Alois Fürstner: Applying Organometallic Chemistry in Total Synthesis

Chris Regens
Denmark Group Meeting

April 22, 2008

Alois Fürstner

- Born in 1962 in Bruck an der Mur (Austria)
- In 1987 he received his doctorate degree from the Technical University in Graz working Prof. H. Weidmann
- Postdoctoral work with W. Oppolzer at the University of Geneva
- He completed his 'habilitation' back in Graz in 1993
- Later that year he started his independent career at the Max-Plank-Institut für Kolenforschung in Mülheim an der Rur (Germany)
- In 1998 he was promoted to director
- He is also affiliated with the University of Dortmund

Awards

Dozentenstipendium of the Fonds der Chemischen Industrie (1994), Leibniz Award (1999), IUPAC-Thieme Prize (2000), Arthur C. Cope Scholar Award (2002), Otto Bayer Prize (2006).

Alois Fürstner Research Interests: Tonight's Overview

New Synthetic Methods and Concepts for Catalysis

-Catalytic Nozaki-Hiyama-Kishi Reaction

-Titanium-induced Heterocycle Synthesis (McMurry)

-Boron Chemistry- 9-Methoxy-9-BBN Variant of the Suzuki Reaction

-*N*-Heterocyclic Carbenes and Silylenes

-Iron Catalyzed Cross-Coupling

-Platinum and Gold Cycloisomerizations

Alkene Metathesis

-Ring Closing Metathesis (RCM)

-Application of RCM in Total Synthesis

-Metathesis in $scCO_2$

-Development of Alternative RCM Catalysts

Alkyne Metathesis

-Ring Closing Metathesis (RCAM)

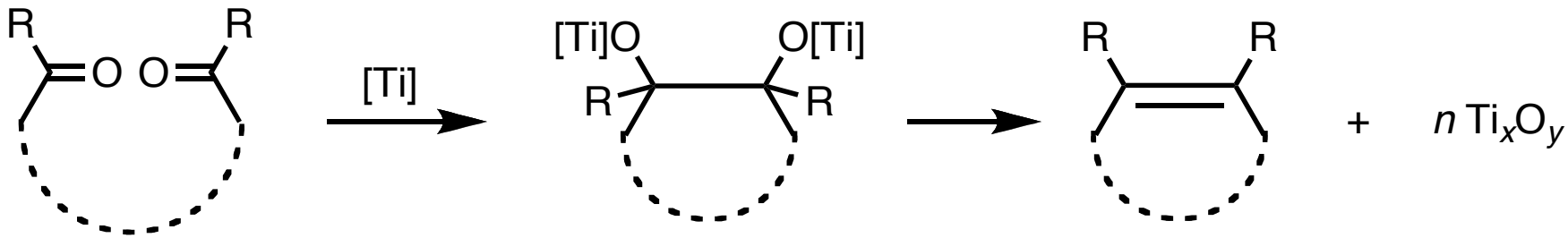
-Application of RCAM in Total Synthesis

-Synthesis of Metalla-Macrocycles

-Application of RCAM in the Synthesis of Materia

-Catalyst Development

Background: Expanding the "McMurray Reaction"

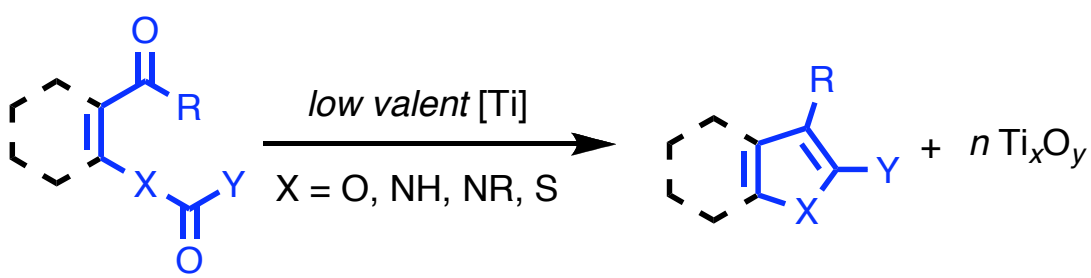


- In the 1970's Mukaiyama, Tyrilk, and McMurray made the discovery that low valent titantium [Ti] effects the coupling of aldehydes and ketones to alkenes.

