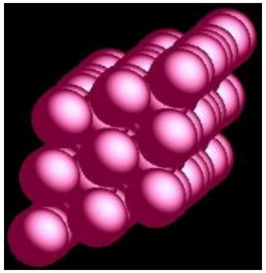
C-C Bond forming Reactions Mediated by SmI_2 via Radical Process

STEREO SEMINAR-Literature Report 02/12/2015

Yajun REN

Samarium (II): SmO, SmS, SmSe, SmTe, **SmI_2**

discovered in *1879*



Sm Crystal Structure
trigonal

21 isotopes of Sm reported so far

$[Xe].4f^6.6s^2$;

bp 1794°C

Outline

I- Introduction

- Preparation of SmI_2
- Common Additives
- Two major Classes of Reactions Mediated by SmI_2

II- Reductive Couplings to Make C−C Bonds via Radical Process

- Cross-Coupling of Ketyl Radicals with Alkenes
- Cross-Coupling of Ketyl Radicals with Arenes
- Pinacol Couplings
- Cross-Coupling of Imines and Equivalents
- Non-Ketyl Radical Cross-Coupling

III- Conclusion and outlook

I- Introduction

Preparation of SmI_2

Kagan's method using ICH_2CH_2I

$$3Sm + 3\ ICH_2CH_2I \xrightarrow[\text{quantitative}]{\text{THF, rt}} 3\ SmI_2 + 3\ CH_2{=}CH_2$$

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

Imamoto's method using I_2

$$3Sm + 3\ I_2 \longrightarrow 2\ SmI_3 + Sm$$

$$2\ SmI_3 + Sm \longrightarrow 3\ SmI_2$$

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

Concellon's method using various oxidants and sonication

$$Sm + \underset{\text{oxidants }(CHI_3,\ CH_2I_2,\ I_2)}{\text{oxidants}} \xrightarrow[\text{THF, 5 min}]{\text{sonication}} SmI_2$$

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

Common Additives

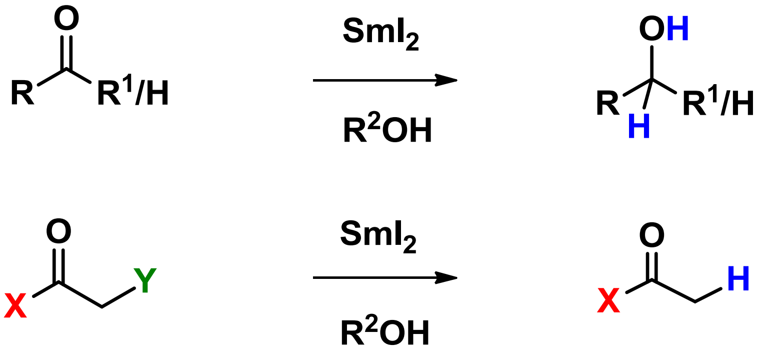
Lewis bases – HMPA and other electron-donor ligands, chelating ethers, etc.

Proton sources– predominantly alcohols and water

Inorganic additives – NiI_2, LiCl, etc.

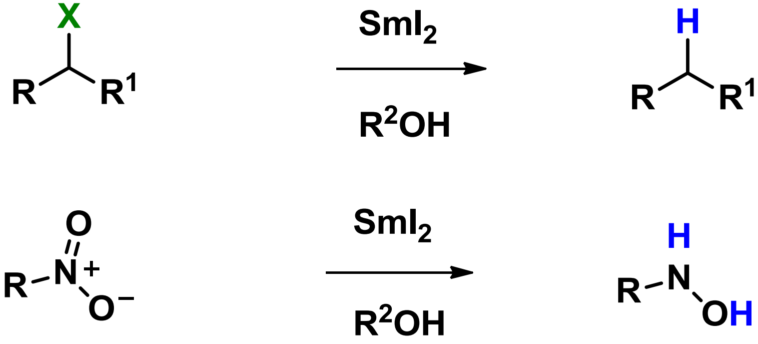
Two Major Classes of Reactions Mediated by *SmI_2*

1. **reductive manipulations of functional groups**



X = R,OR

Y = OH, OR, O_2CR, halide, $OSiR_3$, OSO_2Ar, SAr, SO_2Ar

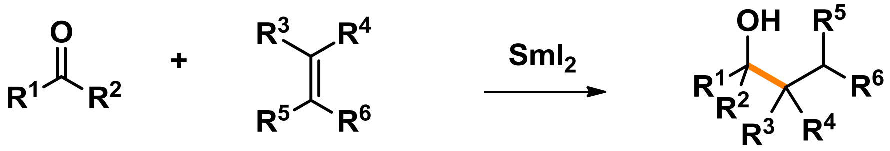


Two Major Classes of Reactions Mediated by *SmI_2*

2. reductive couplings to make C−C bonds

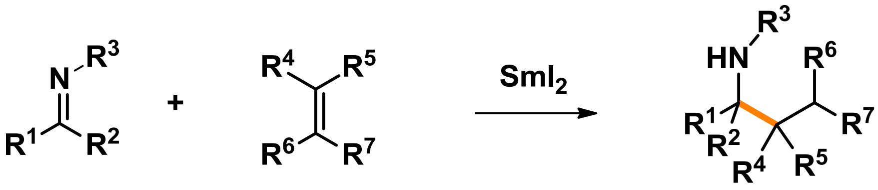
radical process

- ketyl radicals coupling with olefins:

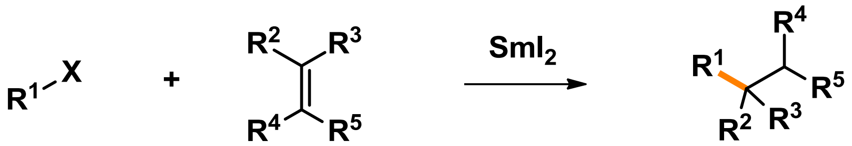


- pinacol couplings:

- imines and equivalents:



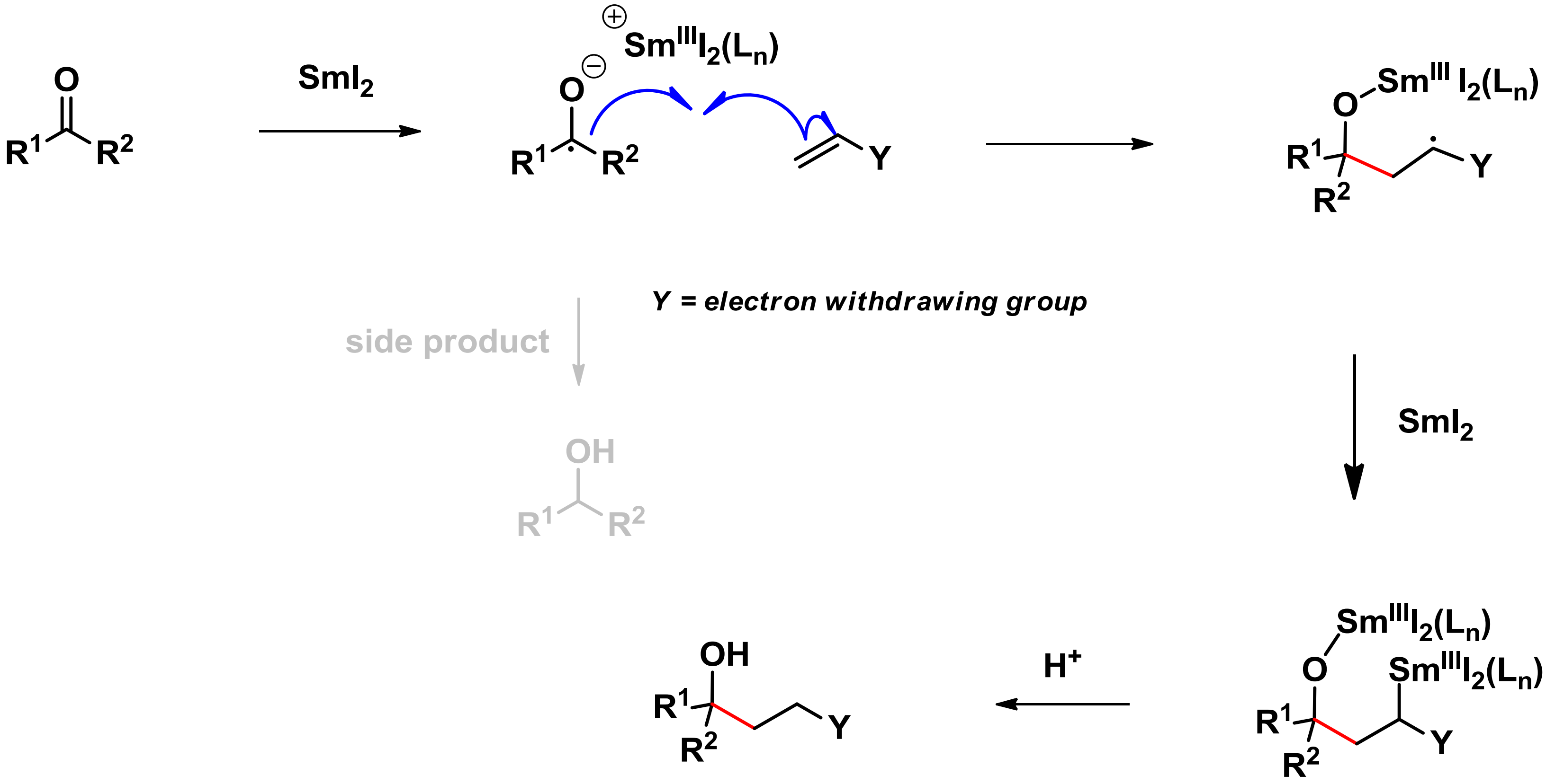
- non-ketyl radicals:



II- Reductive Couplings to Make C−C Bonds via Radical Process

- Cross-Coupling of Ketyl Radicals with Alkenes

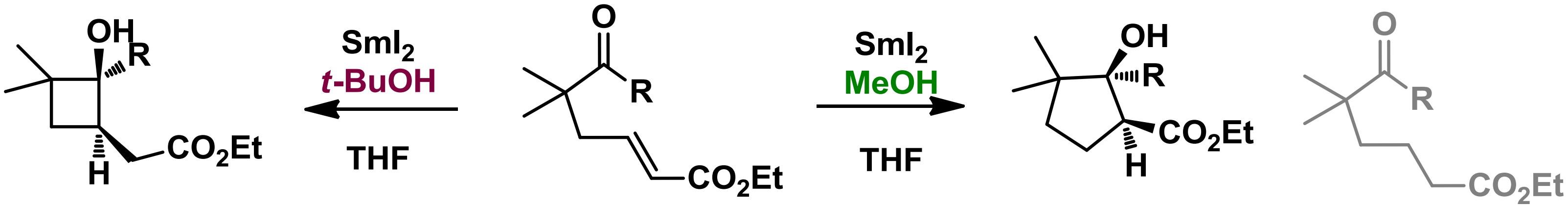
traditional mechanism :



