Seminar outline:
- Introduction and Background
- Intramolecular Barbier Reaction
- Intramolecular Reformatsky Reaction
- Radical Alkene and Alkyne Cyclizations
- Carbonyl-Alkene Reductive Cyclizations
- Intramolecular Pinacol Couplings
- Intramolecular Reductive Couplings of Carbonyls and Hydrazones
- Total Synthetic endeavors utilizing mutiple SmI$_2$ cyclizations

Primary References
Rajapakse, H. Evans Group Seminar 1998
Sml₂ Discovery and Background

Introduction


-Samarium diiodide is the subject of >20 reviews and >850 publications.

-Samarium diiodide is commercially available as an anhydrous powder (5g, $185) or as a 0.1 M solution in THF (100mL, $32). (Aldrich catalog 2003-2004)

-Samarium diiodide can be prepared from Sm metal and CH₂I₂, ICH₂CH₂I, or I₂.

-Reactions are generally performed with an excess of samarium diiodide, degassed reagents and solvents, and in dry THF containing an antioxidant.

-Catalytic amounts of Sml₂ can be used with the addition of mischmetall (alloy of lanthanides [La 33%, Ce 50%, Nd 12%, Pr 4%, Sm and other lanthanides 1%] to regenerate Sml₂. The use of catalytic amounts of Sm(II) and mischmetall is more cost effective. The alloy is unreactive to carbonyls and simple to use.

-The normal work-up usually requires acidic conditions. However, Rochelle's salt and potassium carbonate can be used for acid sensitive substrates. (Little D. J. Org. Chem. 1996, 3240)

-THF appears to be the proton source for the termination of radical cascades. If a second reduction with additional equivalent of Sml₂ occurs the proton source is generally the alcoholic co-solvent. (Curran D. P. J. Am. Chem. Soc. 1988, 5046)

-Samarium diiodide chemoselectively reduces: organic halides, carbonyls, α-hetero-sustituted carbonyls, cyclopropyl ketones, epoxides, amine oxides, sulfoxides, phosphine oxides, sulfones, sulfonates, nitro, nitroso, and azo compounds, allyl acetates, and isoxazoles.

Sml₂ Reduction Potential

-Samarium diiodide is a polyvalent single electron reducing agent.

- The reduction potential (E⁰) of Sm⁺²/Sm⁺³ in water is -1.55 V compared to Na₀/Na⁺¹ of -2.77 V.

- The reduction potential of Sml₂ can be increased by the addition of HMPA, and LiBr or LiCl.

- The addition of transition metal increases the rate of several Sml₂ reactions. (Kagan, H. B. Synlett 1996, 633)

- Changes in protic solvents can alter the rates of Sml₂ mediated reactions and in some cases alter the mechanism.

SmI\textsubscript{2} Barbier Reaction

Basic Mechanism

Reduction of the ketone followed by substitution of alkyl-halide with ketyl-radical ruled out by Kagan, because the use of chiral alkyl-halides leads to racemic products.

-The replacement of HMPA with LiBr predominately leads to the Pinacol product via inner sphere electron transport/reduction of the ketone via formation of SmBr\textsubscript{2}.

- Replacement of HMPA with HMDS leads to the formation of \([\text{Sm(HMDS)}\textsubscript{2}]\textsubscript{2}\), which has a redox potential in between SmI\textsubscript{2} and \([\text{Sm(HMPA)}\textsubscript{6}]\textsubscript{I}\textsubscript{2}\). \([\text{Sm(HMDS)}\textsubscript{2}]\textsubscript{2}\) reacts faster with alkyl halides and ketones via change in mechanism towards an inner sphere ET process.