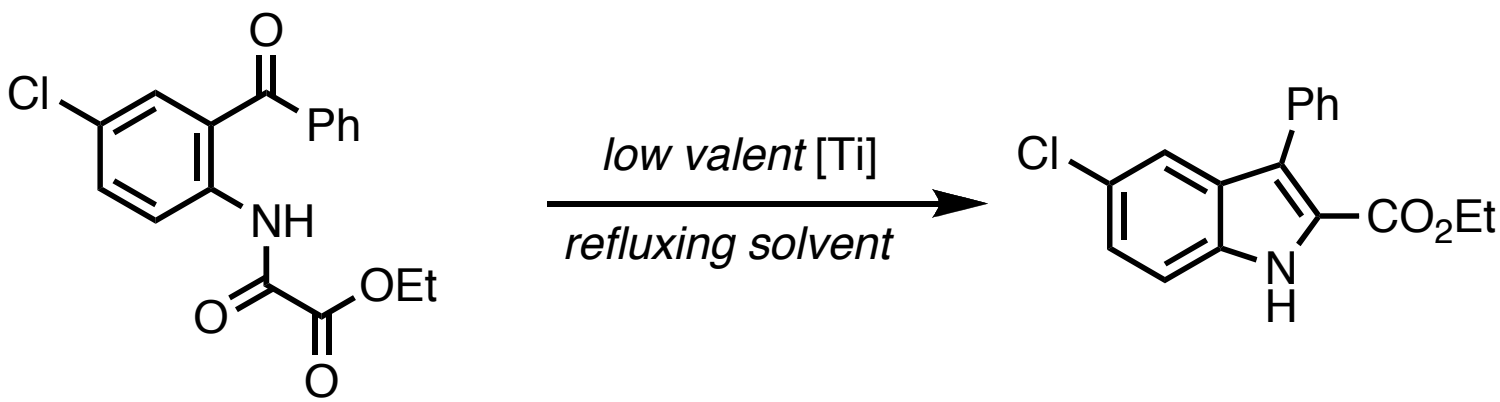
- The active reagent could be prepared by reduction of $TiCl_x$ with the appropriate reducing agent (K, Na, Li, Zn, Zn(Cu), Mg, Mg(Hg), C_8K, $LiAlH_4$, etc).

- Bogdanovic and Bolte demonstrated that reduction to a low-valent species ($TiCl_2$), with zinc, occurs only in the presence of a carbonyl compound (i.e. 'instant method'). *The Lewis-acidic $TiCl_3$ must first coordinate to the Lewis-basic carbonyl group and then reduction occurs*

- Fuerstner applied this idea to the synthesis of heterocyclic compounds.



