ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

SmI_2-Mediated C-C Bond Formation and Application in Natural Product Synthesis

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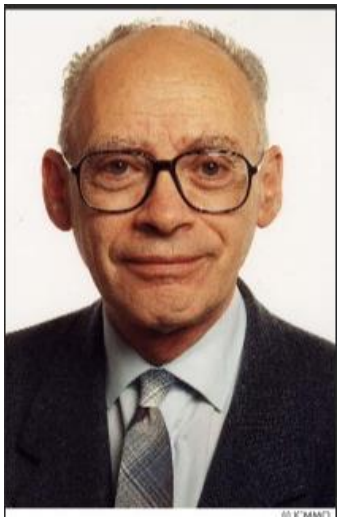
12.05.2022

SmI_2 : Kagan's reagent



Henri Kagan (1930-)

Ph.D. in chemistry from the Collège de France

Professor, University of Paris, then Paris-XI University, France.

Namy, J. L., Girard, P. & Kagan, H. B. New preparation of some divalent lanthanide iodides and their usefulness in organic-synthesis. *Nouv. J. Chim.* **1**, 5–7 (1977).

Outline

1. Introduction

2. Influence of Different Additives

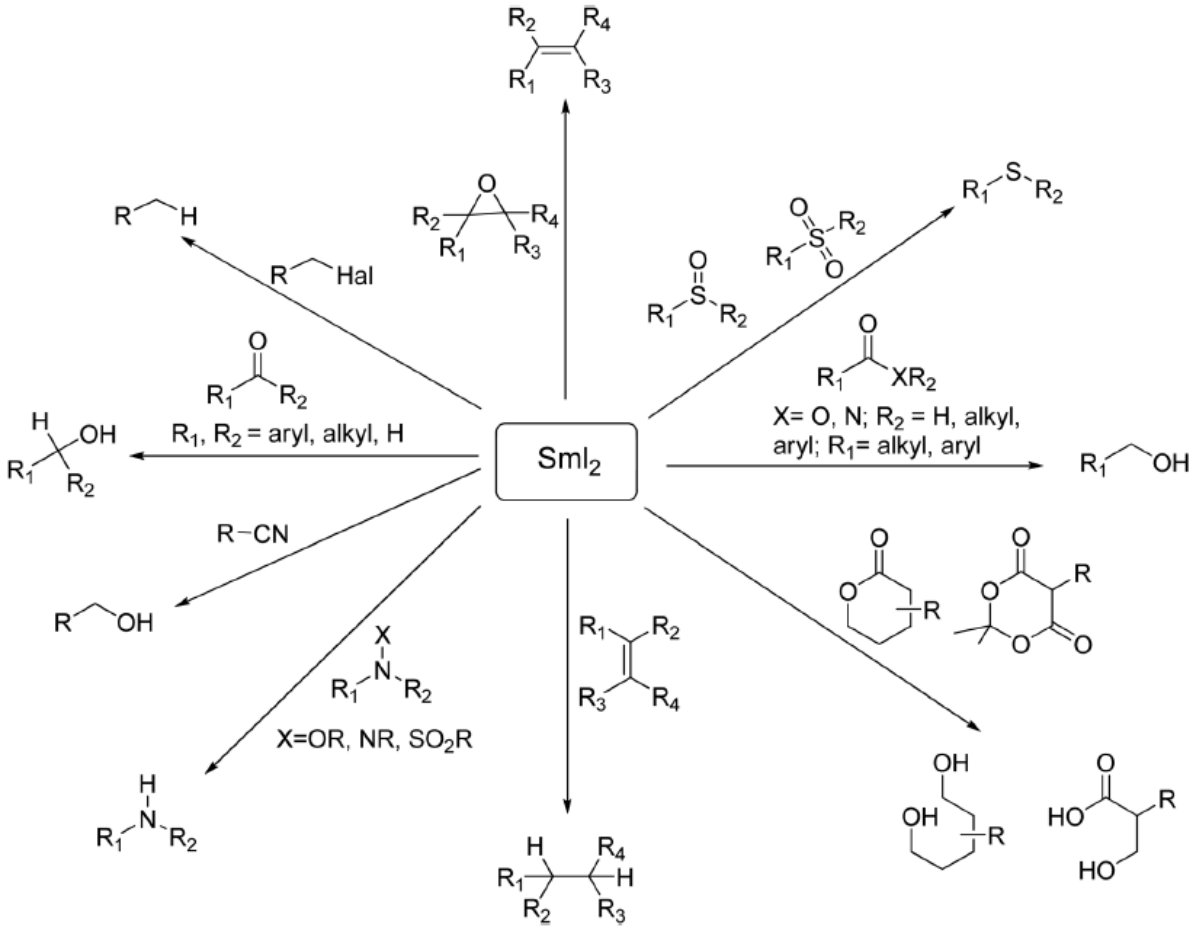
3. Preparation of SmI_2

4. SmI_2 Mediated C-C Formation

5. Summary

Introduction

- ***Selective SmI_2-mediated functional group transformations***

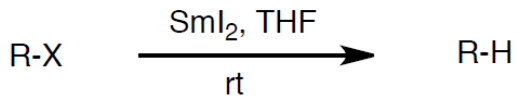


Tetrahedron, **2003**, *59*, 10351–10372
Chem. Rev. **2004,** *104*, 3371–3403
Eur. J. Inorg. Chem. **2004**, 3393–3403
Angew. Chem. Int. Ed. **2009**, *48*, 7140 – 7165

Heterocycles, **2014**, *89*, 1369–1391
Chem. Rev. **2014**, *114*, 5959−6039
RSC Adv., **2022**, *12*, 9944
Nature Synthesis, **2022**, *1*, 275–288

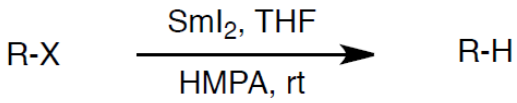
Influence of Different Additives

- ***Influence of HMPA***



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



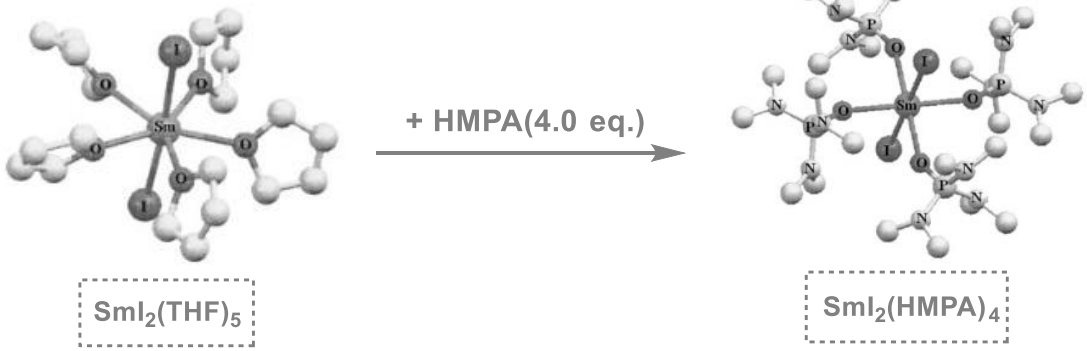
R	X	time	yield (%)
$C_{10}H_{21}$	I	5 min	96
$C_{10}H_{21}$	Br	10 min	97
$C_{10}H_{21}$	Cl	8 h[a]	94

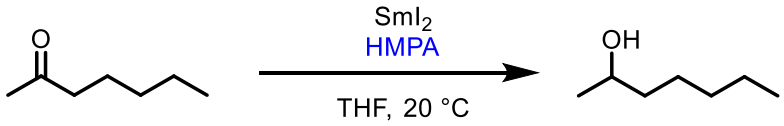
[a] reaction carried out at 60 °C

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

Influence of Different Additives

Influence of HMPA





entry	Additive	time	convertion (%)
1	---	16 days	28%
2	HMPA (1.0 eq)	<1 hour	100%

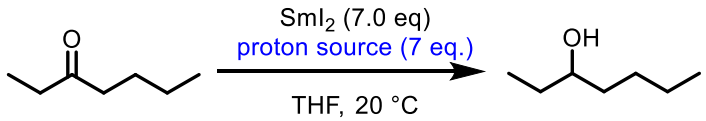
M.-R. S. Fuh, T.-Y. Lin, S.-C. Chang, *Talanta* **1998**, *46*, 861-866.

