Review:

Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Ahn Vu, V. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4302.

General References on the Preparation and Reactions of Grignard Reagents:

Main Group Metals in Organic Synthesis, Yamamoto, H., Oshima, K., Eds.; John Wiley and Sons: New York, **2004**.

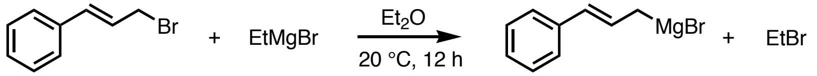
Handbook of Grignard Reagents, Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, **1996**.

Organomagnesium Methods in Organic Synthesis, Wakefield, B. J.; Academic Press: San Diego, **1995**.

Development and General Aspects:

$$\boxed{RX + R'MgX' \rightleftharpoons RMgX' + R'X}$$

- Analogous to lithium-halogen exchange. The position of the equilibrium varies with the stabilities of the carbanion intermediates involved (sp >> sp^2 >> sp^3).



Prévost, C. *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.

- Although the first example was reported in 1931 (above), the preparation of Grignard reagents via metal-halogen exchange has not been widely used until recently. Knochel and coworkers have demonstrated the functional-group tolerance of magnesium-halogen exchange, which is now the method of choice for the preparation of highly functionalized organomagnesium reagents.

- *i*-PrMgCl or *i*-PrMgBr are the most common reagents. In most cases, these reagents can be used interchangeably. *i*-PrMgBr is made by the Grignard reaction of isopropyl bromide and magnesium turnings. It is less soluble than the chloride (solutions are ~0.8 M), and the titre must be checked more often. *i*-PrMgCl is commercially available as a 2.0 M solution in THF or diethyl ether.

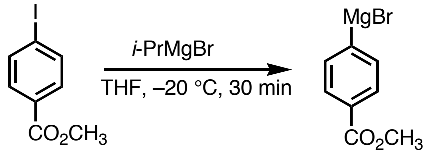
- Solutions of *i*-PrMgX are titrated by the method of Paquette (Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.) According to this procedure, a flame-dried flask is charged with menthol (a non-hygroscopic solid), 1,10-phenanthroline (indicator) and THF. The Grignard reagent is then added until a distinct violet or burgundy color persists.

- Unlike many lithium-halogen exchange protocols, only one equivalent of *i*-PrMgX is used in typical experimental procedures.

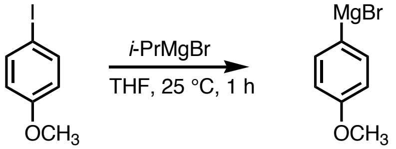
- THF is the most common solvent. Ethyl ether has been employed as a solvent for selective exchange of geminal dihalides to generate magnesium carbenoids.

- The reactivity of Grignard reagents is highly temperature dependant. Only highly reactive electrophiles such as aldehydes and ketones react at significant rates below 0 °C. This allows for the preparation of organomagnesium reagents containing cyano, nitro, ester, and imine functional groups, provided that the rate of the exchange reaction is fast enough to allow for exchange at temperatures below 0 °C.

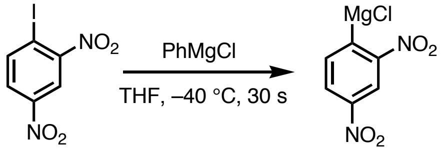
- The rate of magnesium-halogen exchange is accelerated by electron-withdrawing groups on the aromatic ring, and is slowed by electron-donating groups:



Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Ahn Vu, V.; Knochel, P. *Synthesis* **2002**, 565.



Cali, P.; Begtrup, M. *Synthesis* **2002**, 63.



Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1610.

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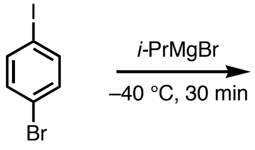
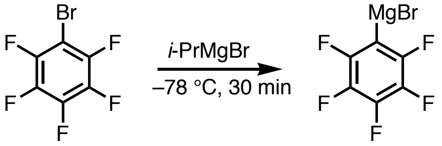
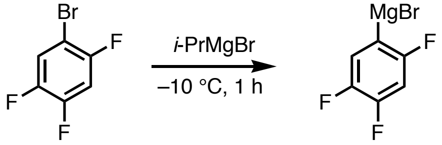
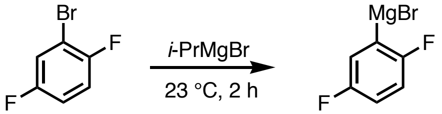
- Aryl bromides undergo exchange more slowly than iodides, but electron-poor aryl bromides can still react at temperatures below 0 °˘C.