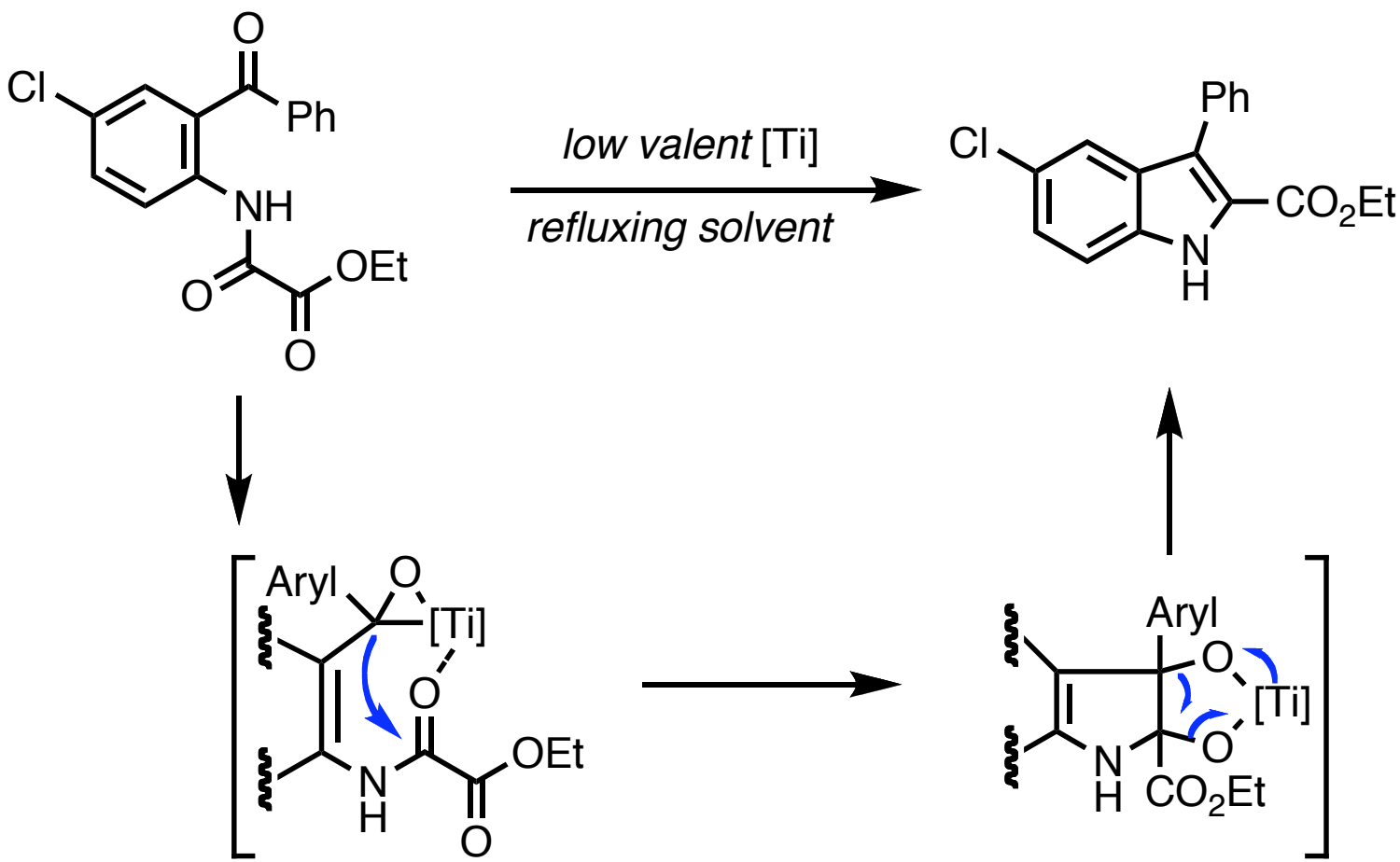
Reduction Heterocyclic Synthesis



[Ti]	Solvent	Isolated yield
$TiCl_3$ / 2 C_8K	DMF	93%
$TiCl_3$ / Zn "instant"	THF	87%
$TiCl_3$ cat., Zn, TMSCl	DME	79%

JOC, **1994**, *59*, 5215
JACS, **1995**, *117*, 4468
Org. Synth., **1999**, *76*, 14

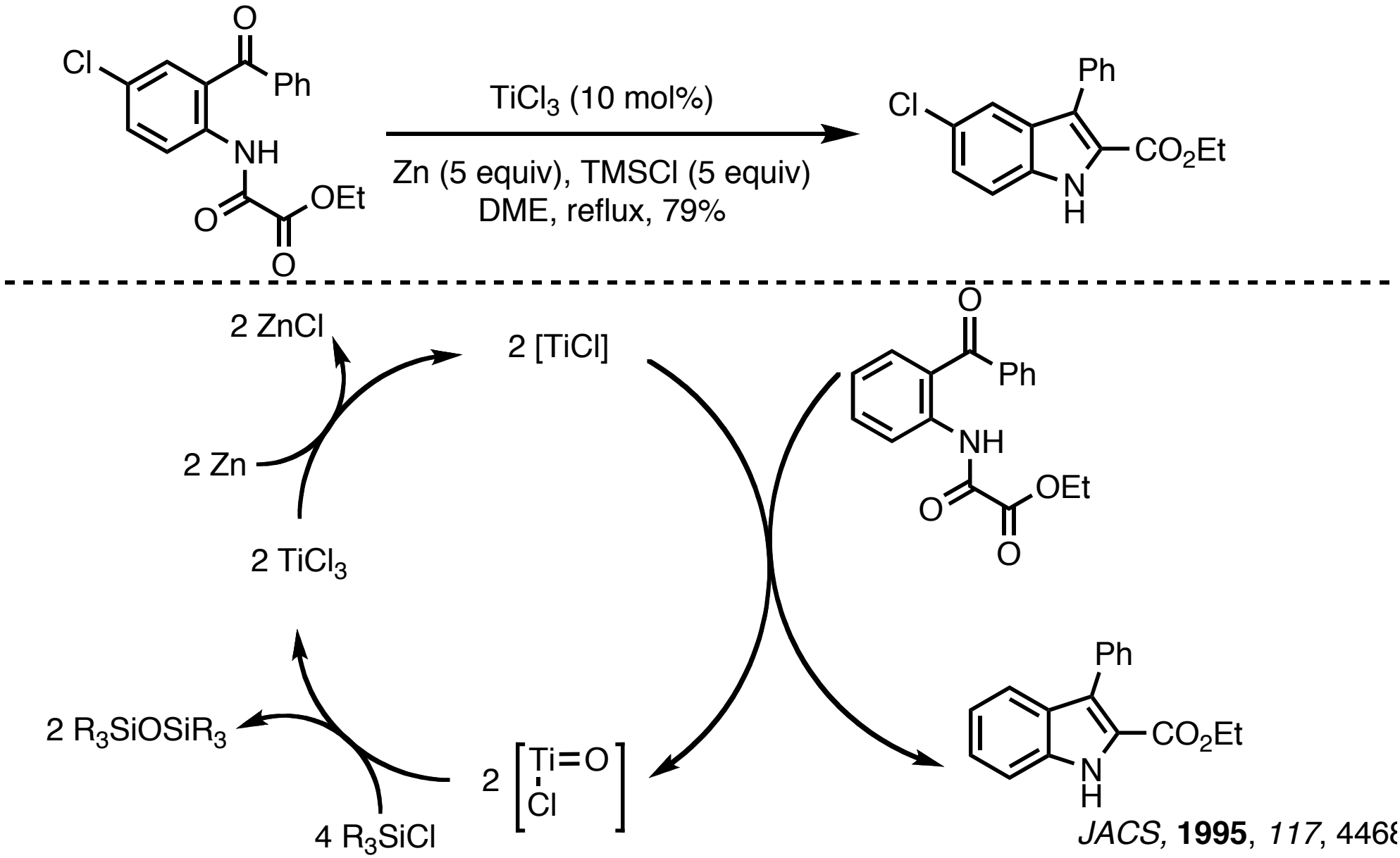
Reduction Heterocyclic Synthesis: Proposed Pathway