Y = electron withdrawing group

♣ *Intramolecular Cross-Coupling of Ketyl Radicals with Alkenes*

A “fake” ketyl radical process:

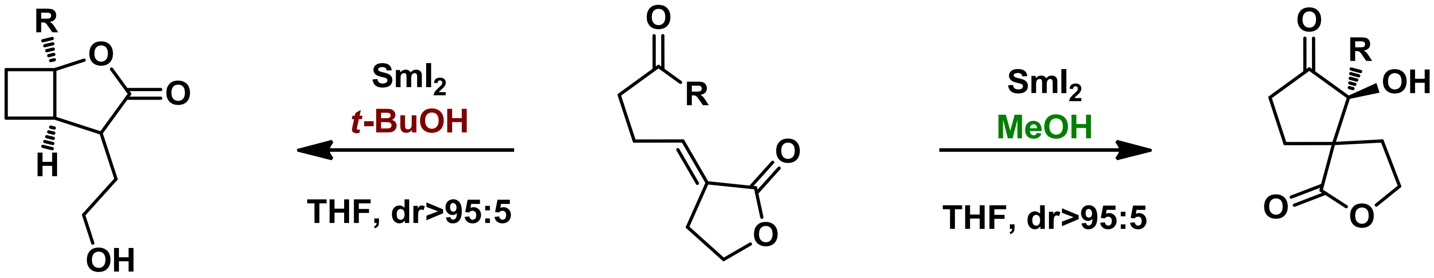


trace-30%

acyclic esters

15-45%

by-product



yield: 31-70%

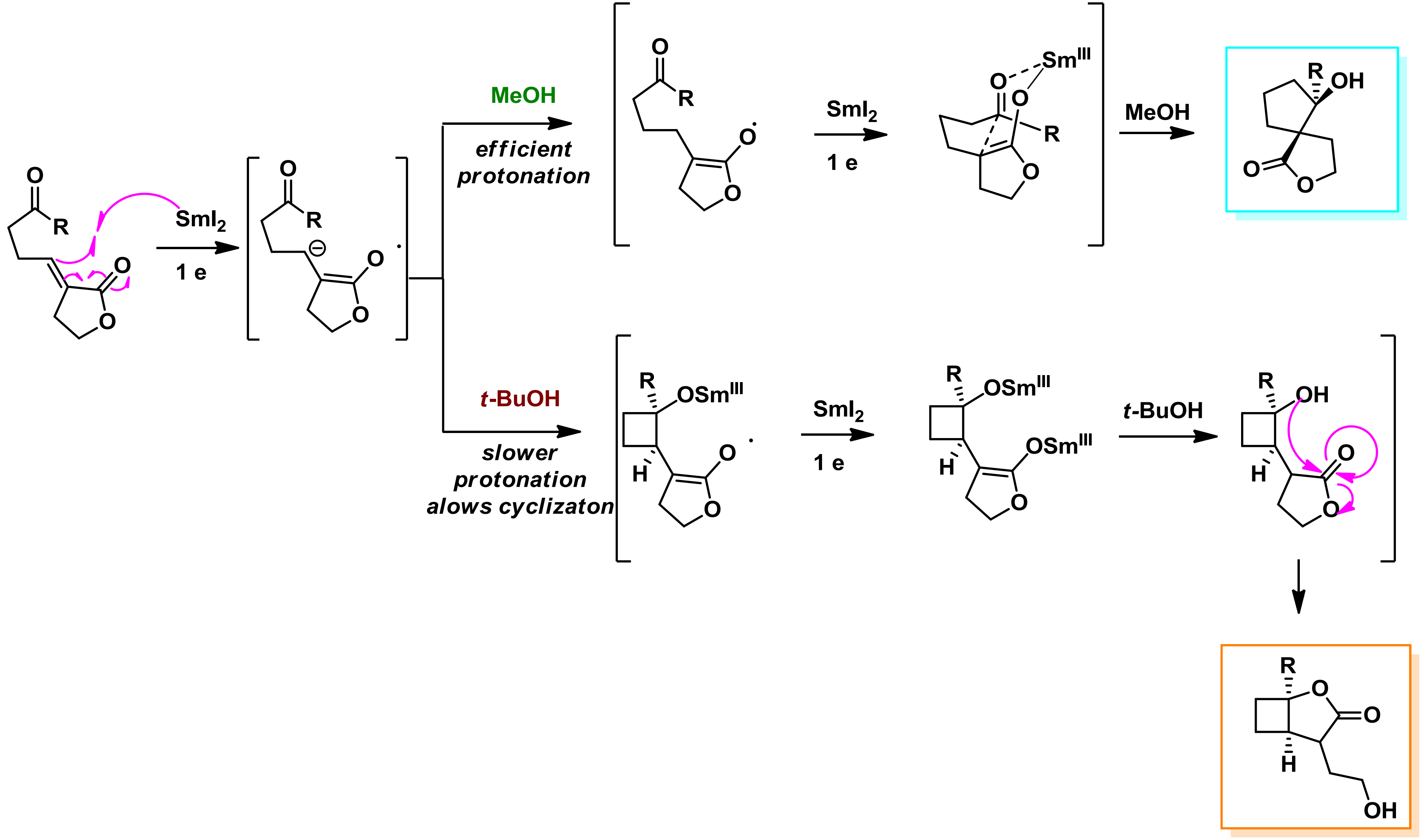
R = Me, Et, *i*-Pr, *c*-Pr

cyclic esters

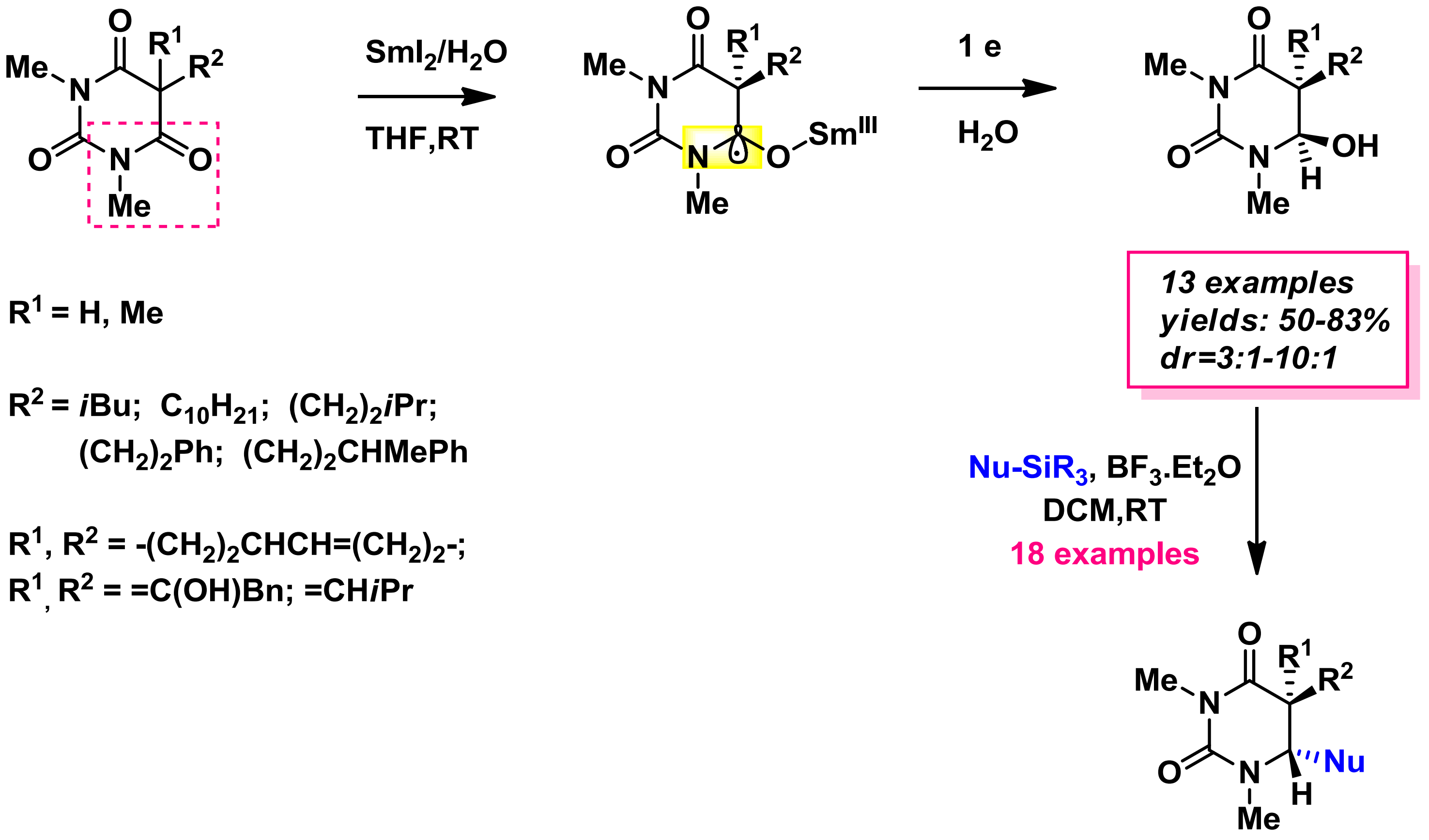
yield: 48-71%

Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345.
Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett*. **2003**, *5*, 4811.

