A quick reintroduction to the periodic table and the s-block:

**Group 1** "Alkali Metals" have ns\(^1\) electron configuration and therefore have a strong tendency to lose an electron to form cations in solution. This makes them powerful reducing reagents that react violently with water. When found in nature they exist as salts. Alkali metals are soft and have low melting points.

**Group 2** "Alkali Earth Metals" have ns\(^2\) electron configuration which makes them more stable than group 1 metals, but they are still only found in nature as salts. Their metals are denser and have higher melting points. They are also powerful reducing reagents and all except beryllium react with water and oxygen. Barium is the most reactive and must be stored under oil.

Earth's relative abundance of s-block elements (ppb-atoms):
1. magnesium: 482,000,000
2. calcium: 11,100,000
3. sodium: 2,000,000
4. potassium: 110,000
5. lithium: 4,100
6. strontium: 3,900
7. barium: 850
8. beryllium: 140
9. rubidium: 120
10. cesium: 7
11 + 12: francium/radium <1

**Sodium, potassium, francium and radium** will not be covered, so here are some fun facts to leave you with:

The Bose-Einstein condensate of Sodium is capable of slowing light down to 17 m/sec (38mph) as opposed to its normal speed of ~3 x 10\(^8\) m/sec in a vacuum.

**Potassium** superoxide KO\(_2\) is a portable source of oxygen and a carbon dioxide absorber. It is widely used in respiration systems (i.e. submarines and spacecraft) as it takes less volume than gaseous oxygen: 4KO\(_2\) + 2CO\(_2\) = 2K\(_2\)CO\(_3\) + O\(_2\)

"Francium" is so fragile it's basically useless, and even though there's barely enough of it in the earth for chemists to detect it directly, no one will ever herd enough atoms of it together to make a visible sample. If they did, it would be so intensely radioactive it would murder them immediately."

- The Disappearing Spoon by Sam Kean

"Radium" was radium infused, radioactive water manufactured by Harvard dropout William Bailey. It was responsible for killing steel tycoon Eben Byers. The Wall Street Journal is famously quoted as saying: "the radium water worked fine until his jaw came off."

**Group 1**

**Lithium**

What one should know about lithium (things I will not cover):
- Dissolving metal reductions with Li and NH\(_2\)Naphthalene/DIBB/etc.
- Making [kinetic] enolates with bases like LDA/LHMDS/etc.
- Deprotonating other acidic protons with organolithium reagents and trapping with electrophiles
- Directed metallations on aryl rings
- Exchanging carbon-halogen bonds for carbon-lithium bonds
- 2 equivalents of \(\text{BuLi}\) needed if using it stoichiometrically
- \(\text{LiNH}_2\) cleaves allyl or benzyl ethers (to deprotect alcohols) as well as removing any base-cleavable functionality (esters/carbonates/etc.)
- Transmettallation with organo-tin species
- Named reaction using \(\text{BuLi}\): Shapiro/Corey-Fuchs/1,2- and 2,3- Wittig rearrangement/Peterson olefination, etc.

Things one may not have seen before:
Shapiro alternative: Cohen et. al. JOC (1990) 4786

\[
\text{PhSH, montmorillonite (83%)} \rightarrow \text{LiDBB, Me}_2\text{NCHO (80%)}
\]

The original acylanion equivalent: Corey et. al. JACS (1968) 3245

\[
\begin{align*}
\text{S} + \text{nBuLi; Br} & \rightarrow (70%) \\
\text{Addition to isonitritles: Niznik et. al. JOC (1974) 600} & \\
\text{PhLi + Me + Me + Me + Na} & \rightarrow \text{Et}_2\text{O, 0 °C} \\
\text{electrophiles} & \rightarrow \text{PhCHO (67%)}
\end{align*}
\]

- primary halide (86%)
- TMSCl (40%)
- CO\(_2\)chloroformate (52% - 80%)
- benzaldehyde (81%)
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Lithium continued:
More isonitrile chemistry: Ito et. al. JACS (1977) 3532


Ynolates: Murai et. al. JACS (1996) 7634

Asymmetric carbolithiation: Bailey et. al. JACS (2000) 6787


Reductive Alkylation:

Electrophilic Trapping:

Electrophiles: zirconacycles, epoxides, aldehydes, ketones/iminines, organo tin
Cesium and Rubidium:

What one should know about organocesium and cesium reagents:
- when organic halides/dialkylmercury reagents are treated with cesium/rubidium, the corresponding organocesium/rubidium compounds rapidly undergo Wurtz coupling (and consequentially are not used often)
- cesium reagents are important for fluorine chemistry and salts of cesium and rubidium are used as bases in organic synthesis (nucleophilic addition, HWE, cross coupling)
- a few complexes with cesium and rubidium (allyl and cyclopentadienyl) have been characterized by X-ray diffraction, but they haven’t been utilized synthetically

Things one may not have seen before:

Nucleophilic fluorination: DesMarceau et. al. JOC (1984) 1467

\[
\text{F}_3\text{C} = \text{N} \xrightarrow{\text{Br}_2, \text{CsF}} \text{Br} \xrightarrow{\text{hv, pyrex}} \text{F}_3\text{C} = \text{N} - \text{CF}_3
\]

must be perfluoroalkyl


\[
\text{C}_6\text{H}_5\text{I} \xrightarrow{\text{CsF, CO (150 atm), PhH, 150 °C}} \text{C}_6\text{H}_5\text{CF} \quad \text{note: LiF, NaF, KF, RbF, and CaF}_2 \text{ all inferior to CsF}
\]

“Si–H bond activation”: Corriu et. al. Tetrahed. (1983) 999


Rubidium in PTC: Jew et. al. JOC (2003) 4514

Rubidium salts: Yamaguchi et. al. ACIE (1993) 1176

Cesium Fluorosulfate in electrophilic fluorination: Stavber et. al. JOC (1987) 919


Fluoro-destannylation: Hodson et. al. Synlett (1992) 831

Acyl fluorides: Stavber et. al. JOC (1992) 5334

note: mechanism of the reaction is unclear—radical inhibitors were introduced (nitrobenzene) that inhibited the reaction but did not stop it (51% in the presence of 2 eq)
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**Group 2**

**Beryllium:**

Asymmetric reduction of ketones: Giacomelli et. al. JOC (1986) 2030

\[
\text{O} \quad \text{Ph} \quad \text{ether, -35 °C, 4h} \quad \text{iPr} \quad \text{Ph} \\
\]

(99% GC yield) (36% ee)

\[
\text{Me} \quad \text{Me} \quad \text{Br} \quad \text{Br} \quad \text{Me} \quad \text{Me} \\
\text{Be} \quad \text{Be} \quad \text{Be} \quad \text{Be} \quad \text{Be} \quad \text{Be} \\
\text{note: MgBr}_2 \text{ gave 100% yield by GC after only 8 hours} \\
\]

Beryllium as a Lewis acid: MeCormick et. al. JOC (1980) 2566

\[
\text{OH} \quad \text{Me} \quad \text{Me} \quad \text{THF, rt, 1.5h} \quad \text{2 nBuLi} + \text{BeCl}_2 \quad \text{2 LiCl} + (\text{Bu}_2)\text{Be} \\
\]

(ratio: 99:1) (78%)

\[
\text{HO} \quad \text{nBu} \quad \text{cyclohexenone} \quad \text{(added directly)} \\
\]

distillation

(54%)

Beryllium Borohydride: Robinson et. al. JACS (2012) 9953

\[
\text{R} \quad \text{BeCl}_2 \quad \text{hexane} \\
\text{Cl} \quad \text{BeCl}_2 \quad \text{2 LiBH}_4 \quad \text{toluene} \\
\]

(quant.) (68%)

\[
\text{R} \quad \text{Be} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{N} \quad \text{N} \quad \text{R} \quad \text{N} \quad \text{R} \\
\]

\[
\text{R} = 2,6-di/PrPh \\
\]

Be(BH₄)₂ was first reported in 1940 but has remained elusive since. The structure was disputed for decades and recently it has become "an intriguing hydrogen storage candidate possessing the highest hydrogen capacity (20.8 wt %) of all metal borohydrides."