- Fuestner proposes a dianion mechanism for the fromation of azoles

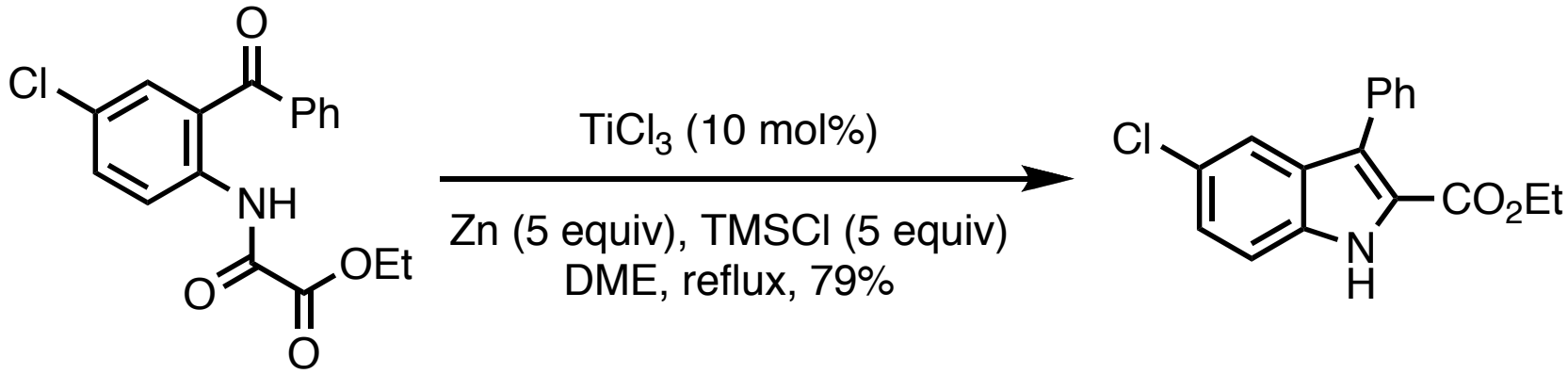
JOC, **1994**, *59*, 521

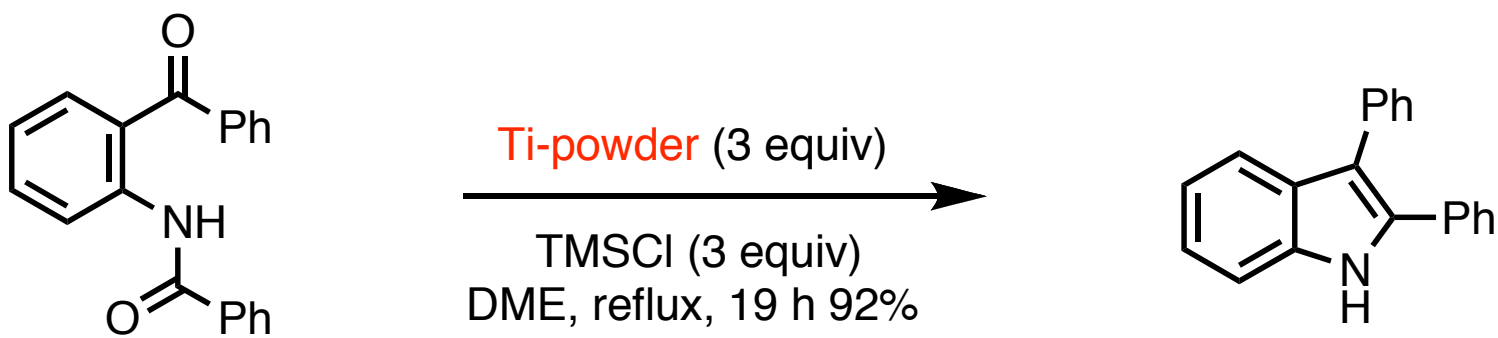
Reduction Heterocyclic Synthesis Using Catalytic [Ti]