HMPA (Equiv)	Peak Potential for the Oxidation of SmI_2(V)
0	**–1.33 V**
1	**–1.43 V**
2	**–1.46 V**
3	**–1.95 V**
4	**–2.05 V**
5	**–2.05 V**

Göran Hilmersson et al. *Eur. J. Inorg. Chem.* **2004**, 3393

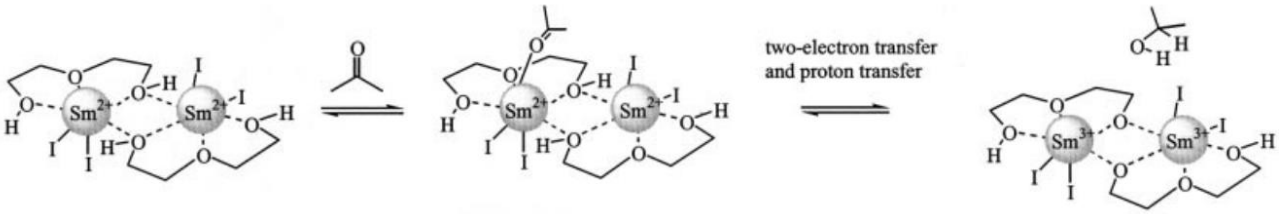
Influence of Different Additives

- ***Influence of proton source***



THF (only)	Me–OH	Me–O–CH2–CH2–OH (Methoxy ethanol)	HO–CH2–CH2–OH ethylene glycol
1.0	**3.5**	**7.1**	**42**

HO–CH2–CH2–O–CH2–CH2–OH di(ethylene glycol)	HO–CH2–CH2–O–CH2–CH2–O–CH2–CH2–OH tri(ethylene glycol)	tetra(ethylene glycol)
255	**95**	**6.9**

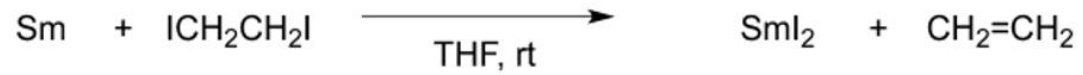


Goran Hilmersson. et al. *Tetrahedron Lett.* **2001**, *42*, 5565–5569

Anders Dahlén and Göran Hilmersson, *Eur. J. Inorg. Chem.* **2004**, 3393-3403

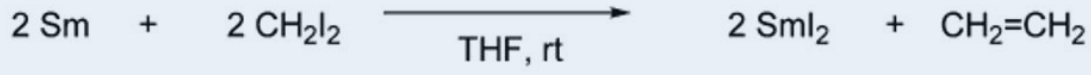
Preparation of SmI_2

Kagan's method



Imamoto's method

Kagan/Molander



Procedure :

To a slurry of Sm metal powder (11 mmol, 1.1 equiv) in degassed THF (100 mL) under N_2 atmosphere at room temperature was added CH_2I_2 (10 mmol, 1.0 equiv). The mixture was stirred at ambient temperature for 3 h. The resulting solution could be used directly.

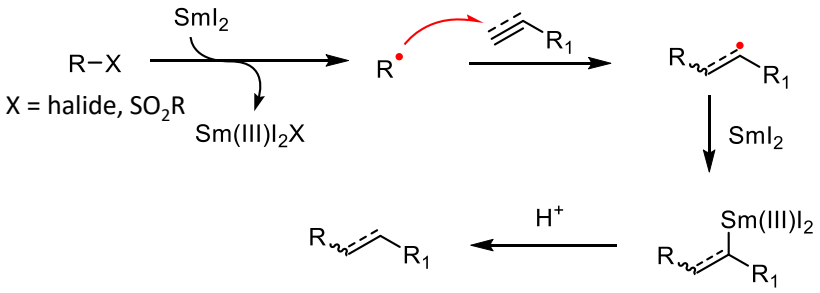
SmI_2 Mediated C-C Formation

SmI_2 Mediated C-C Formation in Natural Products Synthesis

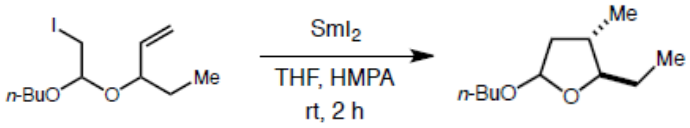
1. **Radical alkene/alkyne coupling**
2. **Barbier and grignard reaction**
3. **Carbonyl-alkene coupling**
4. **Reformatsky / Aldol-type reaction**
5. **Pinacol Coupling**
6. **Fragmentation reaction**
7. **Sequential carbon-carbon bondformation (cascade reaction)**

SmI_2 Mediated C-C Formation

1.Radical–Alkene/Alkyne Reaction

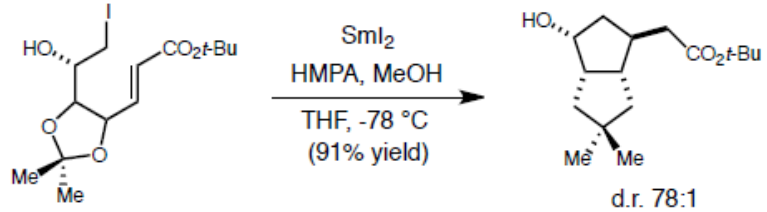


Alkyl radical additions to electron-rich alkene



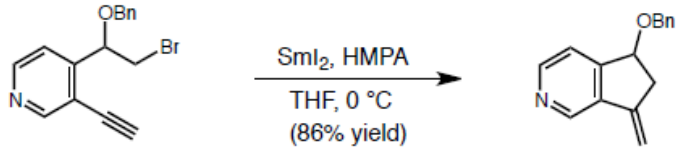
Fukuzawa, S.; Tsuchimoto, T. *Synlett.* **1993**, 803.

Alkyl radical additions to electron-poor alkene



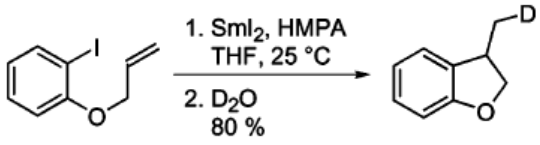
Salari, B. S. F.; Biboutou, R. K.; Bennett, S. M. *Tetrahedron.* **2000**, *56*, 6385.

