Thomas Group

TEXAS A&M UNIVERSITY

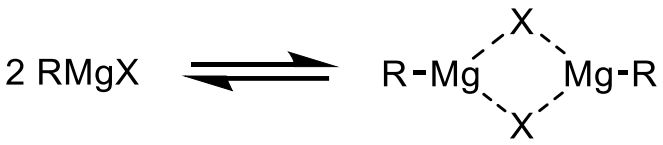
Chemistry of Alkaline Earth Metals

August 1st, 2023
Group Meeting

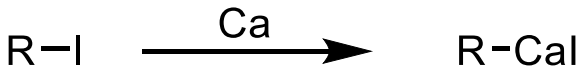
Han-Hsiang Hsu
Texas A&M University

Outline

Part I. History of Grignard Reagents

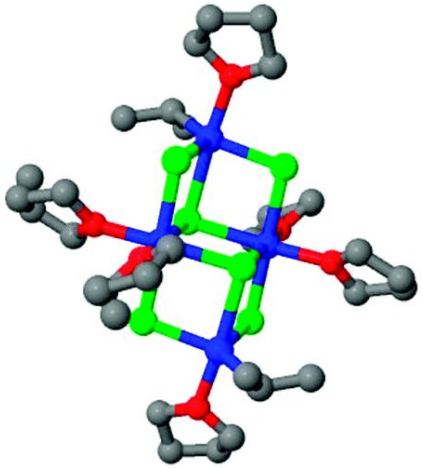


Part II. Calcium Reagents: Synthesis and Reactions



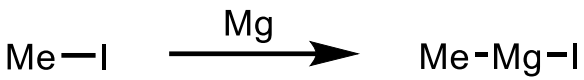
R = 1° alkyl / aryl

Part III. Synergestic Effects with Alkali Metals



Discovery of Grignard Reagent: 1900

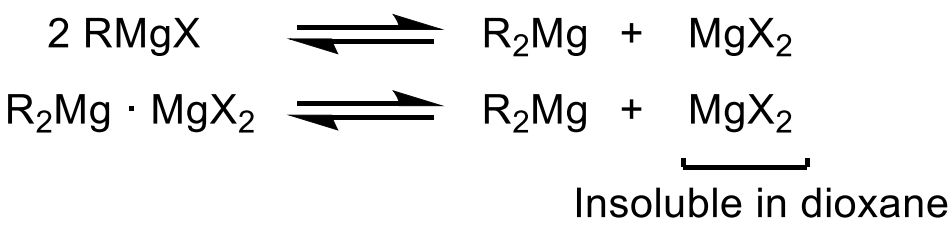
Insertion of Mg into C−I bond

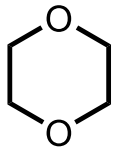


Victor Grignard

The Nobel Prize in Chemistry 1912
"for the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress of organic chemistry"

Schlenk Equilibrium



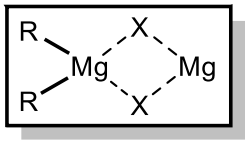


dioxane

V. Grignard, Compt. Rend. Acad. Sci. 1900, 130, 1322.

Constitution of Grignard Reagent

$R_2Mg \cdot MgX_2$ Formulation



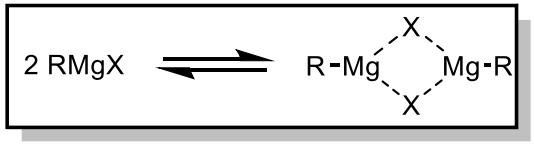
$^{28}MgBr_2 + Et_2{}^{24}Mg \xrightarrow[36h]{} \boxed{\text{"Ethyl Grignard"}} \xrightarrow{\text{dioxane}} \mathbf{Mg}Br_2$

96% Radioactivity

$^{25}MgBr_2 + Et_2{}^{24}Mg \longrightarrow$ Complete Exchange

Dessy, R. E.; Handler, G. S.; Wotiz, J. H.; Hollingsworth, C. A. *J. Am. Chem. Soc.* **1957**, *79*, 3476.
Dessy, R. E.; Handler, G. S. *J. Am. Chem. Soc.* **1958**, *80*, 5824.

RMgX Formulation



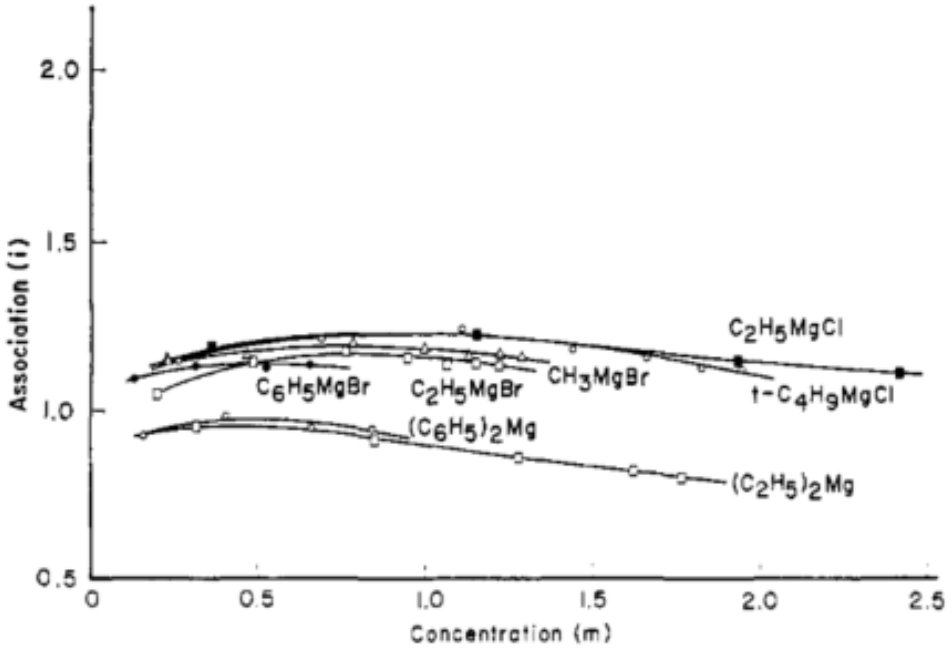
"RMgX" in THF $\xrightarrow{\text{Crystallization}}$ $RMg_2X_3 + R_2Mg$