Bomond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701.



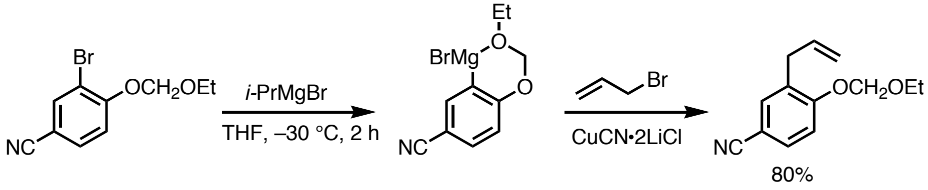




Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

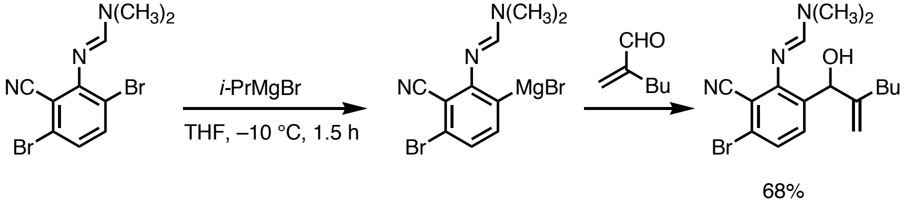
Ortho- **Directing Groups:**

- The presence of a chelating *ortho-* group facilitates exchange, increases the rate of reaction, and allows for low-temperature exchange.



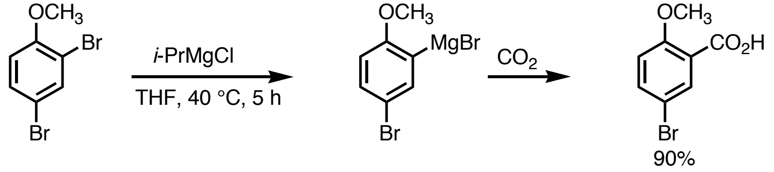
Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Ahn Vu, V. *Angew . Chem., Int. Ed. Engl.* **2003**, *42*, 4302.

- Dibromides undergo regioselective exchange of the bromine *ortho-* to a chelating group. Note also the compatibility of the amidine group with the exchange reaction.



Varchi, G.; Jensen, a. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 477.

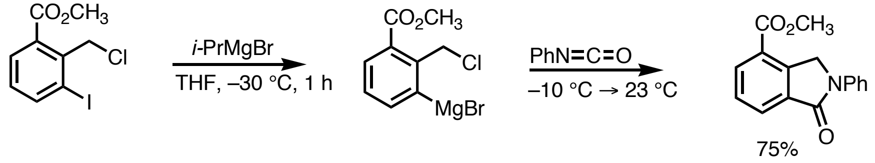
- Higher temperatures are required for the selective exchange with less effective chelators.



Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407.

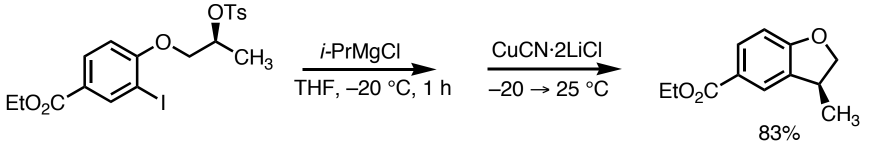
Functional Groups Compatible with the Magnesium-Halogen Exchange:

- Ester, benzylic chloride:



Delacroix, T.; Berillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108.

- Secondary alkyl tosylate:



Kneisel, F. F.; Monguchi, Y.; Knapp, K. M.; Zipse, H.; Knochel, P. *Tetrahedron* **2002**, *43*, 4875.