Intramolecular SmI$_2$ Barbier Reactions

Basic Mechanism

Reactions performed with 2 equiv of SmI$_2$ and 20 equiv of HMPA

Curran, D. P. *Tetrahedron* 1997, 9023
Intramolecular SmI₂ Barbier Reactions
Eunicellin and Muscone


Suginome, H. *Tetrahedron* **1987**, *3963*
Intramolecular SmI$_2$ Barbier Reactions
Polyoxypeptin A

Hamada's Explanation

Procter's Explanation

-Mechanism might proceed through a bis-radical structure

Procter D. *Chem. Rev.* **2004**, *3371*
Intramolecular SmI$_2$ Barbier Cyclizations
Synthetic Studies Towards Variecolin

$\text{OMe}$ $\text{I}$ $\text{O}$ $\text{Cl}$
$\text{+}$
$\text{SmI}_2, \text{cat. NiI}_2$ $\text{THF, 72\%}$

$\text{OMe}$ $\text{O}$ $\text{H}$ $\text{H}$
$\text{OH}$

1:1 Mixture of diastereomers due to racemic starting materials

$\text{RuCl}_3, \text{NaIO}_4$ $\text{MeCN, CCl}_4, \text{H}_2\text{O}$ $65\%$

Molander, G. Org. Lett. 2001, 2257

For increased reaction rates with NiI$_2$ see: Kagan, H. Synlett 1996, 633
For increasing reducing ability of SmI$_2$ with visible light see: Ogawa A. J. Am. Chem. Soc. 1997, 2745
Sml₂ Reformatsky reactions

Basic Mechanism

Due to Sm(III)’s ionic radius, high coordination number, and high oxophilicity: Sml₂ has been used successfully as a chelation element to bring two reaction centers in proximity for the formation of large ring.

<table>
<thead>
<tr>
<th>n</th>
<th>Ring Size</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>8</td>
<td>68%</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>70%</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>74%</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>82%</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>82%</td>
</tr>
</tbody>
</table>

**SmI$_2$ Intramolecular Reformatsky reactions**

(+/−) Paeoniflorigenin and Paeoniflorin

Slow Addition of SmI$_2$ (7 equiv)

THF, -45 °C

10h

[Chem 3D w/ MM2 energy minimization]

93% Single Diastereomer

-Product of the cyclization is base sensitive. Retro-Aldol is observed upon treatment of product with Et$_3$N.

**Smi\textsubscript{2} Intramolecular Reformatsky reactions**

**Uridine Derivatives**

\[
\begin{align*}
\text{Conditions} & \quad \text{Product Yields} \\
\text{rt w/ Zn} & \quad \text{C 22\%} \\
\text{rt} & \quad \text{A 71\%} \\
0 \, ^\circ C & \quad \text{A 75\%} \\
-78 \, ^\circ C & \quad \text{A 90\%} \\
-78 \, ^\circ C \text{ w/ HMPA} & \quad \text{A 76\%, B 11\%}
\end{align*}
\]

-Substrate is Base sensitive

-Uridine Derivatives have been shown to be potent antitumor agents both *in vitro* and *in vivo*

**SmI₂ Intramolecular Reformatsky reactions**

**Taxol-Mukaiyama**

- **Step 1:**
  - 1N HCl, THF
  - (COCl)₂, DMSO, Et₃N, CH₂Cl₂ 94%

- **Step 2:**
  - LHMDS, Me₃, HMPA, THF 100%
  - 1N HCl, THF 83%
  - (COCl)₂, DMSO, Et₃N, CH₂Cl₂ 95%

**Chemical Structures:***

![Chemical Structures](image)

SmI₂ Intramolecular Reformatsky reactions
Taxol-Mukaiyama

Chem 3D Minimized Sm³⁻ Enolate Chelate

Simplified Chair Transition State

- Preliminary modeling suggest reaction proceeds through E-enolate

SmI2 Intramolecular Reformatsky reactions
Model Studies Toward Ciguatoxin

Inoue, M. *JOC* 1999, 9416
Inoue, M. *ACIEE* 1998, 965

66% over 5 steps
Sml$_2$ Intramolecular Reformatsky reactions
Model Studies Toward Ciguatoxin

Chem 3D Minimized Structure of the Sm$^{III}$ Chelated Enolate

Simplified Conformation

Inoue, M. ACIEE 1998, 965
Inoue, M. JOC 1999, 9416
**SmI₂ Radical-Alkene and Alkyne Cyclizations**