Monomeric structure also supported by aggregation studies

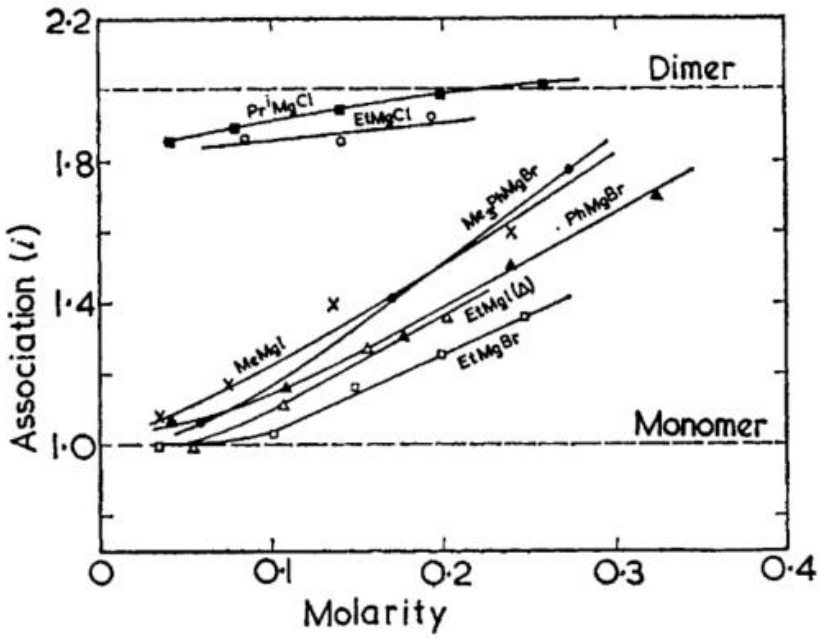
Ashby, E. C. *Quarterly Reviews, Chemical Society* **1967**, *21*, 259-285.

Aggregates of Grignard Reagent – Ebullioscopic Data

Consistently Monomeric in THF



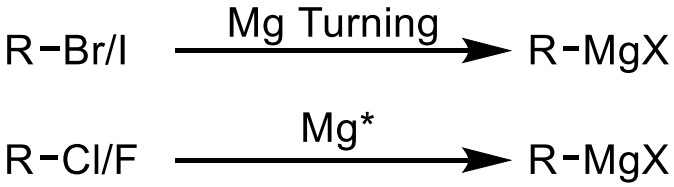
Variable in Et_2O

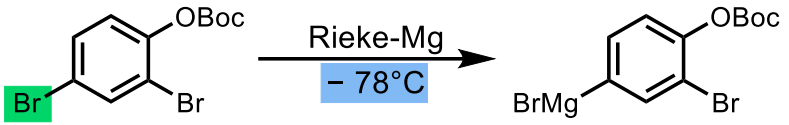


Walker, F. W.; Ashby, E. C. *J. Am. Chem. Soc.* **1969,** *91*, 3845.
Ashby, E. C. *Quarterly Reviews, Chemical Society* **1967**, *21,* 259-285.

Synthesis of Grignard Reagents

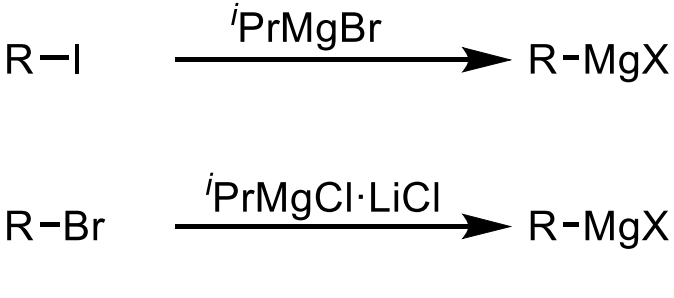
Direct insertion

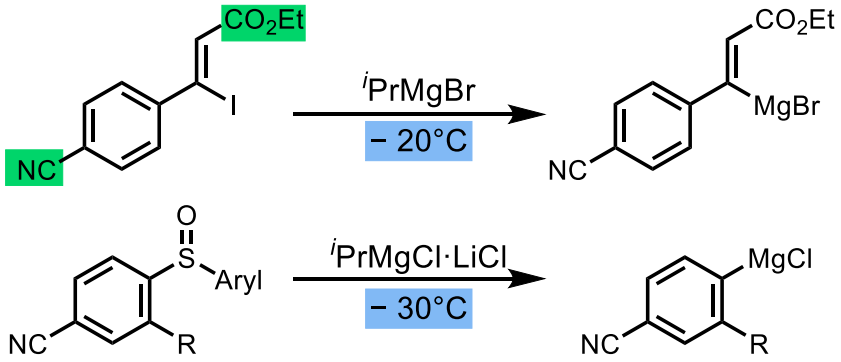




Lee, J.-s.; Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *The J. Org. Chem.* **2000**, *65*, 5428-5430.

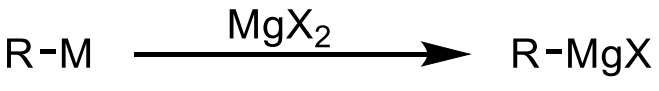
Magnesium-Halogen Exchange

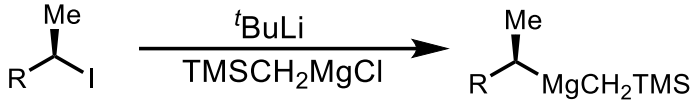




Knochel, P. Et al; *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.
Ziegler, D. S.; Wei, B.; Knochel, P. *Chem. - Eur. J.* **2019**, *25, 2695.*

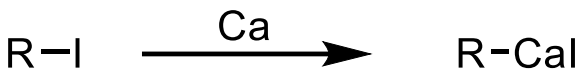
Transmetalation





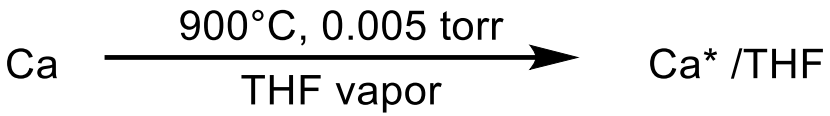
Kremsmair, A.; Wilke, H. R.; Simon, M. M.; Schmidt, Q.; Karaghiosoff, K.; Knochel, P. *Chem. Sci.* **2022,** *13*, 44-49.

Organocalcium Synthesis



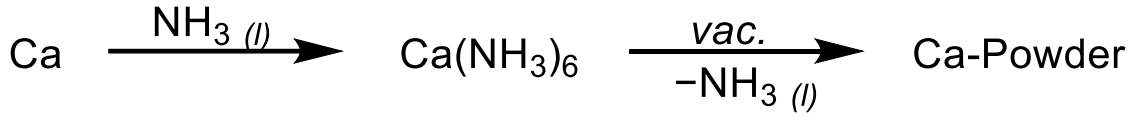
R = 1° alkyl / aryl

Vapor Condensation

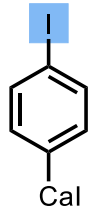


Mochida, K.; Yamanishi, T. *J. Organomet. Chem.* **1987**, *332*, 247.

