Samarium(II) Iodide in Organic Synthesis

Aroop Chandra

January 10th, 2013

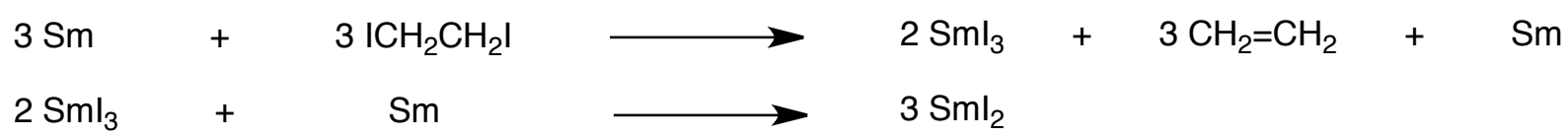
Samarium

- **Derived from Samarskite mineral in 1879**
- **Atomic weight 150.36, atomic number 62, mp 1074 °C, bp 1794 °C**
- **21 Isotopes of Sm reported so far**

The Reagent and the Effect of Additives

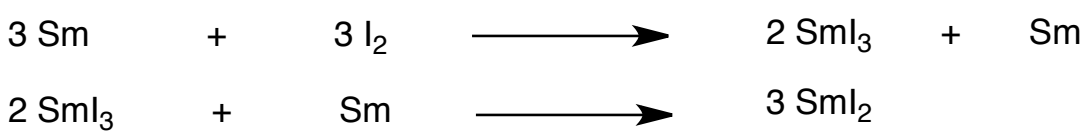
■ Preparation of samarium iodide

Kagan's method using 1,2-diidoethane



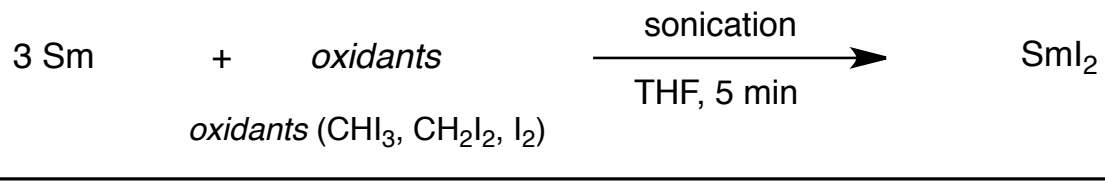
Girard, P.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

Imamoto's method using iodine



Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501.

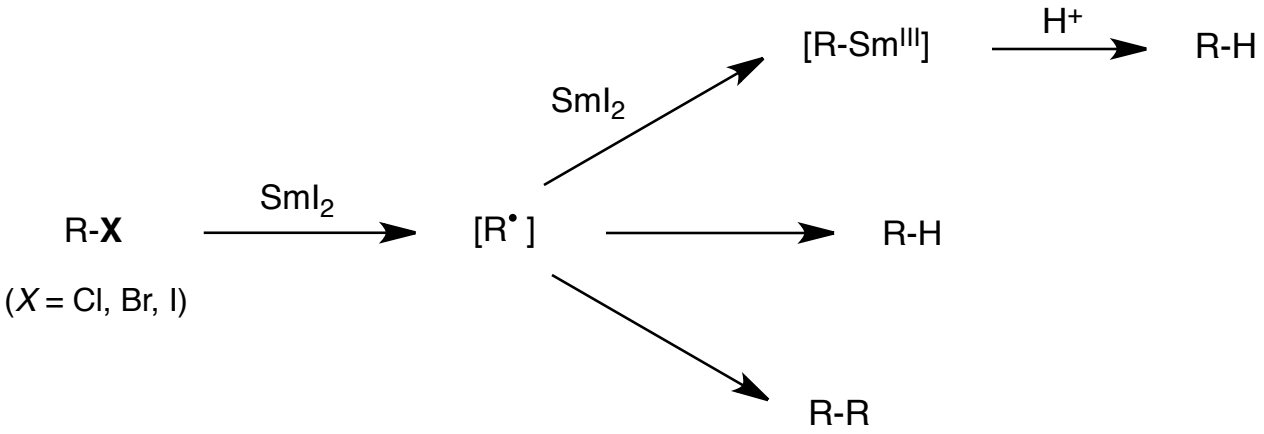
Concellon's method utilizing various oxidants and sonication



Concellon, J. M.; Bardales. E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775.

Mechanism of SmI_2-Mediated Reactions

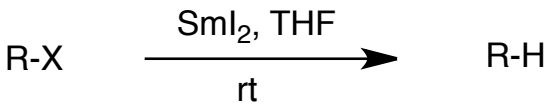
Radicals and anions from organohalides



Reduction of halides: iodides > bromides > chloride

Mechanism of SmI_2-Mediated Reactions

Radicals and anions from organohalides



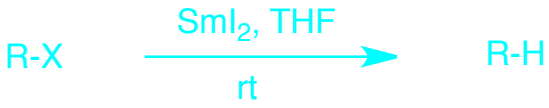
R	X	time	yield (%)
$C_{12}H_{25}$	I	6 h	95
$C_{12}H_{25}$	Br	48 h	82
$C_{12}H_{25}$	Cl	48 h[a]	no rxn

[a] reaction carried out at 60 °C

Inanga, J.; Ishikawa, M. *Chem. Lett.* **1987**, *102*, 1485.

Mechanism of SmI_2-Mediated Reactions

Radicals and anions from organohalides



R	X	time	yield (%)
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$C_{12}H_{25}$	Br	48 h	82
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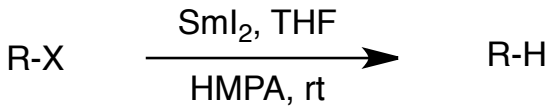
[a] reaction carried out at 60 °C

■ Effect of Lewis bases on the reduction of alkyl halides

HMPA significantly increases the rate of reduction



R	X	time	yield (%)
$C_{10}H_{21}$	I	5 min	96
$C_{10}H_{21}$	Br	10 min	97
$C_{10}H_{21}$	Cl	8 h[a]	94

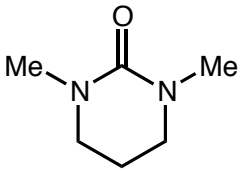
[a] reaction carried out at 60 °C

Inanga, J.; Ishikawa, M. *Chem. Lett.* **1987**, *102*, 1485.

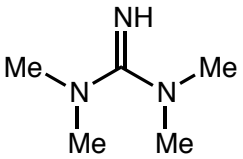
Mechanism of SmI_2-Mediated Reactions

Radicals and anions from organohalides

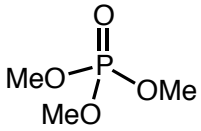
Alternatives to HMPA



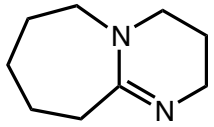
DMPU



TMG



TMP



DBU

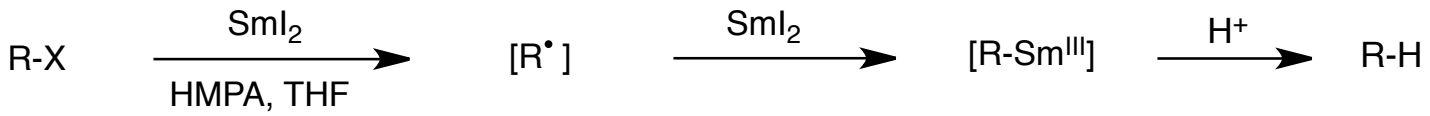
- The basic cosolvents enhances the reducing ability of SmI_2 in two ways:
  1. Basic cosolvents dissociate SmI_2 aggregates in THF
  2. Basic cosolvents may perturb the electron-donating orbital of Sm(II) and raise its energy, thus increasing the Sm(II)/Sm(III) reduction potential

- A relatively large excess of these Lewis basic cosolvents are required as compared to HMPA

- None of these basic cosolvents has as high an affinity of SmI_2 as HMPA

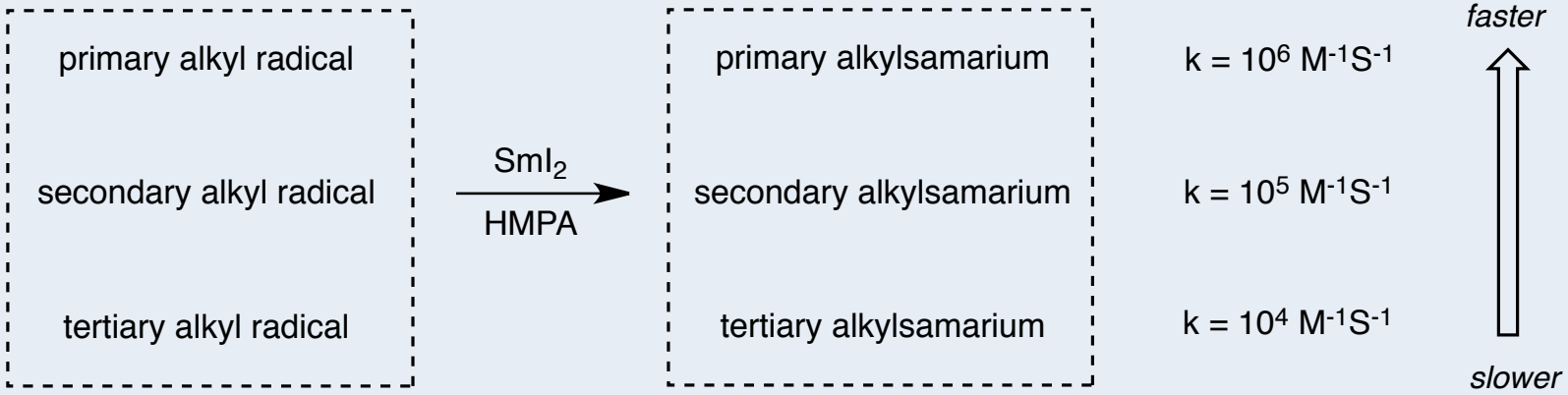
Mechanism of SmI_2-Mediated Reactions

Radicals and anions from organohalides



(*RX* = primary, secondary, and tertiary halides)

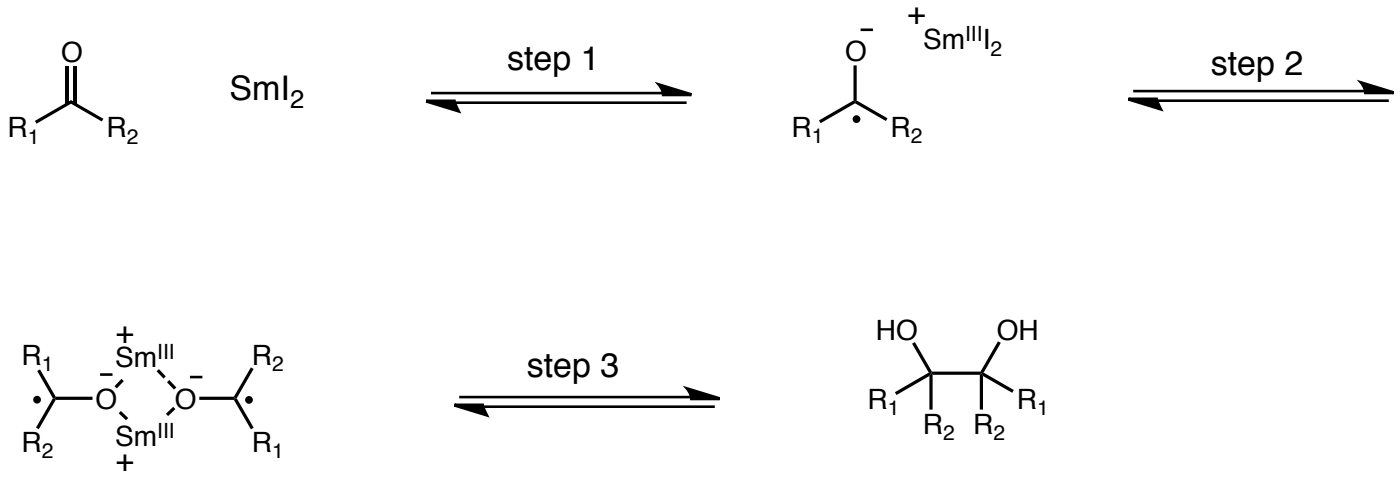
Curran's rate data for the reduction of alkyl radicals to the corresponding anions



Curran, D. P.; Fevig, T. L.; Jasperse, C. P. *Synlett*. **1992**, 943.

Mechanism of SmI_2-Mediated Reactions

Ketyl radical anions from carbonyl groups



Mechanism of SmI_2-Mediated Reactions

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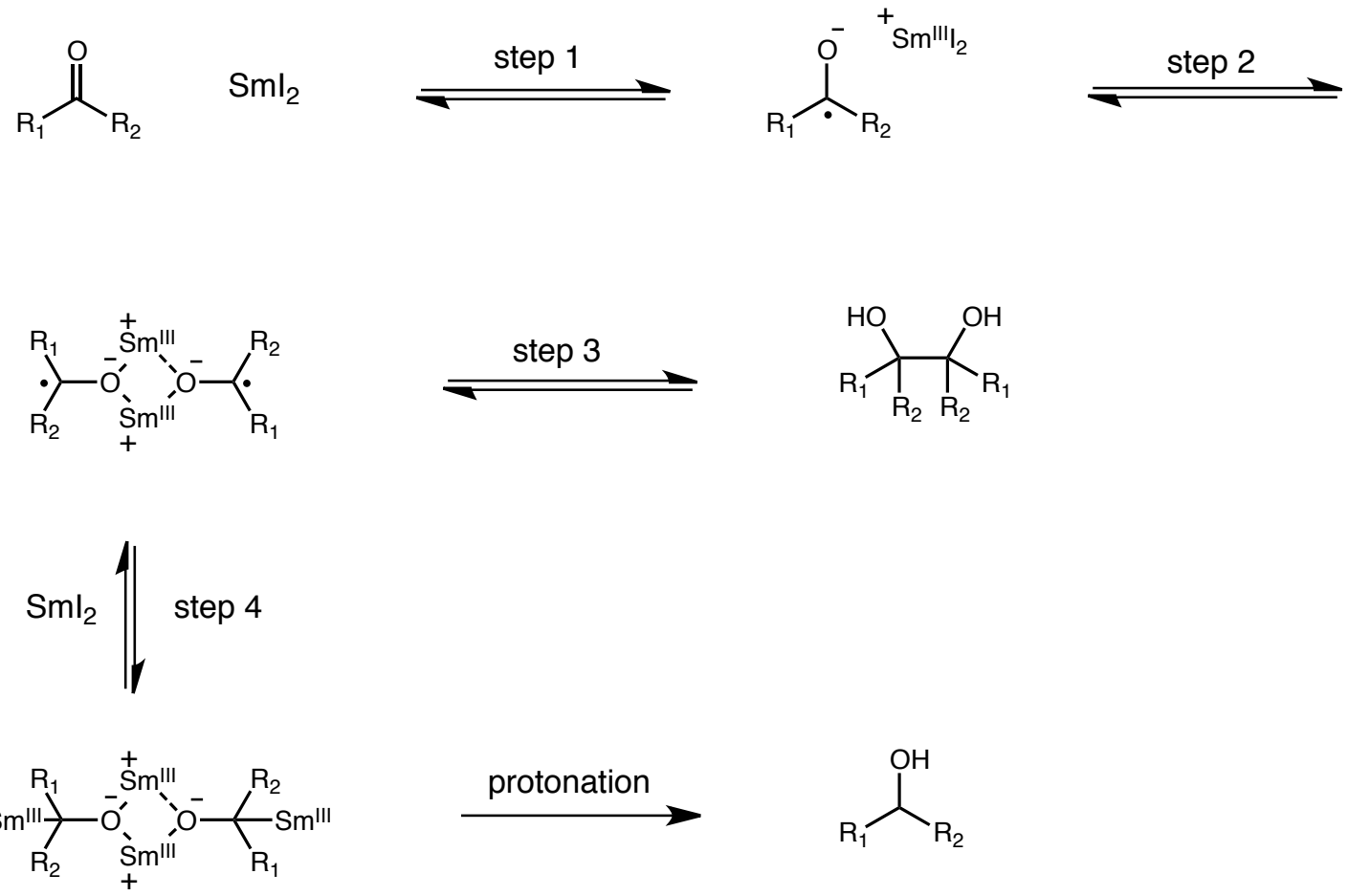
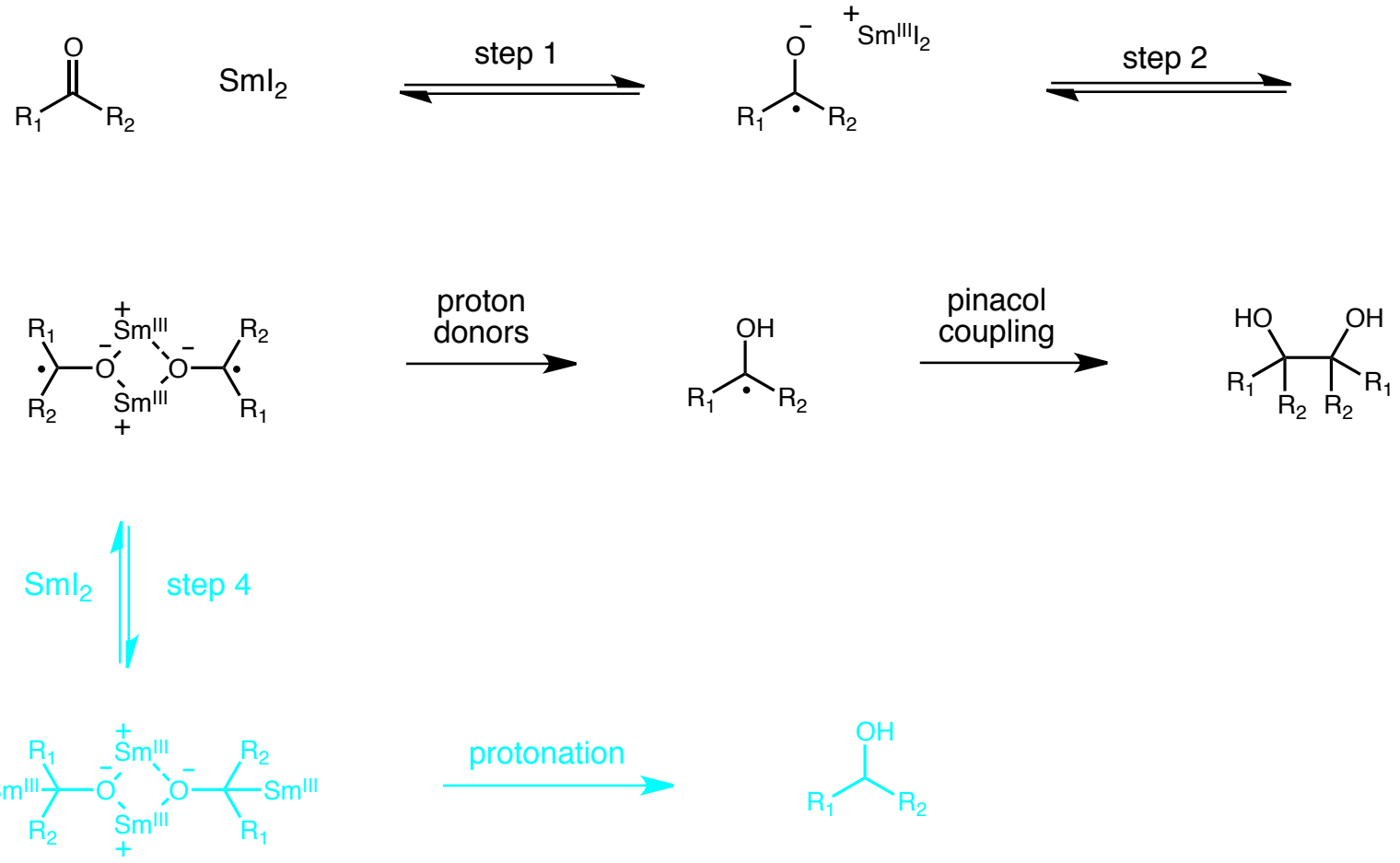