Alkyl radical additions to alkyne



Ohta, A. et al. *Tetrahedron*. **1994**, *50*, 13575

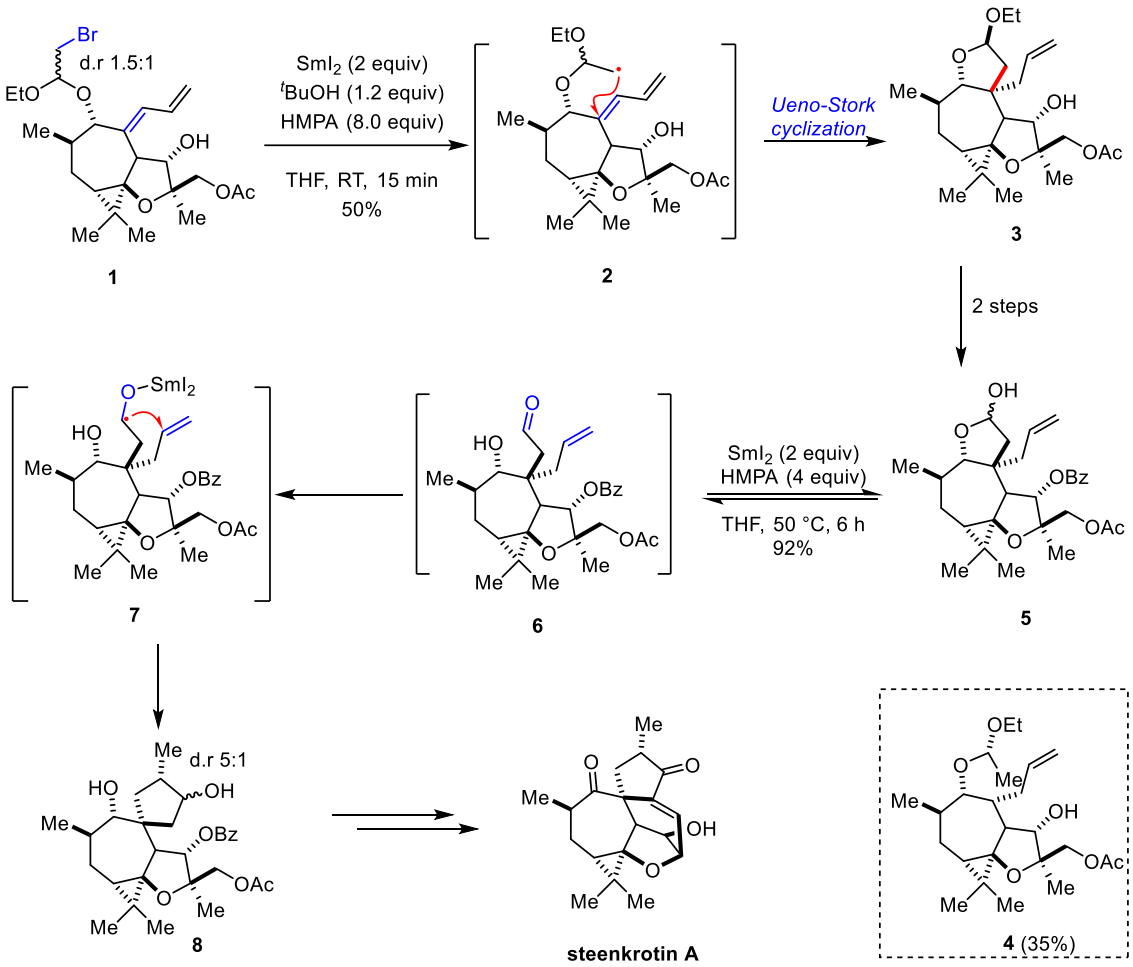
Aryl radical additions to alkene



Totleben, M. J. et al. *Synlett* **1990**, 773.

SmI_2 Mediated C-C Formation

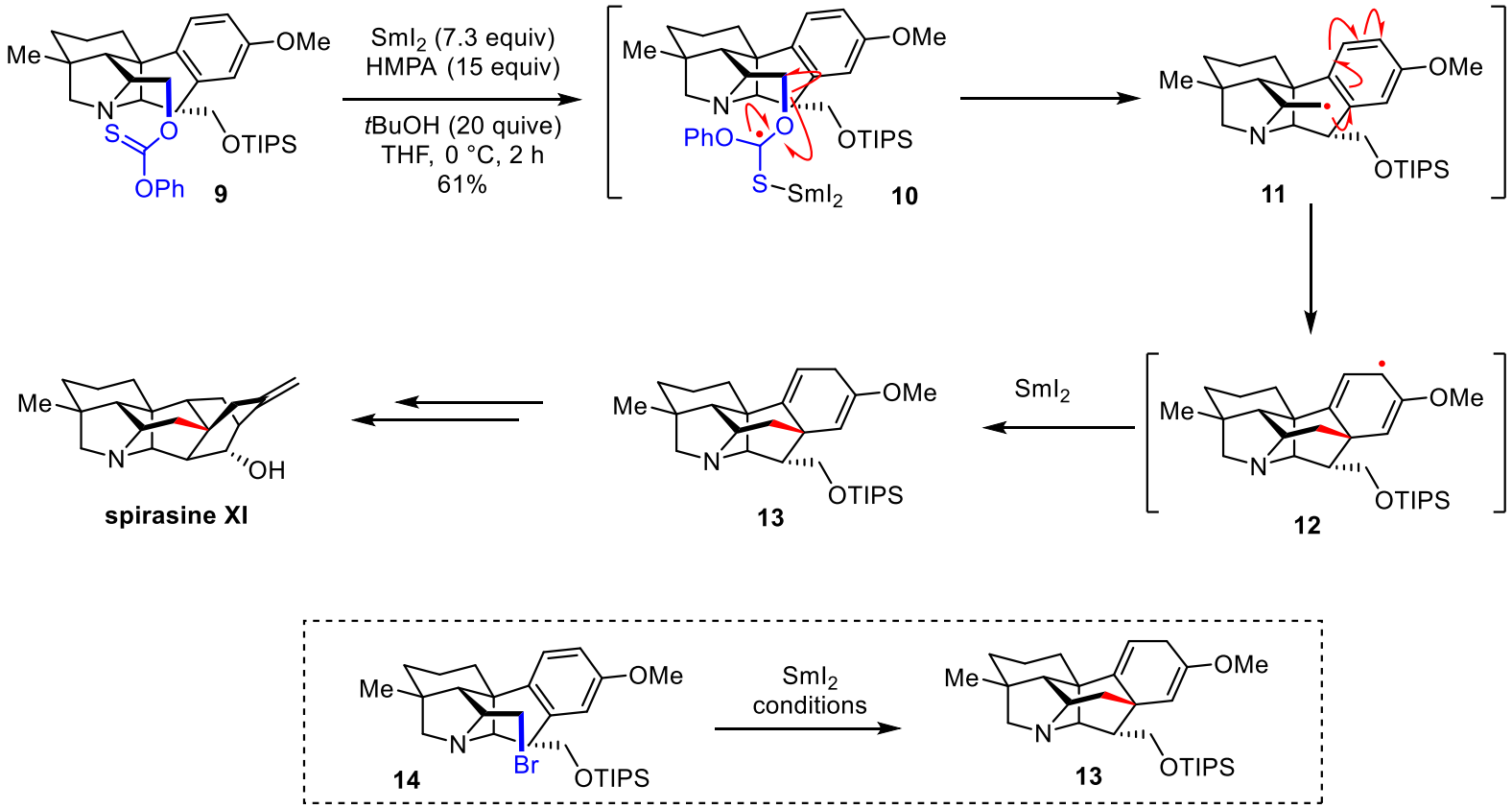
1.Radical–Alkene/Alkyne Reaction



Pan, S. Xuan, J. Gao, B. Zhu, A. Ding, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 6905–6908.
Ding, H. et al. *Chem. Eur. J.* **2016**, *22*, 959–970.

SmI_2 Mediated C-C Formation

1.Radical–Alkene/Alkyne Reaction

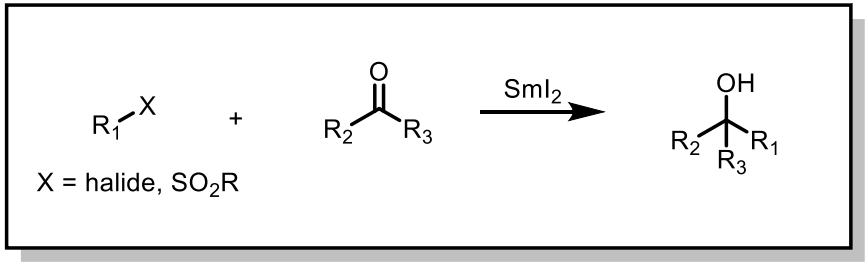


Zhang, M. et al. *Angew. Chem. Int. Ed*. **2018**, *57*, 937–941.

SmI_2 Mediated C-C Formation

2.Barbier Reaction

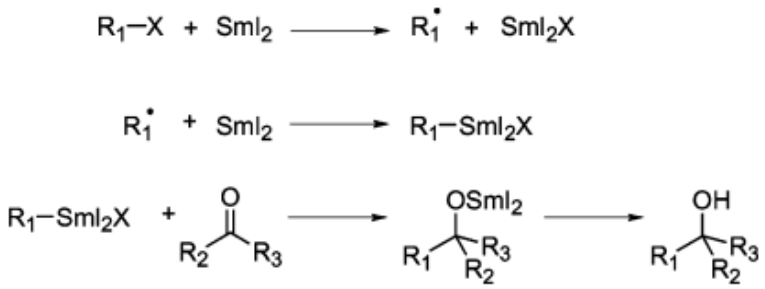
- The Barbier reaction is one of the most commonly employed SmI_2-mediated transformations.
- Popular for the formation of five- to eight membered carbocycles.