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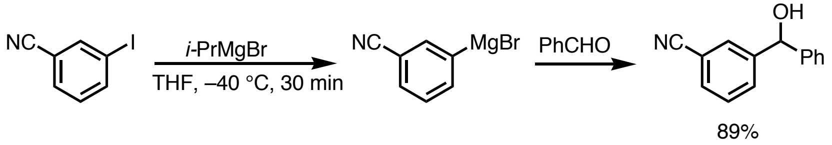
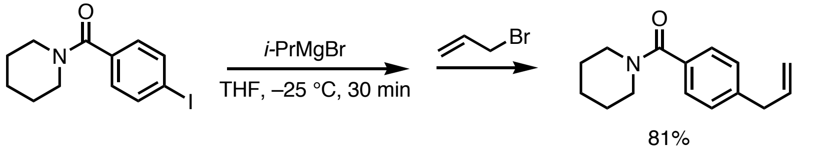
- Nitrile:

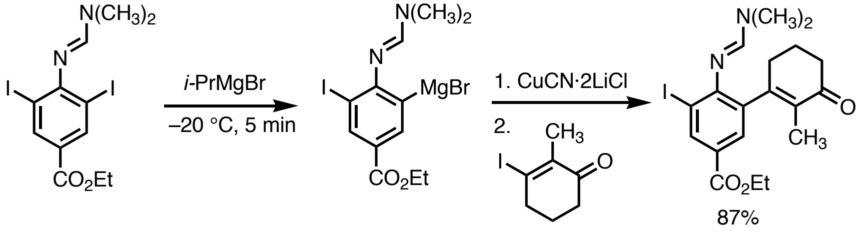


- Tertiary amide:



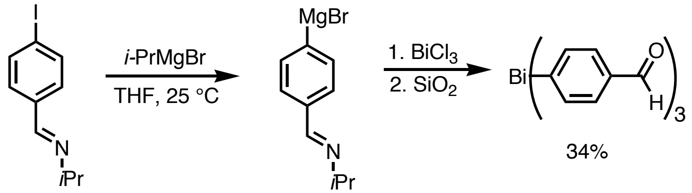
Bomond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701.

- Amidine, note also the selective exchange of a diiodide:



Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, *477.*

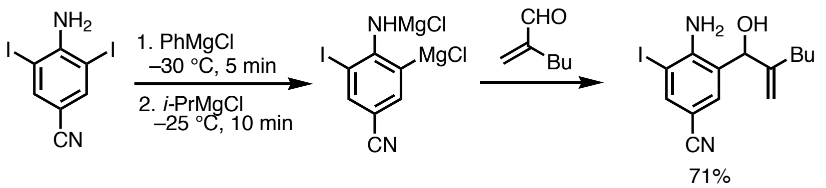
- Imine:



Murafuji, T.; Nishio, K.; Nagasue, M.; Tanabe, A.; Aono, M.; Sugihara, Y. *Synthesis* **2000**, 1208.

- Imines can be used to mask aryl aldehydes during the magnesium halogen exchange. The low yield of the reaction sequence above is likely attributable to the second step of the procedure.

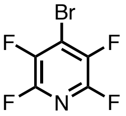
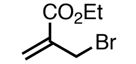
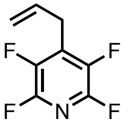
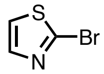
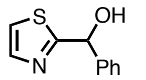
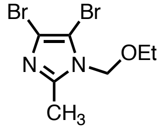
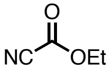
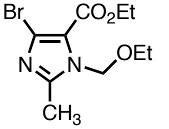
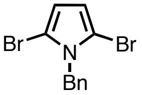
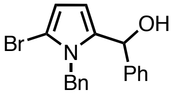
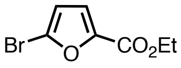
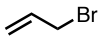
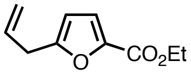
- Unprotected anilines:



Varchi, G.; Kofink, C.; Lindsay, D. M.; Ricci, A.; Seconi, G.; Knochel, P. *Chem. Commun.* **20**

- In the above example, phenyl magnesium chloride is first added because it is a strong base and as a magnesium-halogen exchange reagent it is less reactive than *i*-PrMgX. This allows for quantitative deprotonation before exchange.