Mechanism of SmI_2-Mediated Reactions

Ketyl radical anions from carbonyl groups

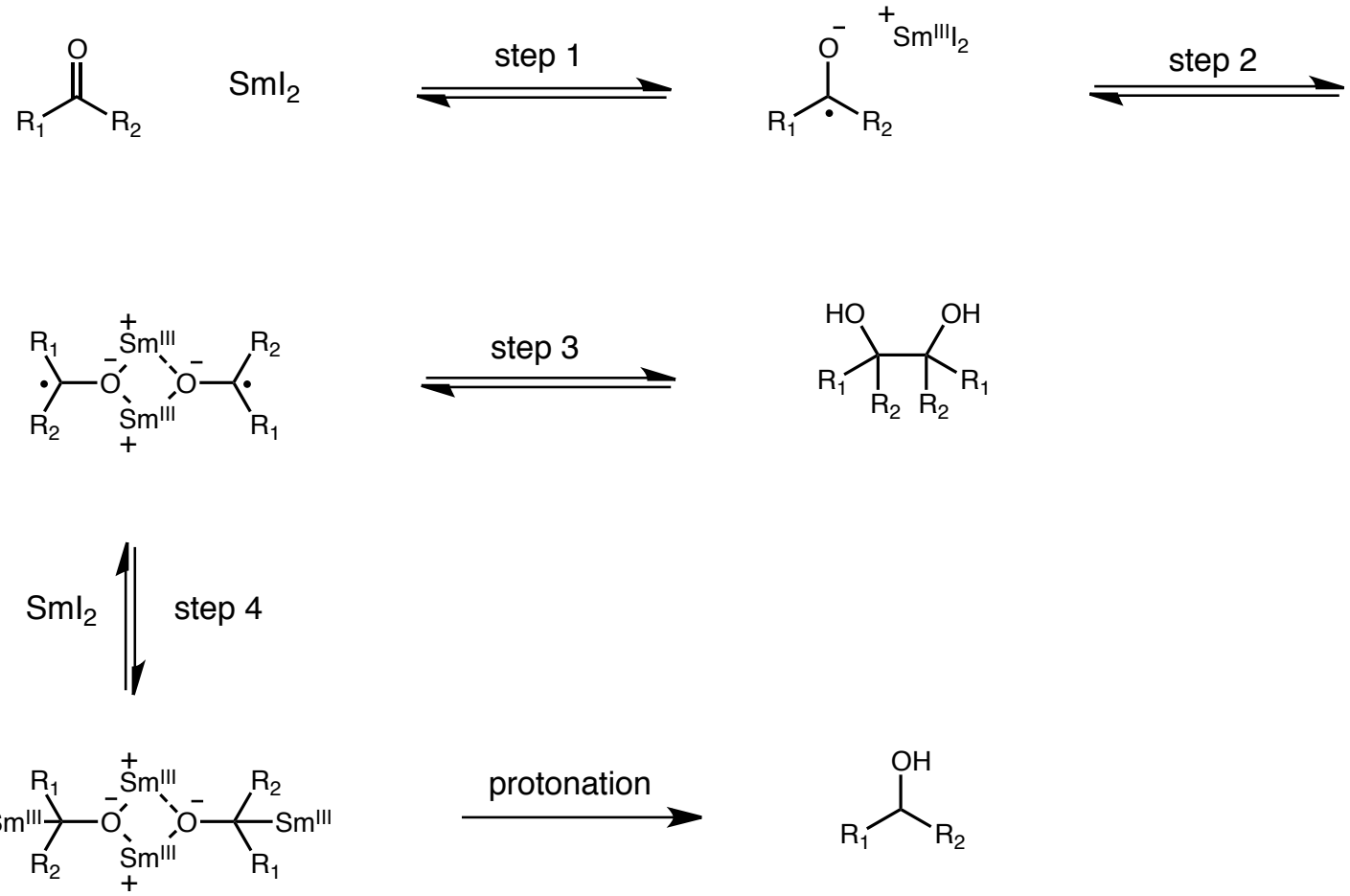
■ **Effect of proton donors (H_2O and alcohols) in carbonyl reduction**



Mechanism of SmI_2-Mediated Reactions

Ketyl radical anions from carbonyl groups

■ **Effect of Lewis basic cosolvents (HMPA) in carbonyl reduction**

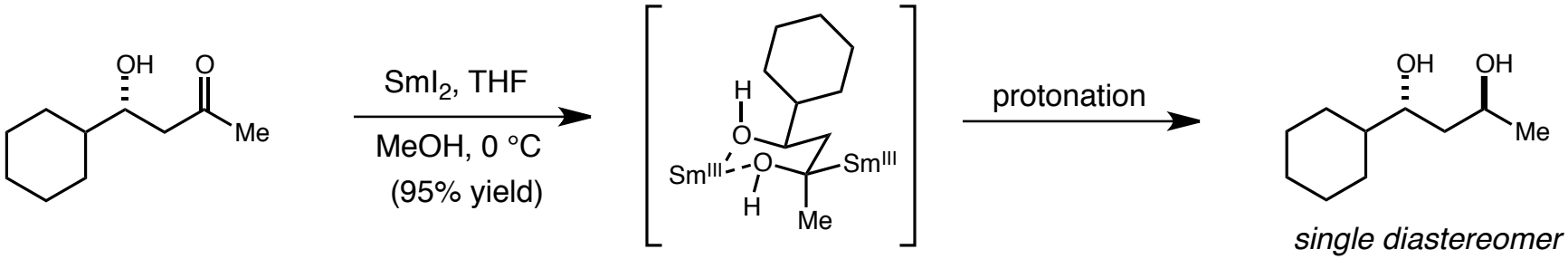


■ Addition of HMPA increases the rate of reduction of dialkylketones by 2 order of magnitude

Mechanism of SmI_2-Mediated Reactions

Ketyl radical anions from carbonyl groups

■ **The role of proximal Lewis basic functional groups in carbonyl reduction**



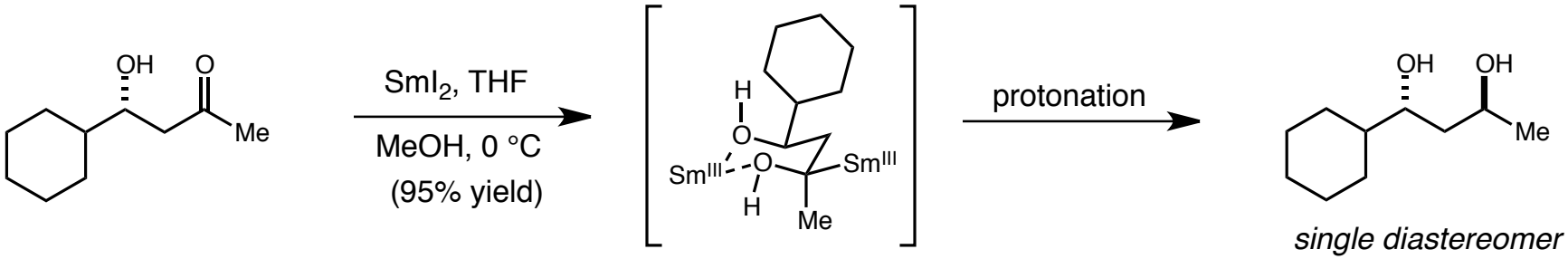
single diastereomer

Keck, G. E.; Wager, C. A. *Org. Lett.* **2000**, *2*, 2307.

Mechanism of SmI_2-Mediated Reactions

Ketyl radical anions from carbonyl groups

■ **The role of proximal Lewis basic functional groups in carbonyl reduction**



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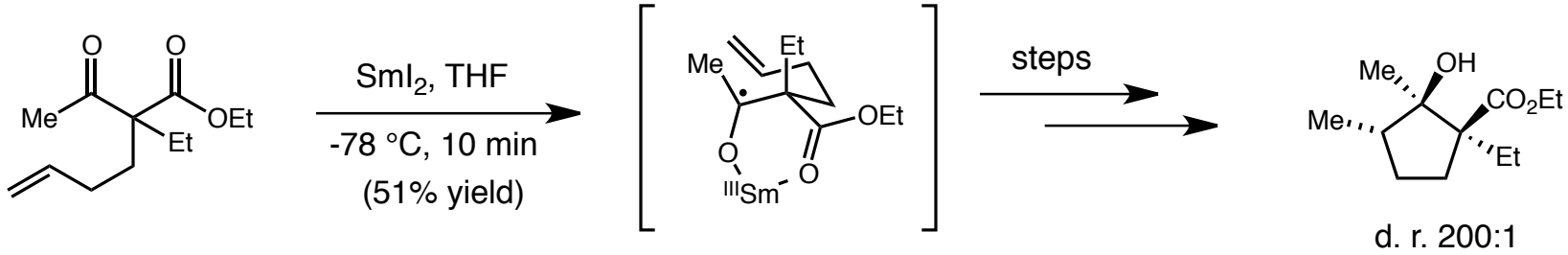


Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

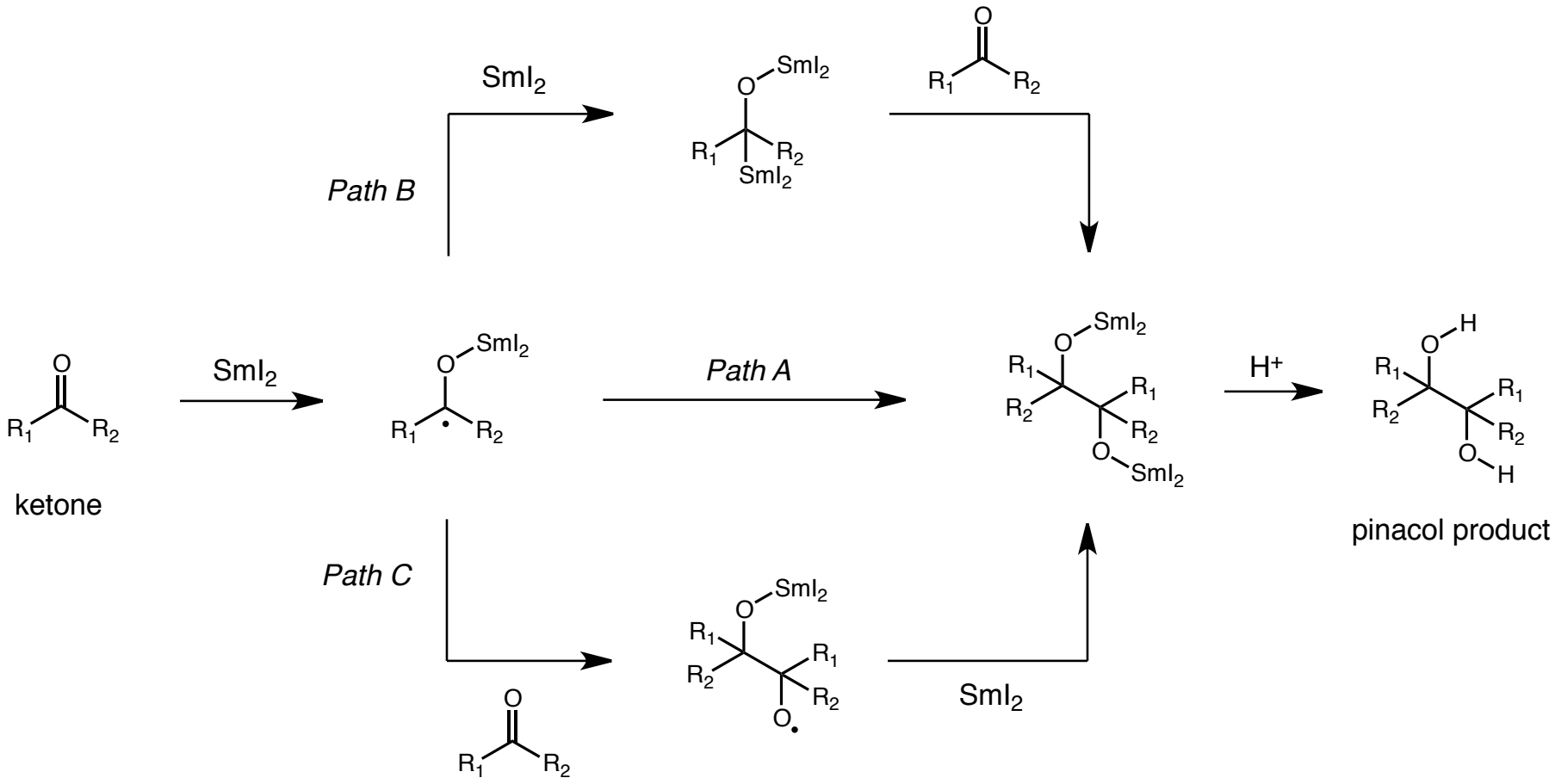
Carbon-Carbon Bond-forming Reactions Using SmI_2

- **Pinacol Coupling**
- **Carbonyl-alkene coupling**
- **Radical alkene/alkyne coupling**
- **Barbier and grignard reaction**
- **Reformatsky reaction**
- **Aldol-type reaction**
- **Fragmentation reaction**
- **Sequential carbon-carbon bond formation (cascade reaction)**
- **Modification of biomolecules**

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Pinacol Coupling

Mechanistic Scenarios

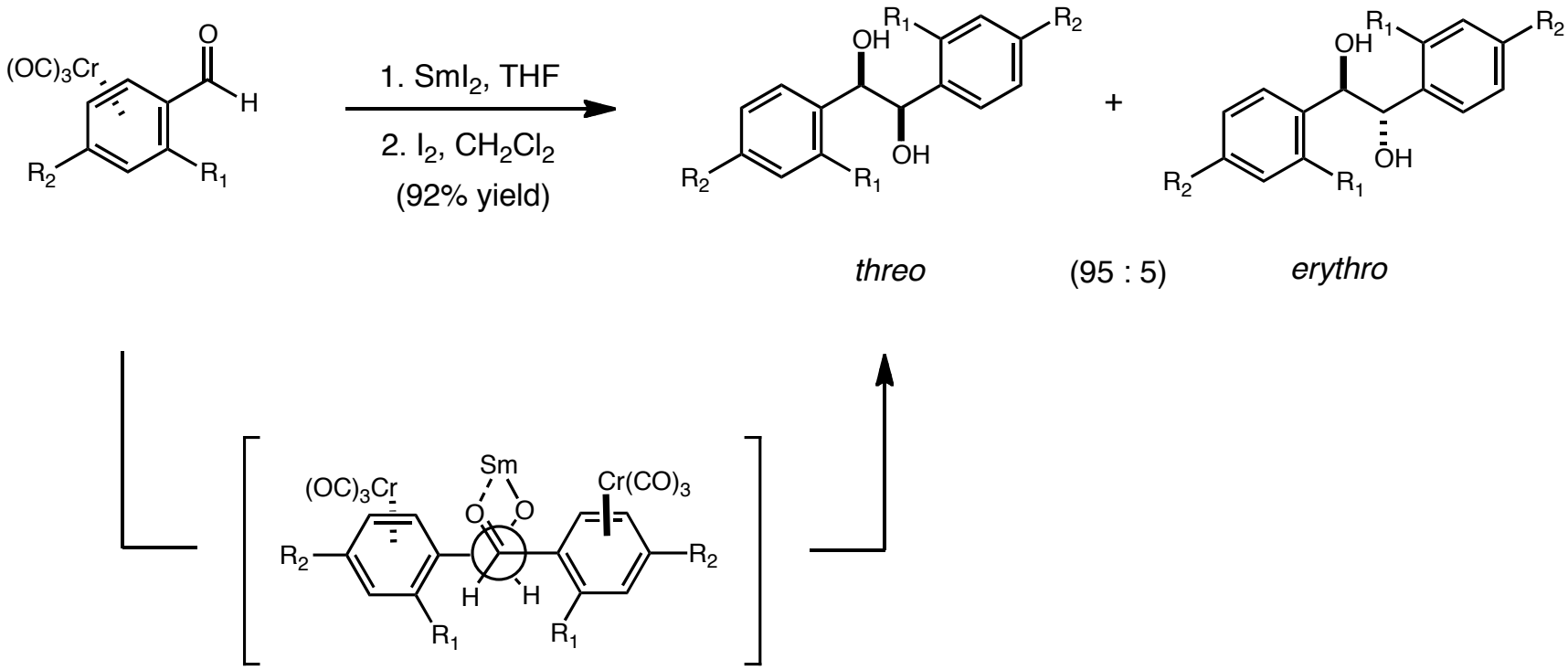


Lebrun, A, Kagan, H. B. *Tetrahedron Lett.* **1993**, *34*, 2311.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intermolecular pinacol coupling

Asymmetric synthesis of hydrobenzoins

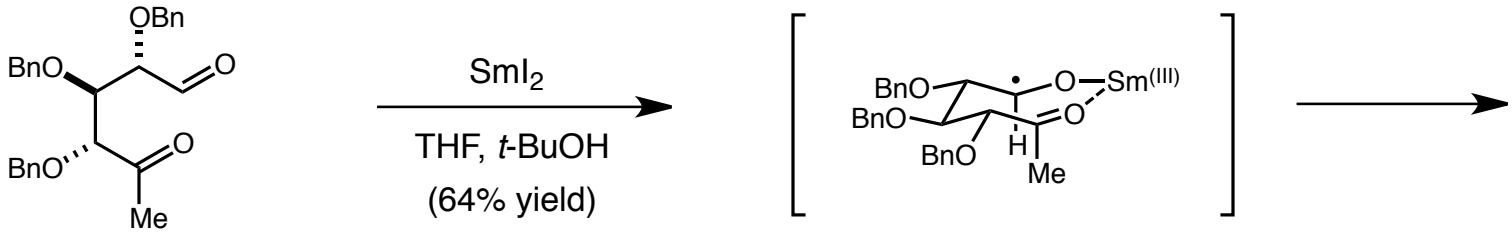


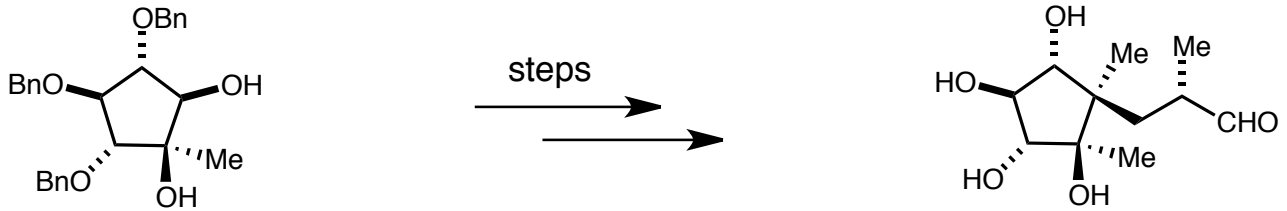
Collin, J.; Machrouhi, F.; Nief, F. *Tetrahedron. Lett.* **1999**, *40*, 3161.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular pinacol coupling

