Radical Reactions (Part 2)

Lecture Notes

Key Reviews:

McMurry Reductive Coupling

Samarium Diiodide-Mediated Reactions

Acyloin Condensation

Dissolving Metal Reductions
The McMurry Reductive Coupling Reaction: Background and General Considerations

Reducing agents: Li, Na, Mg, Zn, LiAlH₄, Zn-Cu
Carbonyl groups: aldehydes and/or ketones

Exact mechanism is unknown because active reagent not entirely known, but involves two key steps: pinacol coupling and deoxygenation to the alkene

Specific intermediates involved depend on the structure of the carbonyl substrate and the exact reaction conditions, making generalizations difficult and yields hard to reproduce

For a review, see: J. E. McMurry, Chem. Rev. 1989, 89, 1513.
The McMurry Reductive Coupling Reaction: Applications in Synthesis

\[ R = \text{TBDPS} \]

McMurry coupling reaction (81%)

13-hydroxyneocembrene

The McMurry Reductive Coupling Reaction: Applications in Synthesis

$\text{TiCl}_3$, Zn-Cu, 
DME 

$\text{McMurry coupling}$

(66% overall; E-isomer only)

1. $\text{KO}_2\text{CN}=\text{NCO}_2\text{K}$
2. $\text{H}_2$, Pd/C 

(72% overall)

The McMurry Reductive Coupling Reaction: Applications in Synthesis

Note the carbonyl selectivity in this reaction

Non-nucleoside reverse transcriptase inhibitor

The McMurry Reductive Coupling Reaction: A Way to Stop at the Diol Product

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{TiCl}_4, \text{Mg-Hg} & \quad \underset{\text{THF}}{\rightarrow} & \quad \text{Me} \\
\text{OH} & \quad \text{OH} \\
(32\%) & & \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{TiCl}_4, \text{Mg-Hg} & \quad \underset{\text{THF}}{\rightarrow} & \quad \text{Me} \\
\text{OH} & \quad \text{OH} \\
(43\%) & & \\
\end{align*}
\]

Syn-disposed alcohol results from this reaction; likely the result of titanium chelation of the reaction intermediates

The only other way to get diol products is in ring systems where the final elimination would impart a great deal of ring strain, an example of which is coming up!

A ring closure of two carbonyls to a diol product is also known as a pinacol cyclization

The McMurry Reductive Coupling Reaction: Applications in Synthesis

Ring strain in product likely prevents formation of the alkene product

Sml₂:
An Incredibly Useful One Electron Reductant

\[
\text{Sm metal} \xrightarrow{\text{THF, } 25 \, ^\circ\text{C}} \text{Sml}_2 + \text{I}_2
\]

Commercially available, but best synthesized prior to use

Addition of the 1,2-diiodoethane must be slow (often added over 20 minutes) and exactly one equivalent. Otherwise, Sml₃ (a yellow-green solid) is formed instead. Sml₂ in THF solution is a beautiful deep blue color.

Sml$_2$:
An Incredibly Useful One Electron Reductant

$$\text{Sm metal} \xrightarrow{\text{I} \quad \text{I}} \text{Sml}_2 + \text{I}$$

THF, 25 °C

Commercially available, but best synthesized prior to use

Addition of the 1,2-diiodoethane must be slow (often added over 20 minutes) and exactly one equivalent. Otherwise, Sml$_3$ (a yellow-green solid) is formed instead.

Sml$_2$ in THF solution is a beautiful deep blue color.

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\[
\text{Sm metal} \quad \text{I} \quad \text{I} \quad \xrightarrow{\text{THF, 25 °C}} \quad \text{Sml}_2 + \quad ||
\]

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Addition of the 1,2-diiodoethane must be slow (often added over 20 minutes) and exactly one equivalent. Otherwise, Sml₃ (a yellow-green solid) is formed instead. Sml₂ in THF solution is a beautiful deep blue color.