**Basic Mechanism**

\[
\text{SmI}_2 + \text{R} \rightarrow \text{R}^* \\
\text{R}^* \rightarrow \text{R} \text{R} \text{R} \text{Sm}^\text{III} \rightarrow \text{R} \text{R} \text{R} \text{R} \text{R} \text{OH} \rightarrow \text{R} \text{R} \text{R} \text{R} \text{R} \text{R} \text{R} \text{OH} \rightarrow \text{A} \\
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Equiv HMPA</th>
<th>A/B ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2.3</td>
<td>08/92</td>
</tr>
<tr>
<td>H</td>
<td>3.2</td>
<td>34/66</td>
</tr>
<tr>
<td>H</td>
<td>3.7</td>
<td>50/50</td>
</tr>
<tr>
<td>H</td>
<td>5</td>
<td>56/44</td>
</tr>
<tr>
<td>H</td>
<td>7</td>
<td>52/48</td>
</tr>
<tr>
<td>Me</td>
<td>0</td>
<td>0/100</td>
</tr>
</tbody>
</table>


For a review on the mechanism of SmI₂ reactions see:

For a review of coupling of organic halides and carbonyl compounds see:
Sml₂ Radical-Alkene and Alkyne Cyclizations
Synthetic Utility of Intermediate Organo-Samarium Compounds

**Sml₂ Radical-Alkene Cyclizations**

**C-Glycoside Formation**

![Chemical structures and reaction schemes](image)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>R</th>
<th>Overall Yield B</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF/HMPA</td>
<td>[Ph]</td>
<td>78%</td>
</tr>
<tr>
<td>THF</td>
<td>[Ph]</td>
<td>37%</td>
</tr>
<tr>
<td>THF</td>
<td>[N]</td>
<td>80%</td>
</tr>
</tbody>
</table>

- Authors propose 2-pyridyl group lowers LUMO thus facilitates initial sulfone cleavage

- Possibility of 2-pyridyl group serving as a chelating point, thus facilitating inner sphere electron transport process for initial sulfone cleavage.


For the use of 2-pyridine as a chelation point see: Yamamoto, H. *JACS* 2004, 4128.
Sml₂ Radical Carbonyl-Alkene Cyclizations
Basic Mechanism

-Radical cyclization of ketones with SmI₂

Chemical reactions:
1) 2.2 equiv Sml₂, 2 equiv t-BuOH, THF/HMPA
2) H⁺

Product yields and reaction times:

<table>
<thead>
<tr>
<th>R</th>
<th>% isolated Yield of A and B (diast ratio, A:B)</th>
<th>% Yield C</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>86 (&gt;150:1)</td>
<td>-</td>
<td>15 min</td>
</tr>
<tr>
<td>i-Pr</td>
<td>85 (23:1)</td>
<td>3</td>
<td>30 min</td>
</tr>
<tr>
<td>t-Bu</td>
<td>78 (3:1)</td>
<td>4</td>
<td>8 h</td>
</tr>
<tr>
<td>Ph</td>
<td>48 (1&lt;150)</td>
<td>-</td>
<td>2 h</td>
</tr>
</tbody>
</table>

-Carbonyl reduction by Sml₂ is well documented

Curran, D. P. Synlett 1992, 943
Rajapaksa, H. Group Seminar 6-1998
Sml₂ Radical Carbonyl-Alkene Cyclizations
Basic Mechanism, an Example of an Activated Alkene

Transition States
Sml₂ Radical Carbonyl-Alkene Cyclizations
Basic Mechanism, an Example of an Activated Alkene

Procter, D. J. Org. Lett. 2003, 4811
Sml$_2$ Radical Carbonyl-Alkene Cyclizations
Basic Mechanism, an Example of an Activated Alkene

$t$-BuOH
Slower Protonation allows cyclization

MeOH
"efficient protonation"

Supporting evidence for the anionic model
SmI$_2$ Radical Carbonyl-Alkyne Cyclizations

**Isocarbacyclin**

<table>
<thead>
<tr>
<th>Reagents</th>
<th>A (C$_6$ dr)</th>
<th>B (C$_5$ dr)</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn, TMSCl, 2,6 Lutidine, in THF, at reflux</td>
<td>28% (ND mix)</td>
<td>51% (1:1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Li-Naphthalene, t-BuOH, in THF at -70 °C</td>
<td>65% (ND mix)</td>
<td>15% (1:2)</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>SmI$_2$, t-BuOH, in THF at -70 °C</td>
<td>71% (9:1)</td>
<td>-</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>hv, Et$_3$N, in CH$_3$CN at rt</td>
<td>60% (2:1)</td>
<td>20% (ND)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ND denotes mixture was defined as an "epimeric mixture" at the defined stereocenter.