Synthesis of carbocyclic monosaccharide (+)-caryose





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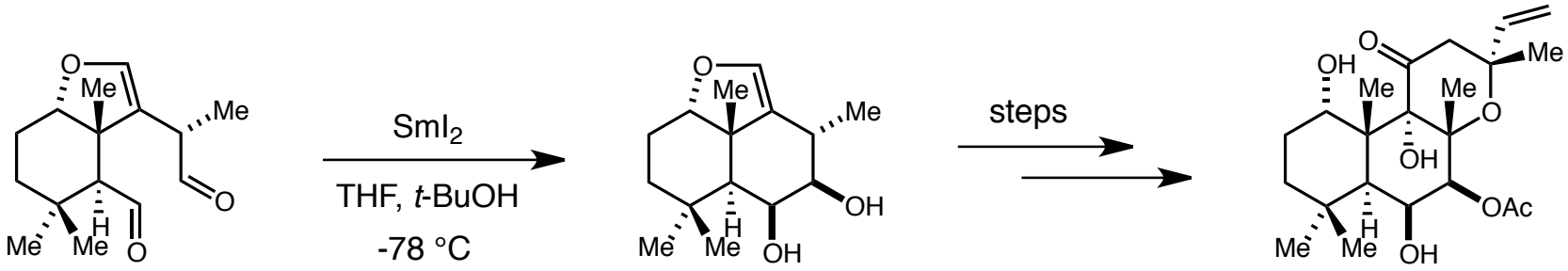
(+)-caryose

Adinolfi. M.; Barone, G.; Iadonisi, L.; Manna, R. *Tetrahedron*. **1997**, *53*, 11767.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Pinacol Coupling

Applications to complex natural products



single diastereomer

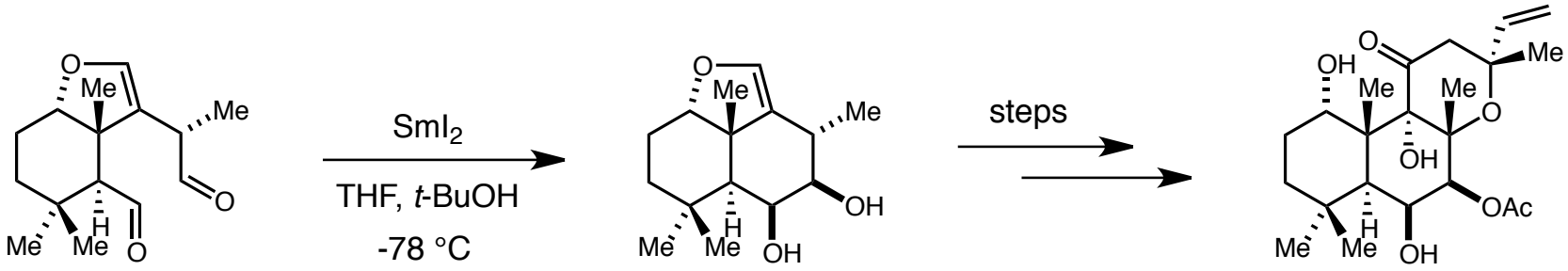
forskolin

Anies, C.; Pancrazi, A; Lallemand, J. -Y.; Prange, T. *Bull. Soc. Chim. Fr.* **1997**, *134*, 203.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Pinacol Coupling

Applications to complex natural products



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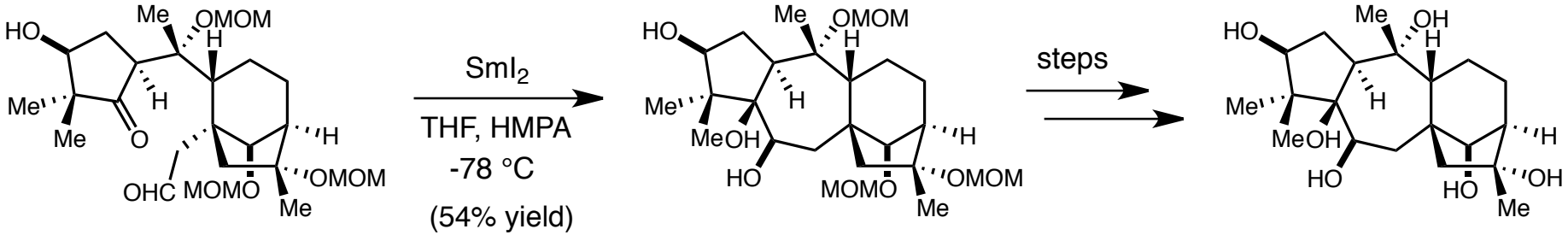


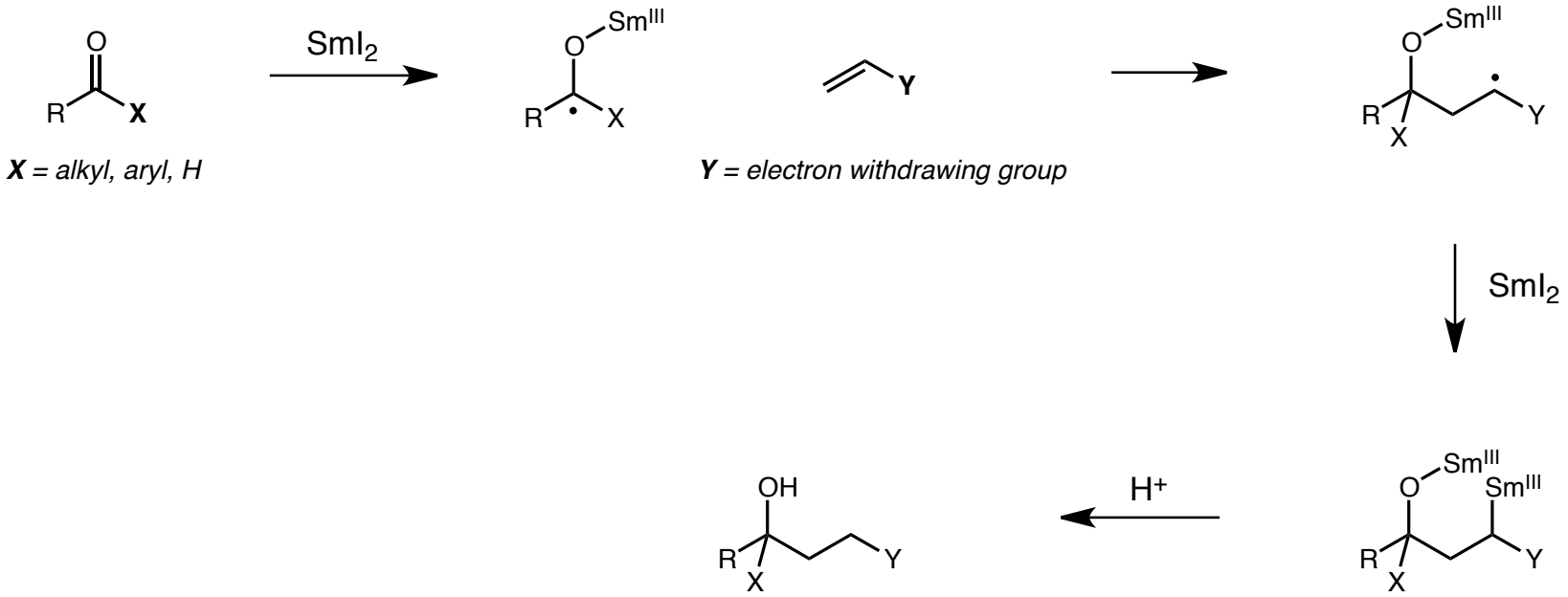
grayanotoxin III

Kan, T.; Hosokawa, S.; Nara, S.; Okisawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Carbonyl-alkene coupling

Traditional mechanism



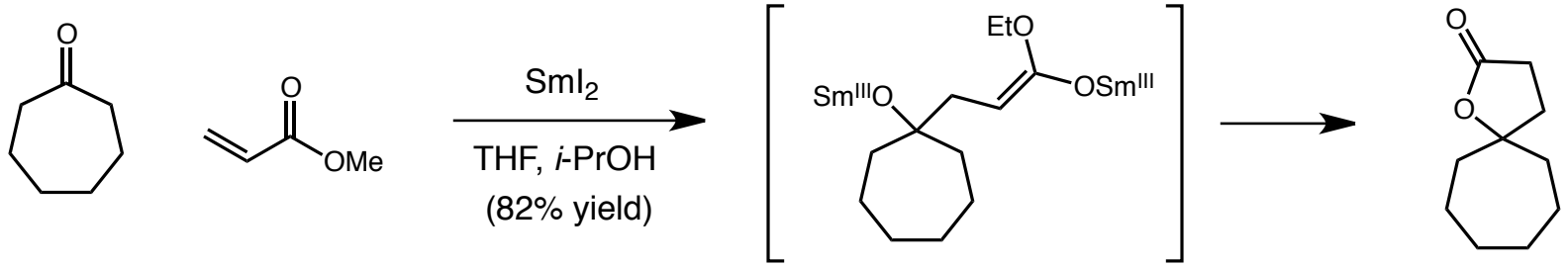
X *= alkyl, aryl, H*

Y *= electron withdrawing group*

■ Intramolecular carbonyl-alkene couplings display a greater degree of tolerance in alkene components

Carbon-Carbon Bond-forming Reactions Using SmI_2

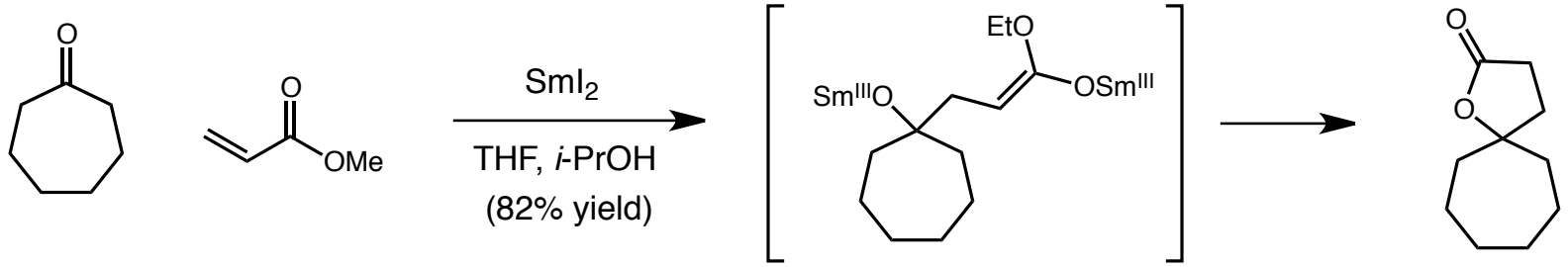
■ Intermolecular carbonyl-alkene coupling



Fukuzawa, S.; Nakanishi, T.; Fujinami, T.; Sakai, S. *Chem. Commun*. **1986**, 624.

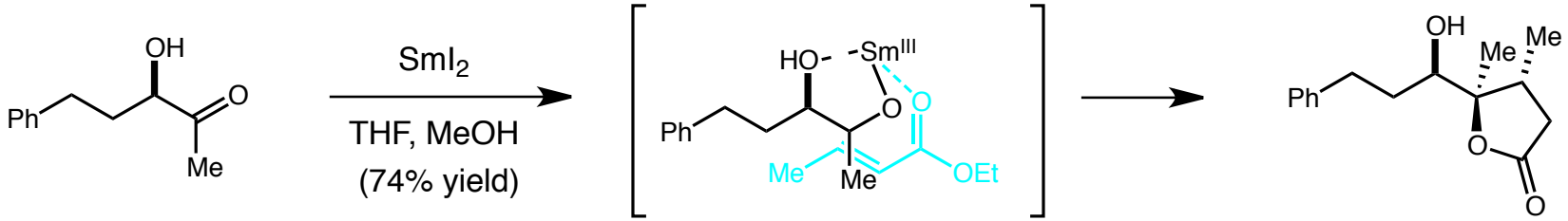
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intermolecular carbonyl-alkene coupling



Fukuzawa, S.; Nakanishi, T.; Fujinami, T.; Sakai, S. *Chem. Commun*. **1986**, 624.

Matsuda's asymmetric synthesis of γ-lactone



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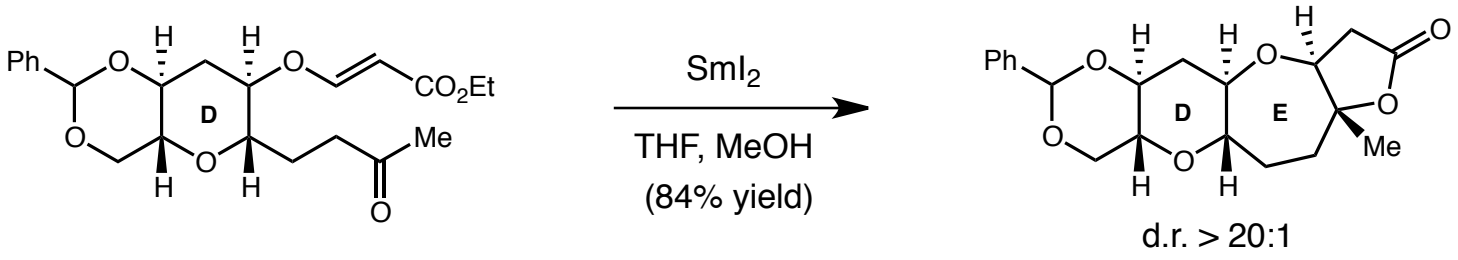
Kawatsura, M.; Matsuda, F, Shrihama, H. *J. Org. Chem*. **1994**, 59, 6900.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular carbonyl-alkene coupling

Applications in complex natural product synthesis



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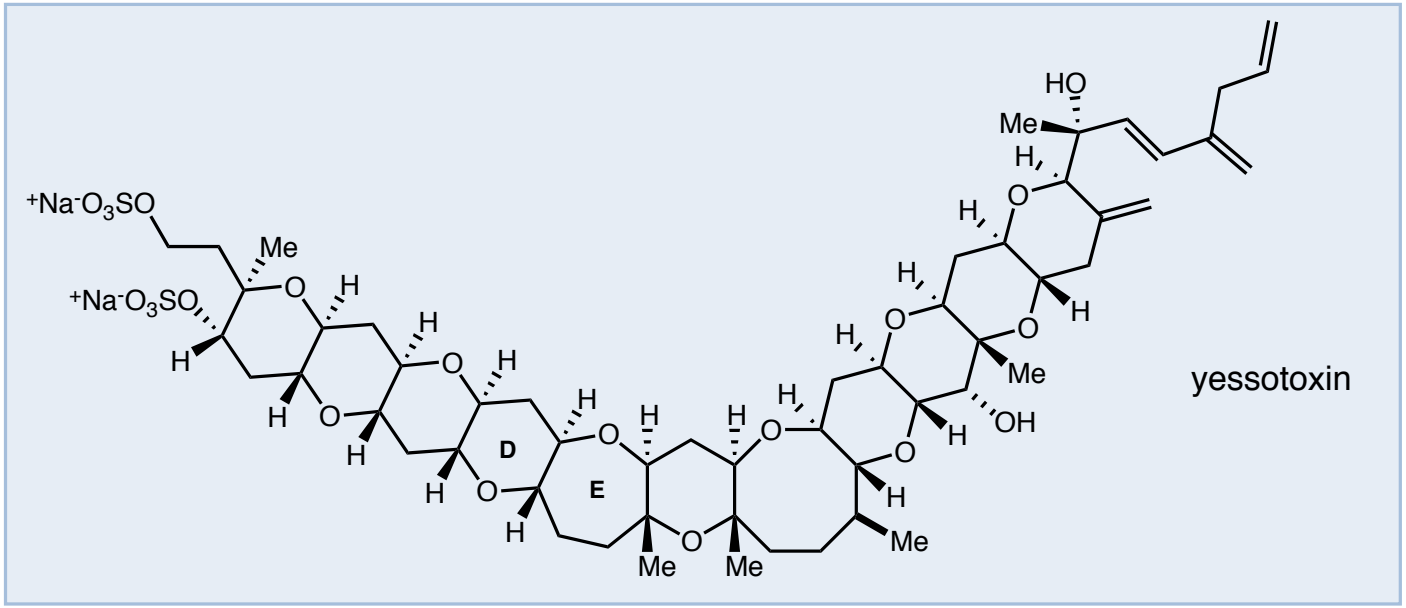
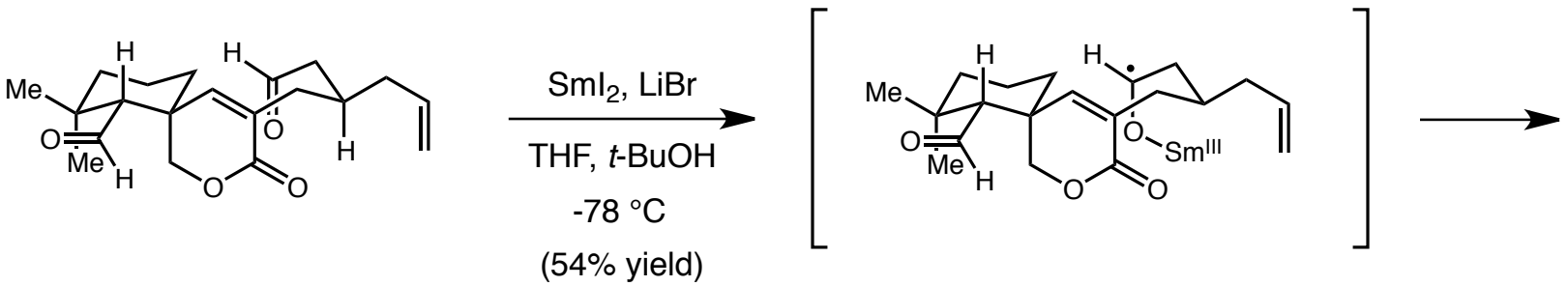


