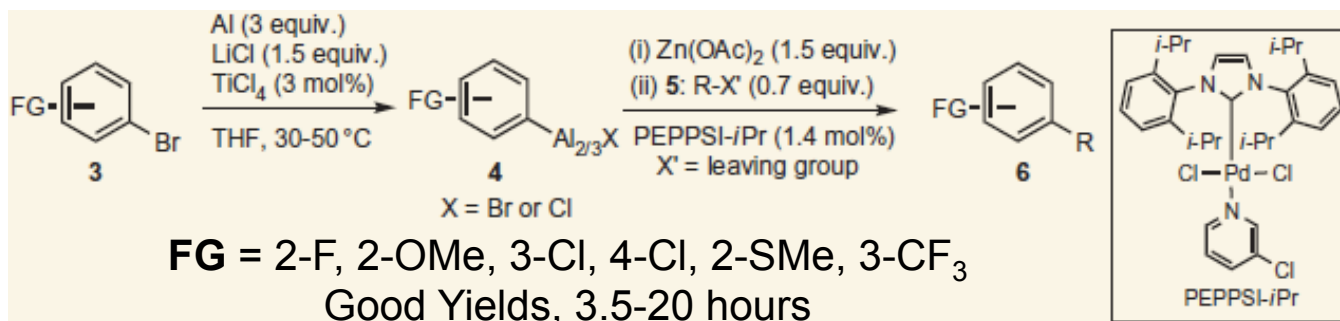
Organoaluminums perform similar chemistry as other metals (Mg, Zn)

Main advantage is due to low cost (1/2 price of Mg) and low toxicity (antiperspirant)

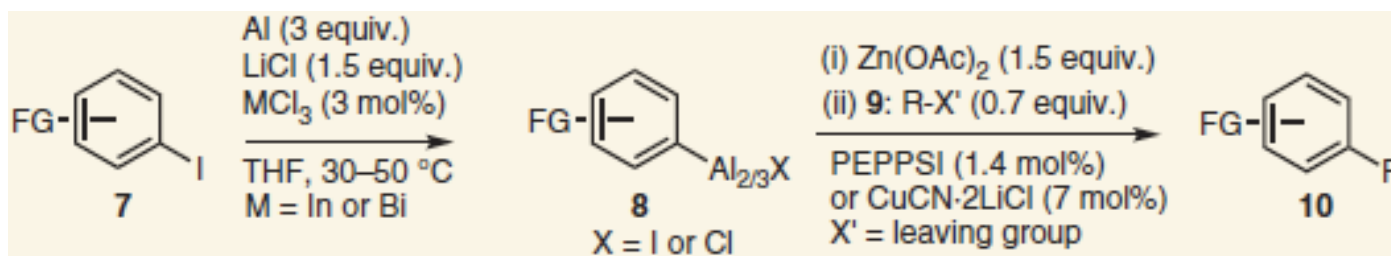
The main challenge is a convenient preparation from simple reagents (Al deactivates in air to Al_2O_3)



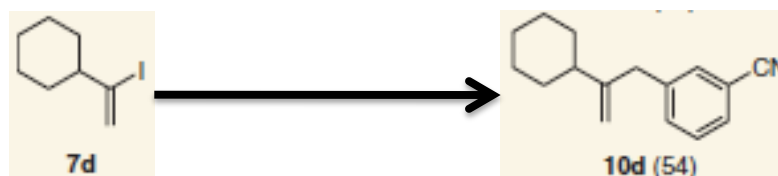
PbCl_2 , VCl_4 , InCl_3 , SnCl_2 , BiCl_3 , TiCl_4 effective catalysts
 TiCl_4 found to be optimum with aryl bromides



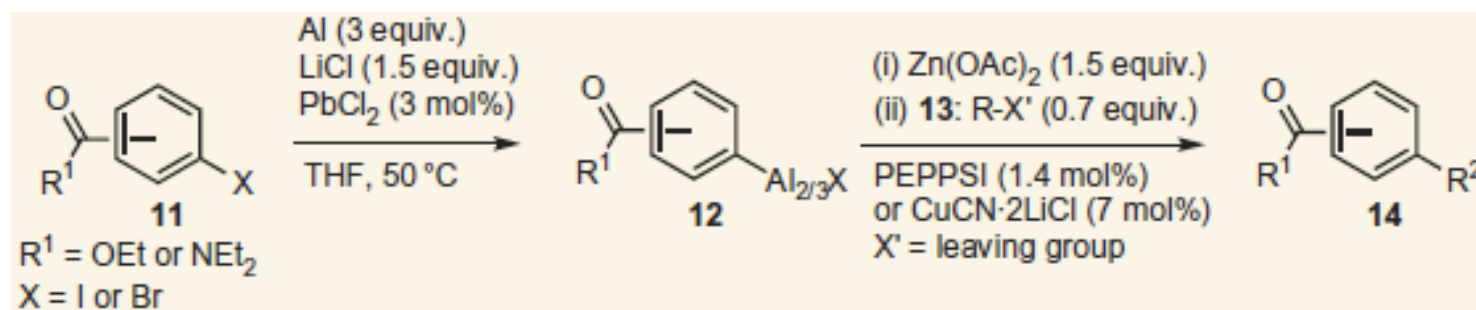
Organoaluminum Synthesis from Aryl Halides