Co-additives can greatly enhance the reducing power of Sml₂, and studies have shown that four equivalents of additive per equivalent of Sml₂ is best.

\[\text{HMPA} = \text{gives a deep purple solution upon complexation}\]
\[\text{H}_2\text{O} = \text{gives a blood red solution upon complexation}\]
\[\text{DMPU} = \text{gives a light purple solution upon complexation}\]

$\text{SmI}_2$: Picanol Coupling Reactions

Usually view mechanism as generation of a single ketyl radical, and then attack onto the remaining, and most active, carbonyl group. Samarium complexation with the ketone acceptor for the ketyl radical is the responsible factor for exceedingly high syn diol selectivity.

Sml$_2$: Picanol Coupling Reactions

\[ \text{Sml}_2 (2 \text{ eq.}), \text{THF/t-BuOH} \rightarrow \text{Product} \]

- 52% yield (J. Org. Chem. 1988, 53, 2132)
- 81% yield (92% de) (Tetrahedron Lett. 1991, 32, 1125)
- 86% yield (96% de) (Tetrahedron Lett. 1994, 35, 2969)
**Sml$_2$-induced Pinacol Coupling:**
*Application to the Original Structure of Diazonamide A*

1. **TBAF**
2. **Dess-Martin [O]**

\[\text{Pd(dppe)}\text{Cl}_2, K_2\text{CO}_3, \text{DME}, 90^\circ\text{C} \] (70%)

**Suzuki coupling**

1. **Sml$_2$ (4 equiv)**, **HMPA (36 equiv)**
   \[\text{THF, 90^\circ\text{C}, 1 h} \] (40%)

**Pinacol cyclization**

*K. C. Nicolaou, S. A. Snyder, unpublished results*
**Sml₂:**
**Hetero Pinacol Coupling Reactions**

5-exo-trig cyclization with hydrazone is infinitely faster the 5-exo-trig cyclization with the alkene

Unlike pinacol couplings, hetero pinacol couplings typically give rise to trans products (in terms of the 1,2-aminoalcohol functionality)

**Hetero Pinacol Couplings Induced by Sml$_2$**

*Intramolecular hetero pinacol couplings:*

$$\begin{align*}
\text{Sml}_2 (3 \text{ eq}), & \quad \text{THF/t-BuOH, 0 °C} \\
& \quad \text{(78%)}
\end{align*}$$

$$\begin{align*}
\text{Sml}_2 (4 \text{ eq}), & \quad \text{THF/HMPA, 25 °C} \\
& \quad \text{(40%)}
\end{align*}$$

**References:**


**Hetero Pinacol Couplings Induced by Sml₂**

**Intramolecular hetero pinacol couplings:**

\[
\text{Sml}_2 \text{ (3 eq), THF/t-BuOH, 0 °C} \quad (78\%) \quad \text{J.L. Chiara, et al.} \\
\text{J. Org. Chem. 1995 60, 6010-6011.}
\]

\[
\text{Sml}_2 \text{ (4 eq), THF/HMPO, 25 °C} \quad (40\%) \quad \text{T. Skrydstrup, et al.} \\
\text{J. Org. Chem. 2000 65, 5382-5390.}
\]

**N-O bond cleavage:**

\[
\text{Sml}_2 \text{ (4 eq), THF, 25 °C, 5 h} \quad (69\%) \quad \text{G.E. Keck, et al.} \\
\text{Tetrahedron, 1999 55, 11755-11772.}
\]

Possible Retroversynthetic Analysis for the Heterocyclic Core of Diazonamide A
Pinacol Coupling to Generate the Heterocyclic Core of Diazonamide A

Failed Approaches To Generate The Macrocyclic Core of Diazonamide A
**Sml₂:**
Ketyl-Olefin Coupling Reactions

Must use alkenes that are activated (i.e. electron poor) for intermolecular reactions.

Simple alkenes do not work for these couplings unless in an intramolecular reaction.