Proposed Mechanism for the Formation of Cyclobutanes/Spirocycles



Reduction of Barbituric Acids Using SmI_2



SmI_2/H_2O

THF,RT

1 e

H_2O

13 examples
yields: 50-83%
dr=3:1-10:1

$Nu\text{-}SiR_3$, $BF_3.Et_2O$
DCM,RT
18 examples

5,6-dihydrouracils

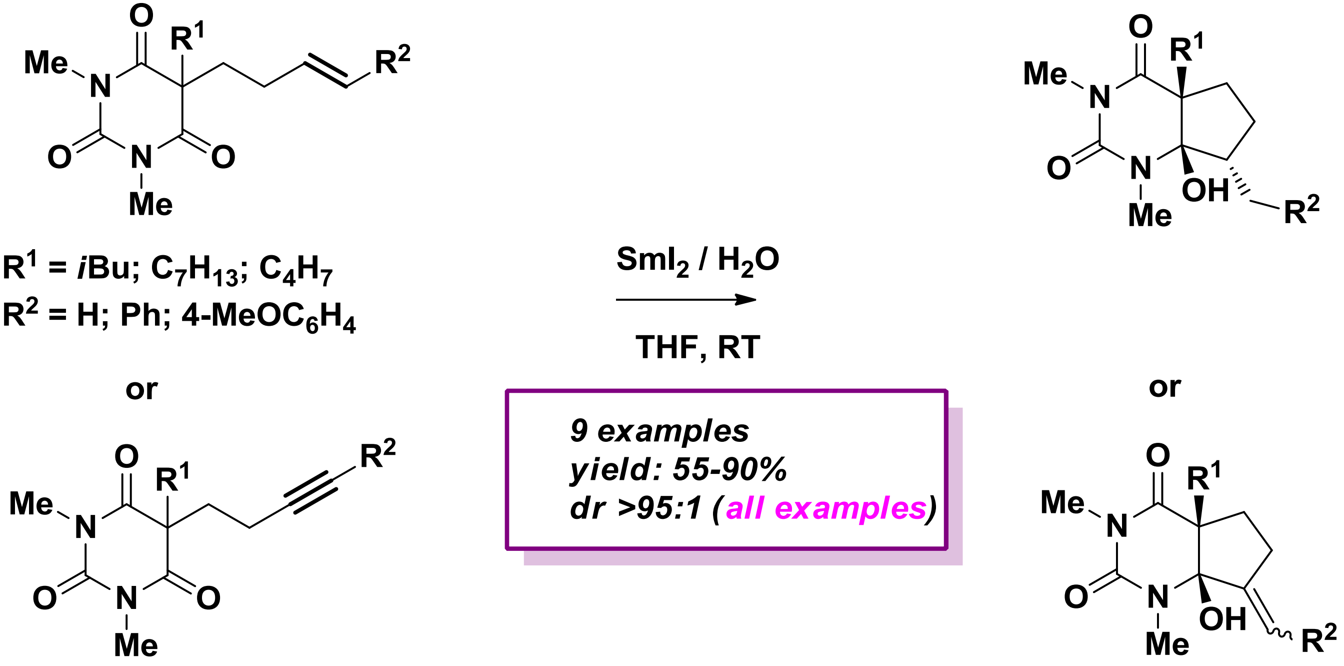
R^1 = H, Me

R^2 = *i*Bu; $C_{10}H_{21}$; $(CH_2)_2$*i*Pr;
$(CH_2)_2Ph$; $(CH_2)_2CHMePh$

R^1, R^2 = $-(CH_2)_2CHCH{=}(CH_2)_2-$;
R^1, R^2 = =C(OH)Bn; =CH*i*Pr

Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed*. **2013**, *52*, 12559
Szostak, M.; Sautier, B.; Procter, D. *J. Org. Lett*. **2014**, *16*, 452.

5-exo-Trig/Dig Cross-Coupling of Cyclic 1,3-Diimides



R^1 = *i*Bu; C_7H_{13}; C_4H_7
R^2 = H; Ph; 4-$MeOC_6H_4$

or

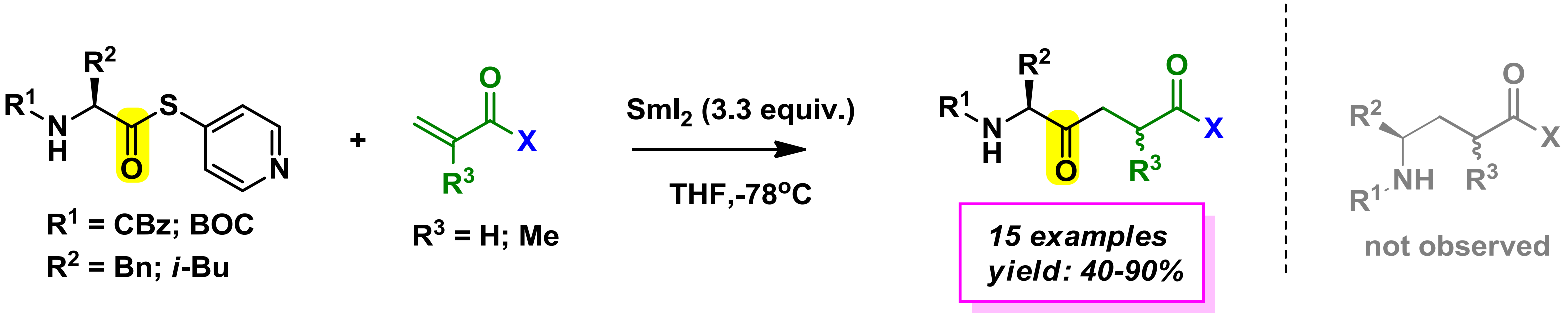
R^1 = *i*Bu; C_4H_5
R^2 = H; Ph; 4-$MeOC_6H_4$

$$\xrightarrow[\text{THF, RT}]{\text{SmI}_2\text{ / H}_2\text{O}}$$

9 examples
yield: 55-90%
dr >95:1 (all examples)

Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed*. **2013**, *52*, 12559
Szostak, M.; Sautier, B.; Procter, D. J. *Chem. Commun*. **2014**, *50*, 2518.

♣ *Intermolecular Cross-Coupling of Ketyl Radicals with Alkenes*



R^1 = CBz; BOC
R^2 = Bn; *i*-Bu

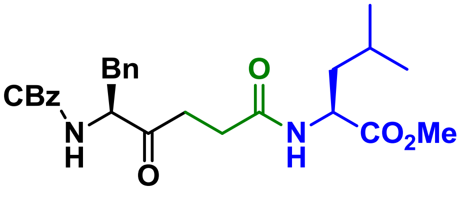
R^3 = H; Me

SmI$_2$ (3.3 equiv.)