Decent to good yields, 3-24 hours



Alkenyl iodide tolerated



Long reaction times (up to 30 hours), good yields

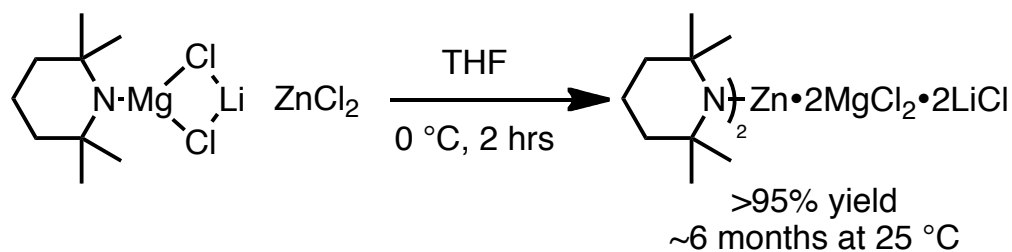
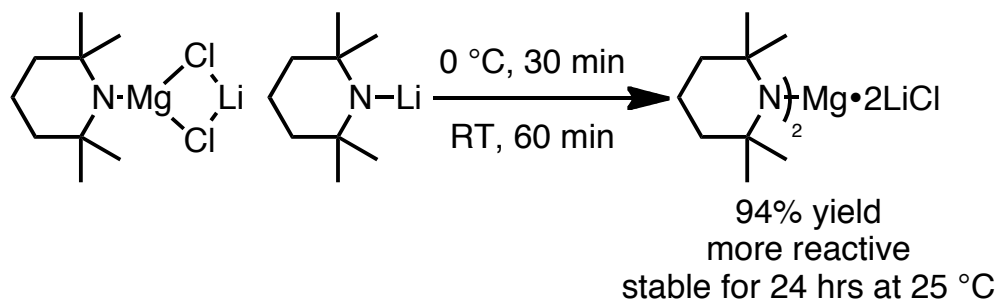
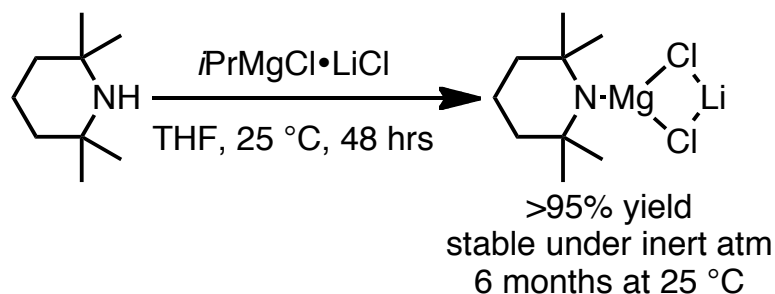
$p\text{-CF}_3\text{-C}_6\text{H}_4\text{-I}$ did not form an organometallic reagent with Pb or Bi metal
 Organoaluminum formation from $p\text{-CF}_3\text{-C}_6\text{H}_4\text{-I}$
 did not proceed with stoichiometric amounts of PbCl_2 , TiCl_2 , or InCl