Ammonia Dissolution



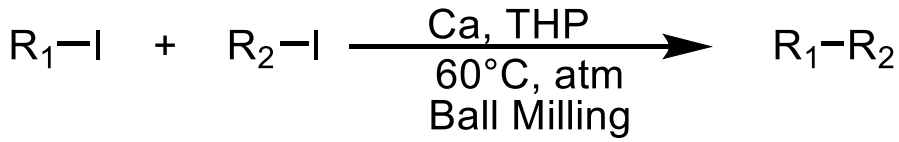
Calcium Bronze

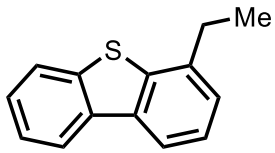


Single Metalation

Westerhausen, M.; Gärtner, M.; Görls, H. *Synthesis* **2007, 725.**

Mechanical Activation



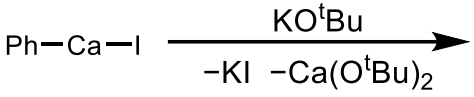


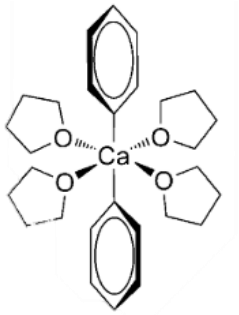
80%

Gao, P.; Jiang, J.; Maeda, S.; Kubota, K.; Ito, H. *Angew. Chem., Int. Ed.* **2022**, *61*, e202207118.

Calcium Grignard Reagents – Reactivities

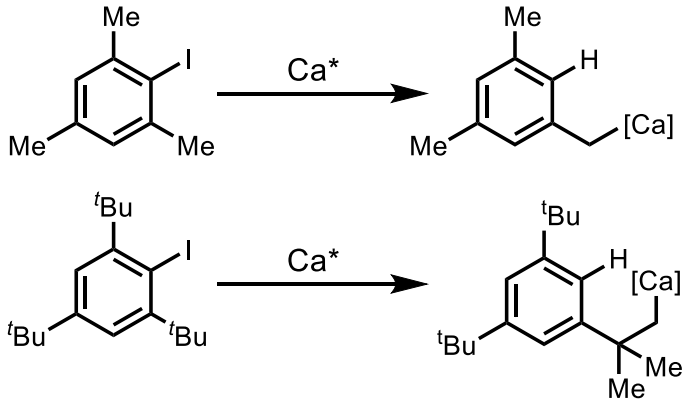
Schlenk Equiribrium





Calcium-Halogen Exchange

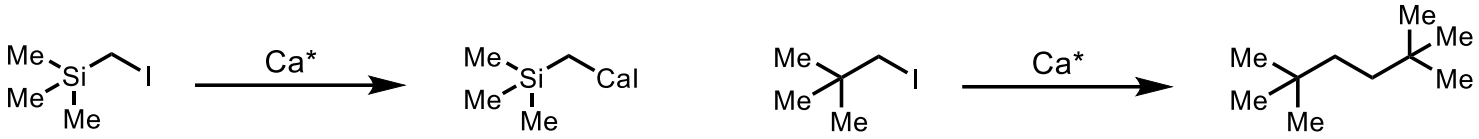
Poor Thermal Stability



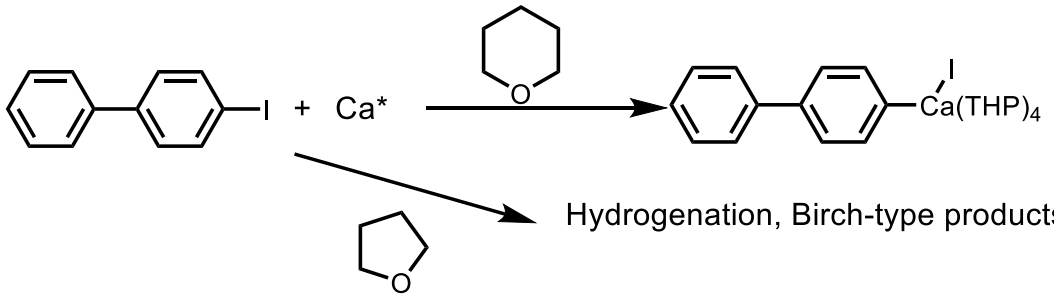
Westerhausen, M.; Koch, A.; Görls, H.; Krieck, S. *Chem. Eur. J.* **2017**, *23*, 1456.

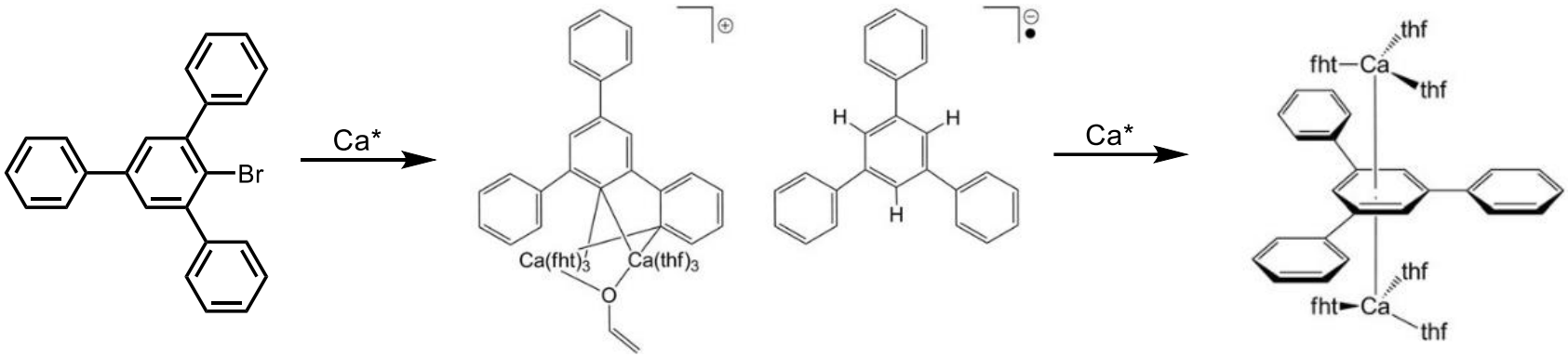
Calcium Grignard Reagents – Reactivities

Stronger Wurtz-Coupling Preference



Side Reactivity (π-affinity?)