JACS, **1995**, *117*, 4468

Reduction Heterocyclic Synthesis: Activation of Ti-Powder

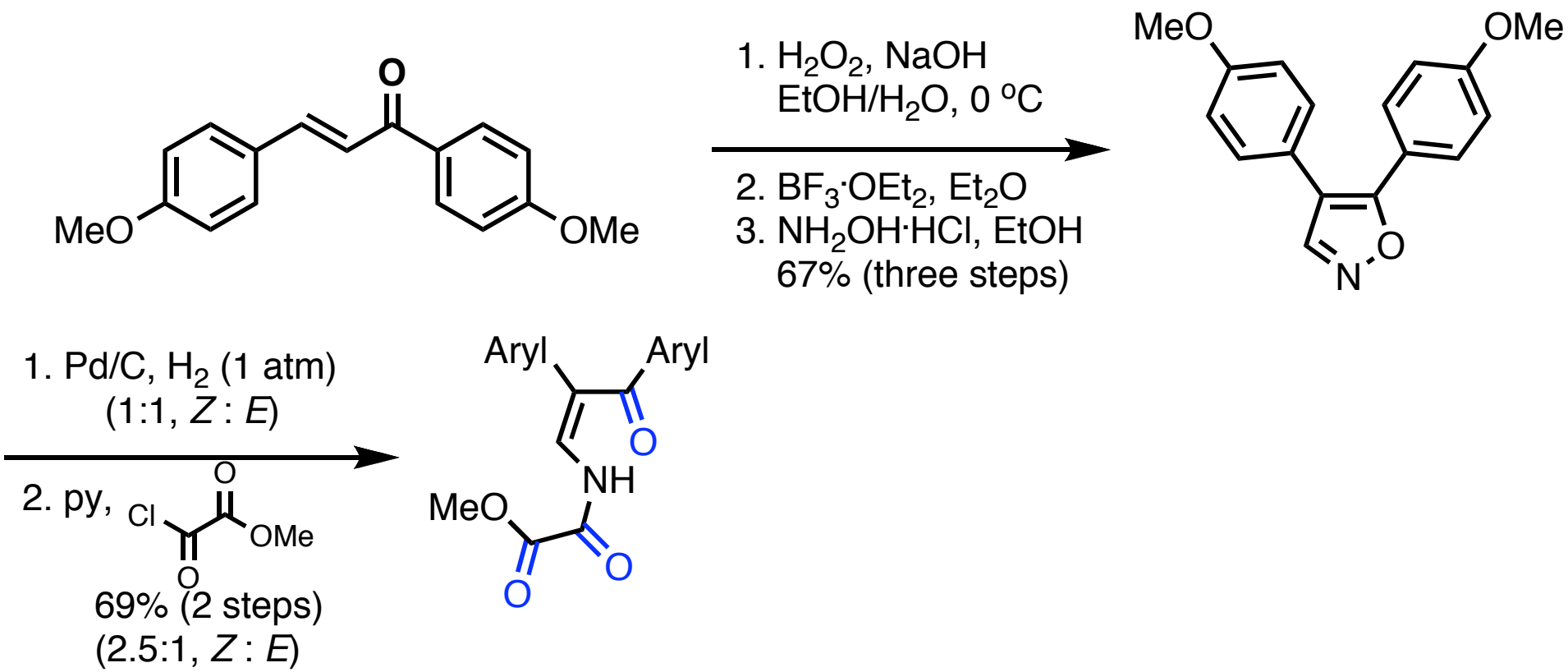




- Commercial powder could be activated using TMSCl for heterocycle synthesis and macrocyclizations without the normal precautions.