Reduction rate: iodides > bromides > chloride

Reduction rate: primary > secondary > tertiary halides

Mechanistic Scenarios



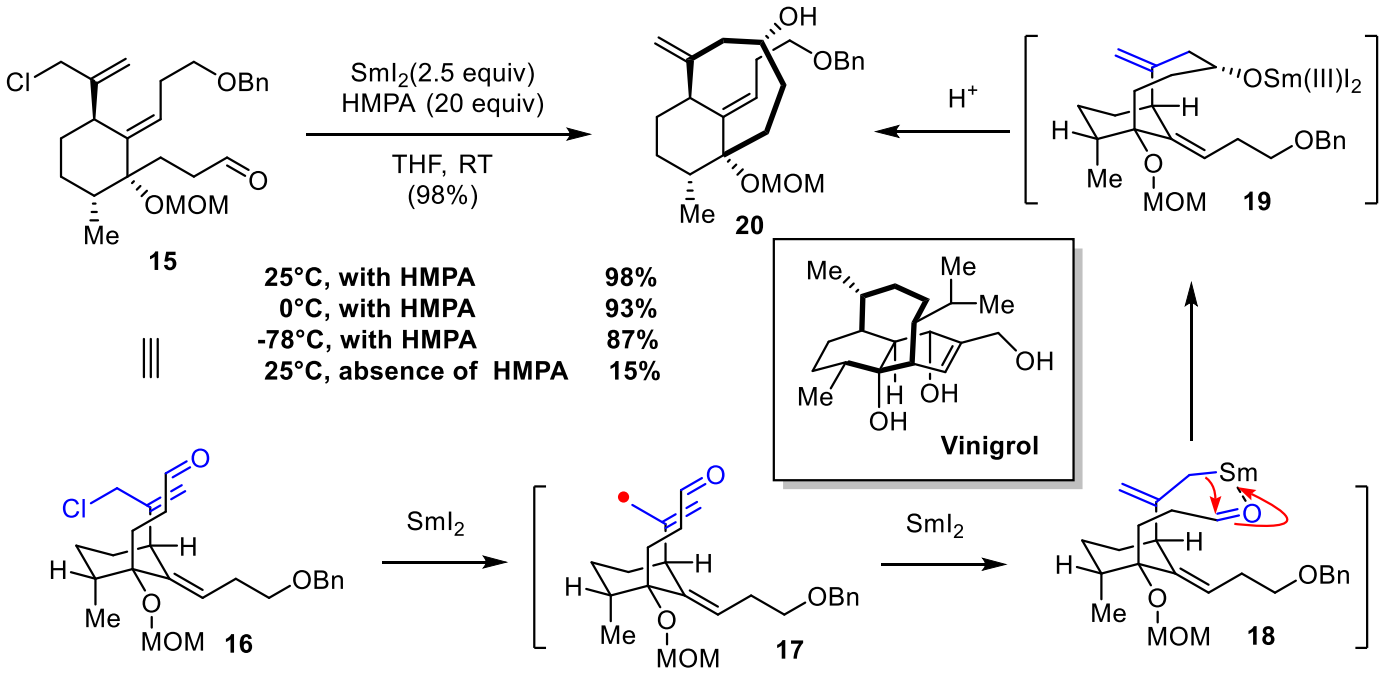
- Through an **organosamarium species** formed through two successive single electron re-ductions

J.-L. Namy, J. Collin, C. Bied, H. B. Kagan, *Synlett* **1992**, 733 – 734;
G. A. Molander, J. A. McKie, *J. Org. Chem.* **1991**, *56*, 4112 – 4120
D. P. Curran, T. L. Fevig, C. P. Jasperse, M. J. Totleben, *Synlett* **1992**, 943 – 961

SmI_2 Mediated C-C Formation

2.Barbier Reaction

Synthesis Applications

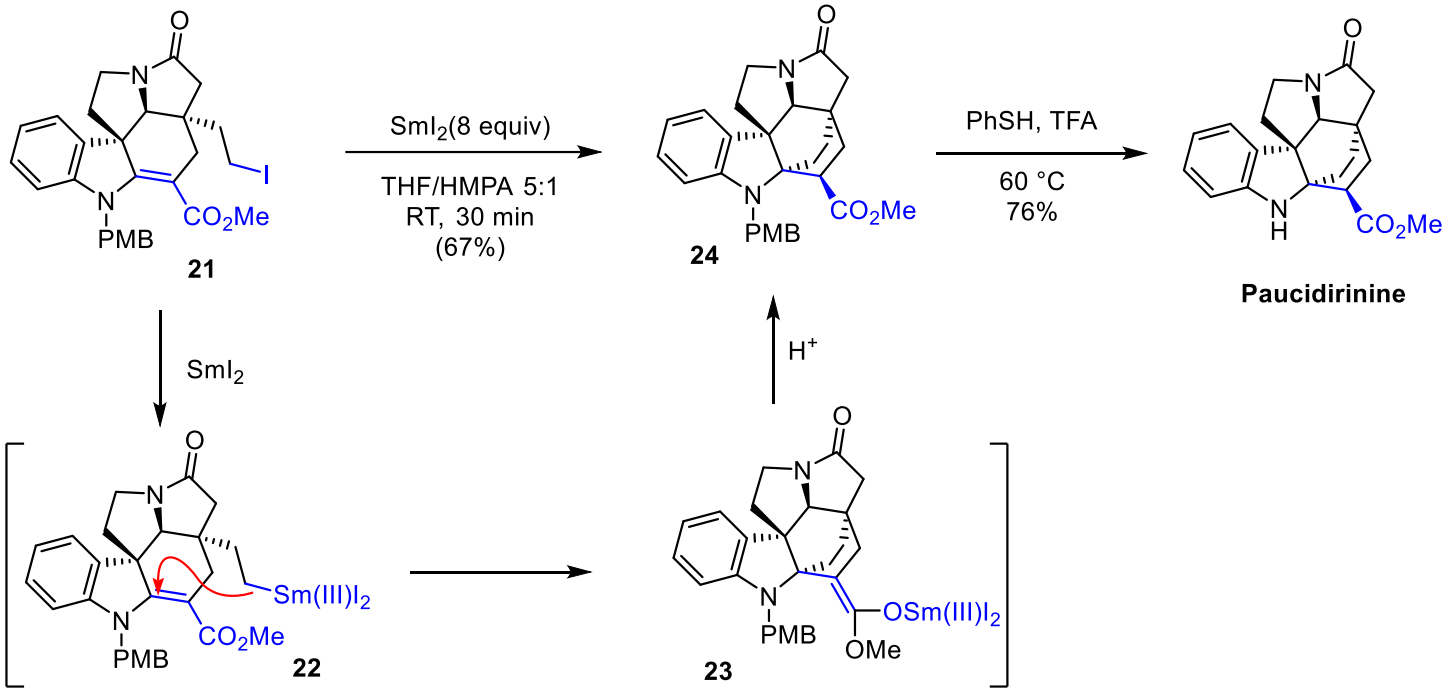


M. Kito, T. Sakai, H. Shirahama, M. Miyashita, F. Matsuda, *Synlett* **1997**, 219 – 220.
F. Matsuda, M. Kito, T. Sakai, N. Okada, M. Miyashita, H. Shirahama, *Tetrahedron* **1999**, 55, 14369 – 14380.