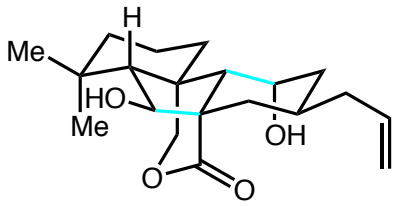
Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 3943.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular carbonyl-alkene Coupling

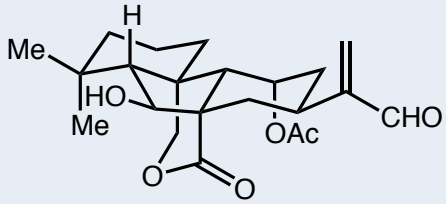
Applications in complex natural product synthesis





single diastereomer

steps



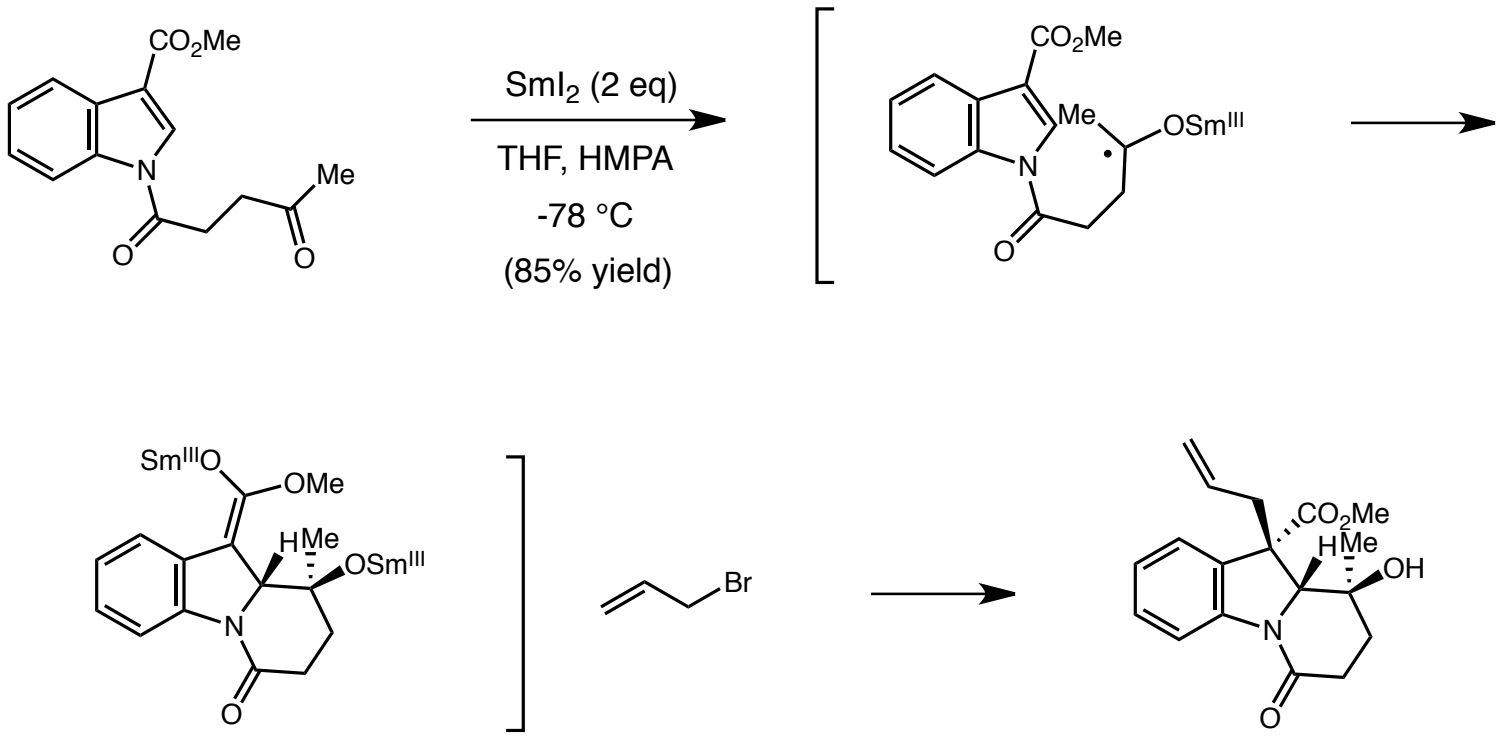
maoecrystal Z

Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Carbonyl-arene coupling

Synthesis of highly functionalized benzannulated indolizidines



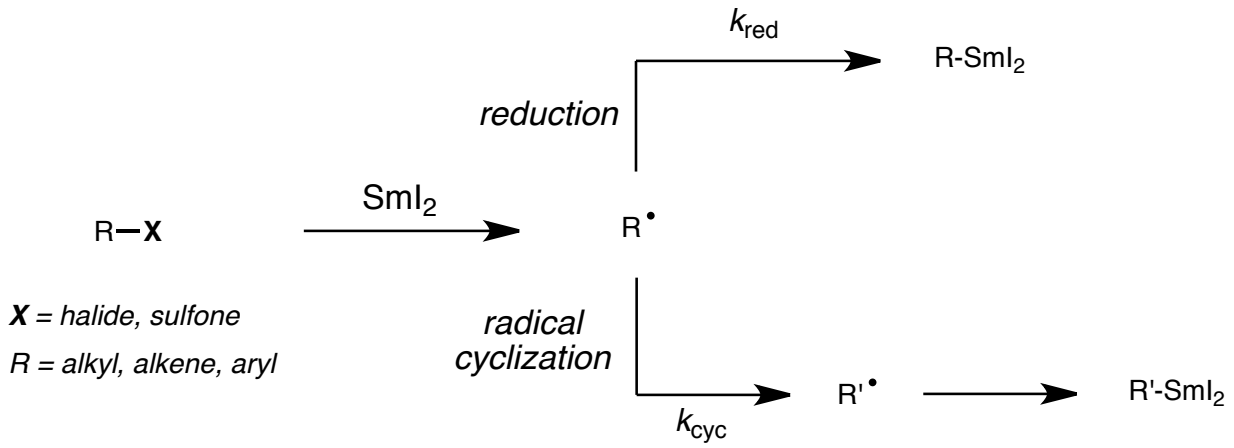
Gross, S.; Reissig, H. -U. *Org. Lett.* **2003**, *5*, 4305.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Radical alkene-alkyne additions

- The addition of sp^2 and sp^3 carbon-centered radicals to unsaturated carbon-carbon bonds
- Halides and sulfones are the most common functional groups used as precursors to radicals
- Intermolcecular variant of this reaction has found only limited applications in organic synthesis

Traditional mechanism

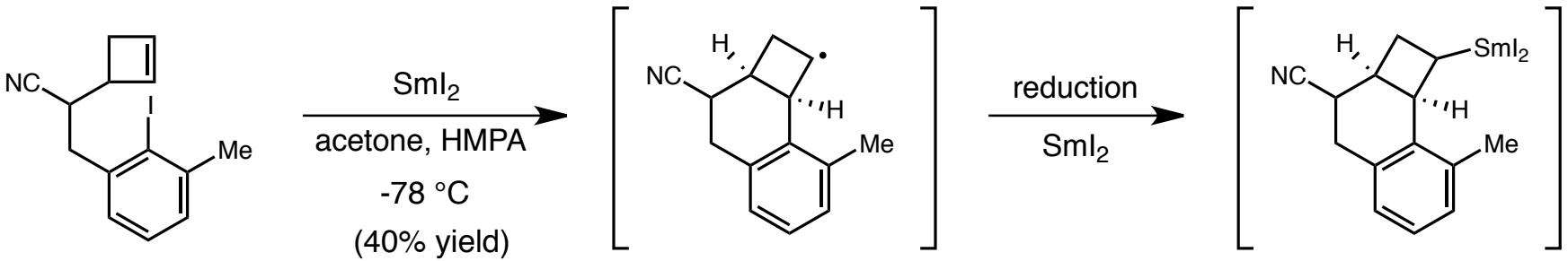


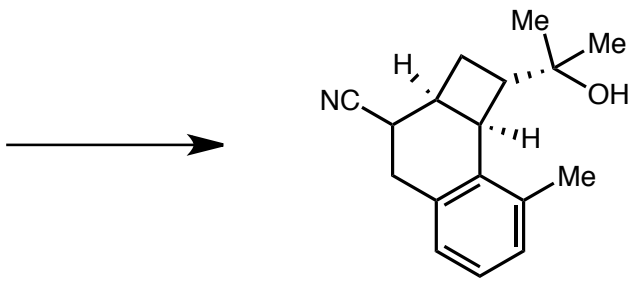
- For successful ring closure, the unimolecular rate constant for cyclization (k_{cyc}) should be sufficiently higher than the bimolecular rate constant for the second reduction step ($k_{red}[SmI_2]$)

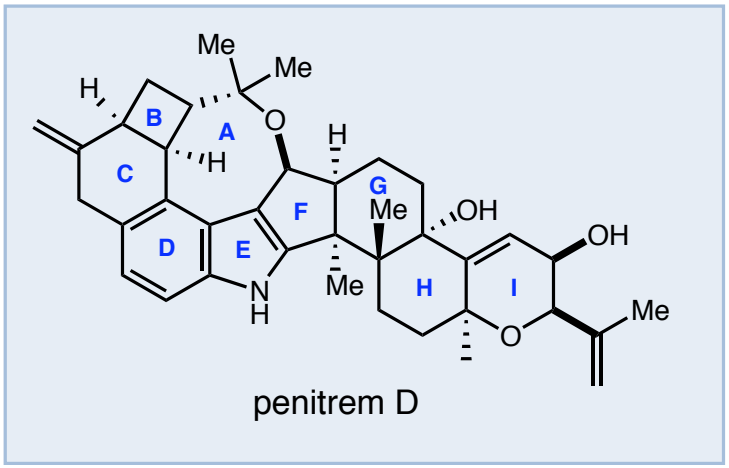
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular radical-additions to alkene

Curran's synthesis of BCD ring-system of penitrem D





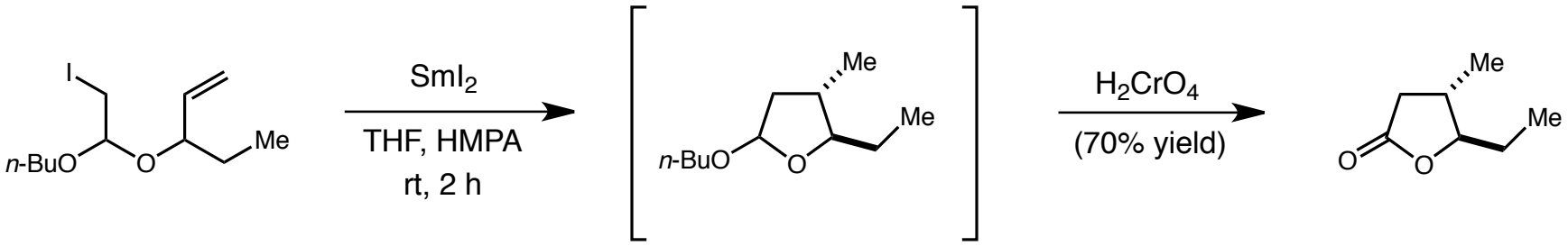


penitrem D

Rivkin, A.; Nagashima, T.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 3719.

Carbon-Carbon Bond-forming Reactions Using SmI_2

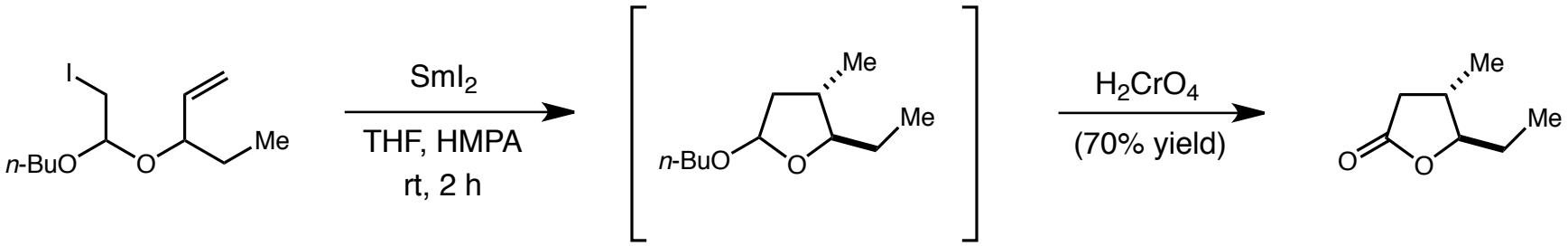
■ Intramolecular radical additions to alkene



Fukuzawa, S.; Tsuchimoto, T. *Synlett*. **1993**, 803.

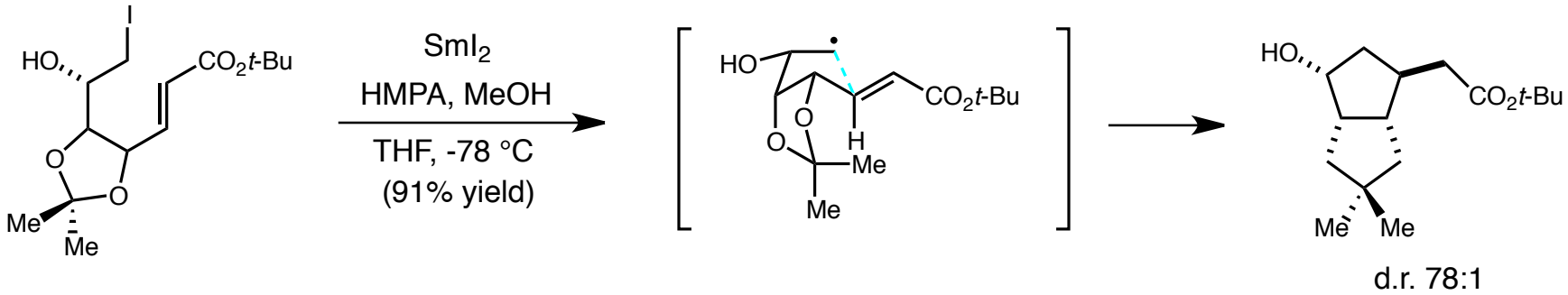
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular radical additions to alkene



Fukuzawa, S.; Tsuchimoto, T. *Synlett*. **1993**, 803.

Highly functionalized cyclopentanes from sugar derived substrate

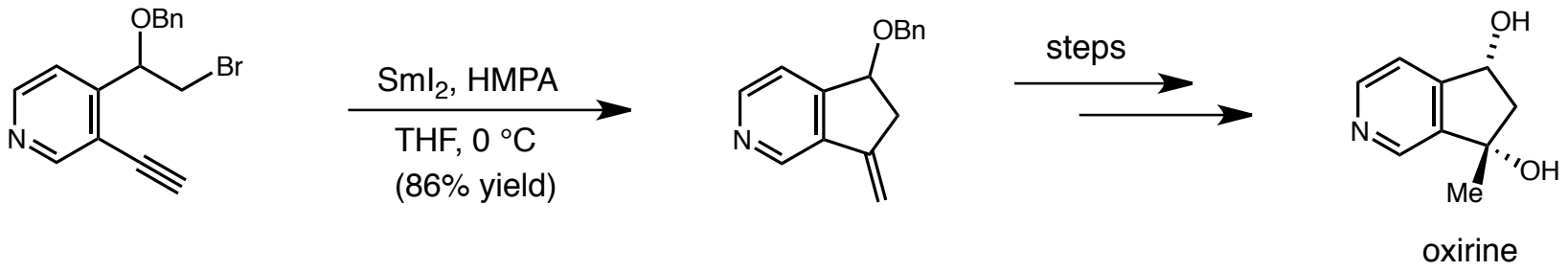


d.r. 78:1

Salari, B. S. F.; Biboutou, R. K.; Bennett, S. M. *Tetrahedron*. **2000**, *56*, 6385.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular radical additions to alkyne

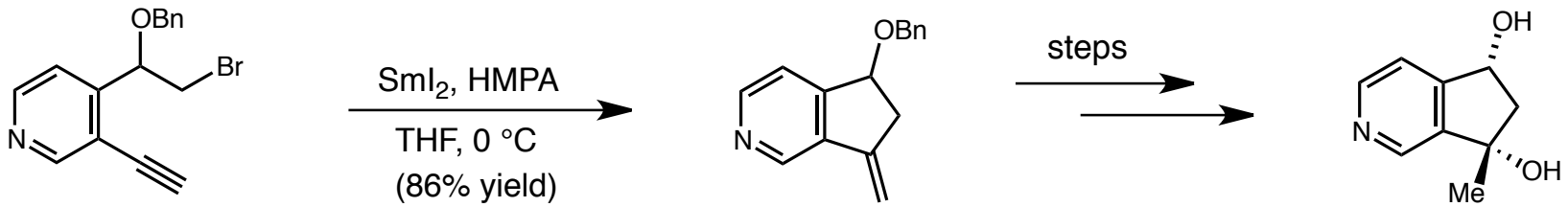


oxirine

Aoyagi, Y.; Inariyama, T.; Arai, Y.; Tsuchida, S.; Matsuda, Y.; Kobayashi, H.; Ohta, A. *Tetrahedron*. **1994**, *50*, 13575.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular radical additions to alkyne