**Plausible Transition States**

SmI\textsubscript{2} Radical Carbonyl-Alkene Cyclizations

(-)-Patchoulenone

![Chemical Structures](image)

X-Ray Structure of A

Model Studies, effects of PhSH additive

<table>
<thead>
<tr>
<th>Additive</th>
<th>Yield B</th>
<th>Yield C</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>39%</td>
<td>54%</td>
</tr>
<tr>
<td>PhSH</td>
<td>71%</td>
<td>0%</td>
</tr>
</tbody>
</table>

-Prins, carbonyl-ene, and Paterno-Buchi reactions proved to be inferior methods in the synthesis

Sml₂ Radical Carbonyl-Alkene Cyclizations

*trans*-Fused Polytetrahydropyrans

![Chemical Structures]

- Issues with simultaneous binding of ketyl radical and conjugated ester, geometrical constraints?

- Alternated Possibilities

*Procter’s Alternative*

*Non-Chelation*

Sml₂ Radical Carbonyl-Alkene Cyclizations

*trans*-Fused Polytetrahydropyrans

Iterative Cyclizations produces Polytetrahydropyrans and Oxepanes

R= Me or H

-Cyclizations proceed in high yield (>80%) and with complete stereocontrol

Hori, N. *Org. Lett.* **1999**, 1099
Sml₂ Radical Carbonyl-Alkene Cyclizations

Natural Product Synthesis and Synthetic Studies

Ciguatoxin
Takakura, H. ACIEE 2001, 1090

Brevetoxin B
Matsuo, Tetrahedron Lett. 2000, 7673

Gambierol
Kadota, I. JACS 2001, 6199
Kadota, I. JACS 2001, 11893


Also, the D and E ring of the A-F fragment of Yessotoxin. Suzuki, K. Org. Lett. 2002, 3943
Sml₂ Radical Carbonyl-Alkene Cyclizations
Synthetic Studies Toward Vinigrol

81%
Single Diastereomer

Matsuda, F. *Synlett* 1996, 1057
Sml$_2$ Radical Carbonyl-Alkene Cyclizations
Synthetic Studies Toward Vinigrol

\[
\text{Vinigrol}
\]

Matsuda, F. *Synlett* 1996, 1057
SmI₂ Radical Carbonyl-Alkene Cyclizations
(+/-) Hypnophilin

- Addition of D₂O lead to no incorporation of deuterium in products.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Pdt</th>
<th>epi-C₁₁</th>
<th>Reduction</th>
<th>Yield of ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>11%</td>
<td>-</td>
<td>18%</td>
<td>NA</td>
</tr>
<tr>
<td>THF/HMPA</td>
<td>91%</td>
<td>-</td>
<td>9%</td>
<td>63%</td>
</tr>
<tr>
<td>THF/DMPU</td>
<td>87%</td>
<td>9%</td>
<td>4%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Sml₂ Radical Carbonyl-Alkene Cyclizations

(-)-C₁₀-Desmethyl Arteannuim B

\[
\text{Me} \quad \text{Me} \quad \text{CO}_2\text{Me} \quad \text{Me} \quad \text{OH} \quad \text{CH}_2\text{CO}_2\text{Me}
\]

\[
\text{THF-MeOH} \quad 0 \degree \text{C} \quad >95\% \quad \text{Single Diastereomer}
\]

(-)-C₁₀-Desmethyl Arteannuim B

\[
\text{Me} \quad \text{Me} \quad \text{CO}_2\text{Me} \quad \text{Me} \quad \text{O}_\text{O}
\]

\[
\text{Sm}^{\text{III}} \quad \text{O} \quad \text{O} \quad \text{Sm}^{\text{III}} \quad \text{O} \quad \text{O} \quad \text{Sm}^{\text{III}}
\]

\[
\text{MeOH} \quad \text{MeOH}
\]

-α,β-unstaturated ester harder to reduce (E_p -2.45 V) than enone (E_p -2.2 V)

-Performing reaction at -78 °C leads to reduction of enone to allylic alcohol.