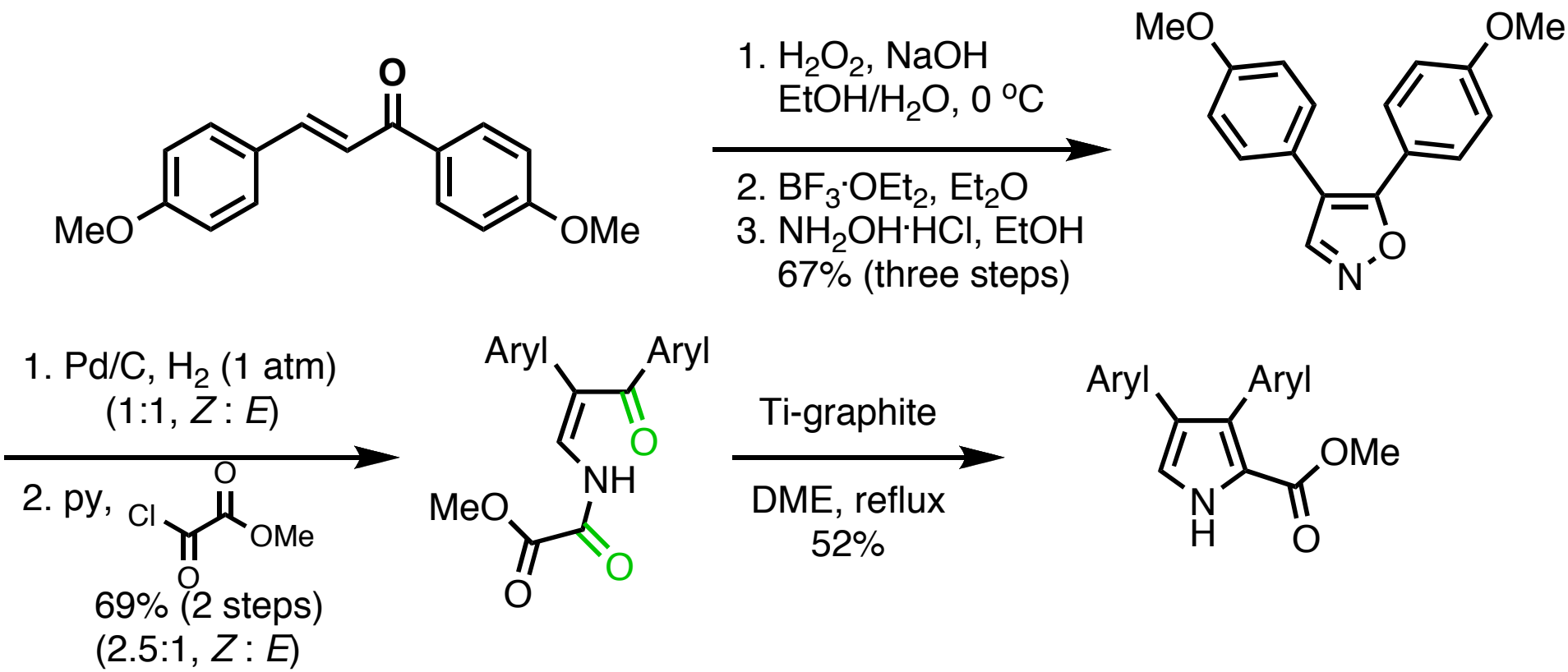
JACS, **1995**, *117*, 4468

Synthesis of Lukianol A: Preparation of the Amido-Enone



J. Org. Chem. **1995**, *60*, 6637-6641

Synthesis of Lukianol A: Key Reductive Coupling Event