**Sml₂: Ketyl-Olefin Coupling Reactions**

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$Sml_2$: Ketyl-Olefin Coupling Reactions

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$\textit{Sml}_2$: Ketyl-Olefin Coupling Reactions

$\text{Me}_2\text{Sm}$, $\text{THF/HMPA}$

$5$-exo-$\text{trig}$

$5$-exo-$\text{dig}$ cyclization

$72\%$

$\textit{coriolin}$

$\text{D. P. Curran and co-workers, J. Am. Chem. Soc. 1988, 110, 5064.}$
**Sml$_2$: Applications in Synthesis**

Sml$_2$: Applications in Synthesis

$\text{Sml}_2$ (2 eq.), THF/HMPA

(86\%) Ketyl-olefin cyclization

$\text{Sml}_2$ (2 eq.), THF/HMPA

(78\%) Ketyl-olefin cyclization

Sml$_2$: Applications in Synthesis

Sml₂:
Applications in Synthesis

Sml₂:
Ketyl-Olefin Coupling Reactions

**Sml₂:**
**Ketyl-Olefin Coupling Reactions**

Same reactivity principles as with Barton deoxygenation example you saw in the last lecture

The Kagan-Molander Sml₂-Mediated Coupling Reaction: Background and General Considerations

A: Add ketone to preformed organosamarium intermediate [samarium Grignard conditions]
B: Ketone in same pot with halide when Sml₂ added [samarium Reformatsky conditions]

Works well with most halides; exceptions are aryl, vinyl, and tertiary halides.

Reactions rates can be greatly accelerated by the addition of Ni(II) or Fe(III) salts.

Addition of HMPA or DMPU as co-solvent to enhance the reducing power of Sml₂ usually helps.

The Kagan-Molander Sml$_2$-Mediated Coupling Reaction: Applications in Synthesis

The Kagan-Molander SmI₂-Mediated Coupling Reaction: Applications in Synthesis

The Kagan-Molander Sml$_2$-Mediated Coupling Reaction: Applications in Synthesis

Due to the reduced reactivity of alkyl chlorides to Sml$_2$, visible light irradiation is needed in the second step to initiate the reaction.

The Kagan-Molander Sml₂-Mediated Coupling Reaction: Applications in Synthesis

Sml₂ (3 eq.)
THF, 0 °C,
10 minutes

Samarium Reformatsky
conditions

TBSCO

(85%)

TBSCO

The Kagan-Molander SmI$_2$-Mediated Coupling Reaction: Applications in Synthesis

The Kagan-Molander Sml₂-Mediated Coupling Reaction: Applications in Synthesis

**Sml₂**: Ketyl-Olefin Coupling Reactions

Esters do not readily form radicals with Sml₂; only aldehydes and ketones possess high reactivity

**aqueous work-up** (61%)
The Acyloin Condensation: Background and General Considerations

One possible mechanism

Note: acyloin derives its name from the older literature as a shorthand notation for α-hydroxy ketones

The Acyloin Condensation: Background and General Considerations

Another possible mechanism

The Acyloin Condensation: Applications in Synthesis

Note: the addition of TMSCl is often done to prevent any base-catalyzed side-reactions such as β-elimination, Claisen, or Dieckmann-type condensations; this simple change greatly expands the scope of this reaction.

bicyclic diketone

The Acyloin Condensation: Applications in Synthesis

Note: the addition of TMSCl is often done to prevent any base-catalyzed side-reactions such as β-elimination, Claisen, or Dieckmann-type condensations; this simple change greatly expands the scope of this reaction.

The Acyloin Condensation: Applications in Synthesis

More sterically accessible enolate is protonated in the final operation; nice example of regioselectivity on a non-symmetrical substrate

anopterine fragment

Birch Reduction: Background and General Considerations

$\text{EDG} = \text{alkyl, OR, } \text{NR}_2$

**Birch Reduction:
Background and General Considerations**

For EDG groups:

- Li or Na, NH₃
- ROH

For EWG groups:

- Li or Na, NH₃
- ROH

**EDG** = alkyl, OR, NR₂

**EWG** = CO₂H, CO₂R, COR, CONR₂, CN, Ar, SiR₃

Birch Reduction: Background and General Considerations

**EDG**

$\text{EDG} = \text{alkyl, OR, NR}_2$

Protonation of the radical anion is determined by the site of maximum electron density

**EWG**

$\text{EWG} = \text{CO}_2\text{H}, \text{CO}_2\text{R}, \text{COR}, \text{CONR}_2, \text{CN}, \text{Ar}, \text{SiR}_3$
Birch Reduction: Background and General Considerations

\[
\begin{align*}
\text{Me} & \quad \text{Li or Na, NH}_3 \quad ROH \\
\text{CONMe}_2 & \quad \text{Li or Na, NH}_3 \quad ROH \\
\end{align*}
\]

\[
\begin{align*}
\text{CONMe}_2 & \quad \text{Li or Na, NH}_3 \quad ROH \\
\text{CONMe}_2 & \quad \text{Li or Na, NH}_3 \quad ROH \\
\end{align*}
\]
Birch Reduction: Background and General Considerations

For any disubstituted system, the groups must reinforce each other for effective Birch reduction. All the examples on this and the previous slide are reinforcing in terms of the regioselectivity of Birch reduction.