Summary

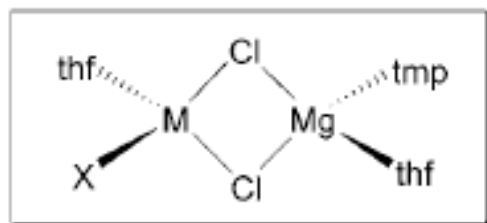
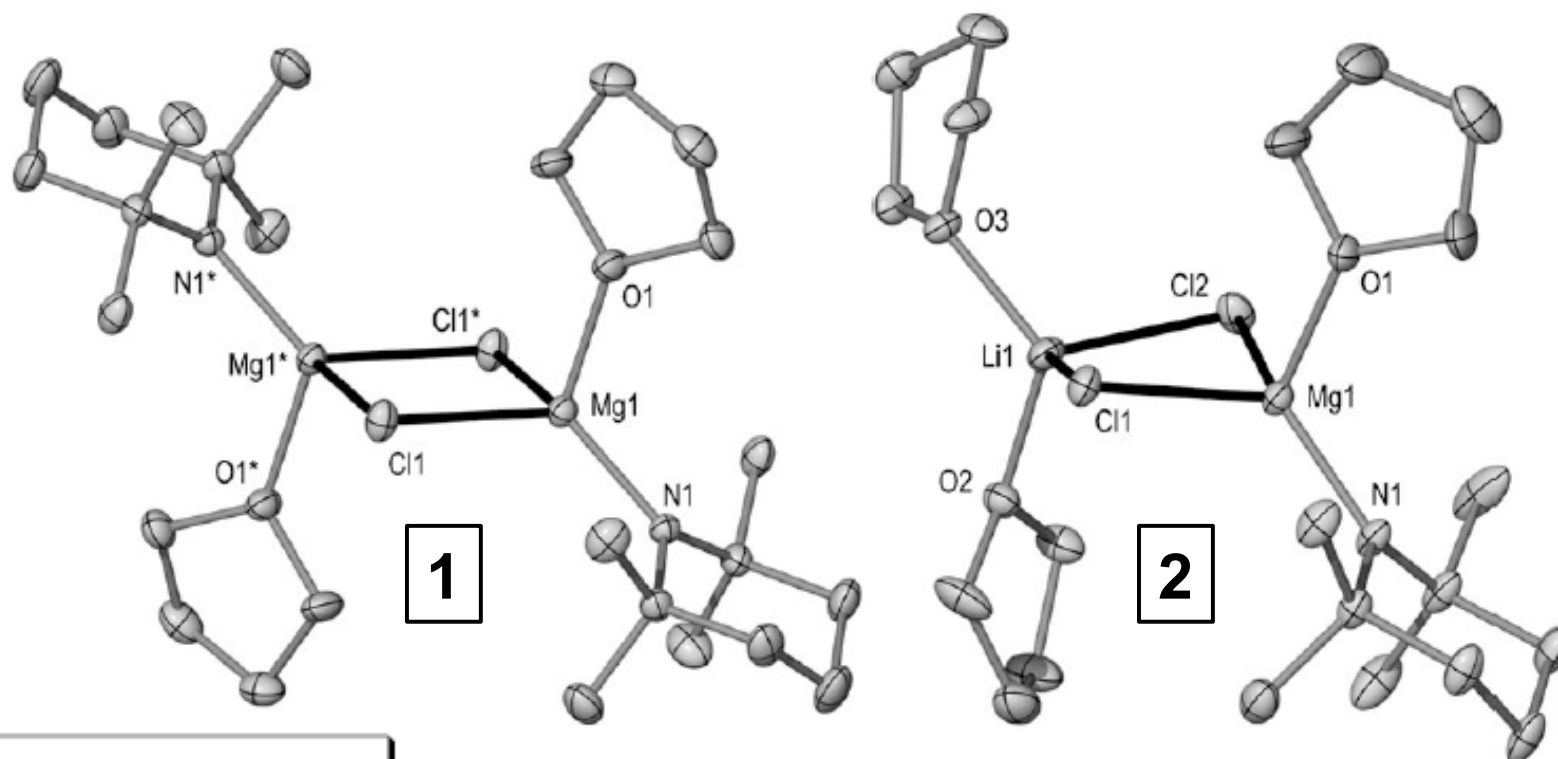
- Chemoselective additions and coupling under mild conditions
- One pot tandem reactions (Cu^I cat. acylation/allylation, Negishi, etc.) are easily accommodated
- Use of organohalide and neutral metal affords organometallic insertion
- Use of aryl/heteroaryl compound with metal-tmp amine base affords metalation product even in the presence of halides
- Metal halide additives have a critical role in reactivity

Grignard reaction not working? Cool it down, add some LiCl.

tetramethylpiperidine Mg/Zn base synthesis



Structure of tmp-based Mg/Zn bases



1 (M = Mg; X = tmp)

2 (M = Li; X = thf)

- 1) **2** is molecular halide like not saltlike
- 2) N is bound to Mg not Li
- 3) Only one bond needs to dissociate to activate the base
- 4) Mg is coordinatively saturated, geminal thf solvate on Mg is labile