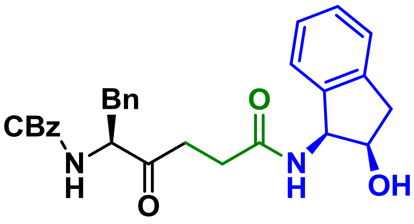
THF,-78°C

15 examples
yield: 40-90%

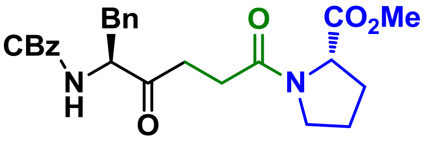
not observed



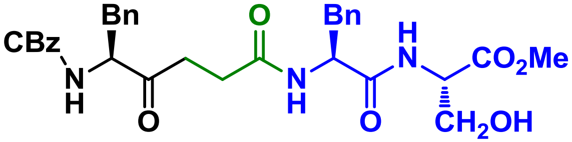
90%



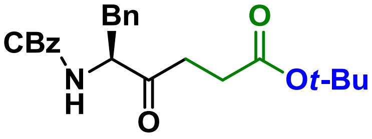
71%



85%



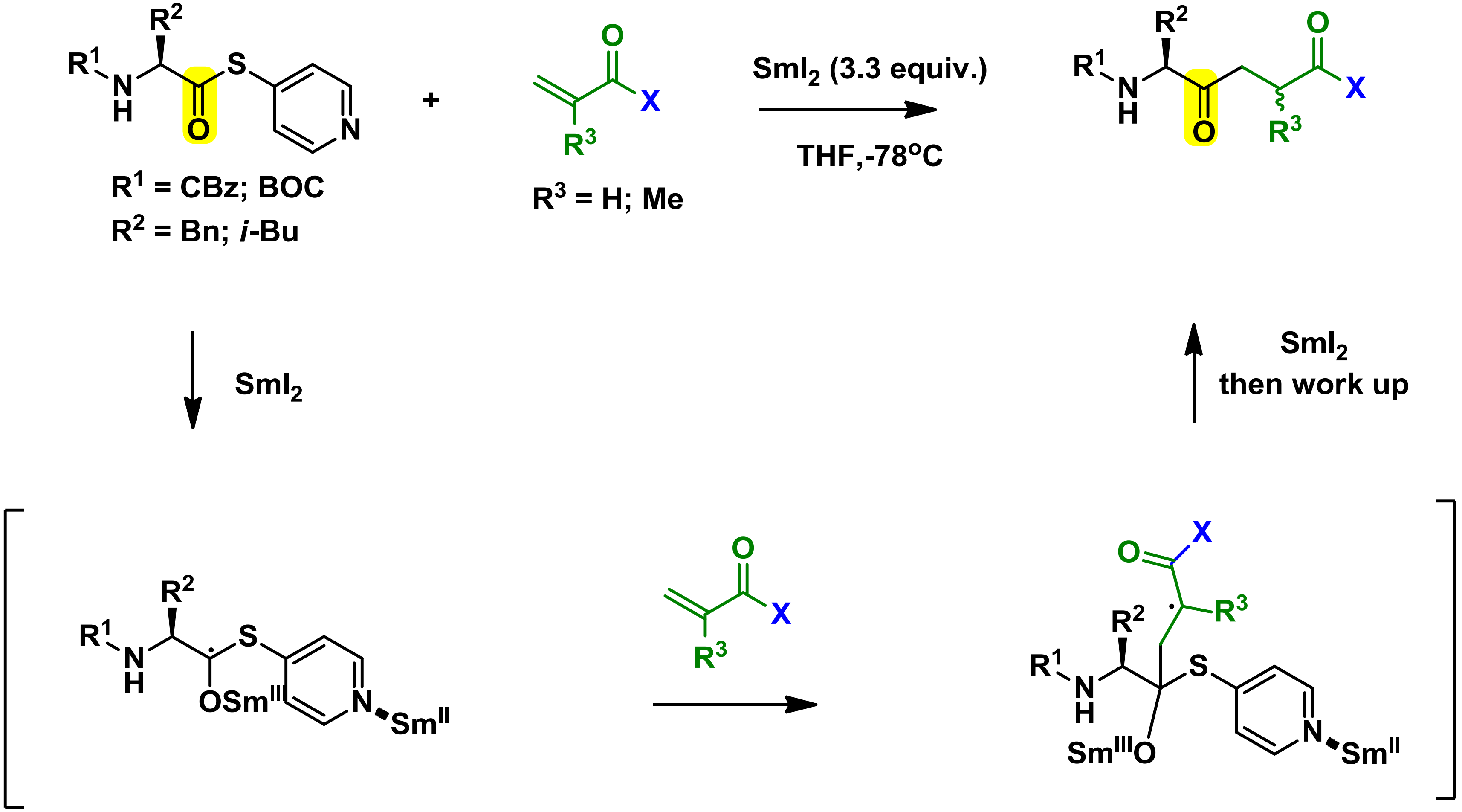
54%



51%

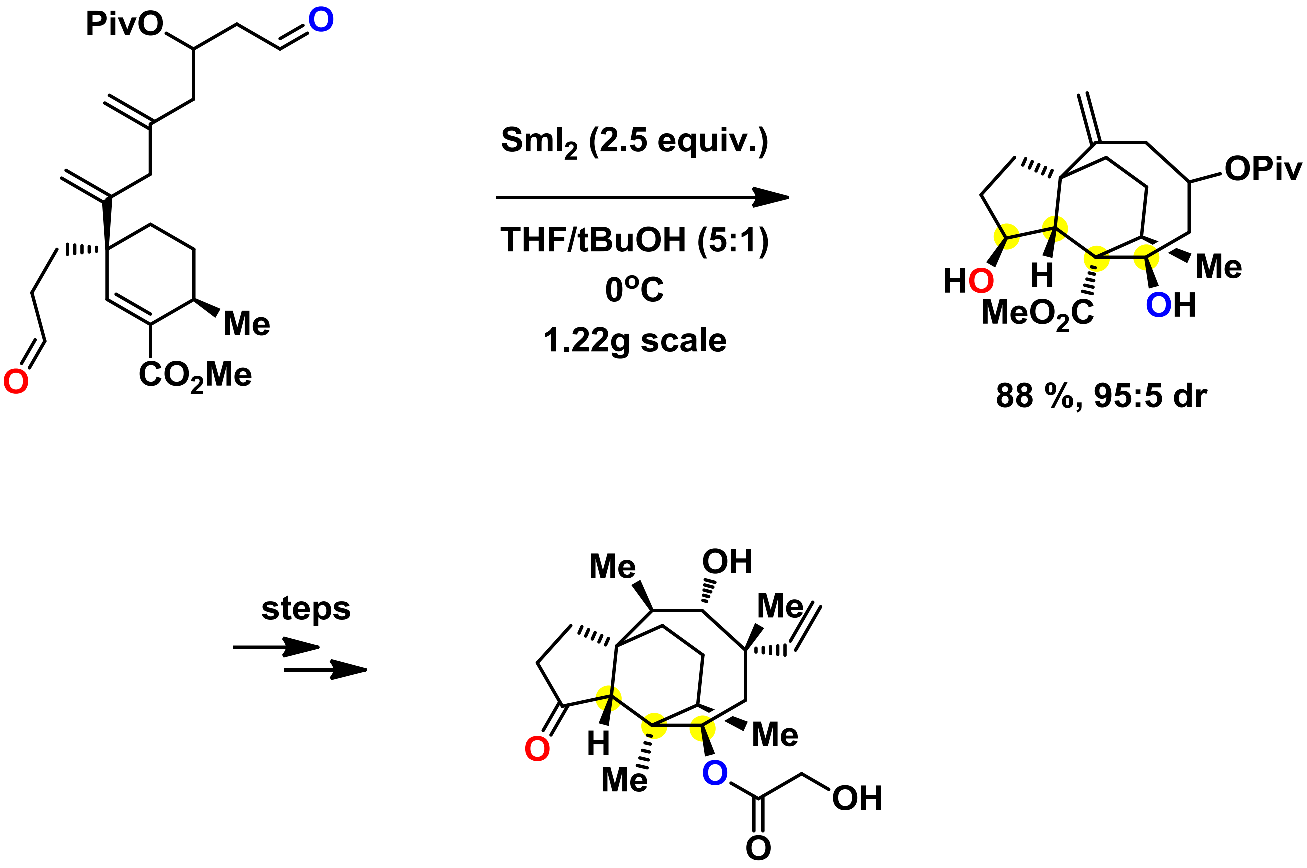
Blakskjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2003**, *125*, 4030
Mikkelsen, L. M.; Skrydstrup, T. *Tetrahedon* **2003**, *59*, 10541.

♣ *Intermolecular Cross-Coupling of Ketyl Radicals with Alkenes*



Application

in the Total Synthesis of (+)-Pleuromutilin



SmI_2 (2.5 equiv.)

THF/tBuOH (5:1)

0°C

1.22g scale

88 %, 95:5 dr

steps

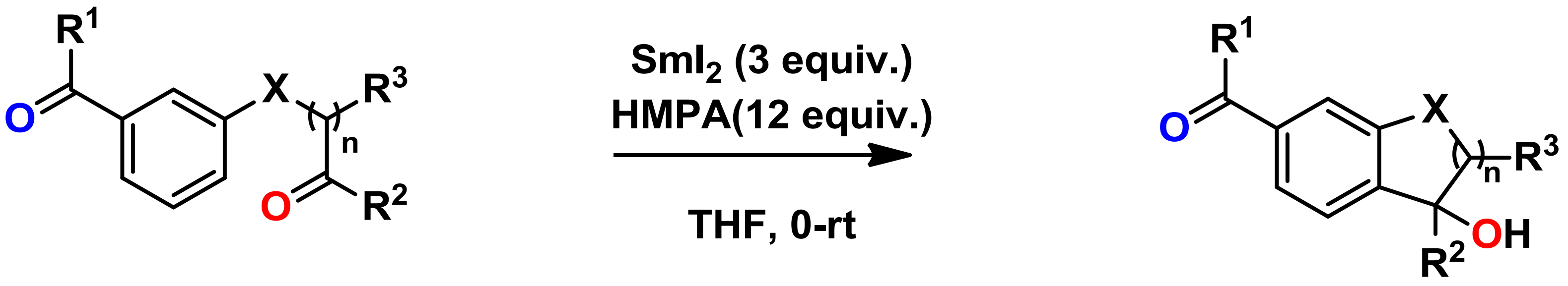
(+)-Pleuromutilin

Fazakerley, N. J.; Helm, M. D.; Procter, D. J. *Chem.- Eur. J.* **2013**, *19*, 6718

II- Cross-Coupling via Radical Intermediates

- Cross-Coupling of Ketyl Radicals with Arenes

Intramolecular 5-exo-Trig and 6-exo-Trig Ketyl/Aryl Cross-Couplings



SmI_2 (3 equiv.)
HMPA(12 equiv.)

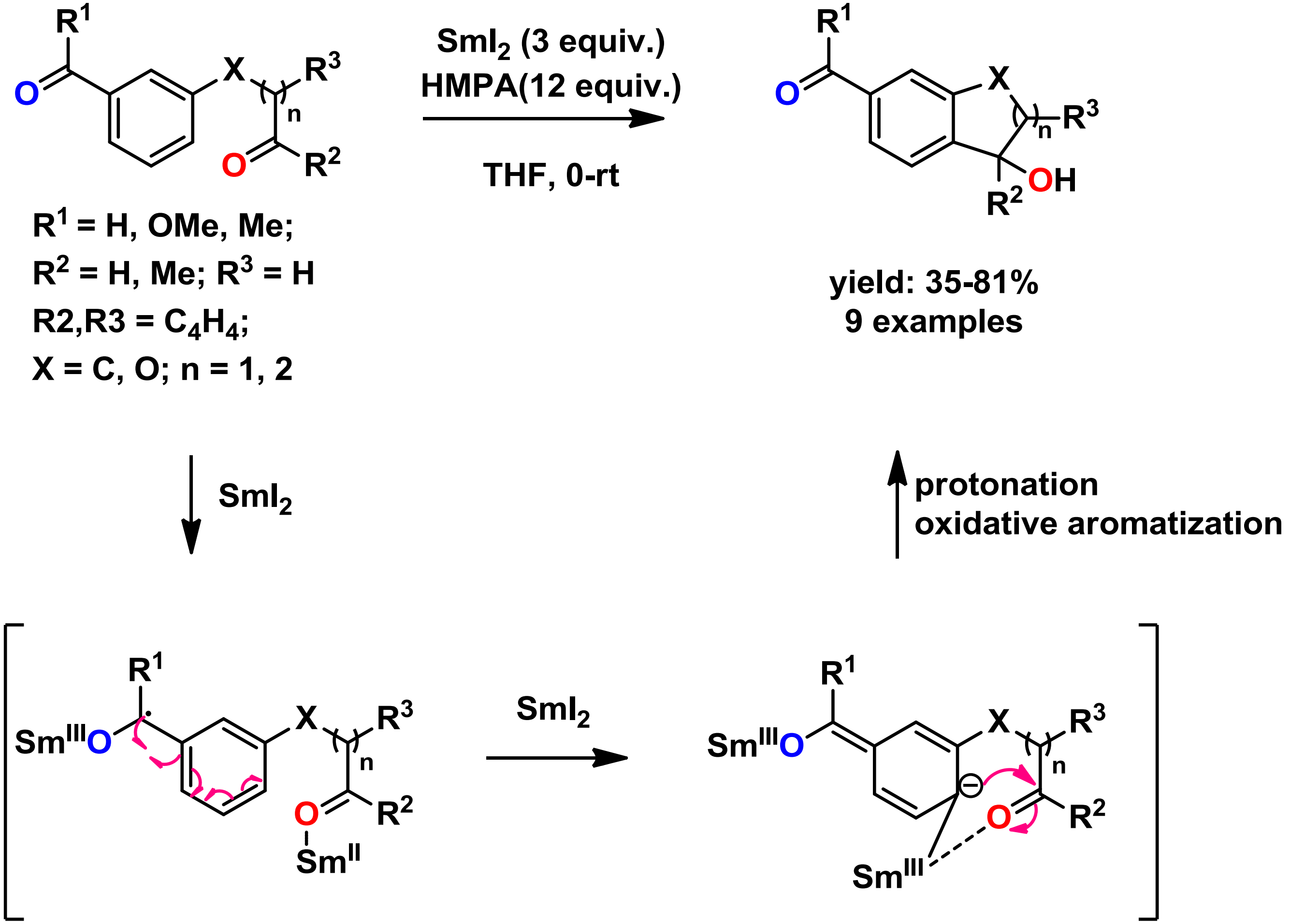
THF, 0-rt

R^1 = H, OMe, Me;
R^2 = H, Me; R^3 = H
R2,R3 = C_4H_4;
X = C, O; n = 1, 2

yield: 35-81%
9 examples

Wefelscheid, U. K.; Berndt, M.; Reissig, H.-U. *Eur. J. Org. Chem*. **2008**, 3635
Montanari, P.; Valenti, P. J. *Heterocycl. Chem.* **1992**, *29*, 259
Kuo, C. W.; Fang, J. M. *Synth. Commun*. **2001**, *31*, 877

Intramolecular 5-exo-Trig and 6-exo-Trig Ketyl/Aryl Cross-Couplings

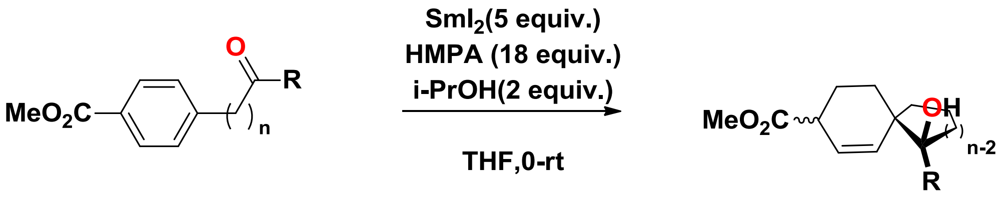


R^1 = H, OMe, Me;
R^2 = H, Me; R^3 = H
R2,R3 = C_4H_4;
X = C, O; n = 1, 2

yield: 35-81%
9 examples

Wefelscheid, U. K.; Berndt, M.; Reissig, H.-U. *Eur. J. Org. Chem*. **2008**, 3635
Montanari, P.; Valenti, P. J. *Heterocycl. Chem.* **1992**, *29*, 259
Kuo, C. W.; Fang, J. M. *Synth. Commun*. **2001**, *31*, 877

***para*-substituted benzoates*:**



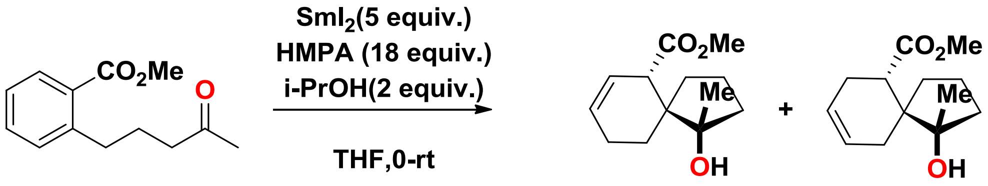
SmI_2(5 equiv.)
HMPA (18 equiv.)
i-PrOH(2 equiv.)