- Heteroaromatics:

Heterocycle	Conditions[a] (°C, h)	Electrophile	Product	Yield (%)
	–40, 0.5	 (CuCN added)		80
	25, 1.5	PhCHO		75
	–20, 1			59
	–5, 1	PhCHO		73
	–30, 1	 (CuCN added)		80

[a] *i*-PrMgBr (1.2 equiv), THF

Abarbi, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

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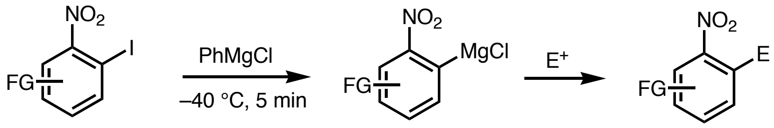
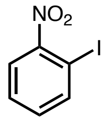
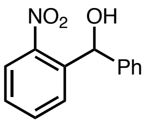
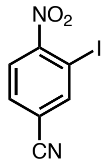
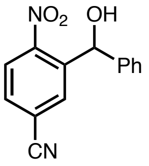
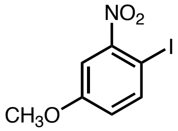
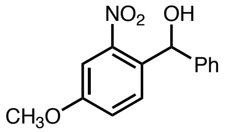
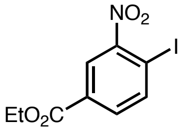
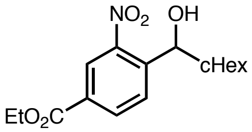
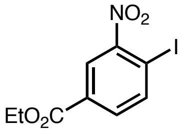
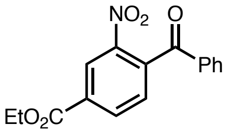
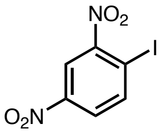
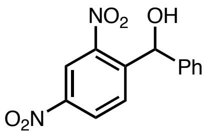
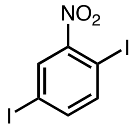
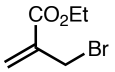
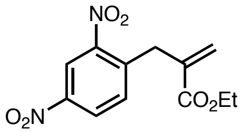
- Nitro arenes:



Nitro arene	Electrophile	Product	Yield (%)
	PhCHO		87
	PhCHO		94
	PhCHO		72
	cHexCHO		64
	PhCOBr		76
	PhCHO		81
			74

Sapountzis, Ioannis; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1610.

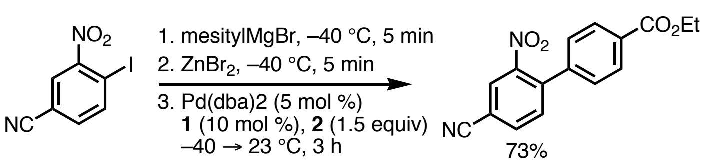
- Nitro-substituted organometallic reagents are difficult to prepare through classical methods. These electron-deficient arenes tend to undergo electron-transfer reactions, and direct oxidative addition with elemental magnesium or zinc often leads to reduction of the nitro group. This new procedure is the best method to date for the preparation of nitroarene organometallics.

- The nitro group must be *ortho* to the iodide exchanged. *Meta-* and *para*-nitro substituted aryl iodides give complex mixtures.

- PhMgCl is necessary for a successful reaction. More reactive Grignard reagents such as *i*-PrMgCl give complex mixtures.

- For successful reactions with reactive electrophiles such as allyl bromides and acid halides, transmetallation of the organomagnesium intermediate with CuCN·2LiCl is necessary.

- Pd-catalyzed Negishi cross-coupling reactions are possible after transmetallation with $ZnBr_2$:



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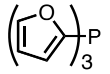

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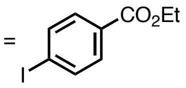
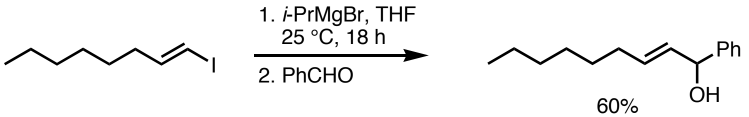


- In the case above, mesityl magnesium bromide is used to prevent competing oxidative addition of the aryl iodide generated in the magnesium-iodide exchange reaction.

Magnesium-Halogen Exchange of Vinyl Iodides:



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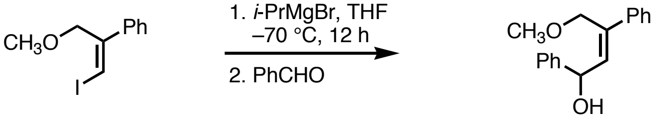

95%

Rottlander, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.