J. Org. Chem. **1995**, *60*, 6637-6641

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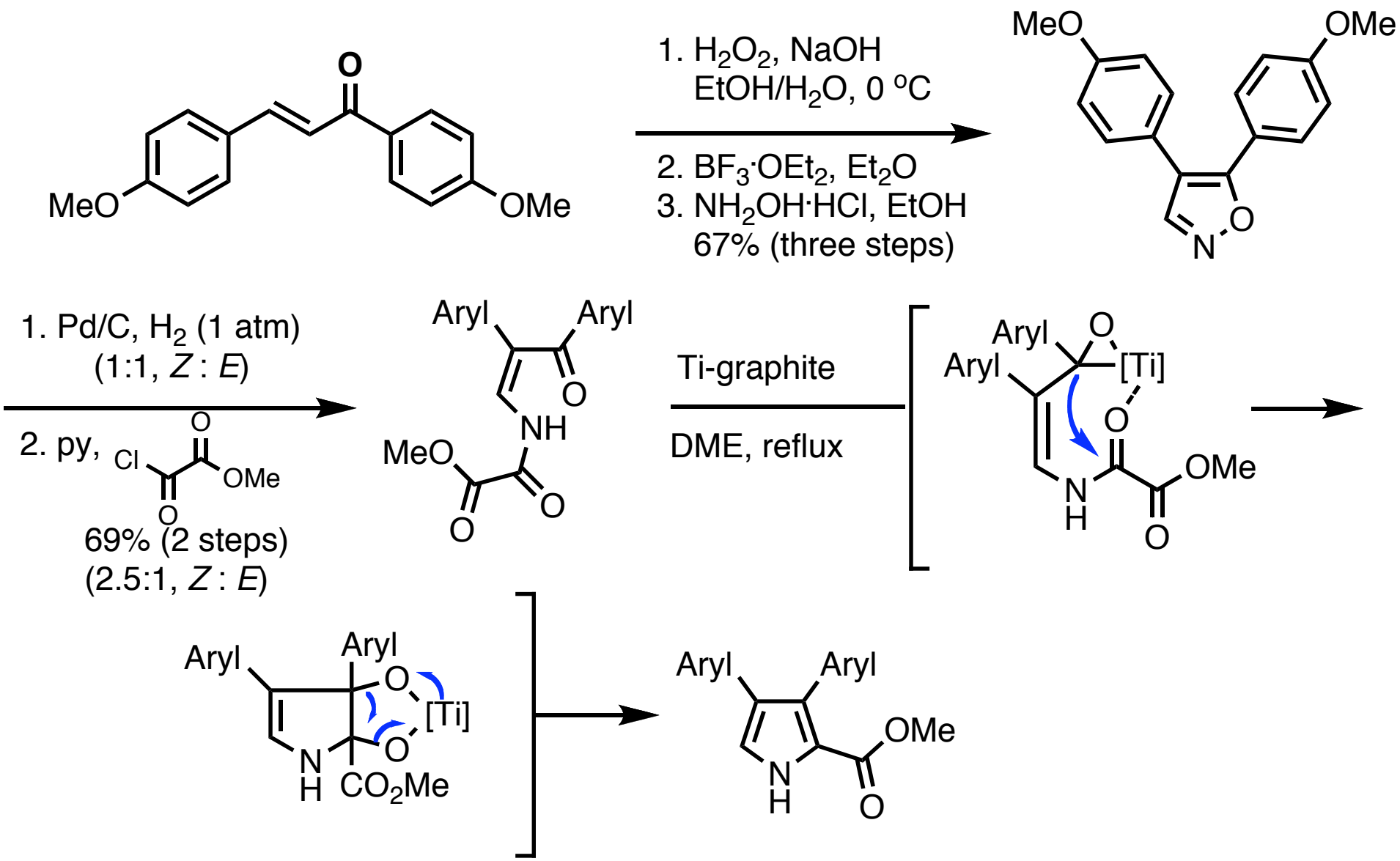
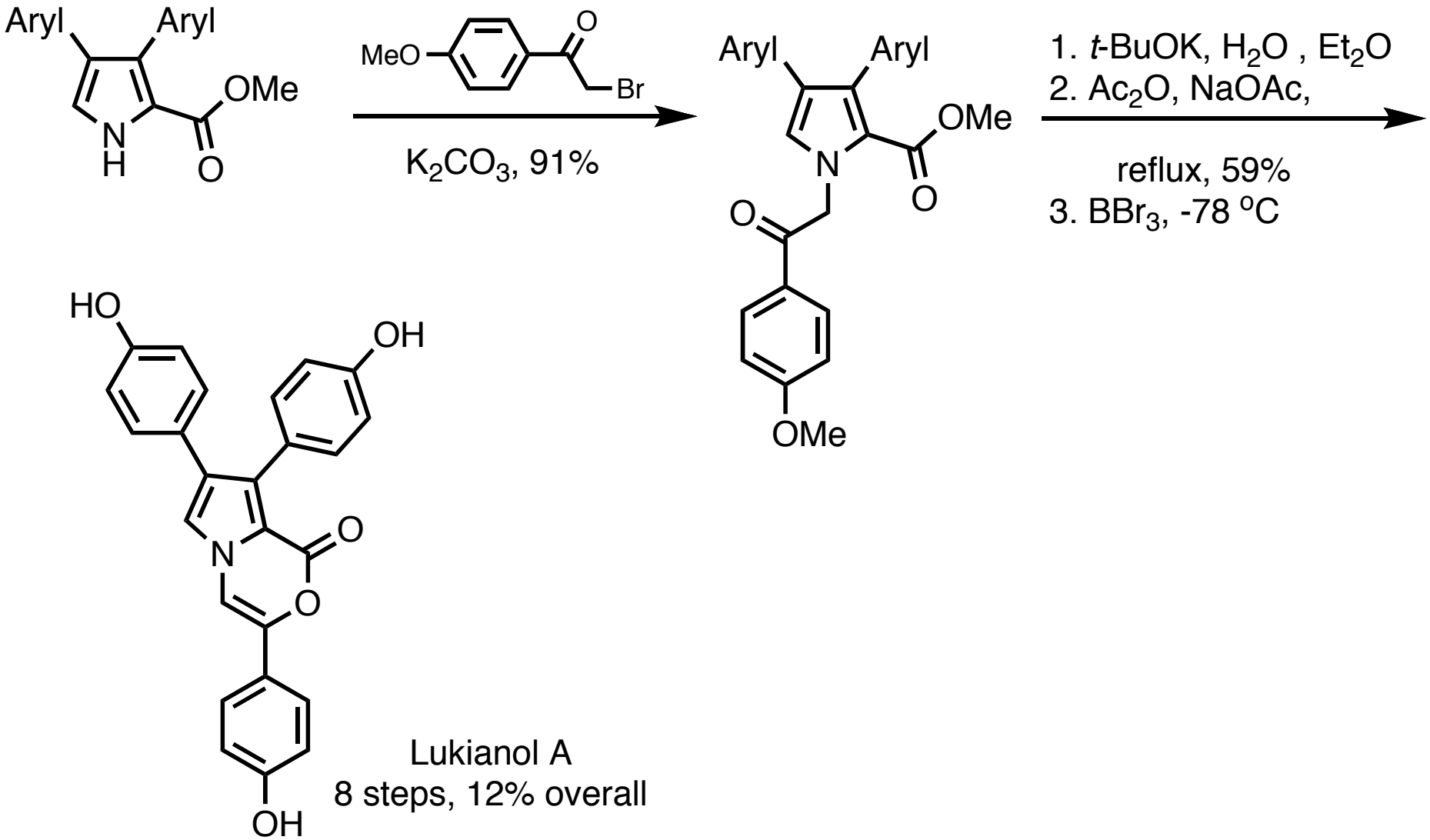
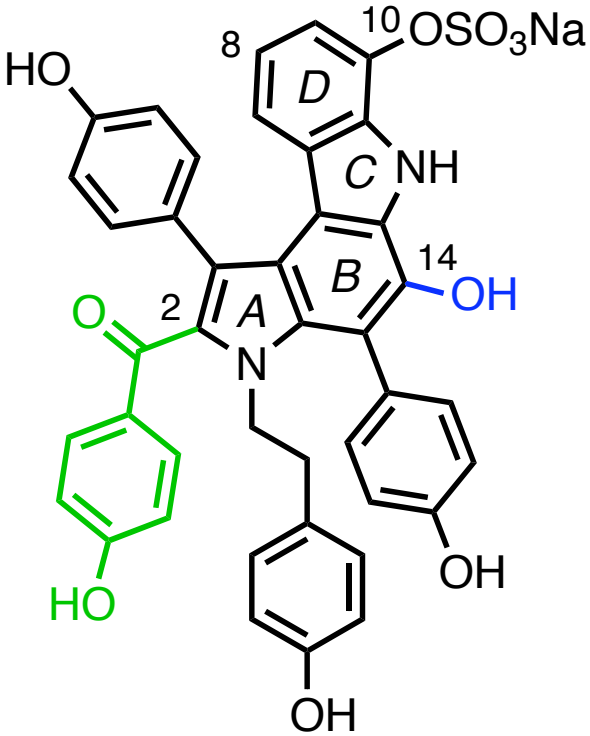