-Reaction required degassed solvents and slow separate addition of MeOH and Sml₂.

-Inital product acid sensitive, utilizing Rochelle's salt and a medium of 10% potassium carbonate significantly improved yields.

SmI$_2$ Radical Carbonyl-Alkene Cyclizations

Mucocin

- Survival of second aldehyde suggests initial SmI$_2$ reduction is reversible
- Increasing reaction time or using larger amounts of SmI$_2$ leads to Pinacol-type coupling and reduction products.

Nakata, T. *ACIEE* 2002, 4751
Curran, D. P. *Synlett* 1992, 943
Sml₂ Radical Carbonyl-Alkene Cyclizations

Upial

2:1 Mixture of olefin isomers

76% Single Diastereomer

Proposed Mechanism

SmI$_2$ Radical Carbonyl-Alkene Cyclizations

Model Studies: Upial

\[
\text{O} \quad \text{CHO} \\
\text{(n)} \quad \text{OCH}_2 \text{OH} \\
\text{SmI}_2 \quad \text{THF-HMPA} \\
\text{O} \quad \text{CHO}
\]

Without HMPA product yields were 5-10%

<table>
<thead>
<tr>
<th>n</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>76%</td>
</tr>
</tbody>
</table>

Supporting Evidence

\[
\text{O} \quad \text{CHO} \\
\text{D} \quad \text{CHO} \\
\text{D} \quad \text{CHO}
\]

SmI₂ Intramolecular Pinacol Couplings
Basic Mechanism, myo-Inositol

-O₃, DMS
MeOH, Py

SmI₂, THF
-78 °C

>B2 : 1
70% over 2 steps

-D-Iditol
or L-Iditol

-Attractive alternative to TiCl₃-Zn/Cu, Mg(Hg)-TiCl₄,
or Ytterbium pinacol couplings.

-Predominately gives cis-diol trans to α-substitution

**SmI₂ Intramolecular Pinacol Couplings**
Caryose and a Jojoba Bean Disaccharide

\[
\begin{align*}
\text{BnO} & \quad \text{BnO} \\
\text{Me} & \\
\text{BnO} & \quad \text{BnO} \\
\text{SmI₂} & \quad \text{BuOH-THF} \\
\text{BnO} & \quad \text{BnO} \\
\text{Me} & \\
\end{align*}
\]

93:7 mixture of cis-Diols
64% Yield

Adinolfi, M. *Tetrahedron* 1997, 11767

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Me} & \\
\text{HO} & \quad \text{OH} \\
\text{CHO} & \\
\end{align*}
\]

Single Diastereomer
40% with Oxidation

Kornienko, A. *Carbohydrate Research* 1998, 144.
Sml$_2$ Intramolecular Pinacol Couplings
Synthetic Studies Toward Taxol

Performing reaction at -78 °C leads to reduction

Corresponding Pinacol with TiCl$_4$/Zn produces pdt in 33% yield.

SmI₂ Intramolecular Pinacol Couplings
Synthetic Studies Toward Taxol

\[ \text{SmI}_2 \text{ (10 equiv)} \rightarrow \] THF, rt

\[ 63\% \]

\[ \text{Sm-Chelated Models Minimized Energies} \]

Minimized structures Utilizing Molecular Mechanics in Spartan 04',
Ground State conformers and restricting carbonyl-carbonyl
distance at 3.0 Å.