THF,0-rt

R = H, alkyl
n = 3, 4

yield: 33-93%
dr: 1:1- 1:2
5 examples

***ortho*-substituted benzoates*:**



SmI_2(5 equiv.)
HMPA (18 equiv.)
i-PrOH(2 equiv.)

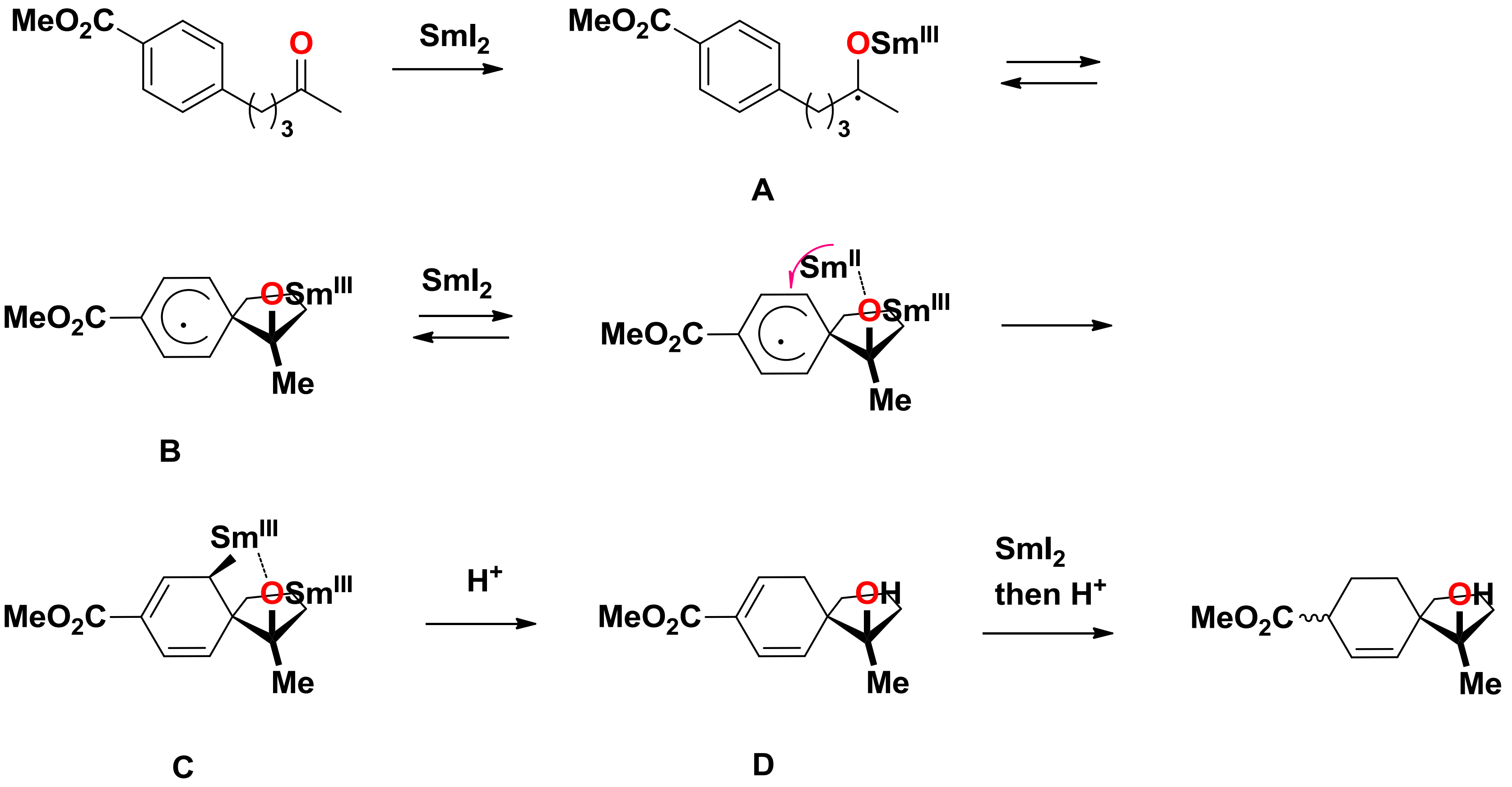
THF,0-rt

D   ***E***

(56%, D:E = 7:1)

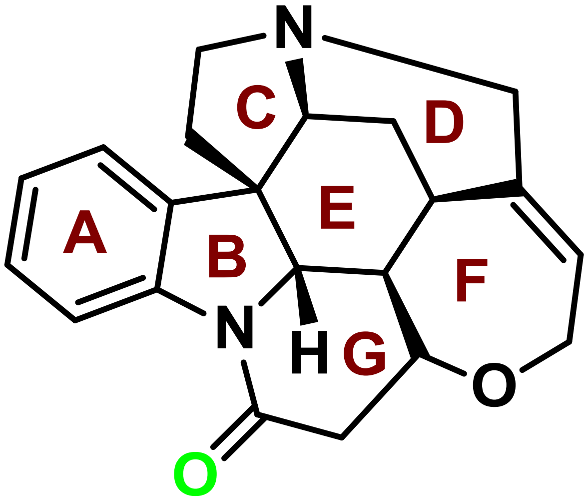
Ohno, H.; Maeda, S. I.; Tanaka, T. *Chem. Commun*. **2002**, 316.

Mechanism of *5-exo-Trig and 6-exo-Trig Ketyl/Aryl Cross-Couplings*



Ohno, H.; Maeda, S. I.; Tanaka, T. *Chem. Commun*. **2002**, 316.

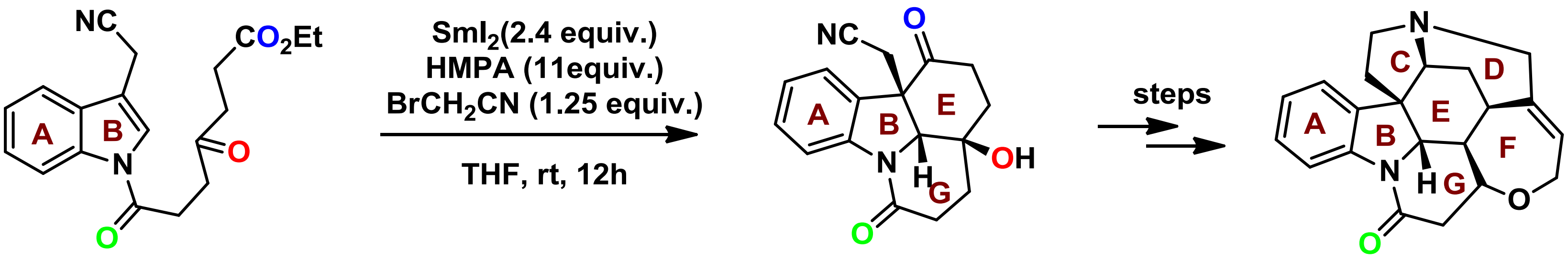
Application



strychnine

Application

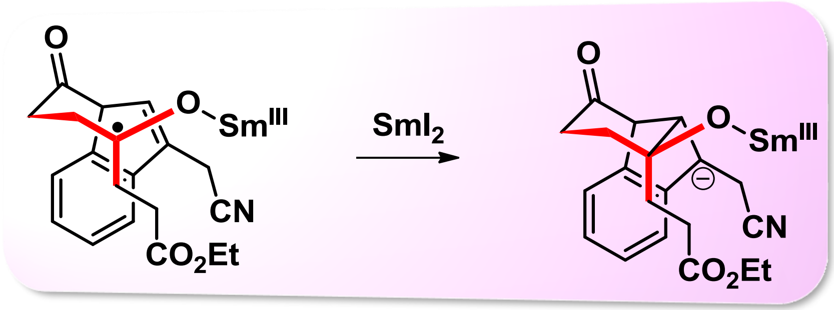
6-exo-Trig/Intramolecular Acylation Cascade in the Total Synthesis of *Strychnine*



77%, >95:5 dr

strychnine

9 steps overall

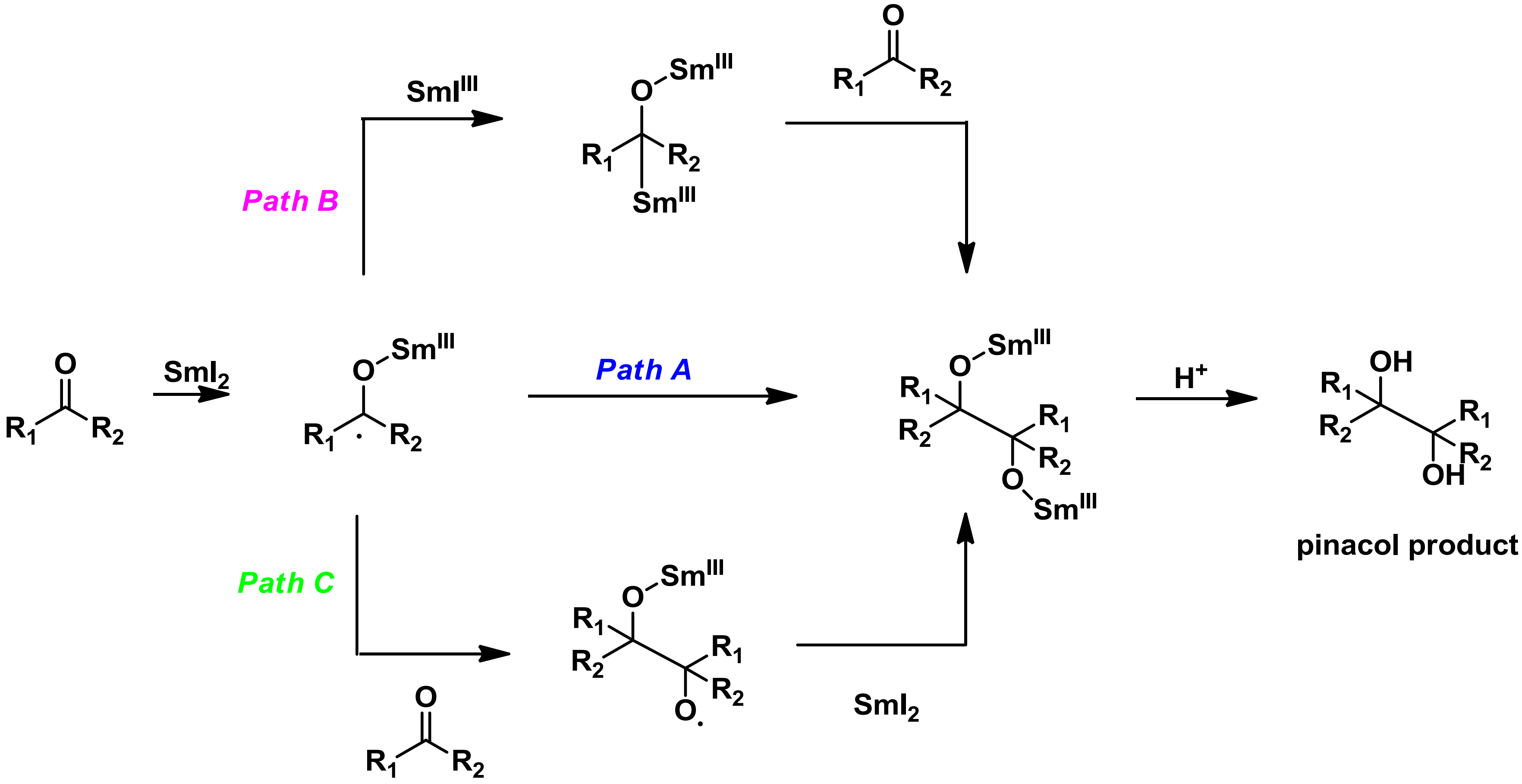


Beemelmanns, C.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **2010**, *49*, 8021