oxirine

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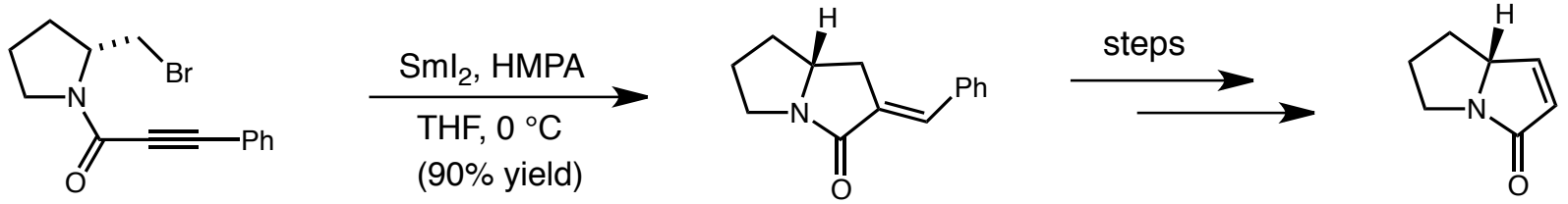
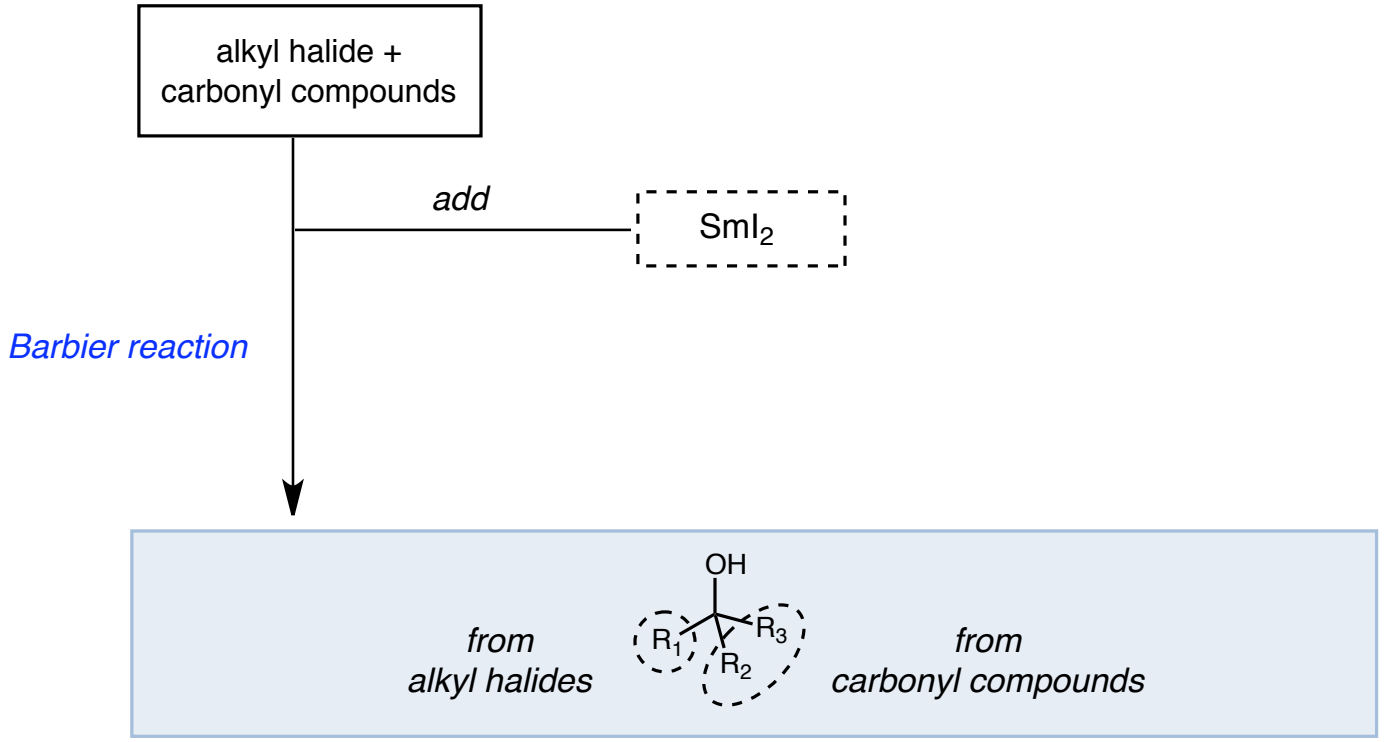


pyrrolam A

Aoyagi, Y.; Manabe, T.; Arai, Y.; Yuhara, T.; Ohta, A. *Tetrahedron*. **1996**, *52*, 869.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Barbier and grignard reactions

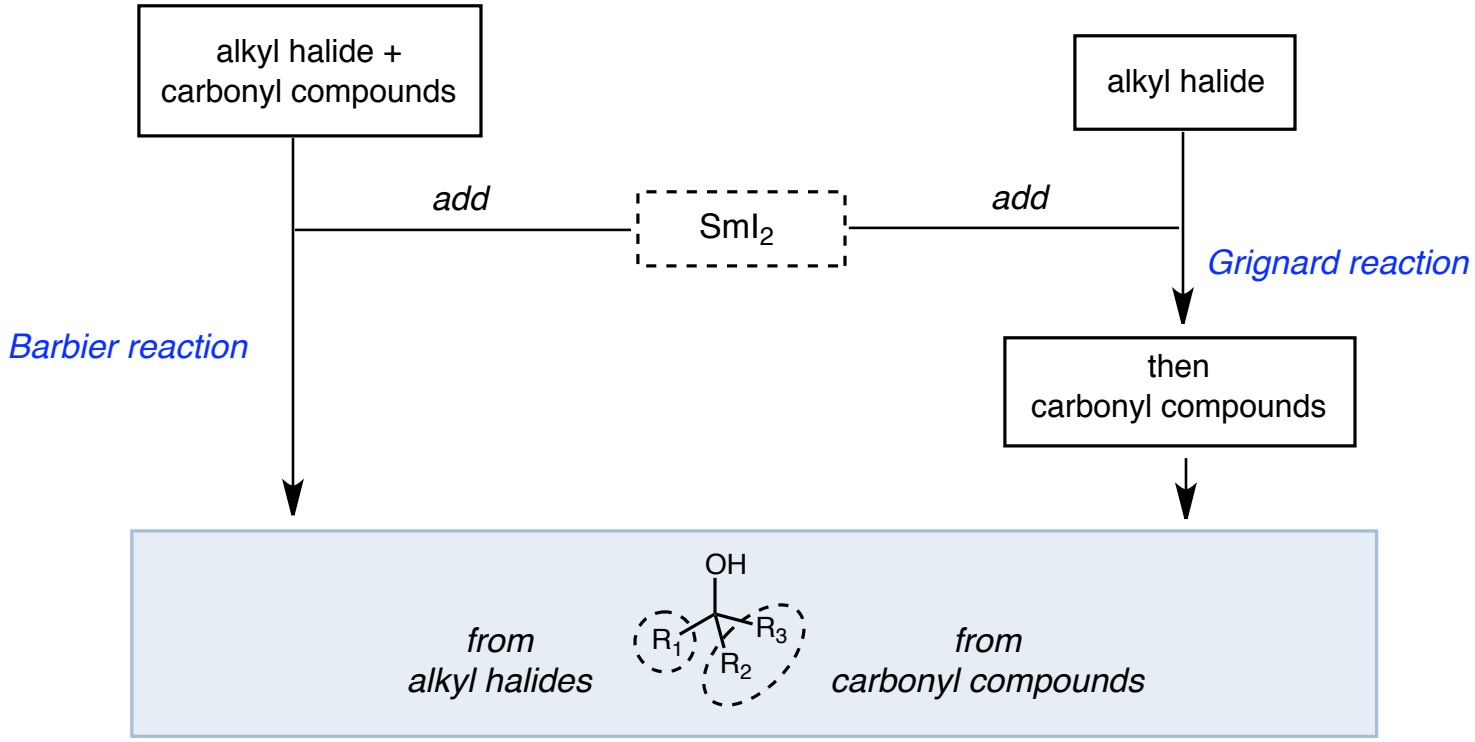


Barbier conditions should be considered for:

- allylic and benzyl halides
- alkyl halides that lead to unstable organosamariums
- alkyl halides that lead to organosamariums that can react with themselves

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Barbier and grignard reactions



Barbier conditions should be considered for:

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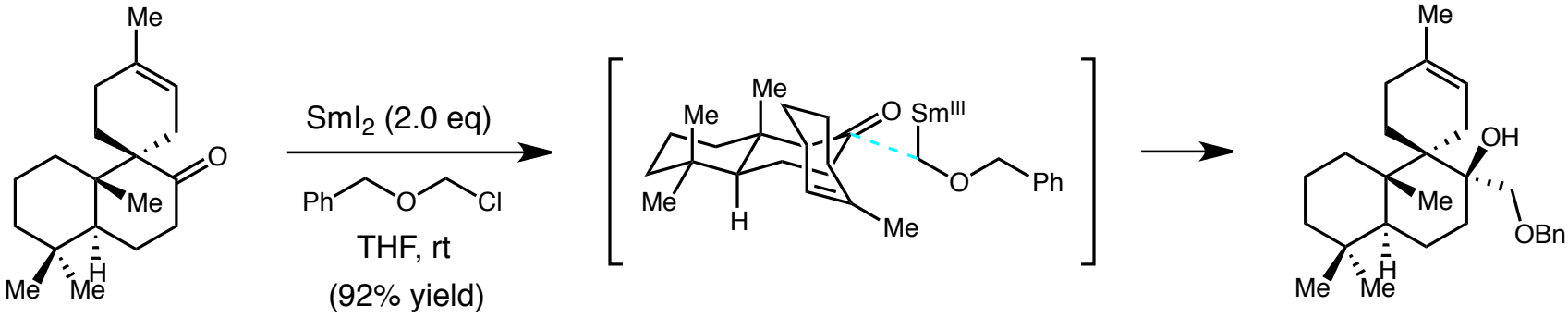
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intermolecular Barbier and grignard reactions

Alkoxymethylation of hindered ketones

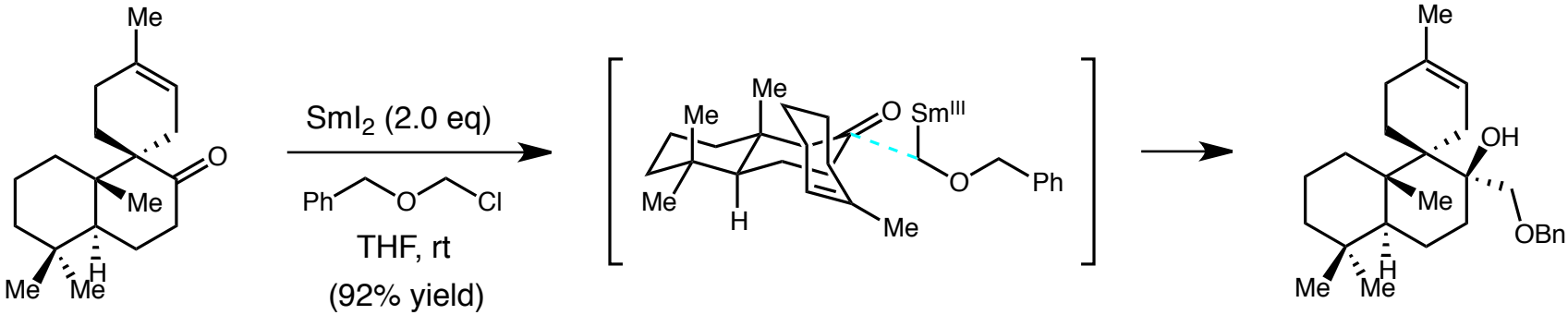


White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.

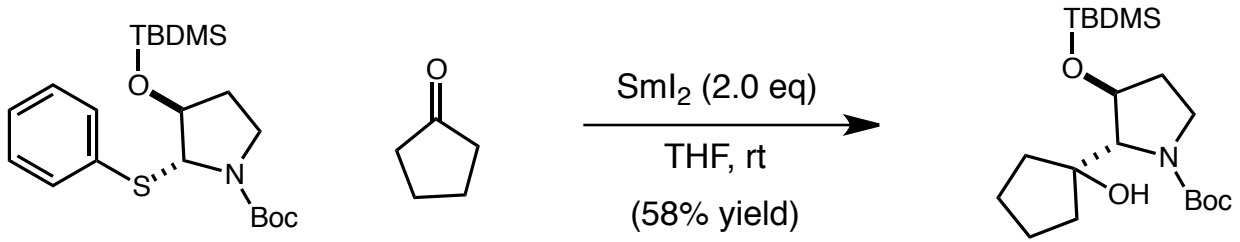
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intermolecular Barbier and grignard reactions

Alkoxymethylation of hindered ketones



White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.

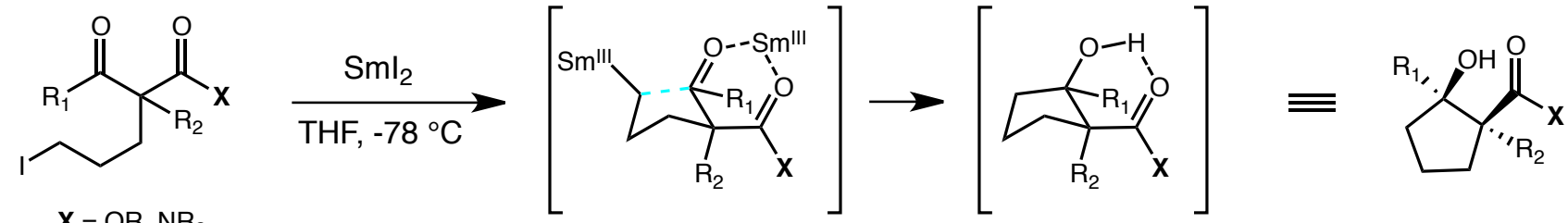


Zheng, X.; Huang, P. -Q. *Org. Lett.* **2005**, *7*, 553.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Barbier reactions

Synthesis of highly functionalized cyclopentanes



X = OR, NR_2

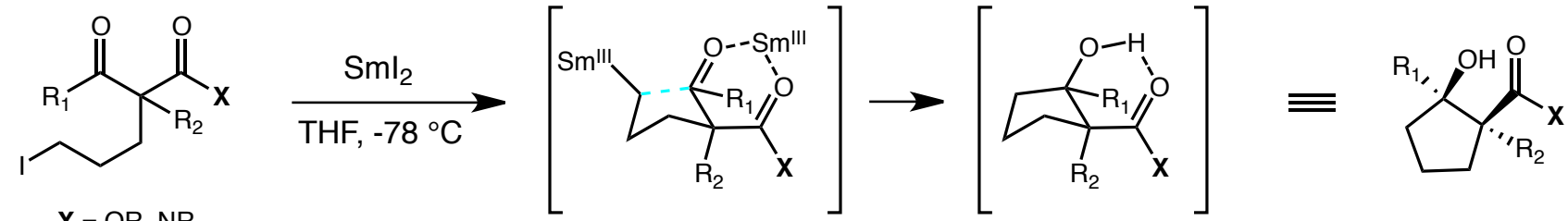
R_1, R_2 = alkyl, H

Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Barbier reactions

Synthesis of highly functionalized cyclopentanes



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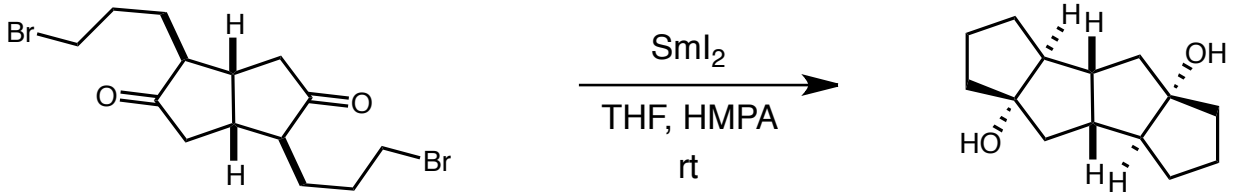
R_1, R_2 = alkyl, H

Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.

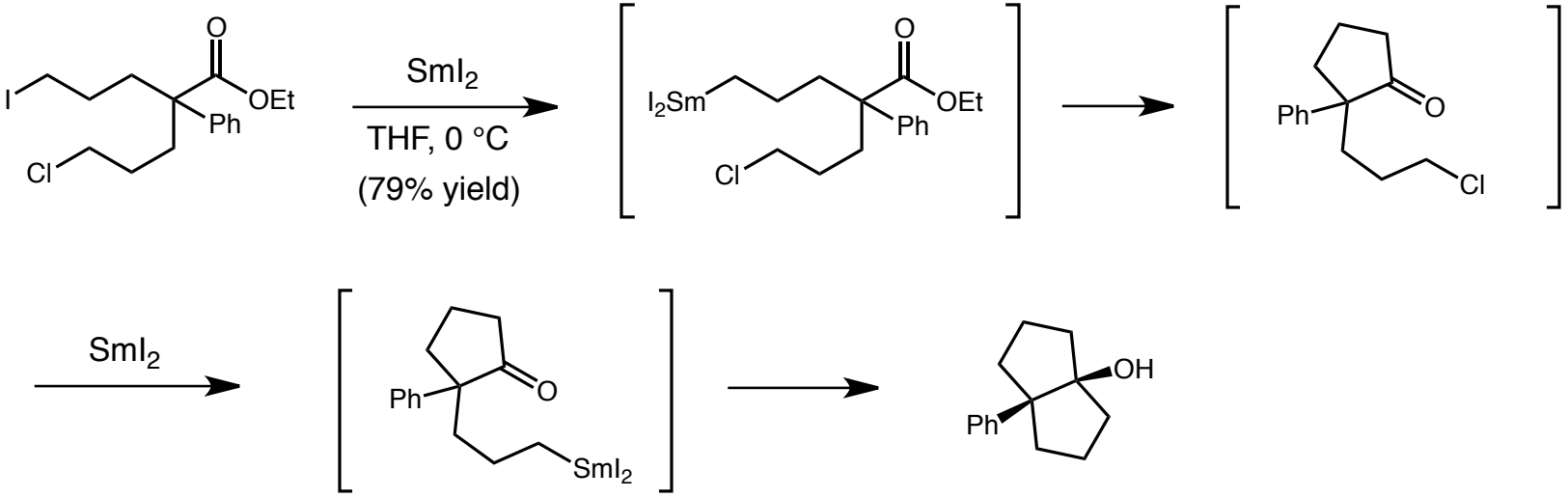


Lannoye, G.; Sambasivarao, K.; Wehrli, S.; Cook, J. M. *J. Org. Chem.* **1998**, *53*, 2327.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Barbier reactions

Organosamarium additions to esters

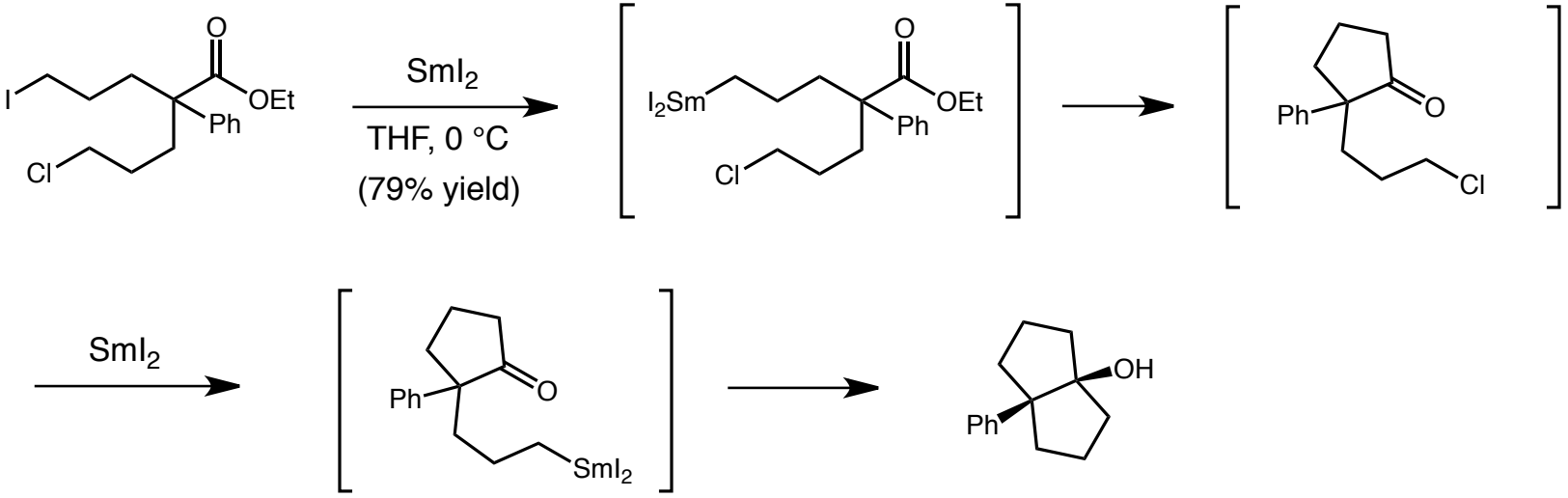


Molander, G. A.; Mckie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.