SmI_2 Mediated C-C Formation

2.Barbier Reaction

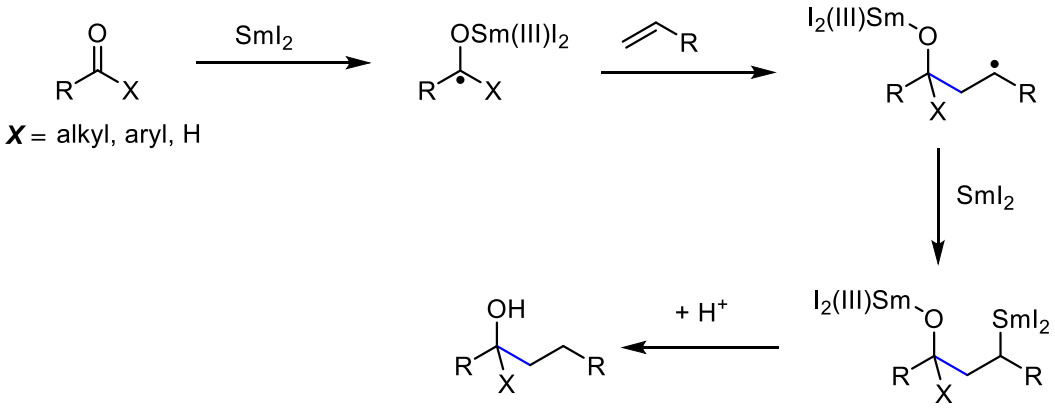
Synthesis Applications



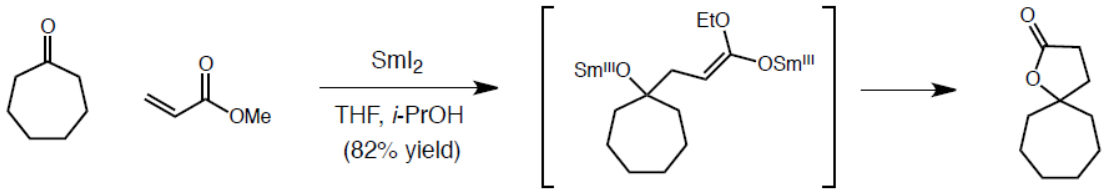
She, X. et al, *J. Org. Chem.*, **2019**, *84*, 1111–1116.

SmI_2 Mediated C-C Formation

3.Carbonyl-alkene coupling



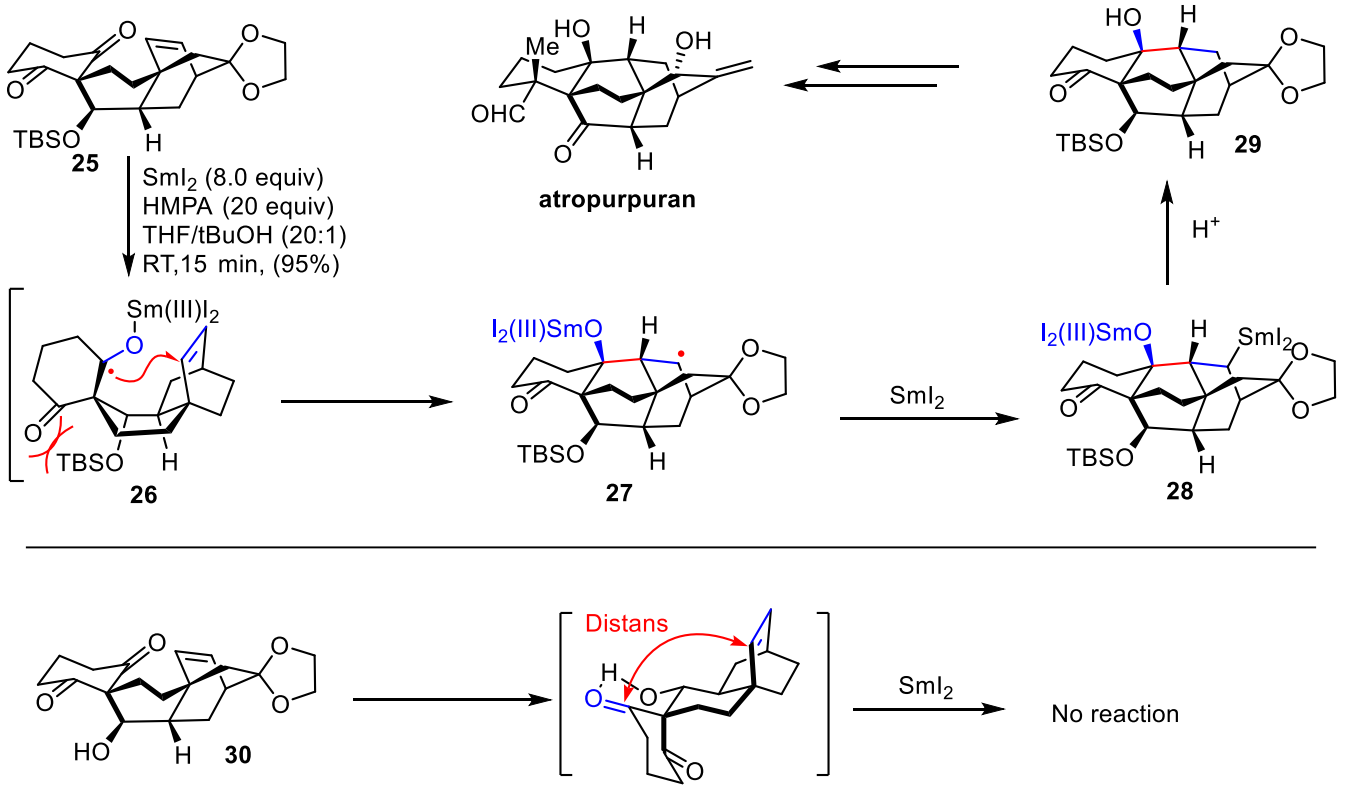
Intermolecular carbonyl-alkene coupling



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

SmI_2 Mediated C-C Formation

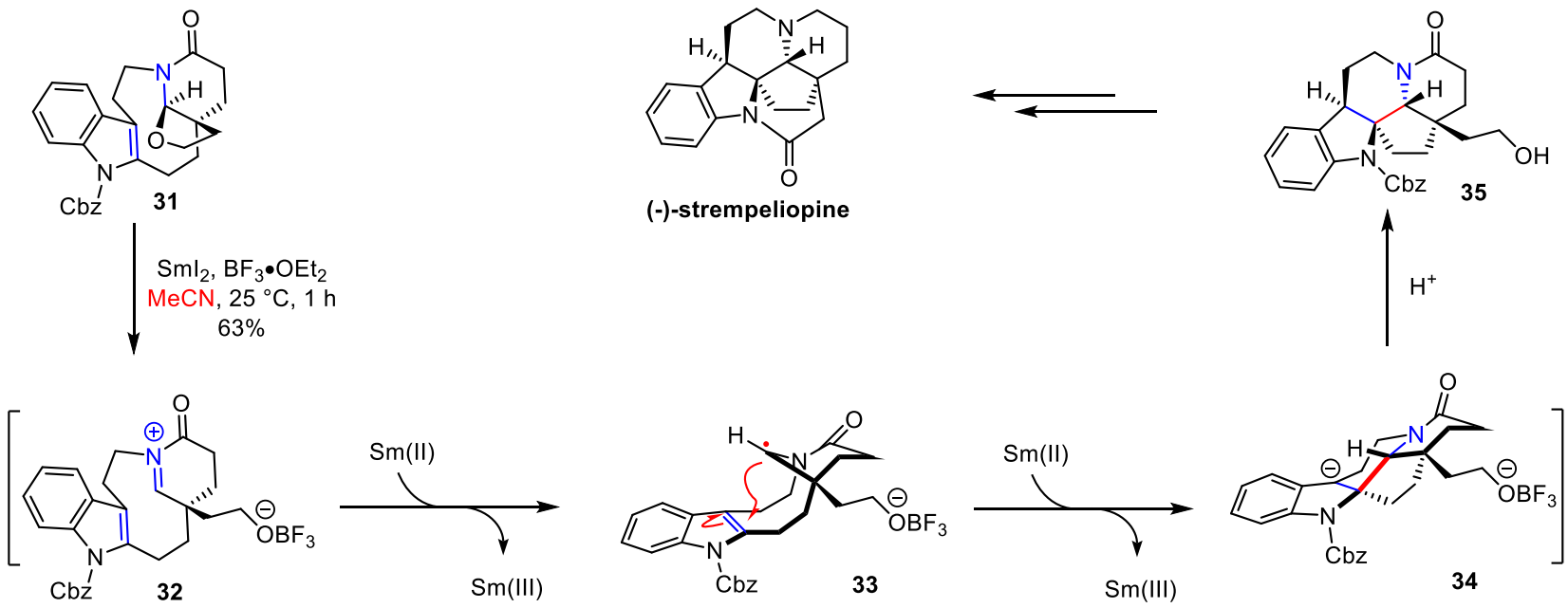
3.Carbonyl-alkene coupling



Gong, J., Liu, X., Chen, H., Wang, Z.-X., Nie, W., Qin, Y., *Nat. Commun.* **2016**, *7*, 12183.