Δ\( E = +9.8 \text{ Kcal} \)

Sml$_2$ Intramolecular Reductive Coupling of Carbonyl-Hydrazones
Basic Mechanism, An Example

\[
\begin{align*}
\text{Ph$_2$N} & \quad \text{OSm}^{\text{III}} \quad \text{H} \\
\text{H} & \quad \text{NPh$_2$} \\
\text{CH$_3$} & \quad \text{OH} \\
\text{Ph$_2$N} & \quad \text{CH$_2$} \\
\text{NPh$_2$} & \quad \text{N$_2$H$\text{H}_2$} \\
\text{Sm$_{\text{II}}$} & \quad \text{(n)} \\
\text{Sm$_{\text{III}}$} & \quad \text{(n)} \\
\text{Sm$_{\text{II}}$} & \quad \text{(n)} \\
\text{Sm$_{\text{III}}$} & \quad \text{(n)} \\
\text{1) Sm$_{\text{II}}$} & \quad \text{2) H}^+ \\
\text{Sm$_{\text{II}}$} & \quad \text{A} \\
\text{Sm$_{\text{III}}$} & \quad \text{B} \\
\hline
n & A : B & \text{Yield} \\
1 & >25 : 1 & 72\% \\
2 & 4.2 : 1 & \text{ND}
\end{align*}
\]
**Sml₂ Intramolecular Reductive Coupling of Carbonyl-Hydrazones**

**Basic Mechanism, An Example**

1) Sml₂
2) H⁺

Additional Evidence

<table>
<thead>
<tr>
<th>n</th>
<th>A : B</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;25 : 1</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>4.2 : 1</td>
<td>ND</td>
</tr>
</tbody>
</table>

Yields from 75-93%

**Sml$_2$ Intramolecular Reductive Coupling of Carbonyl-Oximes**

**Synthesis of Trehazolin**

![Chemical structures and proposed transition states](image)

1. SmI$_2$ (6 equiv) THF-$t$BuOH
2. H$_2$O
3. LiOH, H$_2$O

98%

7 Steps

**Proposed Transition States**

Chiara, J. L. Synlett 1999, 1551.
**Sml₂ Intramolecular Reductive Coupling of Carbonyl-Oximes**

**Synthesis of Trehazolin**


Chiara, J. L. *Synlett* **1999**, *1551.*
Sml$_2$ Intramolecular Reductive Coupling of Carbonyl-Oximes
Synthesis of Diazonamide A

- No reaction in the absence of HMPA

Sml₂ Intramolecular Reductive Arene-Cr(CO)₃-Carbonyl Cyclizations
Synthetic Studies Towards Pseudoterosin G and Helioprin E

2.5 equiv Sml₂
THF-HMPA

51%

Pseudoterosin G
Helioprin E

SmI₂ Intramolecular Reductive Arene-Cr(CO)₃-Carbonyl Cyclizations
Mechanism

Carbonyl-Olefin Reductive Coupling/Intramolecular SmI₂ Barbier Cyclization

Phorbol Skeleton

\[
\text{OBz} \quad \text{O} \quad \text{OBz} \quad \text{CO}_2\text{Me} \\
\text{SmI}_2 \quad \text{t-BuOH} \quad \text{THF, rt} \quad 58\% \\
\rightarrow \quad \text{Single Diastereomer}
\]

1) NaOMe, MeOH
   THF, 85%

2) I₂, PPh₃
   Imidazole
   THF, 90%

\[
\text{Conditions} \quad \text{Time} \quad \text{Yield} \\
\text{No Additive} \quad 5-7\text{h} \quad 43-68\% \\
\text{With NiI₂} \quad 1\text{h} \quad 82-88\%
\]

For increased reaction rates with NiI₂ see: Kagan, H. Synlett 1996, 633
Carbonyl-Olefin Reductive Coupling/Intramolecular Sml₂ Barbier Cyclization
Phorbol Skeleton

\[
\begin{align*}
\text{OBz} & \quad \text{OBz} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{MeO} \\
\text{SmI}_2 & \quad \text{SmI}_2 \\
\text{t-BuOH} & \quad \text{t-BuOH} \\
\text{THF, rt} & \quad \text{THF, rt} \\
58\% & \quad 58\%
\end{align*}
\]