Carbon-Carbon Bond-forming Reactions Using SmI_2

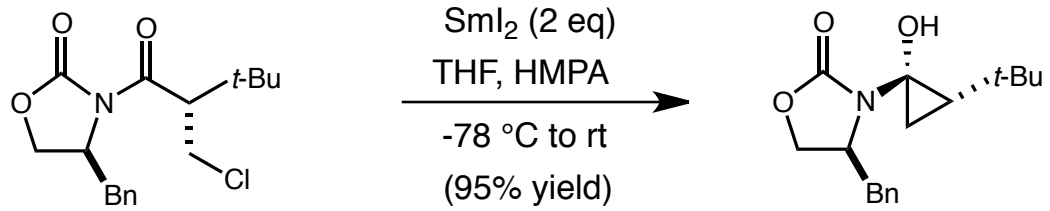
■ Intramolecular Barbier reactions

Organosamarium additions to esters



Molander, G. A.; Mckie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.

Organosamarium additions to amides

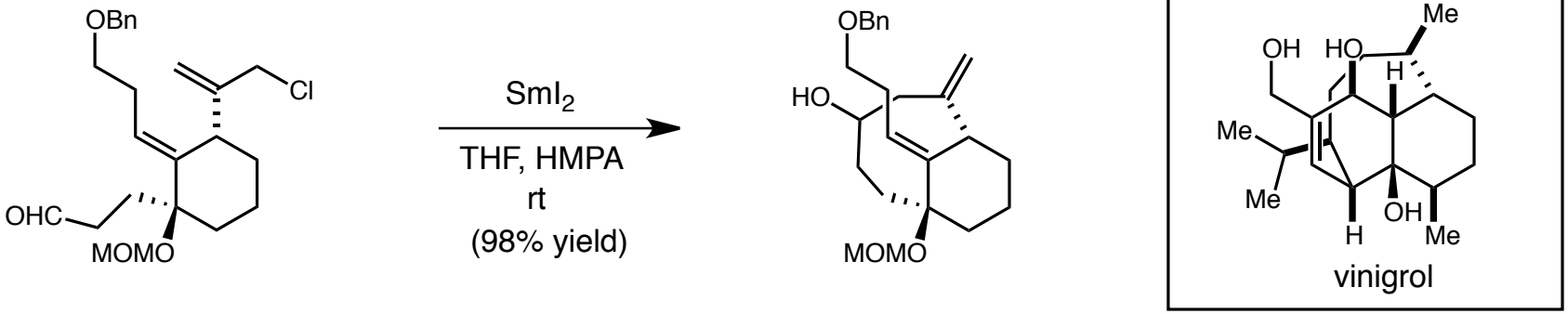


Fadel, A. *Tetrahedron: Asymmetry*. **1994**, *5*, 531.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Barbier reactions

Synthesis of larger rings

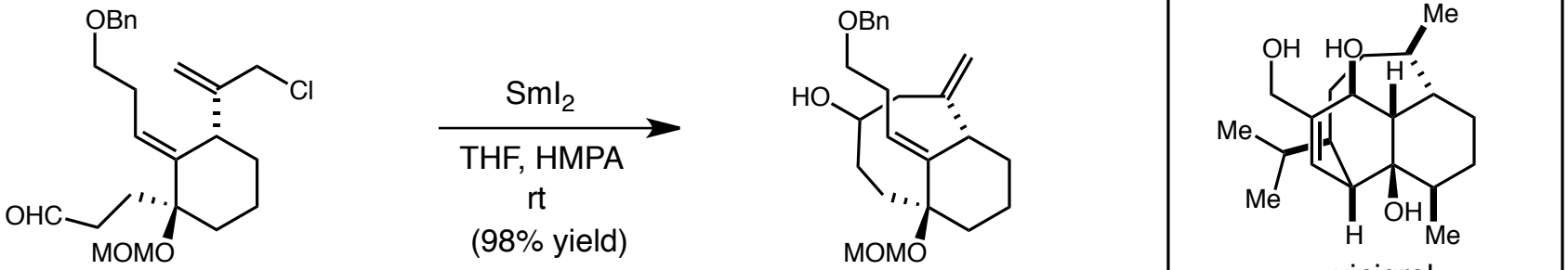


Kito, M.; Sakai, T.; Shirahama, M.; Matsuda, F. *Synlett.* **1997**, *219*.

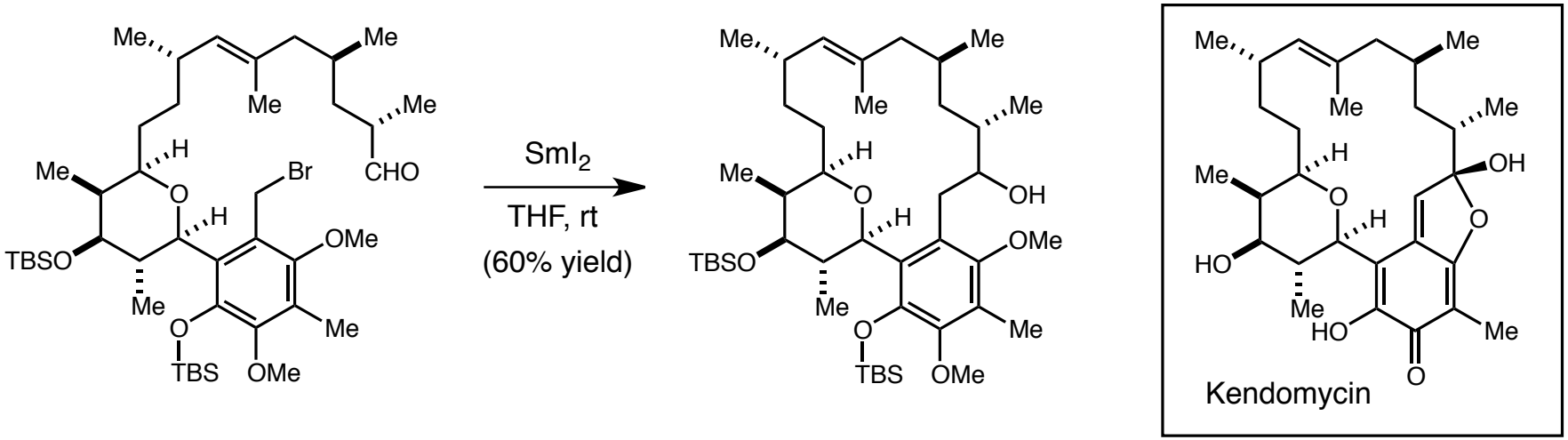
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Intramolecular Barbier reactions

Synthesis of larger rings



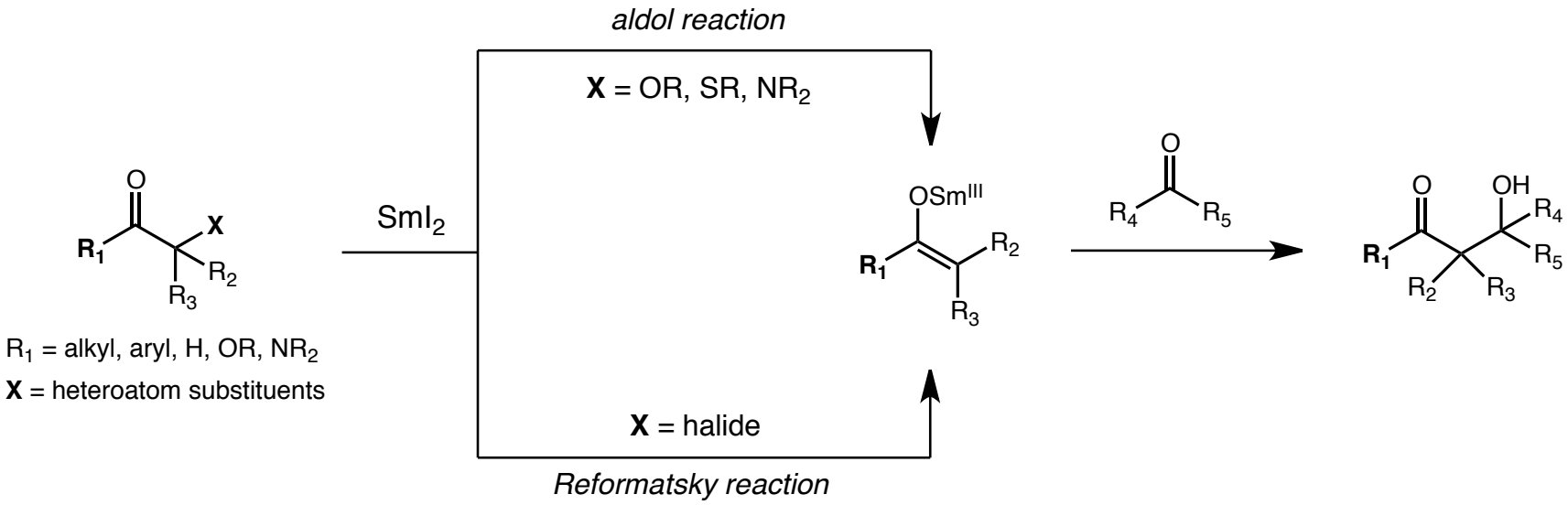
Kito, M.; Sakai, T.; Shirahama, M.; Matsuda, F. *Synlett.* **1997**, *219*.



Lowe, J. T.; Panek, J. S. *Org Lett.* **2008**, *10*, 3813.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Reformatsky and aldol-type reactions

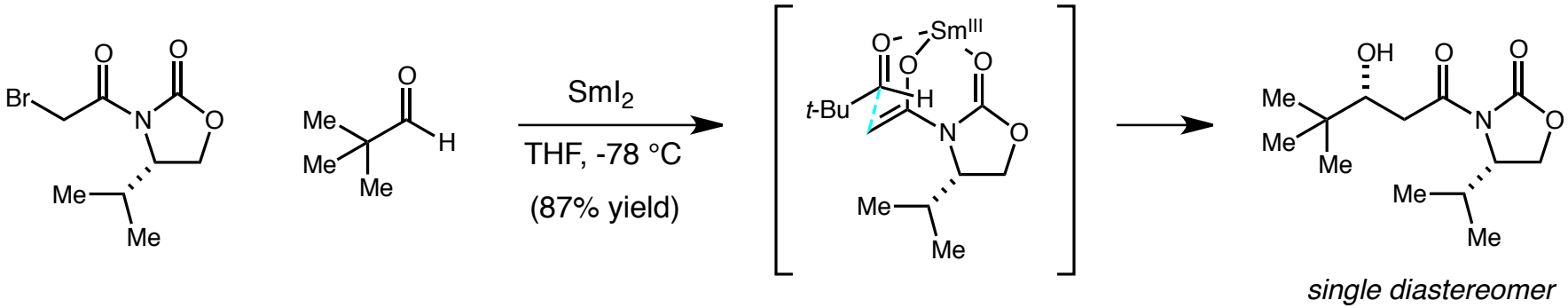


■ Samarium enolate is exploited as nucleophiles

■ Alkylation of Sm(III) enolates with alkyl halides is precedented

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Reformatsky reaction

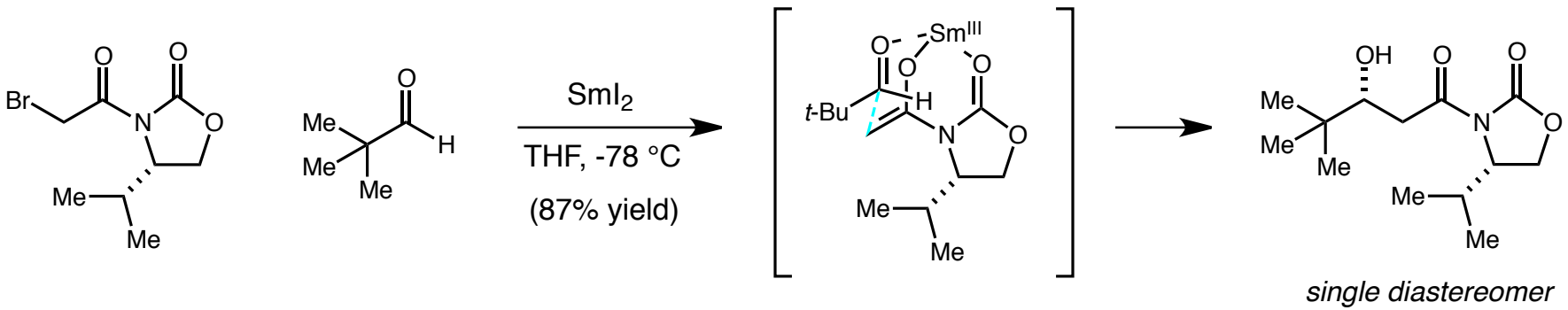


single diastereomer

Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. -I. *J. Org. Chem.* **2000**, *65*, 1702.

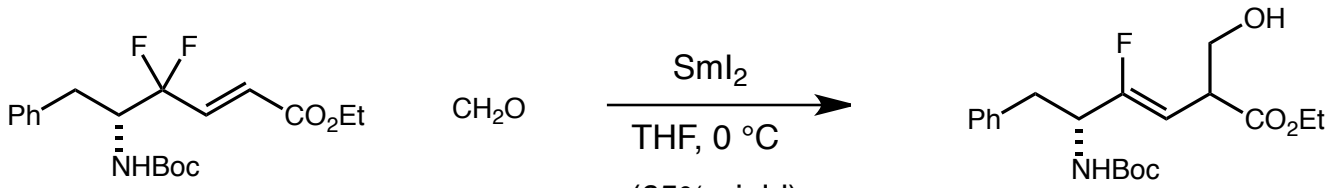
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Reformatsky reaction



single diastereomer

Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. -I. *J. Org. Chem.* **2000**, *65*, 1702.



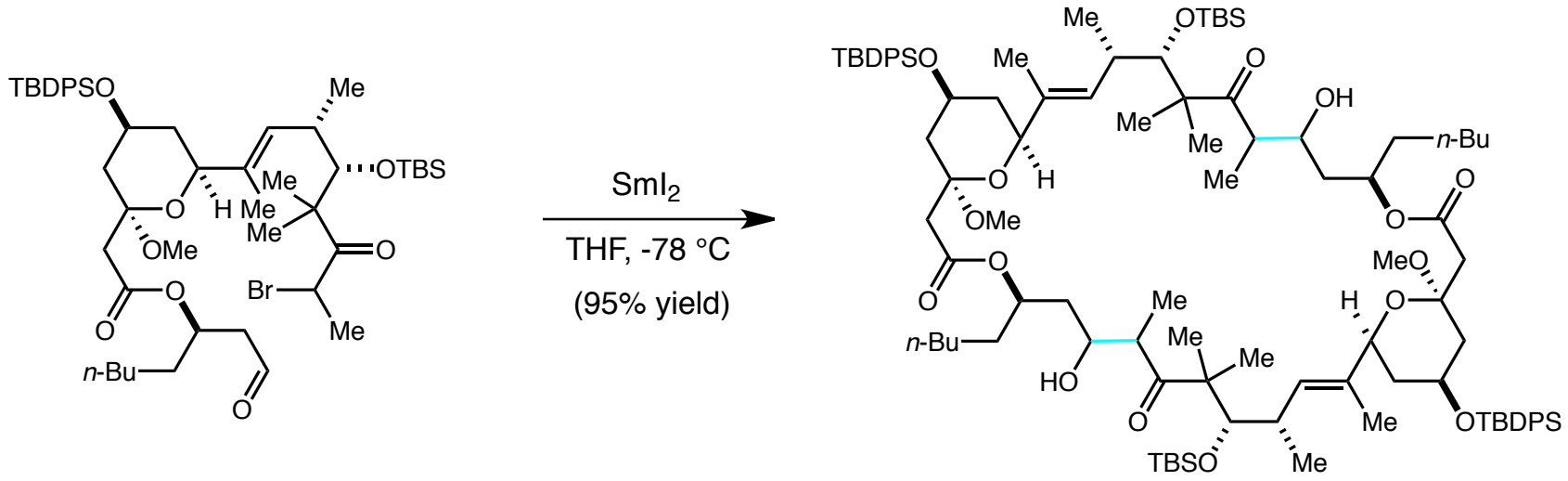
single regioisomer

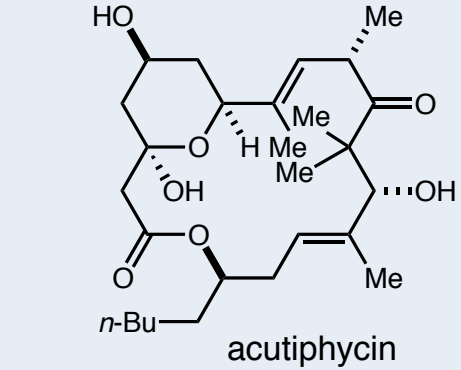
Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Oishi, S.; Fuiji, N. *J. Org. Chem.* **2004**, *69*, 1634.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Reformatsky reaction

Double Reformatsky reaction, dimerization



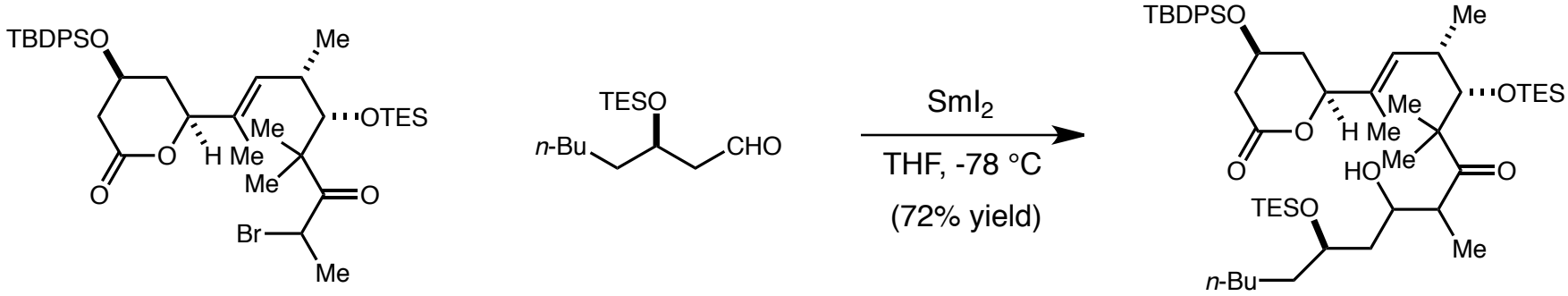


Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106.