- Vinyl Iodides are also suitable substrates for magnesium-halogen exchange. Higher temperatures and longer reaction times are required, which limits the functional-group tolerance of this method.

- When the vinyl iodide is substituted with electron-withdrawing groups or chelating heteratoms, the rate of exchange is enhanced.

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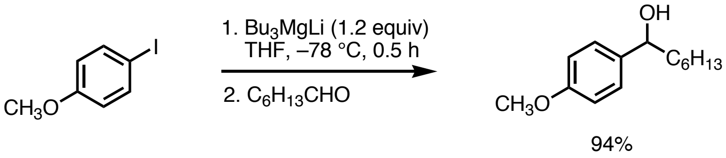
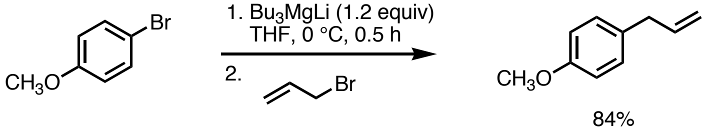
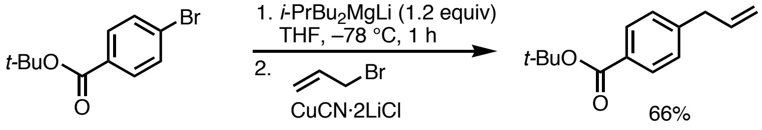
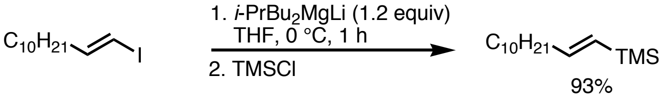
Alternative, More Reactive Reagent Combinations for Magnesium-Halogen Exchange:

- Lithium Trialkyl Magnesium Ate Complexes:









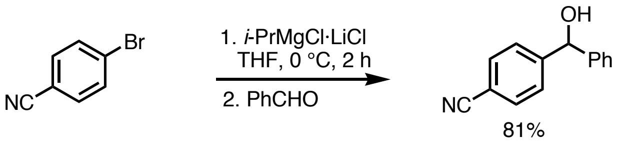
Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.

- The lithium trialkyl magnesiates are prepared in situ by the addition of an alkyl lithium (2 equiv) to an alkyl magnesium halide (1 equiv).

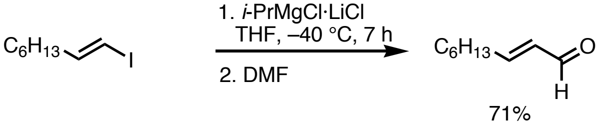
- Magnesiates exhibit a reactivity somewhere between alkyllithium and alkylmagnesium reagents.
- The exchange reaction is faster and less sensitive to electronic effects (arene substitution).

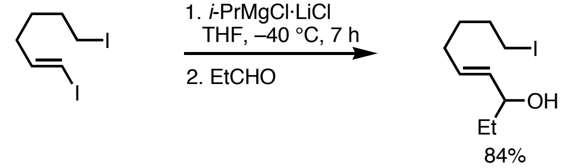
- In accord with their greater reactivity, aryl magnesiates show less funtional group tolerance.

- Enhanced Reactivity by Addition of Lithium Chloride to *i*-PrMgCl prior to exchange (1 equiv):



Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2004***, 43*, 3333.



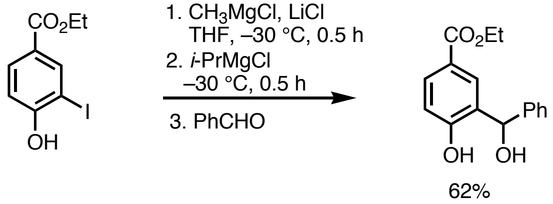


Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004***, 6*, 4215.

- Addition of LiCl to the Grignard reagent produces a more active magnesium-halogen exchange reagent

- It has been proposed that LiCl breaks up aggregates of organomagnesium reagents.

- This more active reagent combination is successful in the exchange of the *ortho*-phenoxy aryl iodide shown below:



Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288.

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