SmI_2 Mediated C-C Formation

3.Carbonyl-alkene coupling

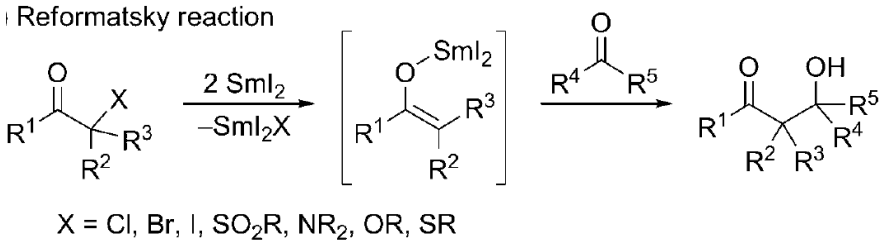


Zeng. X, Boger. D. L., *J. Am. Chem. Soc*., **2021**, *143*, 12412–12417.

SmI_2 Mediated C-C Formation

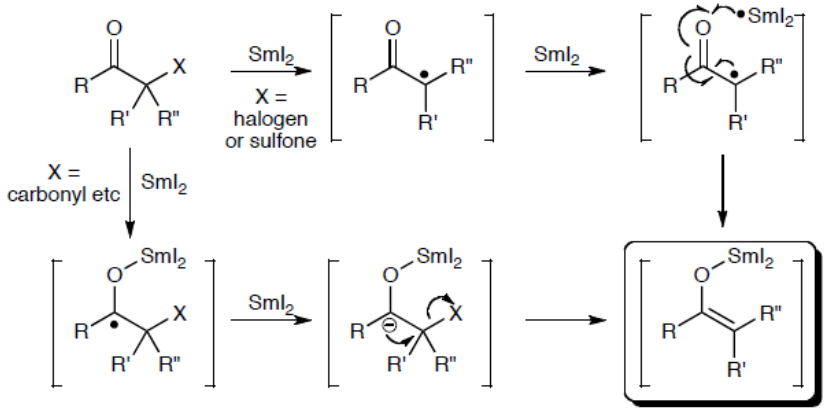
4.Reformatsky / Aldol Type Reaction

SmI_2 mediate Reformatsky / Aldol Type Reaction



- Reductive cleavage of a heteroatom vicinal to carbonyl group.
- Sm^{III} enolate intermediate formation.

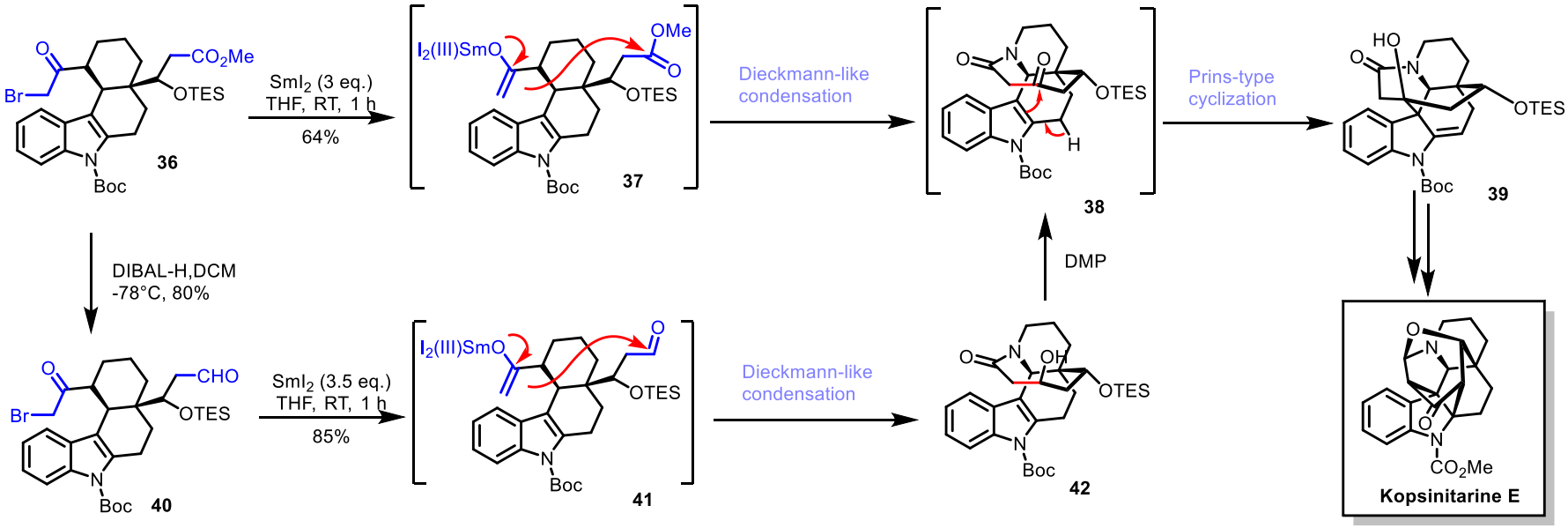
Two possible mechanisms for the formation of the Sm^{III} enolate intermediate



- Single-electron reduction of halide or sulfone to form stabilized radical.
- Initial formation of ketyl radical

SmI_2 Mediated C-C Formation

4.Reformatsky / Aldol Type Reaction

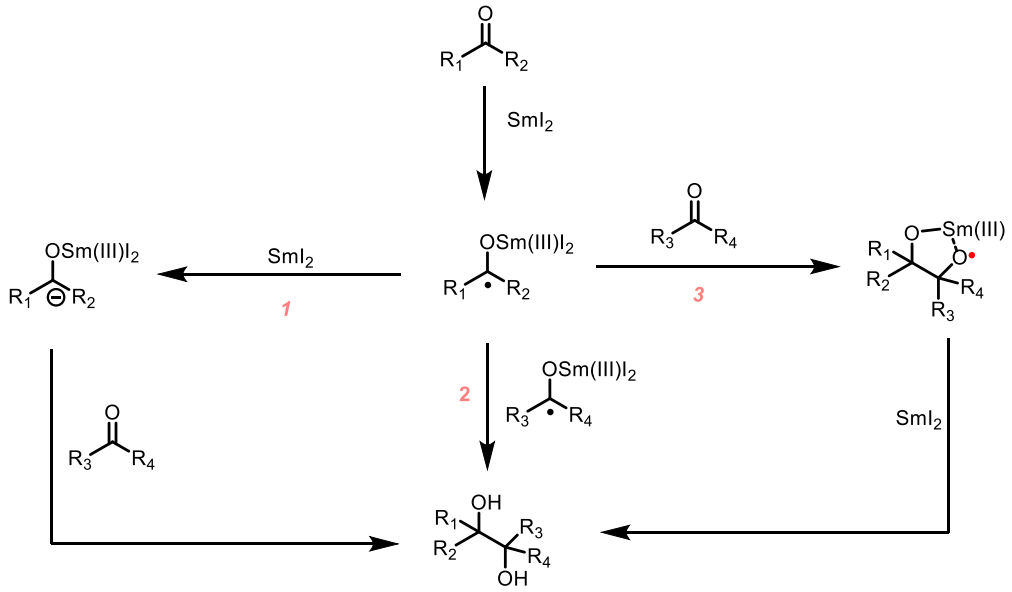


Ma, D. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 22039–22042.