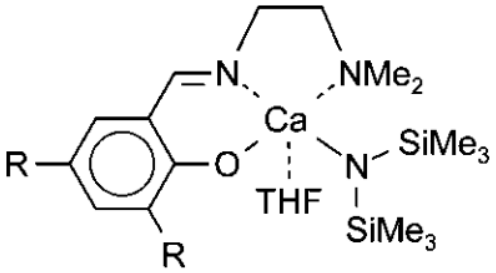
Westerhausen, M.; Koch, A.; Görls, H.; Krieck, S. *Chem. Eur. J.* **2017**, *23*, 1456.

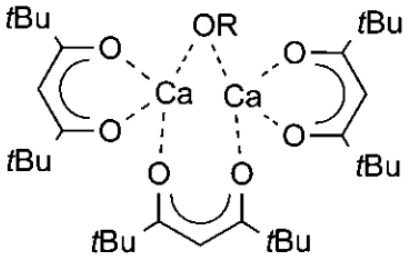
Calcium-Catalyzed Reactions

Nucleophilic Catalyst

[Ca]−Nuc

Nuc = OR, NR_2

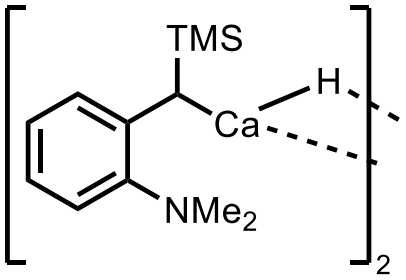




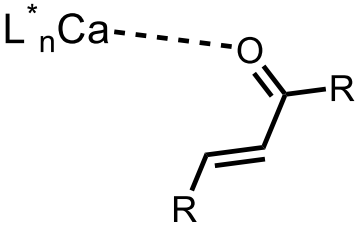
Hydridic Catalyst

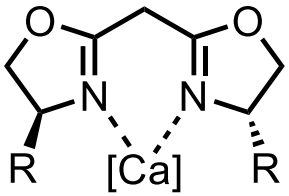
[Ca]−H

(Intermediate)



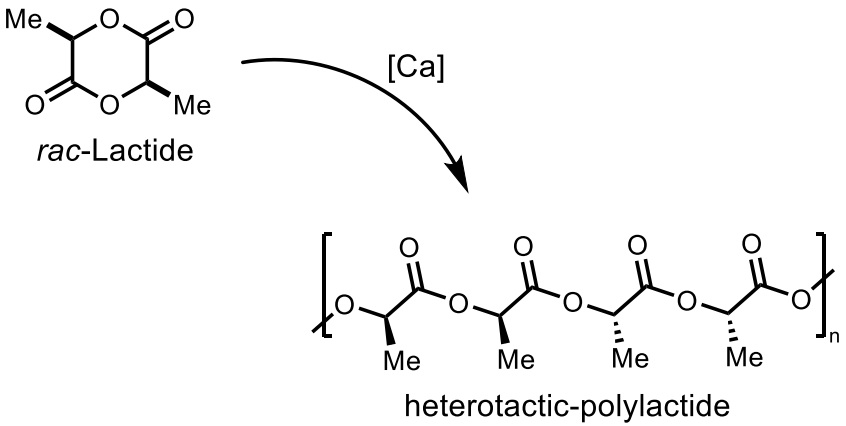
Lewis Acid Catalyst





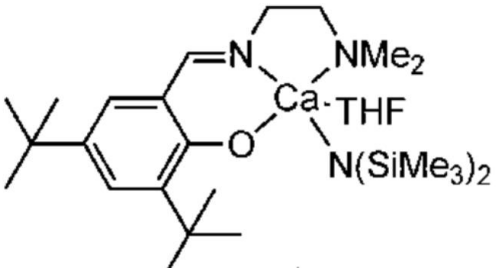
Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

Ring-Opening Polymerization (ROP)



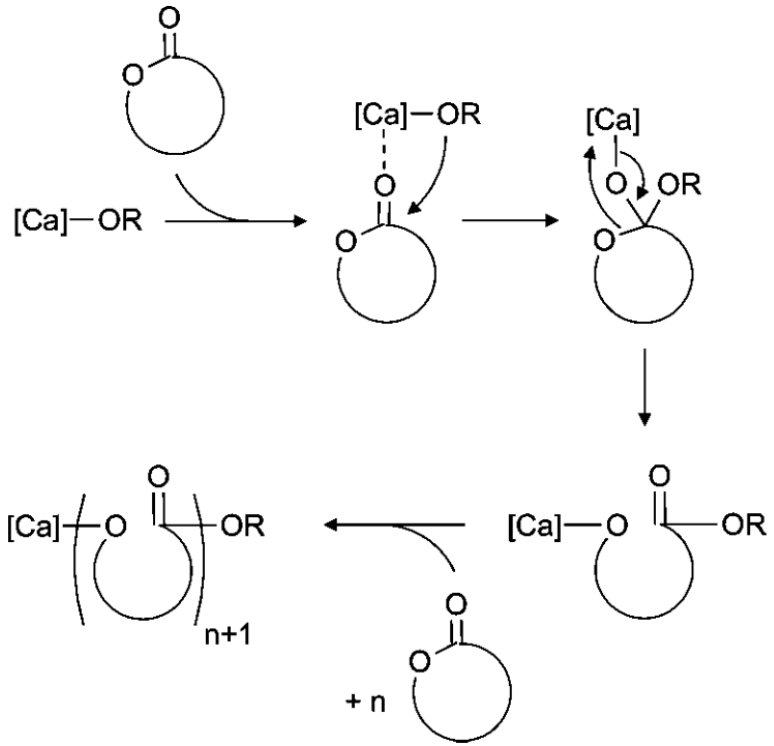
rac-Lactide

heterotactic-polylactide



- Low back-biting
- Tacticity Control

Mechanism:

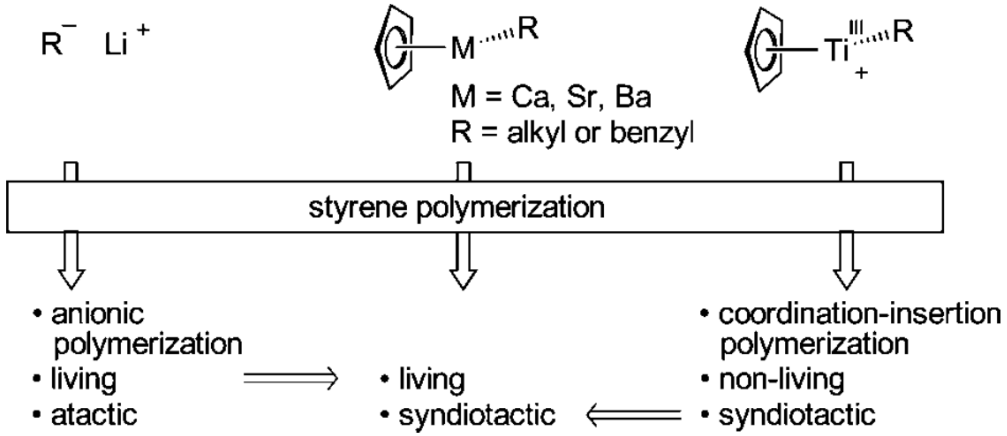


Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

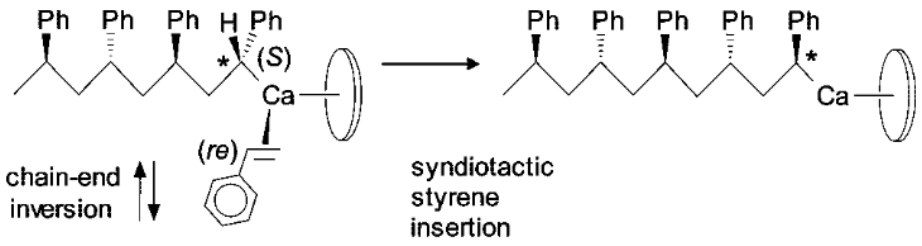
Darensbourg, D. J.; Choi, W.; Karroonnirun, O.; Bhuvanesh, N. *Macromolecules* **2008,** *41*, 3493.

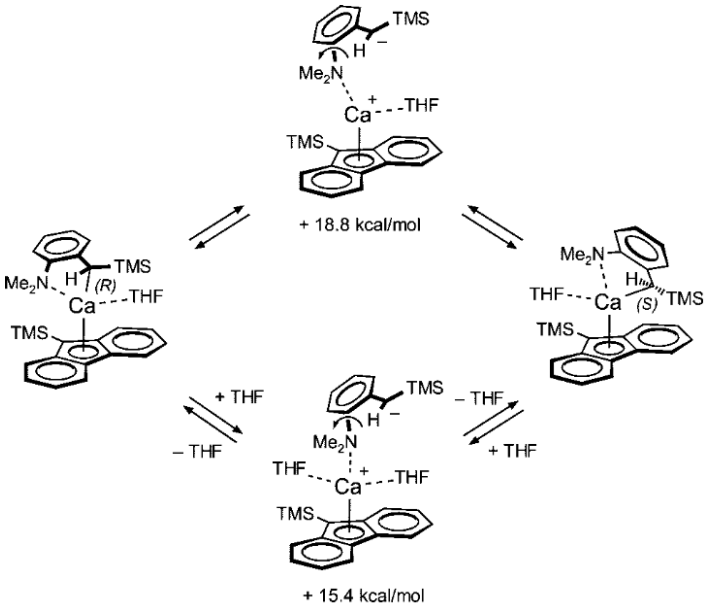
Anionic Polymerization of Alkenes

Intermediate Reactivity of Calcium Complexes



Effect of THF on Tacticity Control

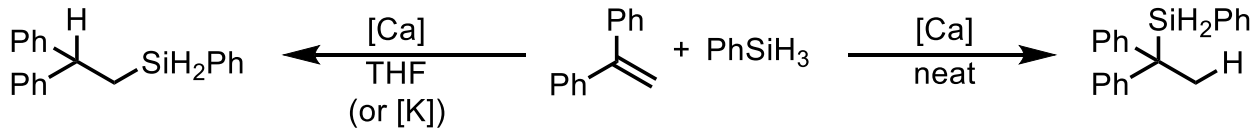




Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

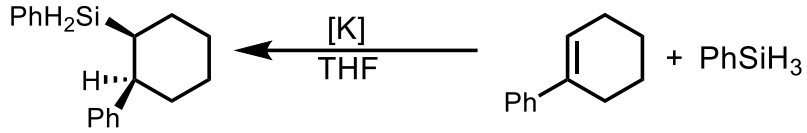
Hydrosilylation

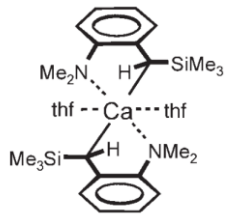
Polarity-Controlled Selectivity



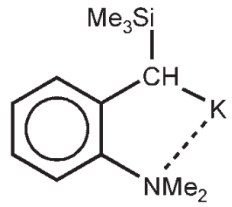
Trans, Steric

Electronic

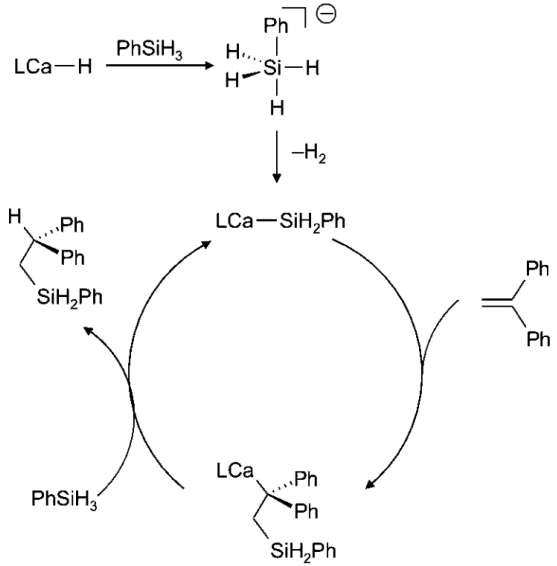


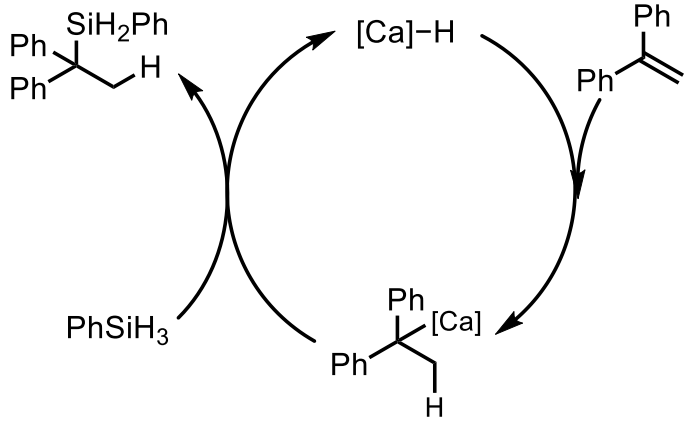


[Ca]



[K]