1) NaOMe, MeOH
THF, 85%
2) I₂, PPh₃
Imidazole
THF, 90%

Model of Intermediate A

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{HO} & \quad \text{HO} \\
\text{SmI}_2 & \quad \text{SmI}_2 \\
\text{NiI}_2 \text{ cat.} & \quad \text{NiI}_2 \text{ cat.} \\
\text{THF, rt, 1 h} & \quad \text{THF, rt, 1 h} \\
88\% & \quad 88\%
\end{align*}
\]

Single Diastereomer

Table:

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Additive</td>
<td>5-7h</td>
<td>43-68%</td>
</tr>
<tr>
<td>With NiI₂</td>
<td>1h</td>
<td>82-88%</td>
</tr>
</tbody>
</table>

Little D. Org. Lett. 2000, 2873
For increased reaction rates with NiI₂ see: Kagan, H. Synlett 1996, 633
Reductive Carbonyl Conjugate and Pinacol Cyclizations
Grayanotosin III

\[
\begin{array}{c}
\text{Me} & \text{H} & \text{Me} \\
\text{O} & \text{O} & \text{OH} \\
\text{Me} & \text{H} & \text{Me}
\end{array}
\xrightarrow{\text{Sml\textsubscript{2}, HMPA, THF, -78 °C}}
\begin{array}{c}
\text{Me} & \text{H} & \text{Me} \\
\text{O} & \text{OH} & \text{OH} \\
\text{Me} & \text{H} & \text{Me}
\end{array}
\]

MM2 Minimized Structure of A

86% Single Diastereomer

Grayanotoxin III

Reductive Carbonyl Conjugate and Pinacol Cyclizations

Grayanotoxin III

-Both $E$ and $Z$-allyl sulfides gave the same product in similar yields

**Model Studies**

R = Bn 83% 86% 91%

R = Ac 47% 78%

$X = \text{SPh}$

$X = \text{SO}_2\text{Ph}$

Plausible Transition States

Reductive Carbonyl Conjugate and Pinacol Cyclizations
Grayanotosin III

\[
\begin{align*}
\text{X} &= \text{MOM} \\
\text{HO} & \quad \text{HO} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{OX} & \quad \text{OX} \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{Sml}_2 & \quad \text{HMPA/THF} \\
\text{Grayanotoxin III}
\end{align*}
\]

Model Studies

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

Conditions: 

<table>
<thead>
<tr>
<th>Conditions</th>
<th>R</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium-pinacol</td>
<td>NA</td>
<td>decomposition</td>
<td></td>
</tr>
<tr>
<td>SmI(_2), HMPA-THF</td>
<td>MOM</td>
<td>ND</td>
<td>Sole prd</td>
</tr>
<tr>
<td>SmI(_2), HMPA-THF</td>
<td>H</td>
<td>50%</td>
<td>ND</td>
</tr>
</tbody>
</table>

Reductive Carbonyl Conjugate and Pinacol Cyclizations
Grayanotosin III

\[
\text{Grayanotoxin III}
\]

Concluding Remarks

**Benefits of Samarium Diiodide Cyclizations**

-Samarium diiodide shows great functional group tolerance.

-The redox potential of SmI$_2$ can be altered by changes in: solvent, co-solvents, ligands, additives, light, and counter ions. This allows fine tuning of the one electron reduction so that relative rates of functional group reductions can be estimated and controlled. (For the reduction potential of several functional groups see: Fry, A. J. *Synthetic Organic Electrochemistry*, 2nd ed.; John Wiley and Sons: New York, 1989.)

-Samarium diiodide has been used succesfully in multiple total synthetic endeavors as a mild single electron chelating reducing agent.

-Due to samarium diiodide's large ionic radius, high coordination number, and high oxophilicity samarium diiodide has been used succesfully as a chelating element to bring two reacting centers in proximity to form large ring systems.

-Samarium diiodide has been shown to be a superior alternative to traditional methods for Barbier, Pinacol, Reformatsky, Carbonyl-Alkene, and Carbonyl-Alkyne cyclizations.

**Drawbacks of Samarium Diiodide Cyclizations**

-The uncertainty in the mechanism of the transformations limits the stereochemical predictive potential of the reagent.