For early examples of this effect, see:
Birch Reduction: Background and General Considerations

For any disubstituted system, the groups must reinforce each other for effective Birch reduction. All the examples on this and the previous slide are reinforcing in terms of the regioselectivity of Birch reduction.

For early examples of this effect, see:
Birch Reduction:
What Other Products Can You Get?

With controlled use of 1 equivalent of a proton source, several alkylating agents can be added to give quaternary carbons and products that cannot aromatize.
Birch Reduction: What Other Products Can You Get?

Birch Reduction:
What Other Products Can You Get?

Birch Reduction:
What Can You Do With the Reaction Products?

\[
\begin{align*}
\text{MeO-} & \quad \xrightarrow{\text{Na/NH}_3, \ t-\text{BuOH}} \quad \text{MeO-} \\
\text{Birch Reduction} & \\
\text{O} & \quad \xrightarrow{H^+} \quad \text{O}
\end{align*}
\]

Robinson annulation-type product
Birch Reduction:
What Can You Do With the Reaction Products?

Birch Reduction: What Can You Do With the Reaction Products?

Birch Reduction:  
What Can You Do With the Reaction Products?

\[
\text{MeO} \quad \text{MeO}
\]

\[
\begin{align*}
\text{Li/NH}_3, & \quad \text{dioxane/ether, } -78 \degree C \\
\text{Birch Reduction} & \quad \text{aq. NH}_4\text{Cl}
\end{align*}
\]

thermodynamic ring fusion

Birch Reduction: What Can You Do With the Reaction Products?

\[ \text{Birch Reduction} \]

\[ \text{Li/NH}_3, \text{ dioxane/ether, -78 °C} \]

thermodynamic ring fusion

\[ \text{aq. NH}_4\text{Cl} \]

less stable cis-fusion

Birch Reduction:
What Can You Do With the Reaction Products?

- $t$-BuOH protonates enone reduction intermediate in situ
- Equatorial alcohol is most stable
- Higher temperature of reaction ensures that Birch reduction happens as well

Dissolving Metal Reduction: What Can You Do With the Reaction Products

**Rule:** Dissolving metal reduction gives the thermodynamically most stable product
Dissolving Metal Reduction: What Can You Do With the Reaction Products

\[ \text{t-Bu} \text{C}_{6}\text{H}_{11} \text{O} \xrightarrow{\text{Li/NH}_3, \text{Et}_2\text{O, t-BuOH}} \{\text{Li(0) to Li(I)}\} \]

\[ \begin{align*} &\xrightarrow{} \text{t-Bu} \text{C}_{6}\text{H}_{11} \cdot \text{O}^- \\ &\xrightarrow{} \text{t-Bu} \text{C}_{6}\text{H}_{11} \cdot \text{OH} \\ &\xrightarrow{1 \text{e}^-} \text{t-Bu} \text{C}_{6}\text{H}_{11} \cdot \text{OH}^- \end{align*} \]

**Rule:** Dissolving metal reduction gives the thermodynamically most stable product

**Exception:** Strained or sterically hindered ketones

\[ \begin{align*} &\text{C}_{6}\text{H}_{11} \text{C} = \text{O} \xrightarrow{\text{Li/NH}_3, \text{EtOH}} \{87:13 \text{ endo:exo}\} \\ &\xrightarrow{} \text{endoh} \text{C}_{6}\text{H}_{11} \text{C} = \text{OH} \\ &\xrightarrow{} \text{exo} \text{C}_{6}\text{H}_{11} \text{C} = \text{OH} \end{align*} \]
Dissolving Metal Reduction: Other Synthetic Opportunities