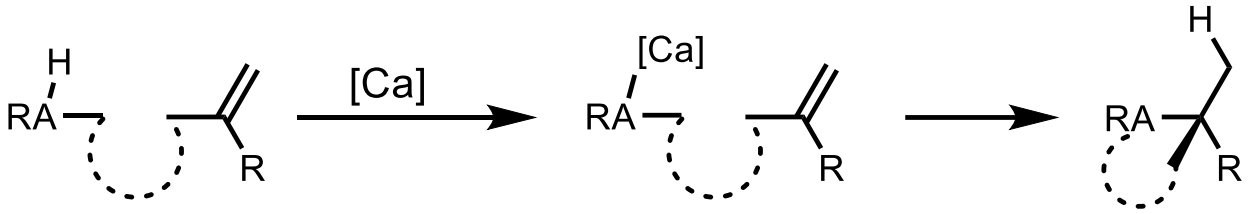




Buch, F.; Brettar, J.; Harder, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2741

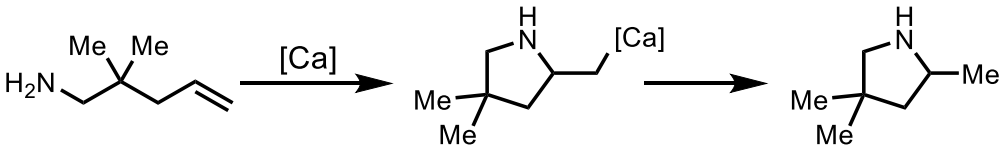
Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

Hydroamination/Hydrophosphination



A = N, P

Hydroamination

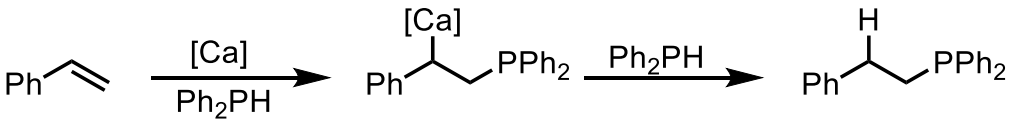


Ring size: 5>6>7

LCaX =

1, Ar = 2,6-diisopropylphenyl

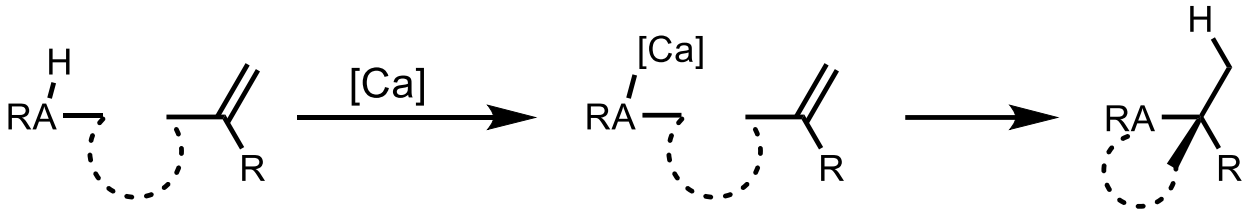
Hydrophosphination



Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

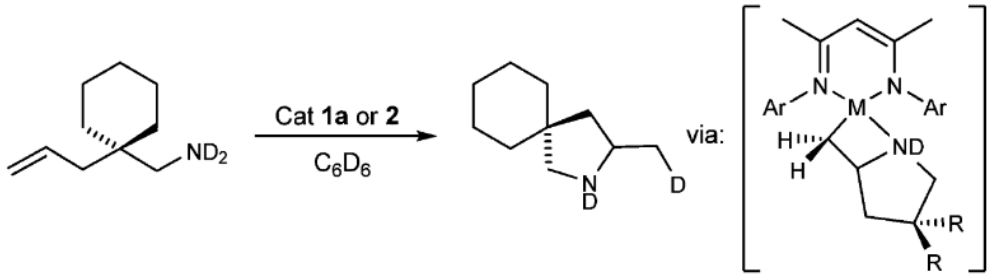
Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009,** *131* , 9670.

Hydroamination/Hydrophosphination

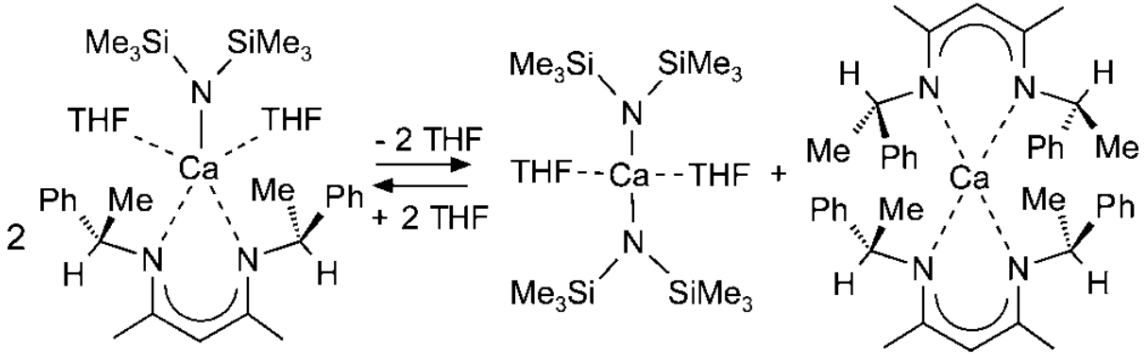


A = N, P

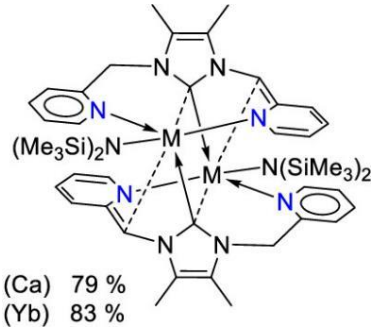
Unusual Uphill Ca-N to Ca-C transformation