Another paper on Be-hydride complexes: Hill et. al. ACIE (2012) 2098 (Seems most are NHC stabilized and are capable of reducing the NHC)

---

**Magnesium:**

What one should know about (things I will not cover):

- Grignard reagents adding to obvious things and other boring example of Barbier coupling
- generation of Grignard reagents (what transmetallates first, initiators, Wurtz coupling, etc.)

Things one may not have seen before:

Hydromagnesiation of alkynes: Cooper et. al. JOC (1962) 3395

\[
\text{Me} \quad \text{Me} \quad \text{Br} \quad \text{Br} \quad \text{Me} \quad \text{Me} \\
\text{HCHO} \quad \text{Me} \quad \text{OH} \\
\]

(45%)


Carbomagnesiase with silyl group stabilization: Yoshida et. al. ACIE (2001) 2337


Carbomagnesiase with Zr: Hoveyda et. al. JACS (1993) 6614

Carbomagnesiase with Zr: Hoveyda et. al. JACS (1993) 6614

EtMgCl, Cp₂ZrCl₂ (6 mol %)

Et₂O, rt, 12hr;
then O₂ bubbled at 0 °C

OH

(70%, 95:5 syn:anti)

nC₉H₁₉

nC₉H₁₉

See also: Carbomagnesiase of alkynes: Snider et. al. Tet. Lett. (1979) 1679 and Nozaki et. al. JACS (1983) 4491


PhMe₂SiMgMe/Cul;
Mel

(77%)
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**Emily Cherney**

### Baran Group Meeting

#### Magnesium:

Directed mettallation with Mg-amides: Eaton et al. JACS (1989) 8016

\[
\begin{align*}
\text{Pr}_2\text{NOC} & \quad \text{CONPr}_2 \quad \text{CONPr}_2 \\
\text{MeO}_{2}C & \quad \text{MeO}_{2}C \\
\end{align*}
\]

(80%)

\*also o-metallation on aryl rings directed by esters and sulfoxides


![Chemical structure diagram]

Geminal difunctionalization of magnesium carbenoids: Hart et al. JOC (1990) 881

\[
\begin{align*}
\text{CH}_2\text{Br}_2 & \quad \text{Mg} \quad \text{THF}, -78 \degree C; \\
\text{PhCHO; Et}_2\text{NH} & \quad \text{OH} \\
\end{align*}
\]

(50%)


![Chemical structure diagram]

Girard reagents and gem-dibromo cyclopropanes and methylsilanes:

![Chemical structure diagram]


\[
\begin{align*}
\text{Me}_2\text{SiLi} & \quad \text{E}^+; \text{THF}, -78 \degree C \text{ to } -30 \degree C; \\
\text{R} & \quad \text{n-Bu} \\
\end{align*}
\]

(65-80%)

R = n-hexyl, Ph

E+ = I2, allylBr, Mel, PhCHO


![Chemical structure diagram]

Radical heterocoupling with Grignard reagents: Ohno et al. JOC (1988) 729

![Chemical structure diagram]

Radical THF synthesis: Oshima et al. OL (2000) 6770

![Chemical structure diagram]

Mg-metal coupling of aldehydes and enones: Ohno et al. JOC (1995) 458

![Chemical structure diagram]

Cobalt catalyzed Heck-type reactions: Oshima et al. JACS (2002) 6514

![Chemical structure diagram]

for further explanation: see KFoo group meeting on Cobalt (2009)
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Calcium:

What you should know about organocalcium and calcium reagents:
- Reducing strength of dissolving metals: Li > K > Rb > Na > Ca so it can have better selectivity.