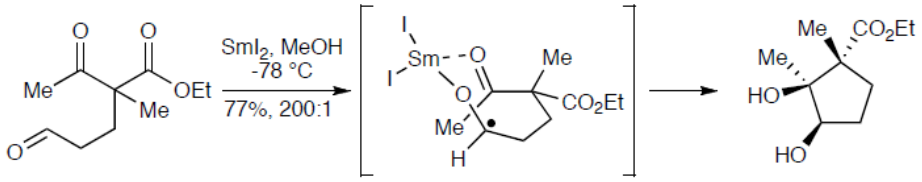
SmI_2 Mediated C-C Formation

5.Pinacol Coupling

Mechanistic Scenarios



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

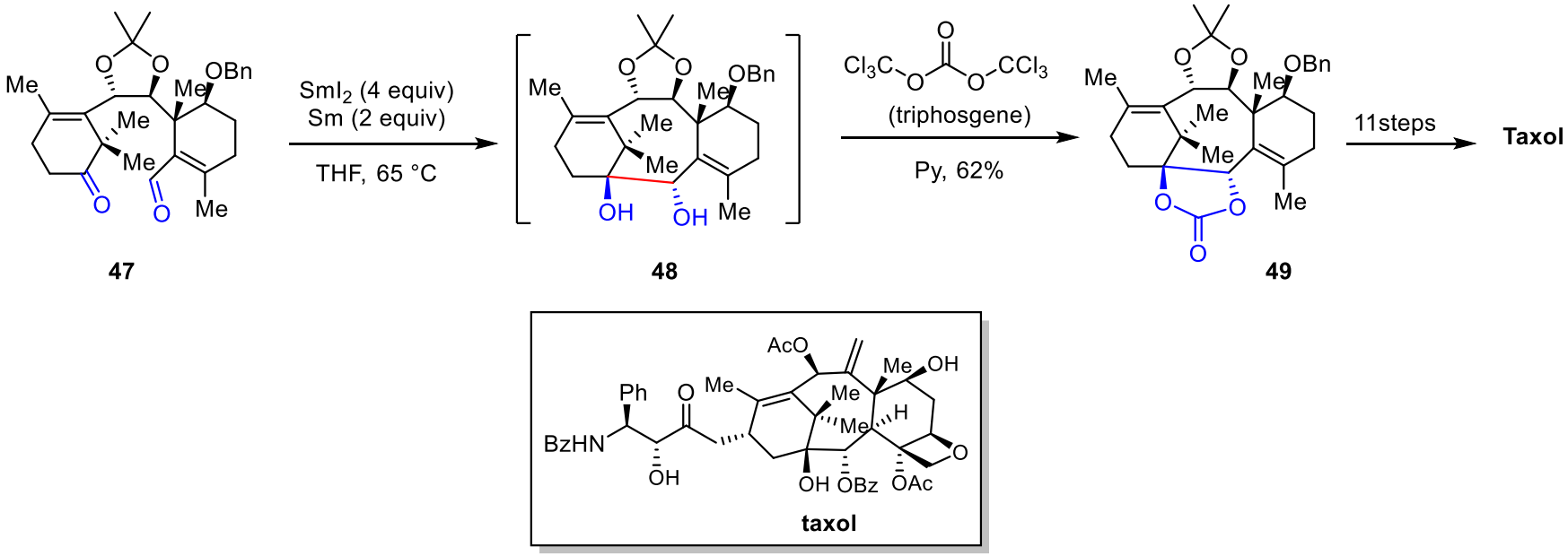


- High degree of stereoselectivity for intramolecular cyclizations

Molander, *J. Org. Chem.* **1988**, *53*, 2132

SmI_2 Mediated C-C Formation

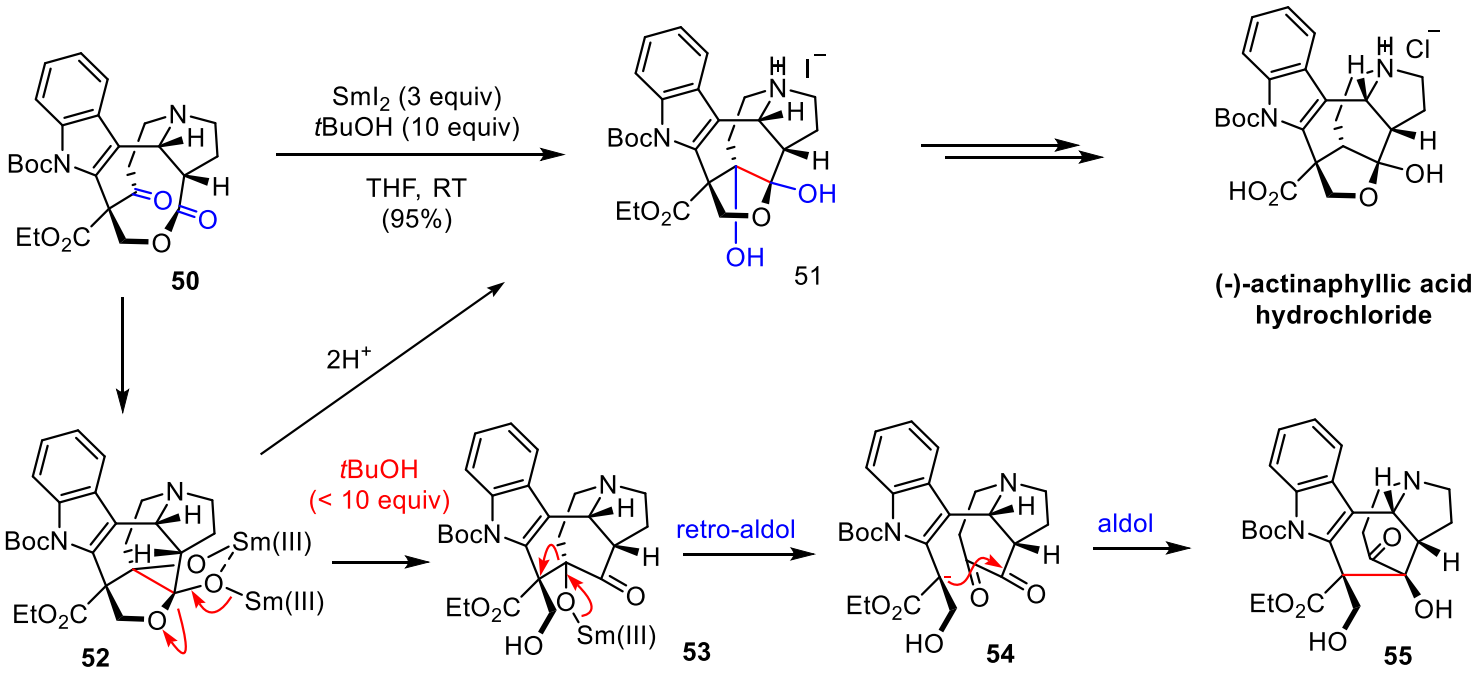
5. Pinacol Coupling



Li, C.-C. et al. *J. Am. Chem. Soc.* **2021**, ***143***, 17862–17870.