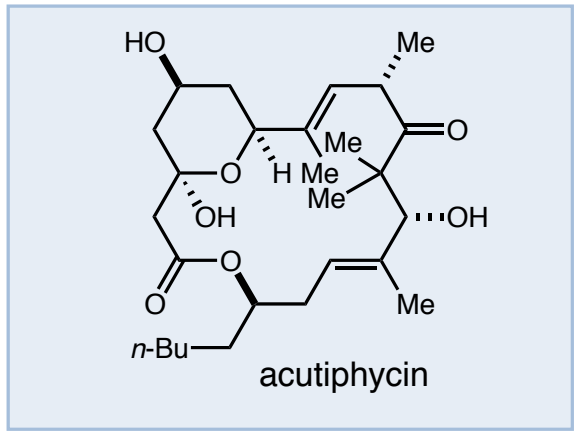
Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Reformatsky reaction

Modified approach to acutiphycin



steps

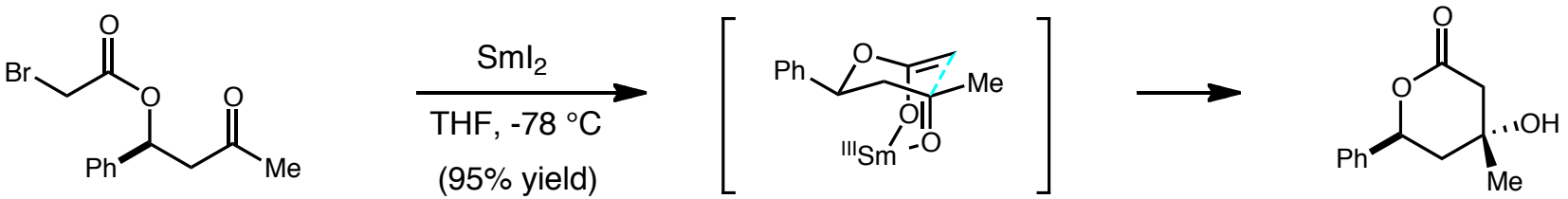


Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Reformatsky reaction

Intramolecular variant

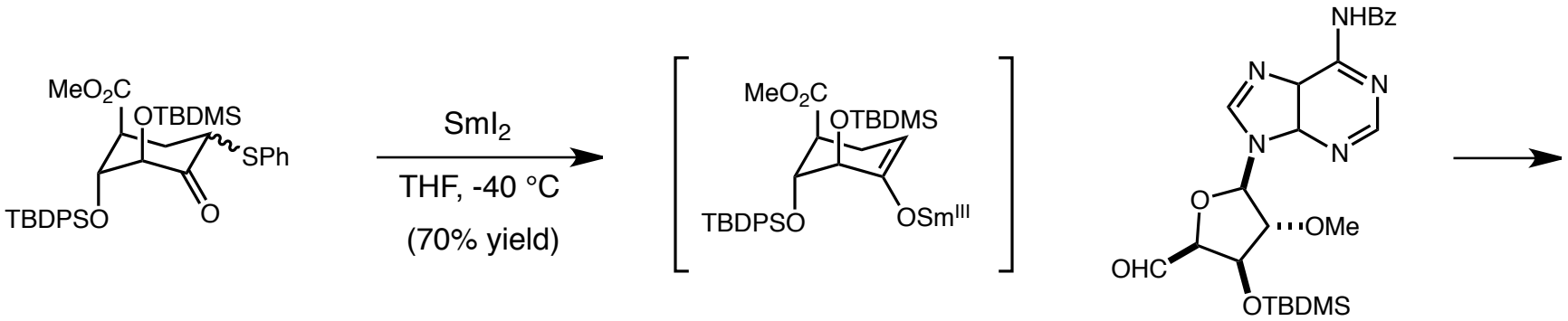


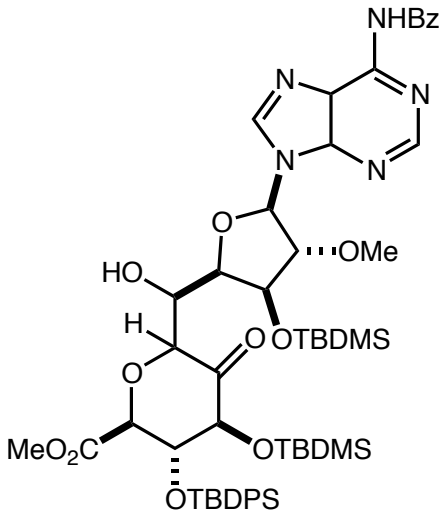
single diastereomer

Molander, G. A.; Etter, J. B.; Harring, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Aldol-type reactions





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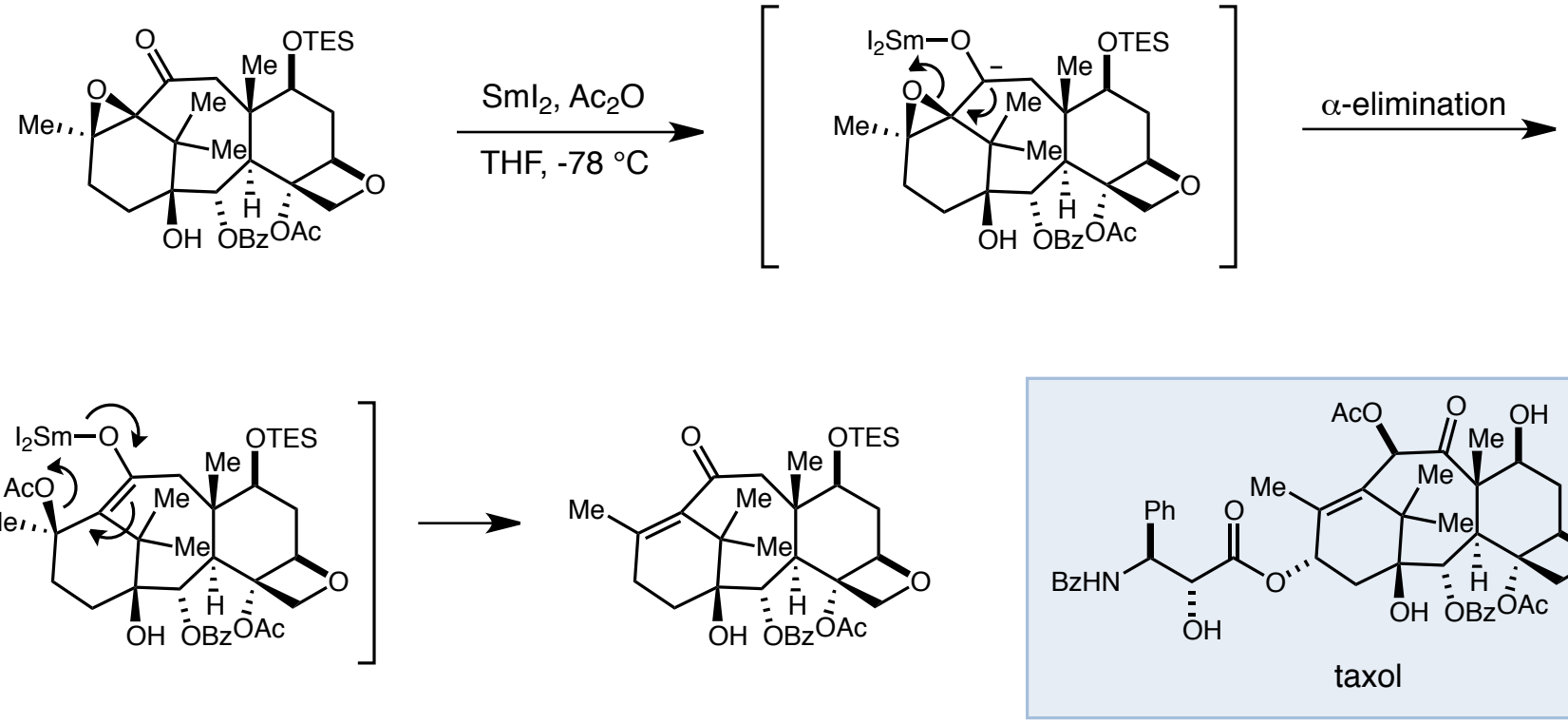
Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106.

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Elimination reaction

Danishefsky's total synthesis of taxol



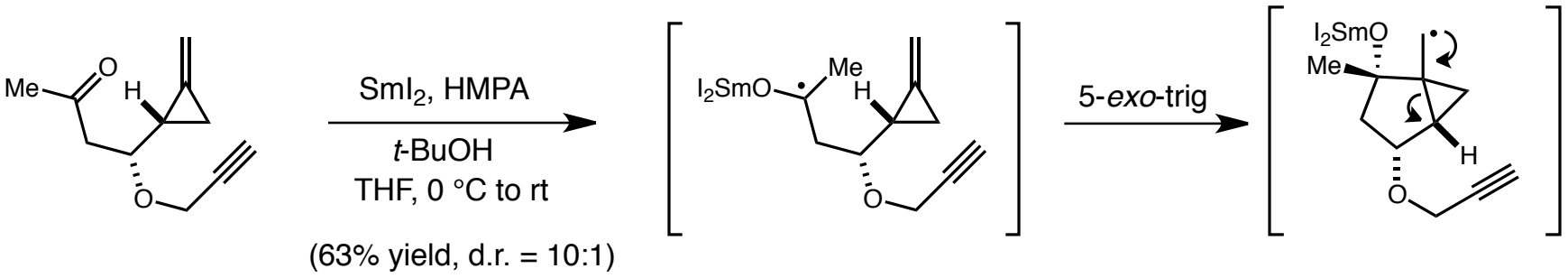
Masters, J. L.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 1723.

Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. B.; Jung, D. K.; Isaacs, R. C. A.; Bornmann. W. G.; Alaimo, C. A. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

Sequential Carbon-Carbon Bond Formation Reactions Using SmI_2

■ Sequences initiated by radical cyclizations

Radical-radical sequence



Boffey, R. J.; Santagostino, M.; Whittingham, W. G.; Kilburn, J. D. *J. Chem. Soc., Chem Commun.* **1998**, 1875.

Sequential Carbon-Carbon Bond Formation Reactions Using SmI_2

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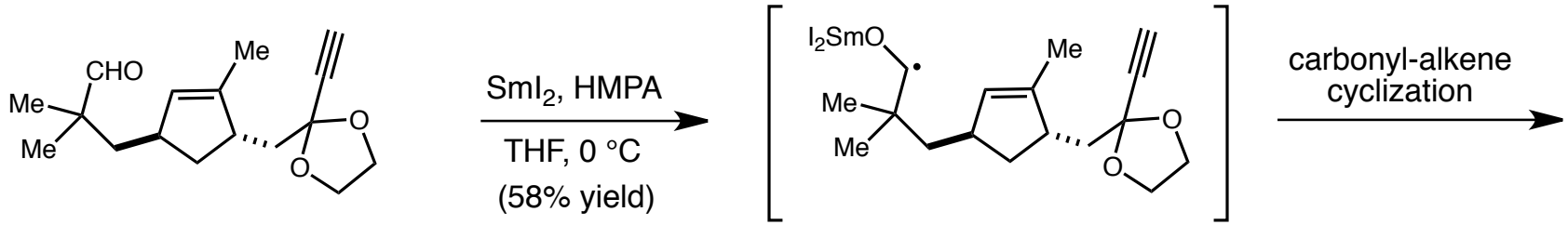
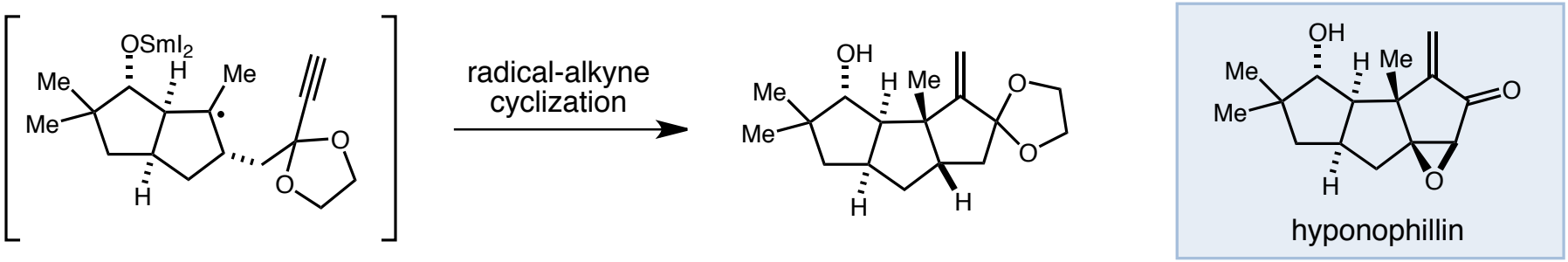


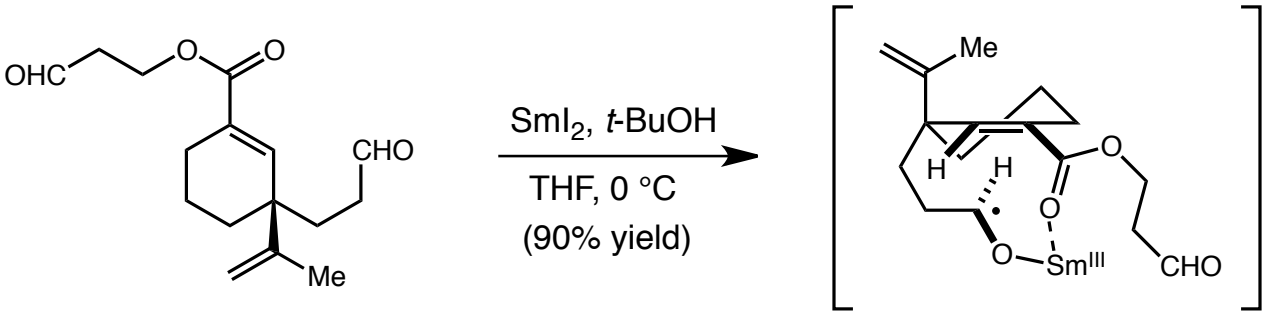


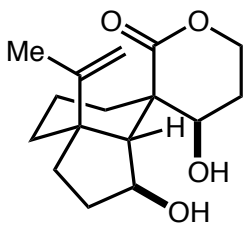
Fevig, T. L.; Elliot, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064.

Sequential Carbon-Carbon Bond Formation Reactions Using SmI_2

■ Sequences initiated by radical cyclizations

Radical-anionic sequence





single diastereomer

Helm, M. D.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224.

Sequential Carbon-Carbon Bond Formation Reactions Using SmI_2

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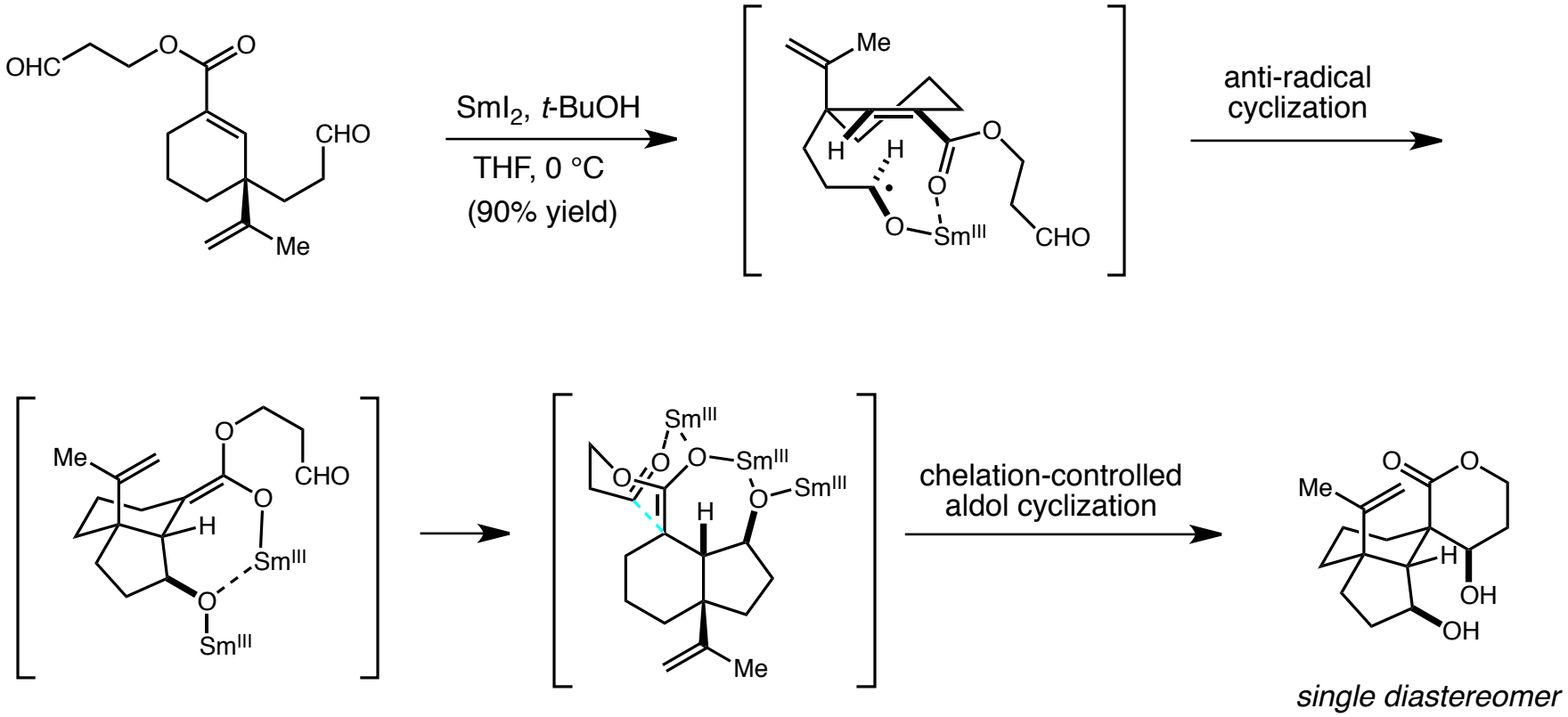


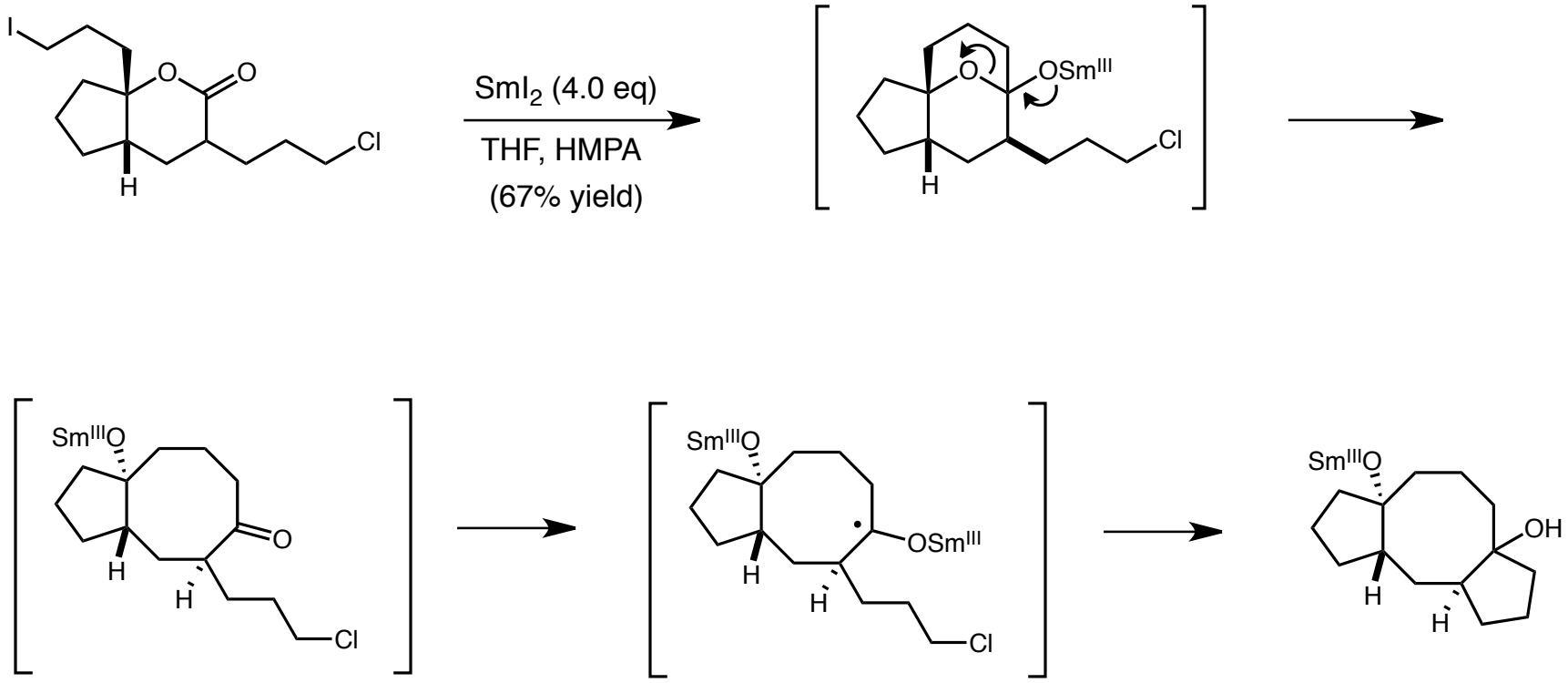
single diastereomer

Helm, M. D.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224.