II- Cross-Coupling via Radical Intermediates

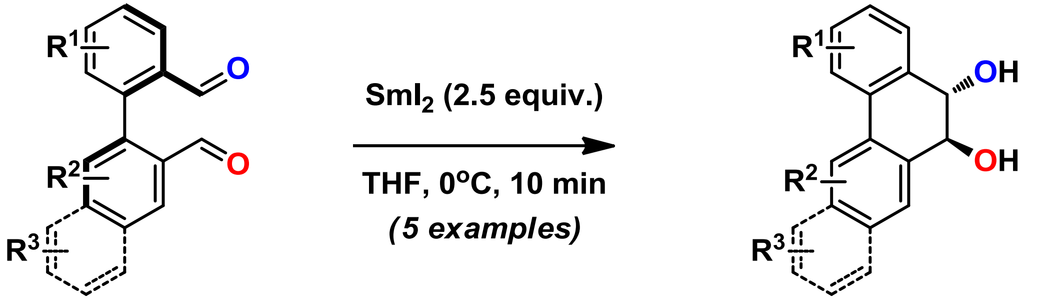
- Pinacol-Type Couplings

mechanism :



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

Chirality Transfer via Aldehyde/Aldehyde Pinacol Coupling



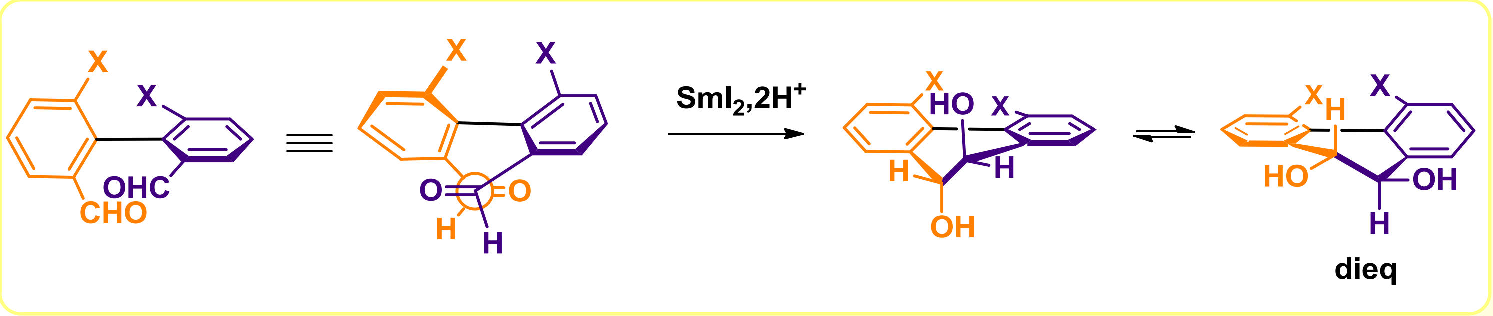
SmI_2 (2.5 equiv.)

THF, 0°C, 10 min

(5 examples)

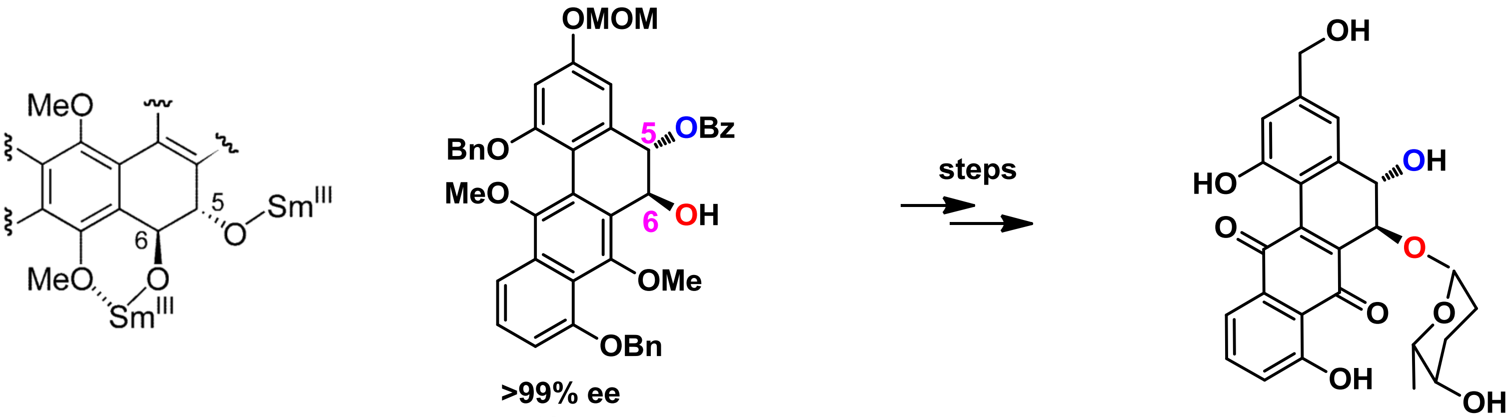
>99% ee

71-99% yield



Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.***1999**, *38*, 1226
Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed*. **2004**, *43*, 3167

Chirality Transfer via Aldehyde/Aldehyde Pinacol Coupling



>99% ee
86% yield

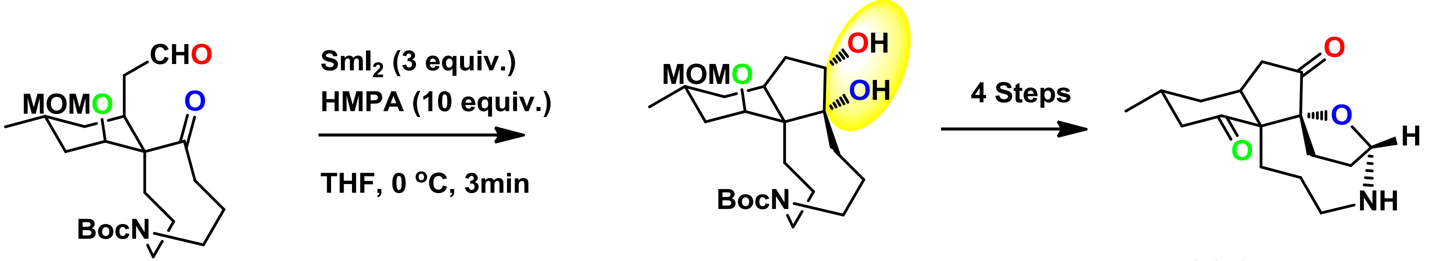
quenching reaction with (BzCl,1.5 equiv.)

TAN-1085

Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.*1999, *38*, 1226
Ohmori, K.; H.; Suzuki, K. *Angew. Chem., Int. Ed*. **2004**, *43*, 3167

Aldehyde/Ketone Pinacol Coupling in the Total Synthesis of Lycopodium Alkaloids

Zhang and coworkers

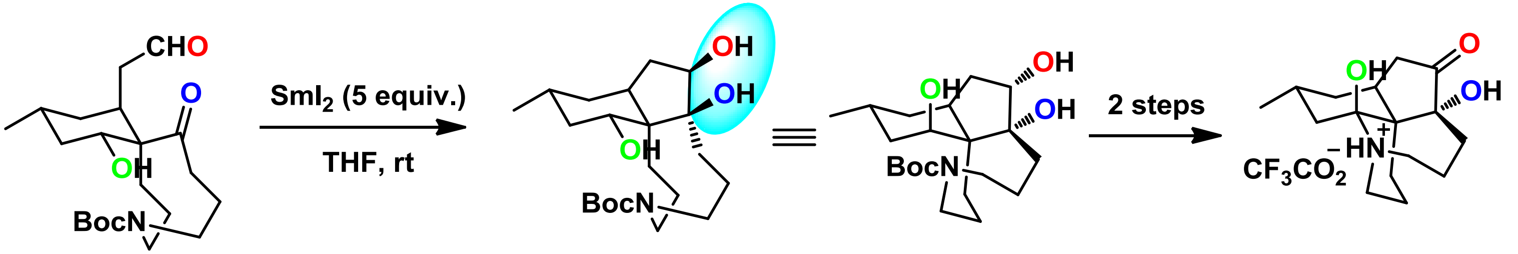


60 %, >95:5 dr

(+)-Sieboldine A

Zhang, X. M.; Meng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 3916.
Zhang, X. M.; Wang, S. H. *J. Org. Chem*. **2012**, *77*, 8174.