SmI_2 Mediated C-C Formation

5.Pinacol Coupling

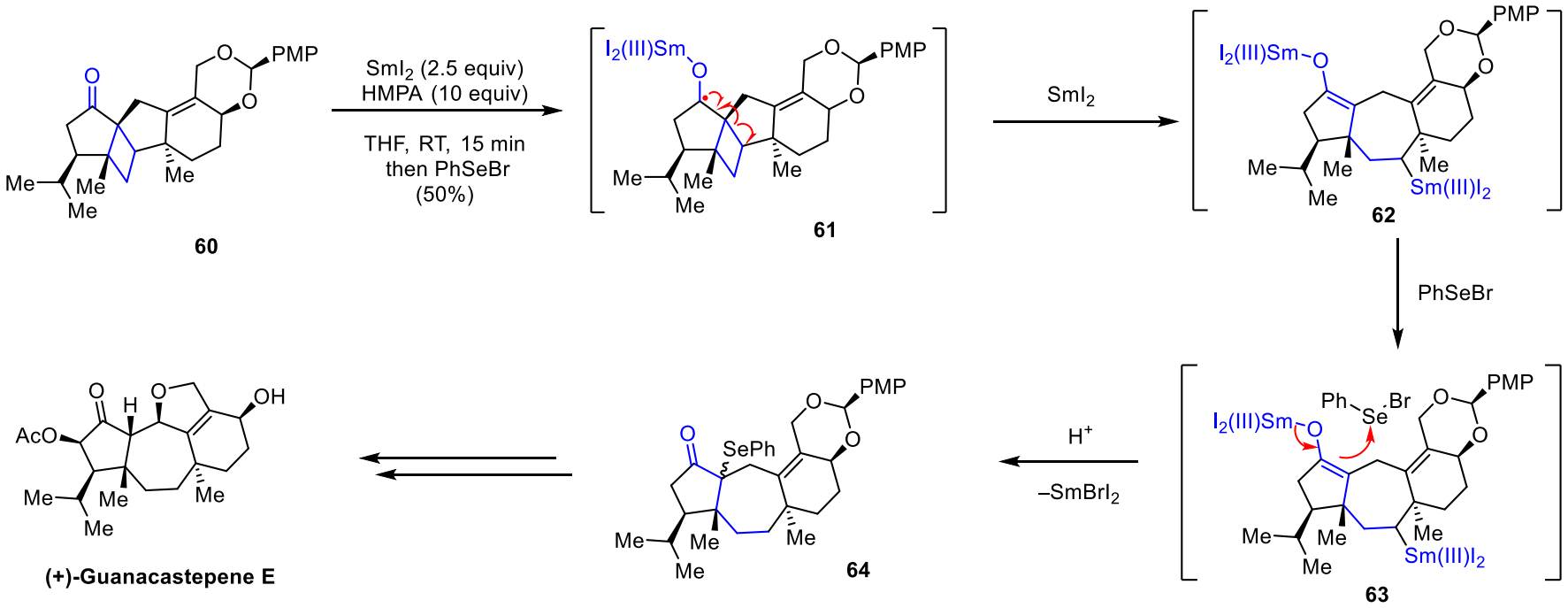


Cai, L., Zhang, K. Kwon, O. *J. Am. Chem. Soc.* 2016, **138**, 3298–3301.

SmI_2 Mediated C-C Formation

6.Fragmentation

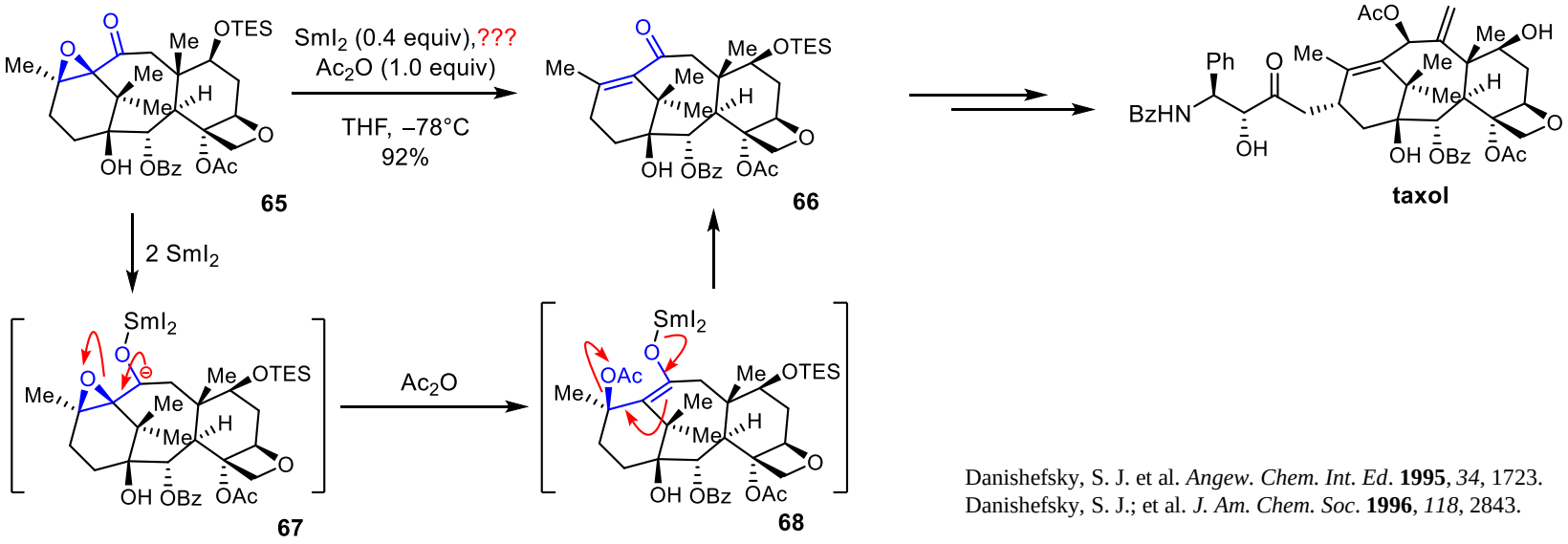
Fragmentation of Cyclobutane



Sorensen, *Org. Lett.* **2002**, *4*, 2063.
Sorensen, *J. Am. Chem. Soc.* **2006**, *128*, 7025.

SmI_2 Mediated C-C Formation

6.Fragmentation

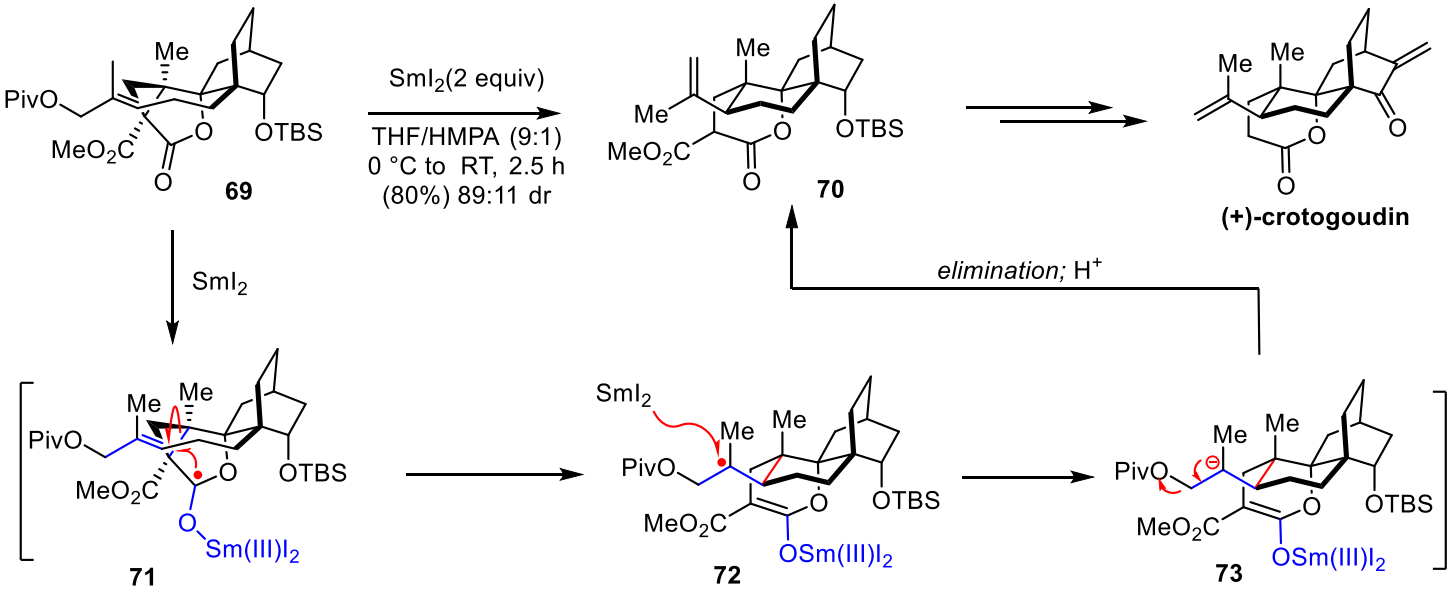


Danishefsky, S. J. et al. *Angew. Chem. Int. Ed*. **1995**, *34*, 1723.
Danishefsky, S. J.; et al. *J. Am. Chem. Soc*. **1996**, *118*, 2843.

SmI_2 Mediated C-C Formation

7.Sequential carbon-carbon bond formation (cascade reaction)

Cyclopropyl opening/6-*exo*-trig/elimination cascade



Breitler, S.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2013**, *52*, 11168.

Summary

- **Additives play crucial parts in SmI_2–mediated transformations.**
- **Many types of intramolecular reaction always provide high stereoselectivity**
- **SmI_2 has a great successful application in total synthesis of complex natural products.**

Thanks for your attention !