Attempts of Enantioselectivity: Hindered by Schlenk Equilibrium



Inactive



Recent Heteroleptic Complex

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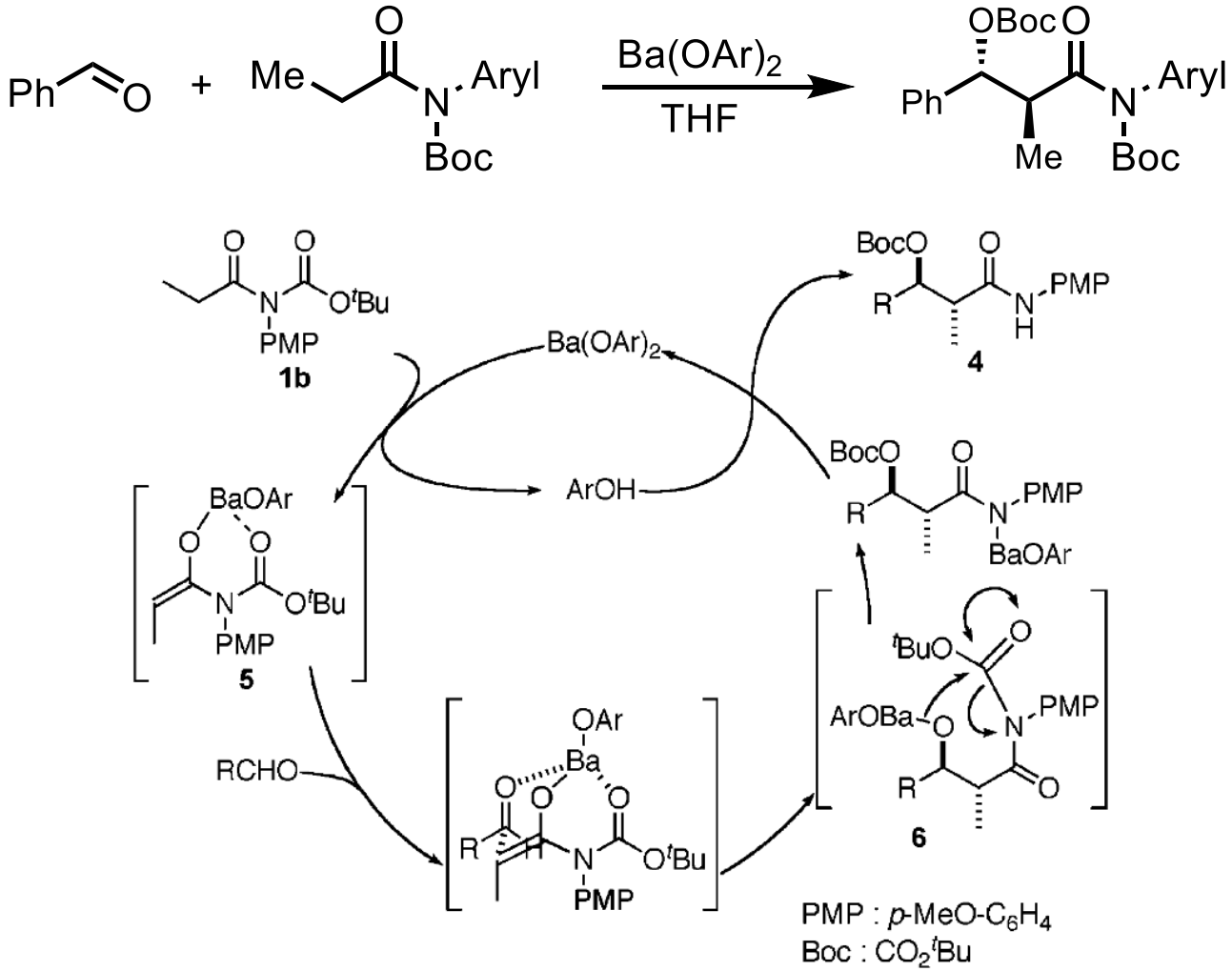
Lewis Acid Catalyst – Unusual anti-aldol from Z-enolate



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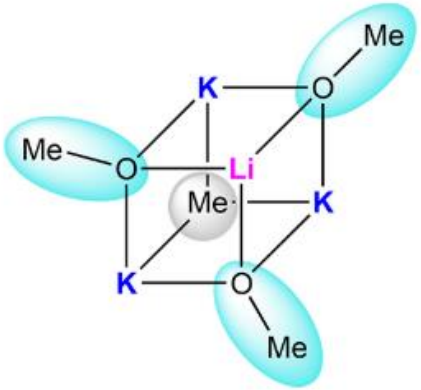
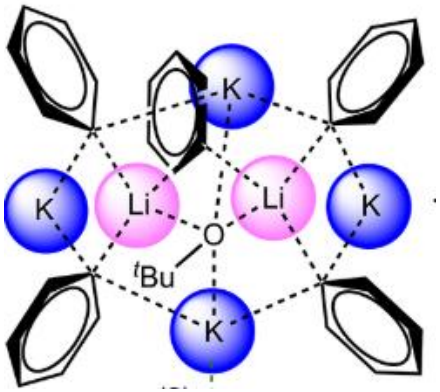
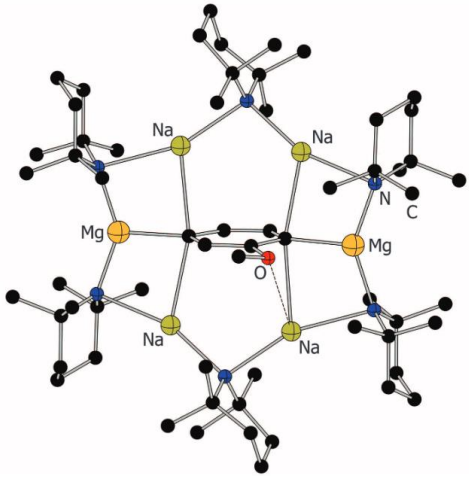
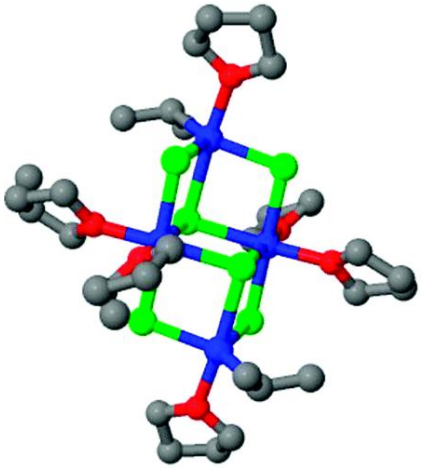
Synergistic Effects



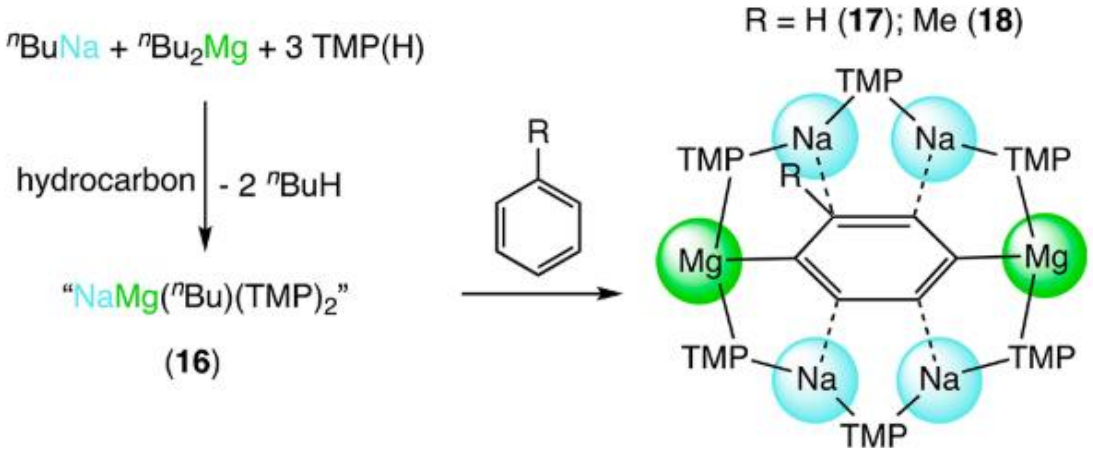


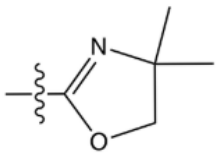




Robertson, S. D.; Uzelac, M.; Mulvey, R. E. *Chem. Rev.* **2019,** *119* , 8332-8405.