Lei and coworkers

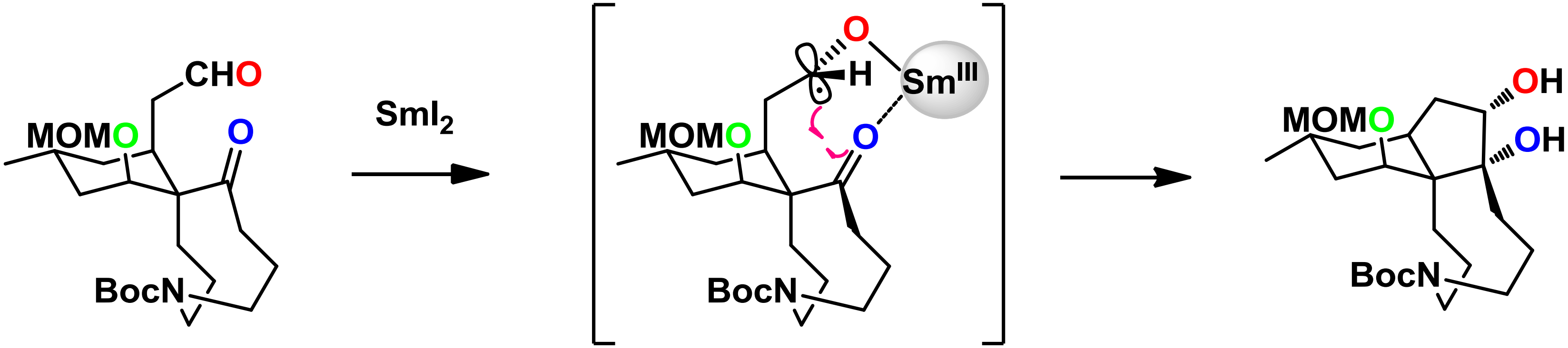


90 %, 4:1 dr

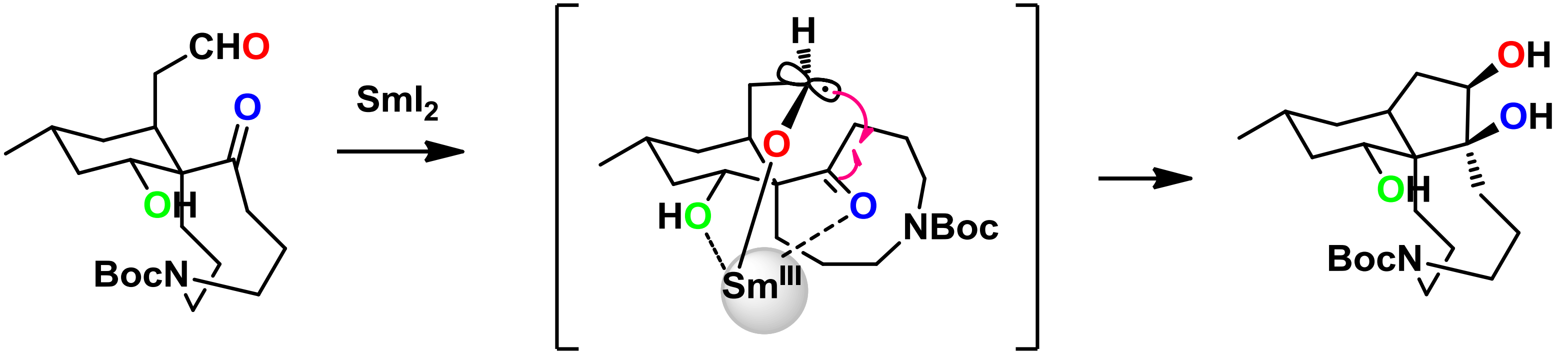
(+)-alopecuridine-TFA

Li, H.; Lei, X. *Angew. Chem., Int. Ed*. **2012**, *51*, 491.
Li, H.; Lei, X. *J. Org. Chem*. **2013**, *78*, 800

Zhang and coworkers



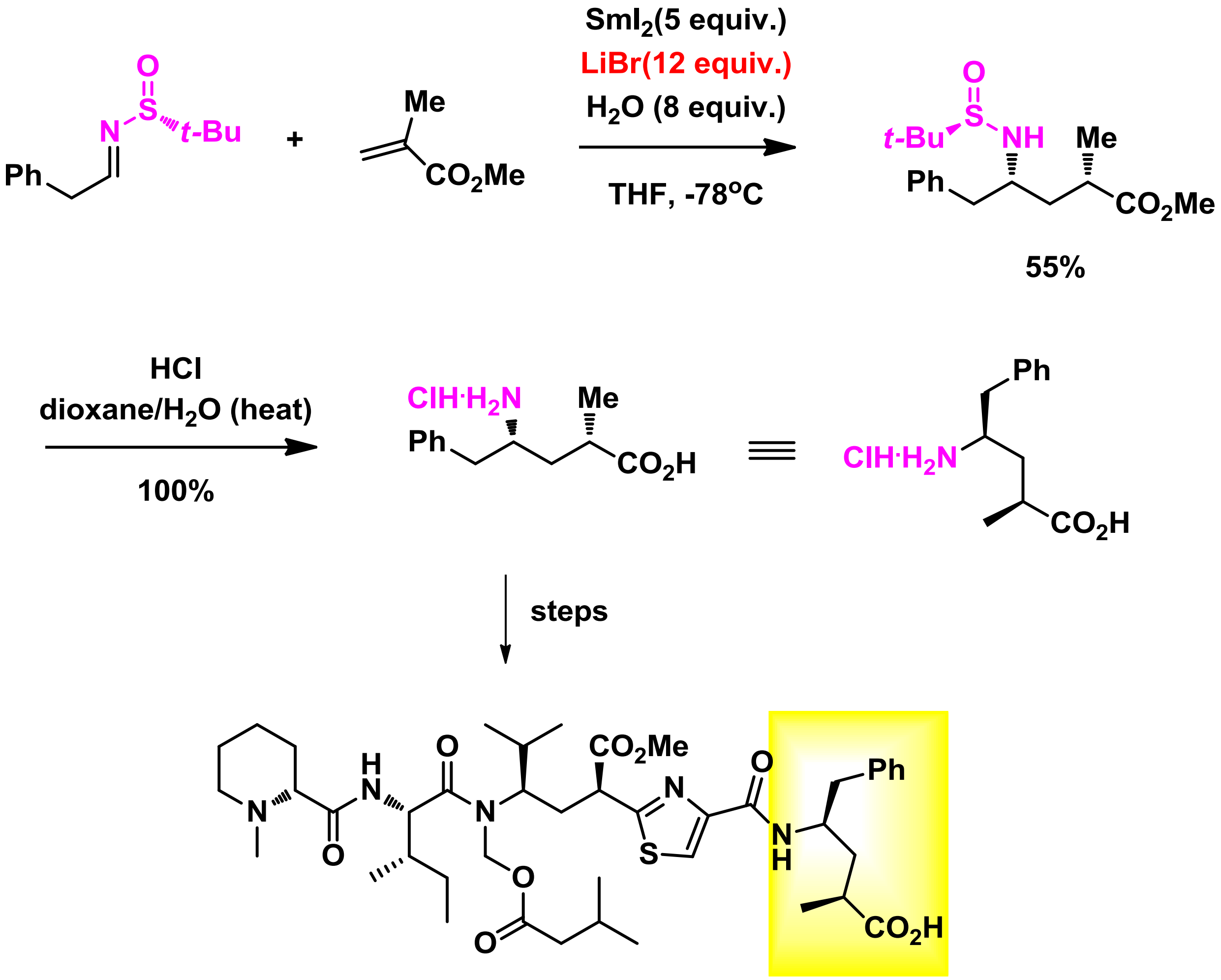
Lei and coworkers



II- Cross-Coupling via Radical Intermediates

-Cross-Coupling of Imines and Equivalents

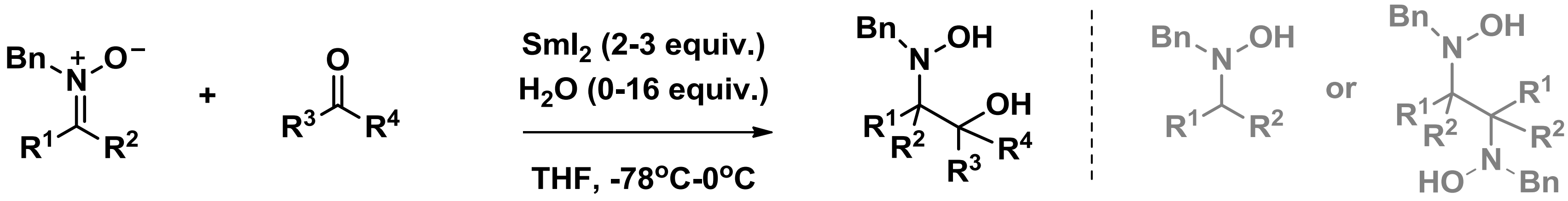
Cross-Coupling with C=C/ C≡C Bonds



tubulysin D

Peltier, H. M.; Ellman, J. A. *J.Am. Chem. Soc*. **2006**, *128*, 16018

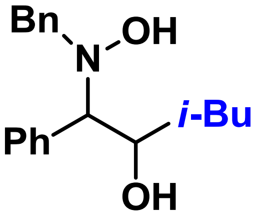
Cross-Coupling with C=O



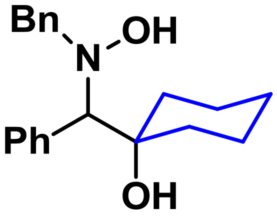
66-99 %

(18examples)