<table>
<thead>
<tr>
<th>Relative reactivities for functional group reduction by Ca/NH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
</tr>
<tr>
<td>R'₂OR → HOR</td>
</tr>
<tr>
<td>alkyne → trans-alkene</td>
</tr>
<tr>
<td>O</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>O</td>
</tr>
<tr>
<td>R₃Si - R₃Si</td>
</tr>
<tr>
<td>R₃SiO -</td>
</tr>
</tbody>
</table>


- Organocalcium:
  - calcium metal is less reactive than alkali metals or magnesium so it needs to be activated before use (reduction of Ca₀ with K metal by Rieke)
  - organocalcium compounds have high reactivity (cleave ethereal solvents) and decompose quickly so they need to be handled at very low temperatures or shielded with bulky ligands (or extremely bulky substrates i.e. 2,6-disub aryl)
  - alkyl halides undergo Wurtz coupling rapidly and aryl iodides represent the major (if not all) substrates used.
  - organocalcium compounds are highly ionic and suffer from low solubility--shielding with ligands also increases solubility

Ca catalyzed Friedel-Crafts alkylation: Niggeman et. al. ACIE (2010) 3648

Coupling of alcohol with organosilanes: Niggeman et. al. EJOC (2011) 3761


Ca catalyzed cyclopropanation: Niggeman et. al. ACIE (2013) ASAP

Calcium catalyzed Pictet-Spangler: Stambull et. al. OL (2006) 5289
Calcium:

Hydroamination: Hill et al. JACS (2005) 2042

\[
\text{C}_6\text{D}_6, 30 \text{ min} \\
(\text{Ar}=2,6\text{-disopropyl ph}) \\
(10 \text{ mol%}) \\
(>99\% \text{ conversion by NMR})
\]


\[
\text{(DCC)} \\
\text{B} (1.5 \text{ mol%}) \\
\text{C}_6\text{D}_6, 30 \text{ min} \\
(85\%)
\]

Hydrosilation of alkenes: Harder et al. ACIE (2006) 2741

\[
\text{PhSiH}_3 (1 \text{ eq}) \\
\text{neat, } 50^\circ \text{C}
\]


Hydrogenation of alkenes: Harder et al. ACIE (2008) 9434

for 1,1'-diphenylethylene, 1 mol% cat., in C\text{6}H\text{6} at 60 \degree \text{C} for 17 hr gave 49\% conversion to product

C–F bond activation: Barrett et al. ACIE (2007) 6339

\[
\begin{align*}
\text{F}_3\text{C} & \text{C} & \text{CF}_3 \\
\text{C}_6\text{H}_5 & \text{N} & \text{H} & \text{N} & \text{C}_6\text{H}_5 \\
\text{Ca}_2 & \text{KHMDS} (2 \text{ eq}) & \text{THF, rt, } 14 \text{ hr} \\
\text{THF} & & & & (X\text{-Ray})
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{D}_6, 50^\circ \text{C, } 2 \text{ hr} \\
\text{LnCa} & \text{F}_2 & \text{CF}_3 \\
\end{align*}
\]

Enantioselective 1,4-additions: Kumaraswamy et al. TL (2001) 8515

\[
\begin{align*}
\text{MeO} & + \\
\text{Ph} & \text{MeO} \\
\text{[(R)-CaBINOL]} & \text{KCl} (15 \text{ mol%}) & \text{Toluene, } -15^\circ \text{C}, 24 \text{ hr}
\end{align*}
\]

(90\%, 42\% ee)

See also: enantioselective Bayliss-Hillman with Ca-BINOL TL (2000) 2165

Enantioselective cross aldols: Noyori et al. TL (2001) 4669

Enantioselective 1,4-additions: Kobayashi et al. ACIE (2009) 9117

\[
\begin{align*}
\text{MeO} & + \\
\text{Ph} & \text{MeO} \\
\text{Ca(O} & \text{OPhMeOC}_6\text{H}_4\text{)} (10 \text{ mol%}) & \text{Ligand C} (10 \text{ mol%}) \\
\text{Toluene, } -20^\circ \text{C, } 4 \text{ A.M.S.} \\
\text{p-MeC}_6\text{H}_4 & \text{MeO} & \text{p-MeC}_6\text{H}_4 \\
\end{align*}
\]

(92\%, 95\% ee)

See also: asymmetric Mannich with malonates and imines: JOC (2010) 963


\[
\begin{align*}
\text{Ph} & \text{N} & \text{MeO} \\
\text{Ca(O} & \text{OPhMeOC}_6\text{H}_4\text{)} (10 \text{ mol%}) & \text{BOX-Ligand*} (10 \text{ mol%}) \\
\text{THF, } 0^\circ \text{C, } 18 \text{ hr} \\
\text{nBu} & \text{MeO} & \text{MeO} \\
\end{align*}
\]