Sequential Carbon-Carbon Bond Formation Reactions Using SmI_2

■ Sequences initiated by anionic reactions

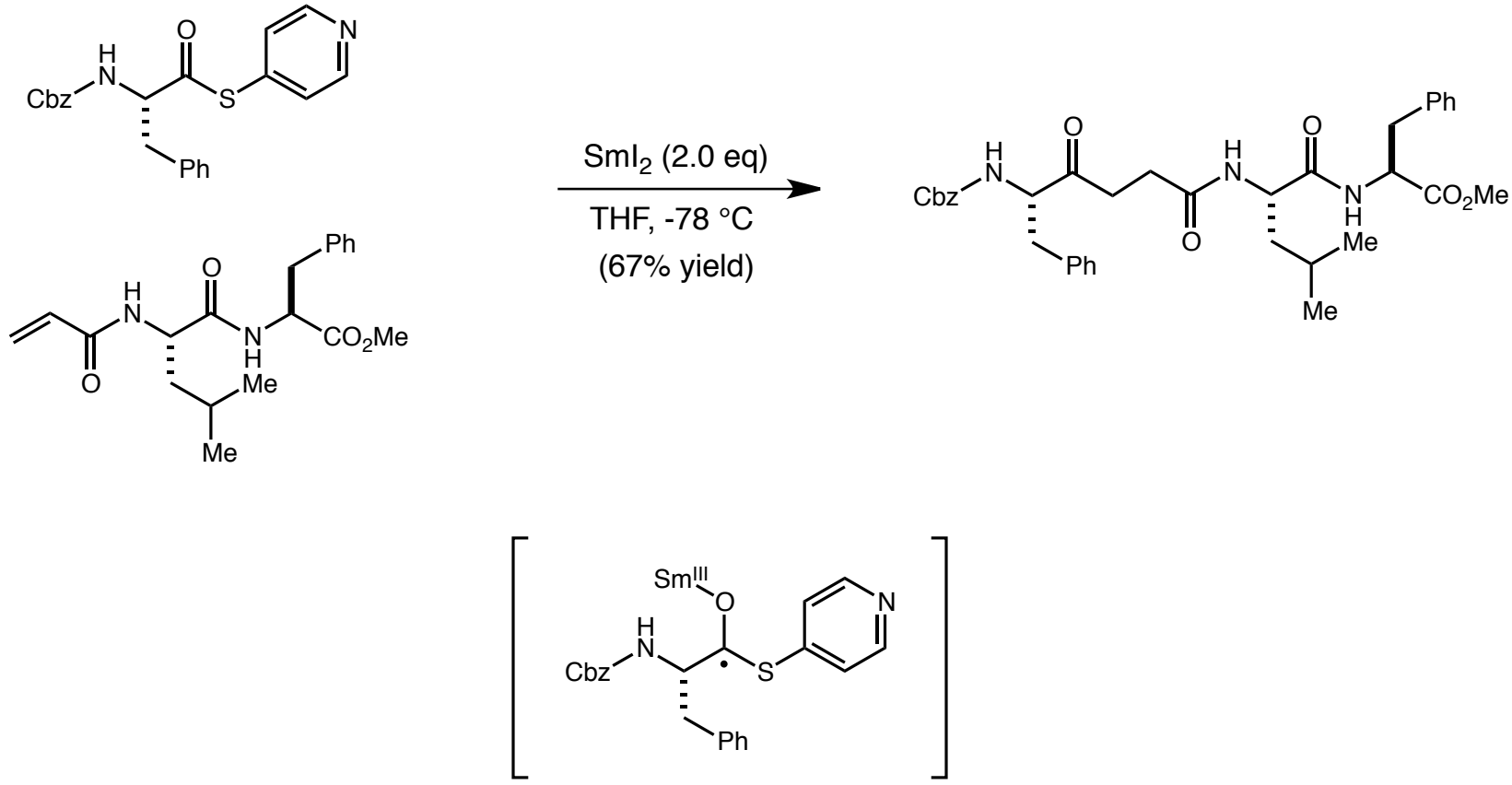
anionic-radical sequence



Helm, M. D.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224.

Modification of Biomolecules Using SmI_2

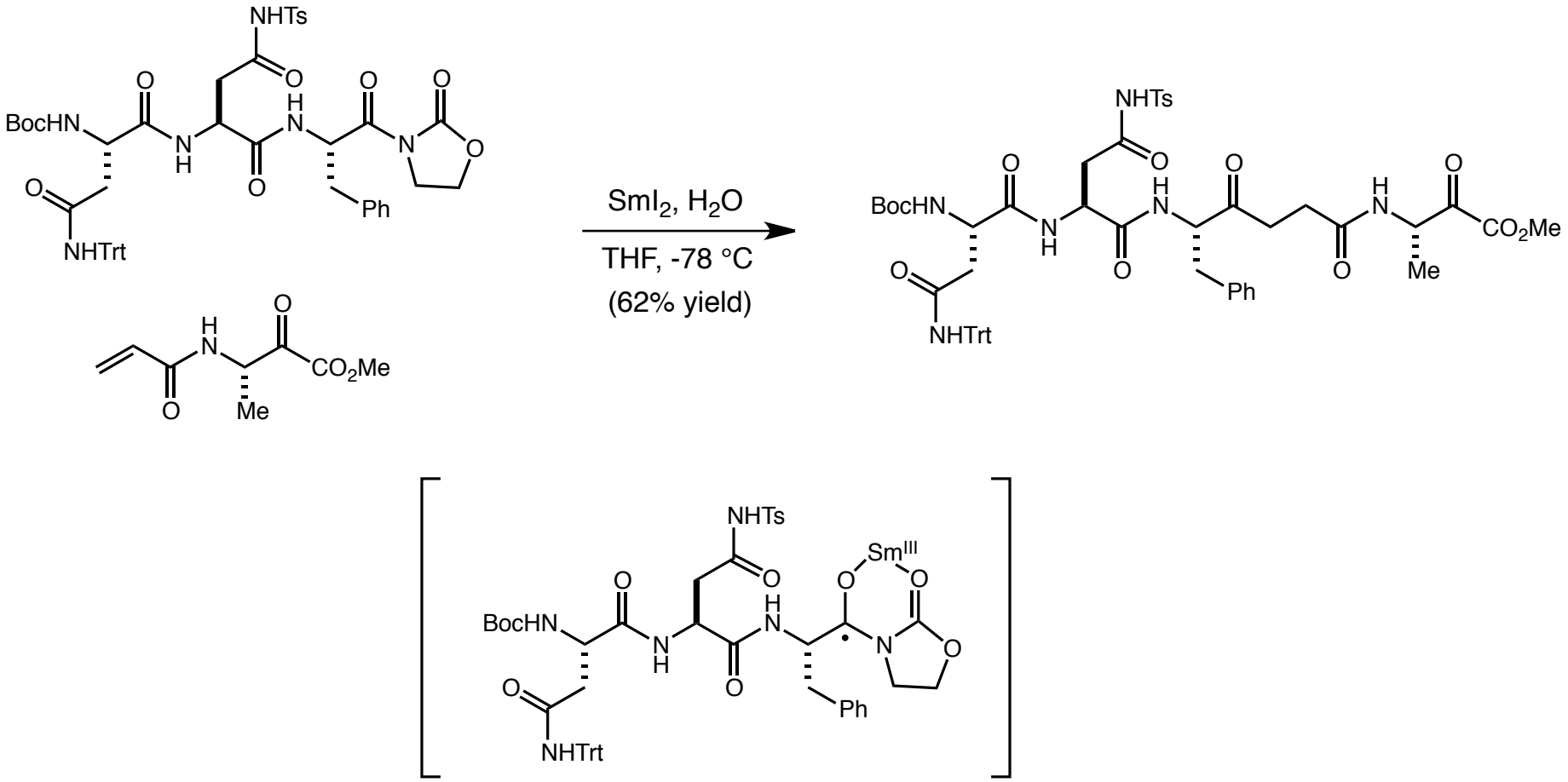
■ Modification of peptides



Hoj, B.; Skrydstrup, T. *J. Am. Chem. Soc*. **2003**, *125*, 4030.

Modification of Biomolecules Using SmI_2

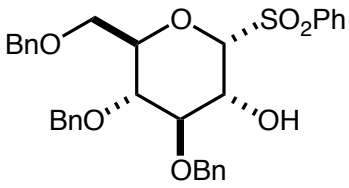
■ Modification of peptides

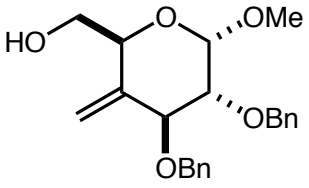


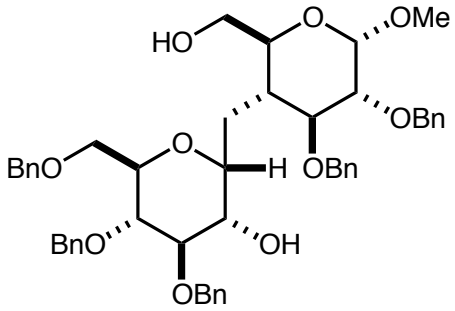
Handen, A. M.; Lindsay, K. B.; Karaffa, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, *128*, 9616.

Modification of Biomolecules Using SmI_2

■ Modification of carbohydrates



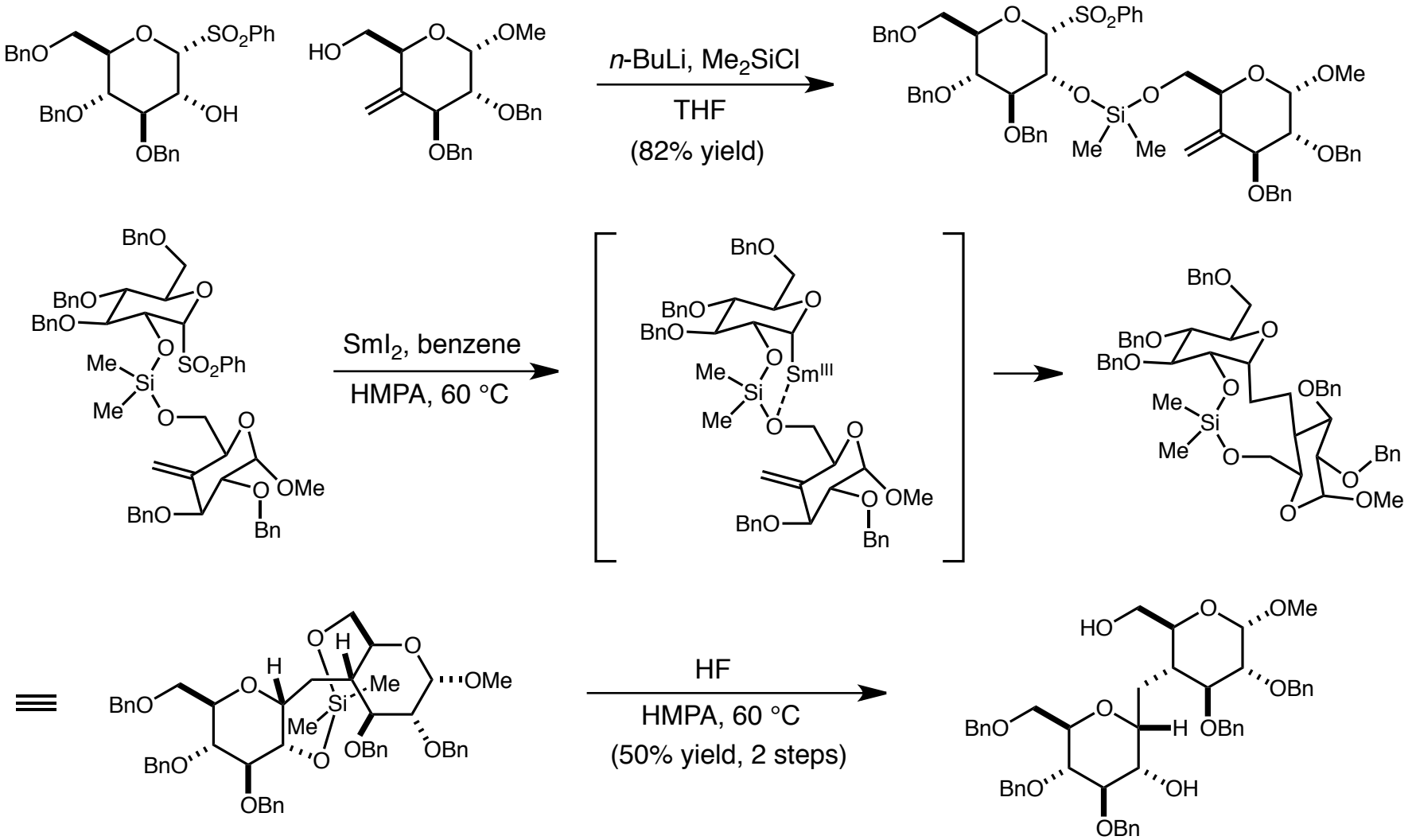




Perrin, E.; Sinay, P. *Synlett.* **1994**, 420.

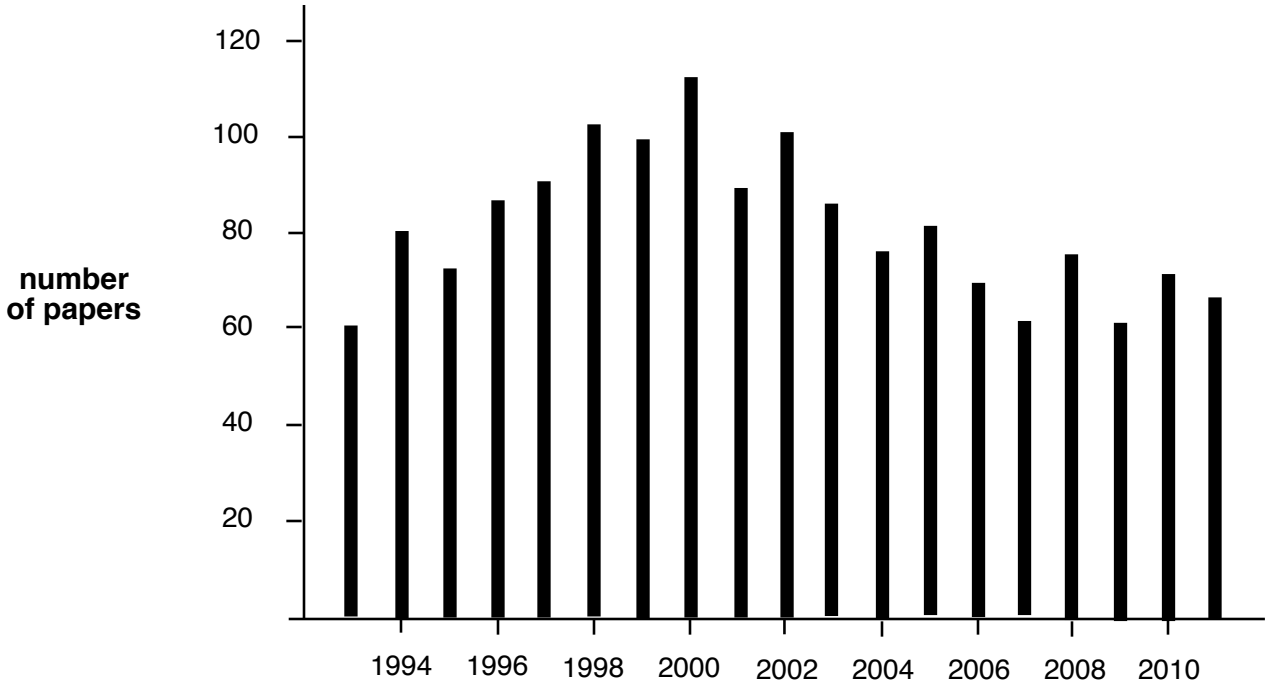
Modification of Biomolecules Using SmI_2

■ Modification of carbohydrates



Perrin, E.; Sinay, P. *Synlett.* **1994**, 420.

Conclusion



- Solvent rates plays a large role on reactivity and regioselectivity in SmI_2 mediated reactions
- Intramolecular reactions can provide high levels of enantio - and diastereoselectivity
- There is a still a potential for the discovery of new reaction types using SmI_2