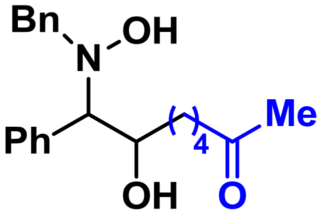
not observed



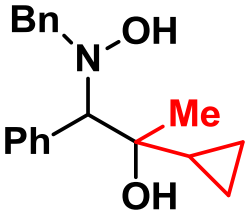
75%
50:50 dr



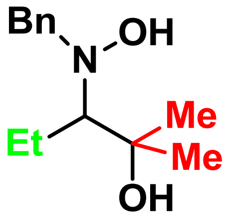
80%



80%
50:50 dr



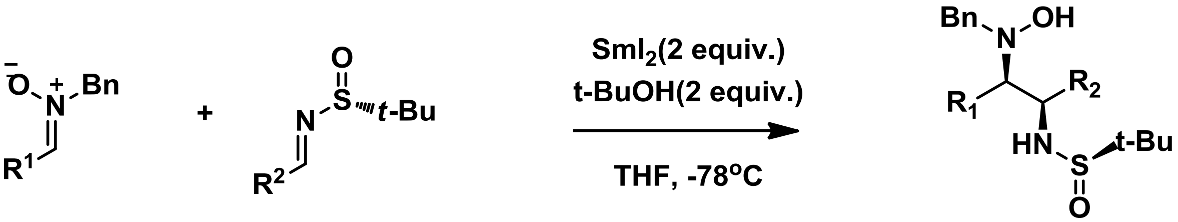
93%
50:50 dr



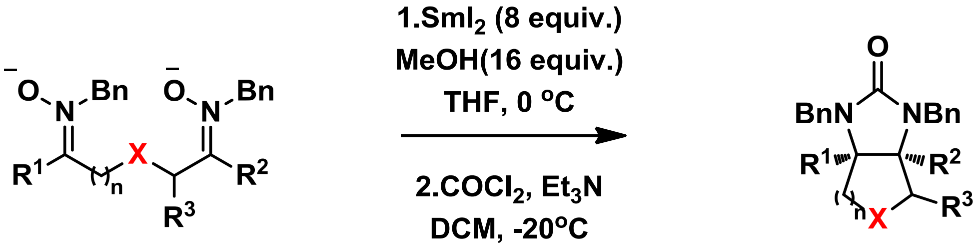
69%

Masson, G.; Vallée ,Y. *Angew. Chem., Int. Ed.* **2002**, *41*,1772

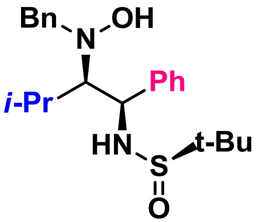
Cross-Coupling with C=N



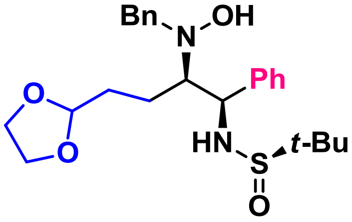
14 examples
22-85%



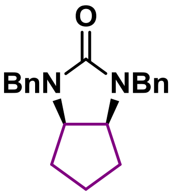
12 example
28-76%



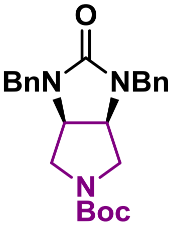
75 %
>95:5 dr



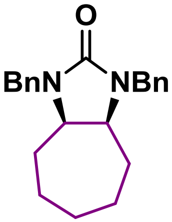
71 %
>90:10 dr



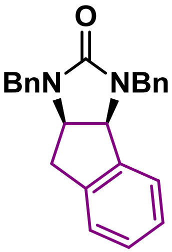
66%
>95:5 dr



59%
>95:5 dr



35%
>75:25 dr



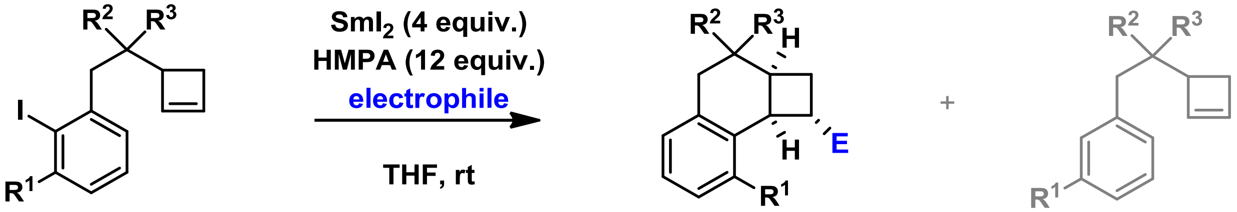
58%
80:20 dr

Zhong, Y. W.; Xu, M. H.; Lin, G. Q. *Org. Lett*. **2004**, *6*, 3953
Ebran, J. P.; Skrydstrup, T. *Chem. Commun*. **2005**, 5402

II- Cross-Coupling via Radical Intermediates

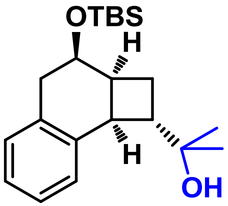
-Non-Ketyl Radical Cross-Coupling

- **Cross-Coupling of Aryl Iodides and Cyclobutenes Using SmI2/HMPA**

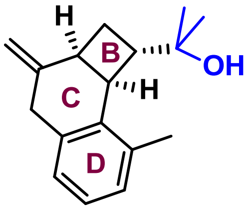


SmI_2 (4 equiv.)
HMPA (12 equiv.)
electrophile
THF, rt

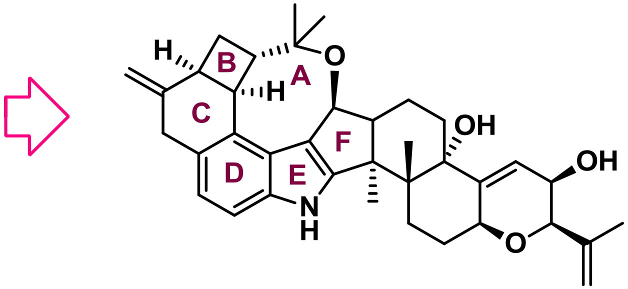
8 examples
40-60% yield



45%



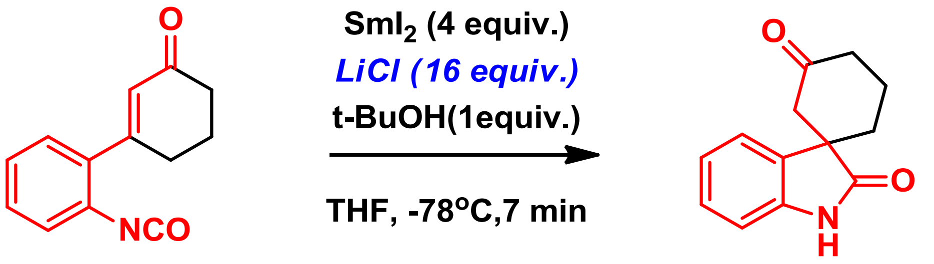
41%



Penitrem D

Rivkin, A.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419

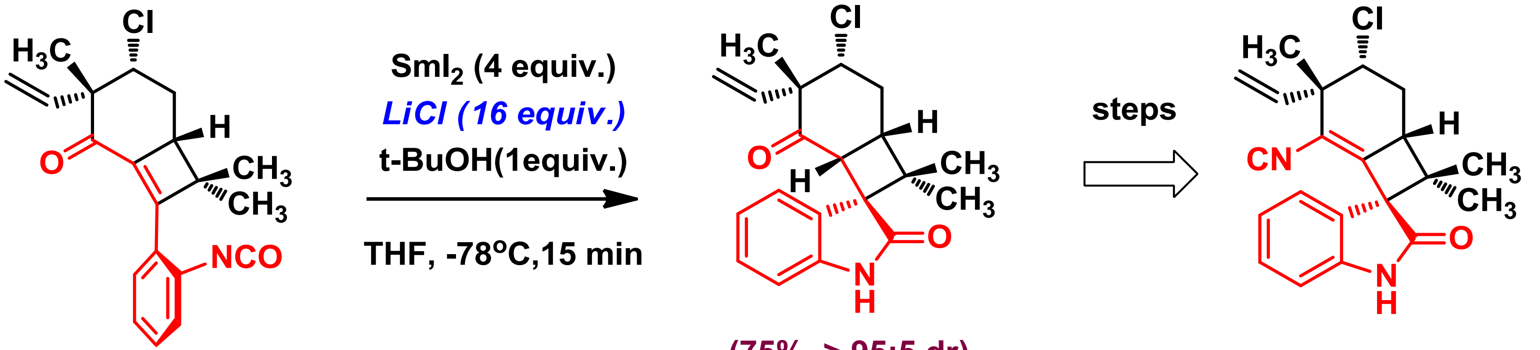
Cross-coupling of Radicals Generated from α,β- Unsaturated Carbonyls



SmI_2 (4 equiv.)
LiCl (16 equiv.)
t-BuOH(1equiv.)

THF, -78°C,7 min

88% (5% without LiCl)



SmI_2 (4 equiv.)
LiCl (16 equiv.)
t-BuOH(1equiv.)

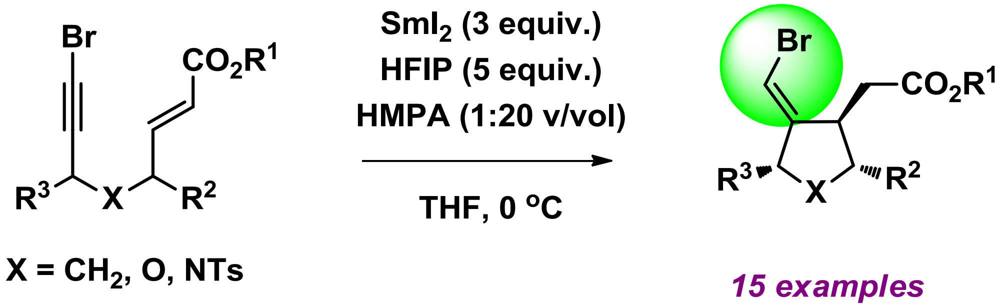
THF, -78°C,15 min

(75%, > 95:5 dr)

Welwitindolinone A Isonitrile

Ready, J. M.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270
Reisman, S. E.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087

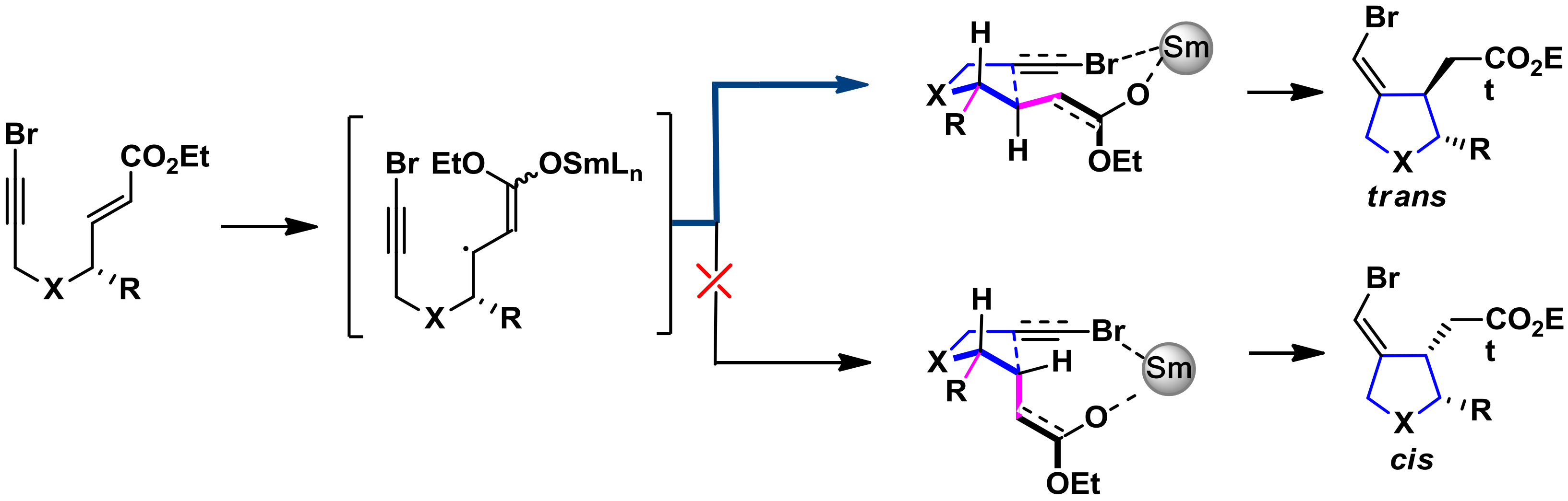
Cross-coupling of Radicals Generated from α,β- Unsaturated Carbonyls



SmI_2 (3 equiv.)
HFIP (5 equiv.)
HMPA (1:20 v/vol)
THF, 0 °C

X = CH_2, O, NTs

15 examples
60-91%
up to >99:1 dr



Takahashi, K.; Honda, T. *Org. Lett*. **2010**, *12*, 3026

III- Conclusion and outlook

- Additives have a remarkable effect
- a wide use in the synthesis of complex natural products

- the development of new intermolecular cross couplings
- the design of new ligands

Thank you for your attention