(81\%, 98\% ee)
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**Calcium:**

Enantioselective Benzoylxylation: Antilla et al. *ACIE* (2011) 1135

\[
\]

\[
\begin{align*}
\text{PhCHO} + \text{enone} & \rightarrow \text{product} \\
\text{cyclohex:toluene, 9:1, -10 °C} & \rightarrow \text{product} (85\%, 70\% \text{ ee})
\end{align*}
\]


\[
\begin{align*}
\text{MeO}-\text{H} & \rightarrow \text{product} (91\% \text{ by } ^1H-NMR) \\
\end{align*}
\]

2,6-diPrPh

2,6-diPrPh

X-ray for L= 2,6-diPrPh

**Strontium:**


\[
\begin{align*}
\text{1,4-Addition of cyanide: Shibasaki et al. *JACS* (2010) 8862} \\
\end{align*}
\]

\[
\begin{align*}
\text{1,4-Addition of malonates: Kobayashi et al. *JACS* (2008) 2430} \\
\end{align*}
\]

Strontium in polymer chemistry: Sarazin et al. *JACS* (2011) 9069

\[
\begin{align*}
\text{MeO} & \rightarrow \text{product} (57\%, M_n = 4200, M_w/M_n = 1.10)
\end{align*}
\]

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Emily Cherney
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**Strontium:**
- Asymmetric Mannich: Shibasaki et. al. ACIE (2011) 4382
- Asymmetric Mannich: Matsunaga et. al. ACIE (2012) 7007
- Hydroammoniation: Barrett and Hill et. al. JACS (2009) 12906

**Strontium ranelate** is a medication for osteoporosis. It is "dual action" because it not only increases bone formation by being incorporated into the bone in place of calcium but also prevents bone resorption. It is an approved prescription drug in more than 70 countries, however the US isn't one of them. The FDA did not approve it, but two major Phase III clinical students showed it is generally well tolerated.

**Barium**
- Asymmetric Diels-Alder reactions: Shibasaki et. al. ACIE (2009) 1070
- Mannich-type reactions: Shibasaki et. al. OL (2007) 3387

**For more examples of hydroamination see also: JACS (2012) 2193 and Organomet. 2011) 1493**
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**Barium**


\[
\text{BaH}_2 (1 \text{ eq}) + \text{HMPA} (5 \text{ eq}) \rightarrow \text{BaH}_2 = \text{62/gram from Strem}
\]

(70%)


\[
\text{PhMeCHO} + \text{PhCHO} \rightarrow \text{PhMe}_2 \text{CHO} \rightarrow \text{PhMe}_2 \text{CHO}
\]

(99%, 70% ee)


\[
\text{Ba(HMDS)}_2 (10 \text{ mol %}) + \text{H} (10 \text{ mol %}) + 4 \text{Å MS, MTBE:THF, 9:1, rt, 24 hr} \rightarrow \text{product}
\]

(89%, 96% ee)


\[
\text{MeMeMeBr} \rightarrow \text{product}
\]

(47%) 1:2:3 = 96:1:3

Note excellent selectivity for \(\alpha(E),\alpha'(E)\) product


\[
\text{nC}_5\text{H}_11\text{OP(O)(OCH}_2\text{CF}_3)_2 \rightarrow \text{nC}_7\text{H}_{15}\text{OP(O)(OCH}_2\text{CF}_3)_2
\]

\[
\text{THF, -78 °C} \rightarrow \text{product}
\]

(99%, 98:2, \(\alpha,\gamma\))

1,2-Addition to Aldehydes: Yamamoto et. al. *Synlett* (1997) 1090

\[
\text{PhCHO, 18-crown-6 (1 eq) THF, -78 °C, 30 min} \rightarrow \text{product}
\]


\[
\text{sBuLi, THF} \rightarrow \text{product}
\]

(95%, \(94.6: \gamma,\gamma\))

(see also: 1,2-Addition to imines and asymmetric 1,2-addition to imines (SAMP)


Triterpenes: Corey et. al. *JACS* (2008) 8865