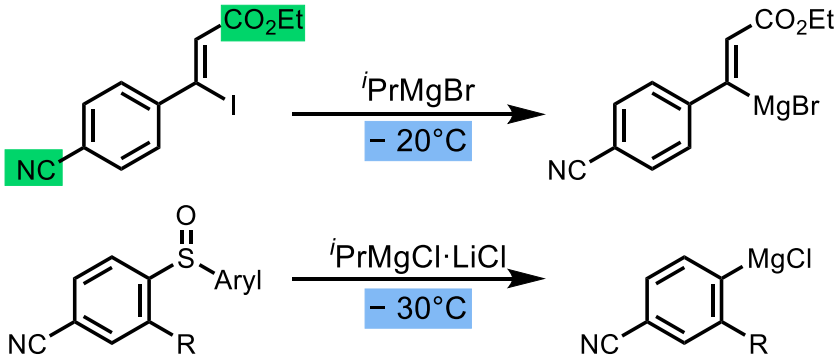
^{n}BuNa +^{n}Bu$_2$Mg – Template Base

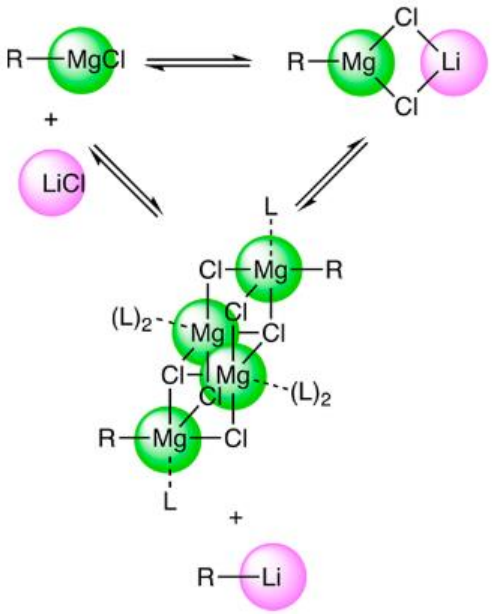


DG	Conditions	Electrophile	Yield (%)
OMe	101°C, 12 h	$D_2O/I_2/CO_2$	80/78/68
CH_2OMe	101°C, 5 h	I_2/CO_2	73/65
O^{t}Bu	25°C, 12 h	I_2	72
CF_3	101°C, 3.5 h	I_2	67
CON^{i}Pr$_2$	25°C, 3.5 h	I_2/CO_2	82/65
	25°C, 1 h	I_2	69*
$OCONEt_2$	25°C, 20 mins	I_2	77

Robertson, S. D.; Uzelac, M.; Mulvey, R. E. *Chem. Rev.* **2019,** *119* , 8332-8405.
Martínez-Martínez, A. J.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T. *Science* **2014,** *346*, 834-837.

Turbo Grignard – Mg-Halogen Exchange





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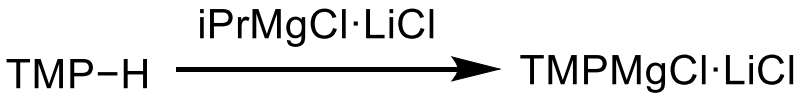
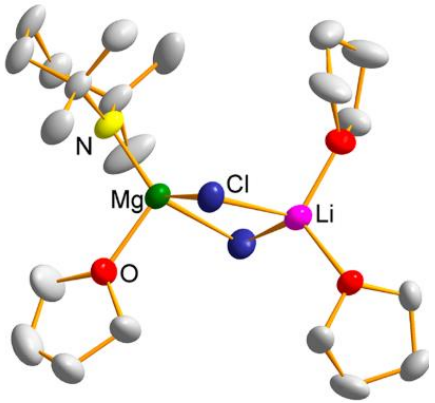
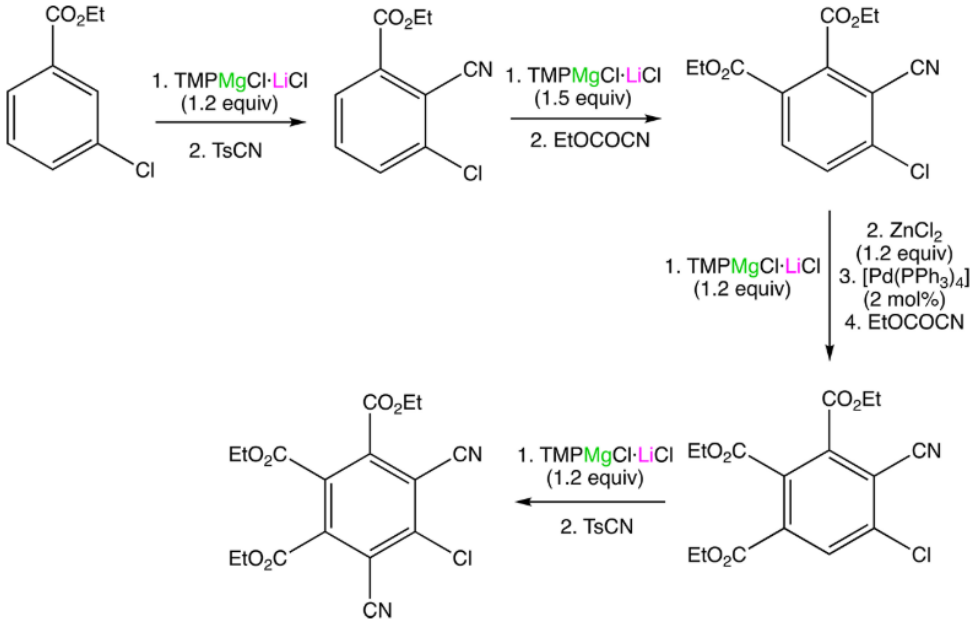
Turbo Grignard – For deprotonation

Salt-Supported Complex





Myriad Deprotonation



Robertson, S. D.; Uzelac, M.; Mulvey, R. E. *Chem. Rev.* **2019,** *119* , 8332-8405.