Synthesis of Lukianol A: Completing the Synthesis

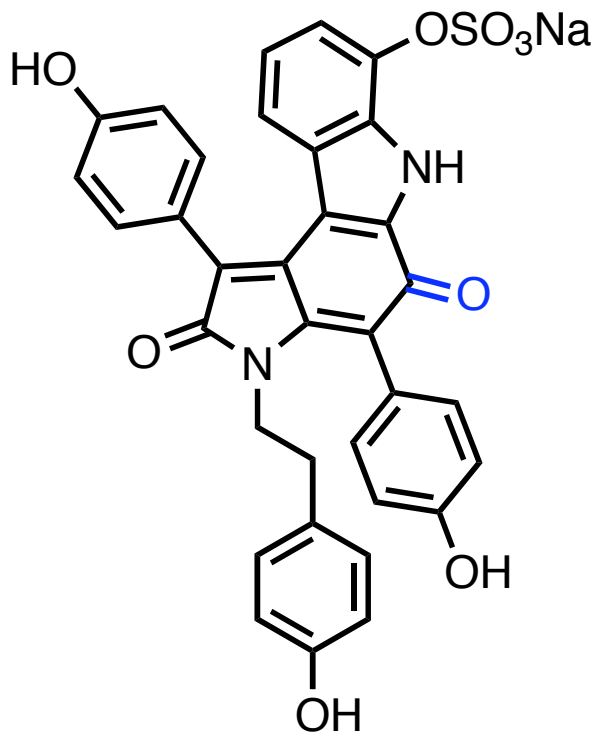


Lukianol A
8 steps, 12% overall

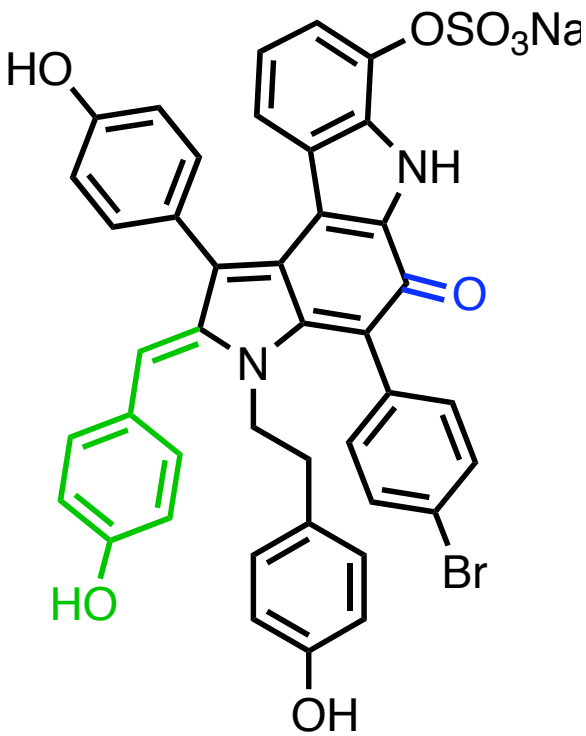
Total Synthesis of Dictyodendrins B, C, E



Dictyodendrin B



Dictyodendrin C

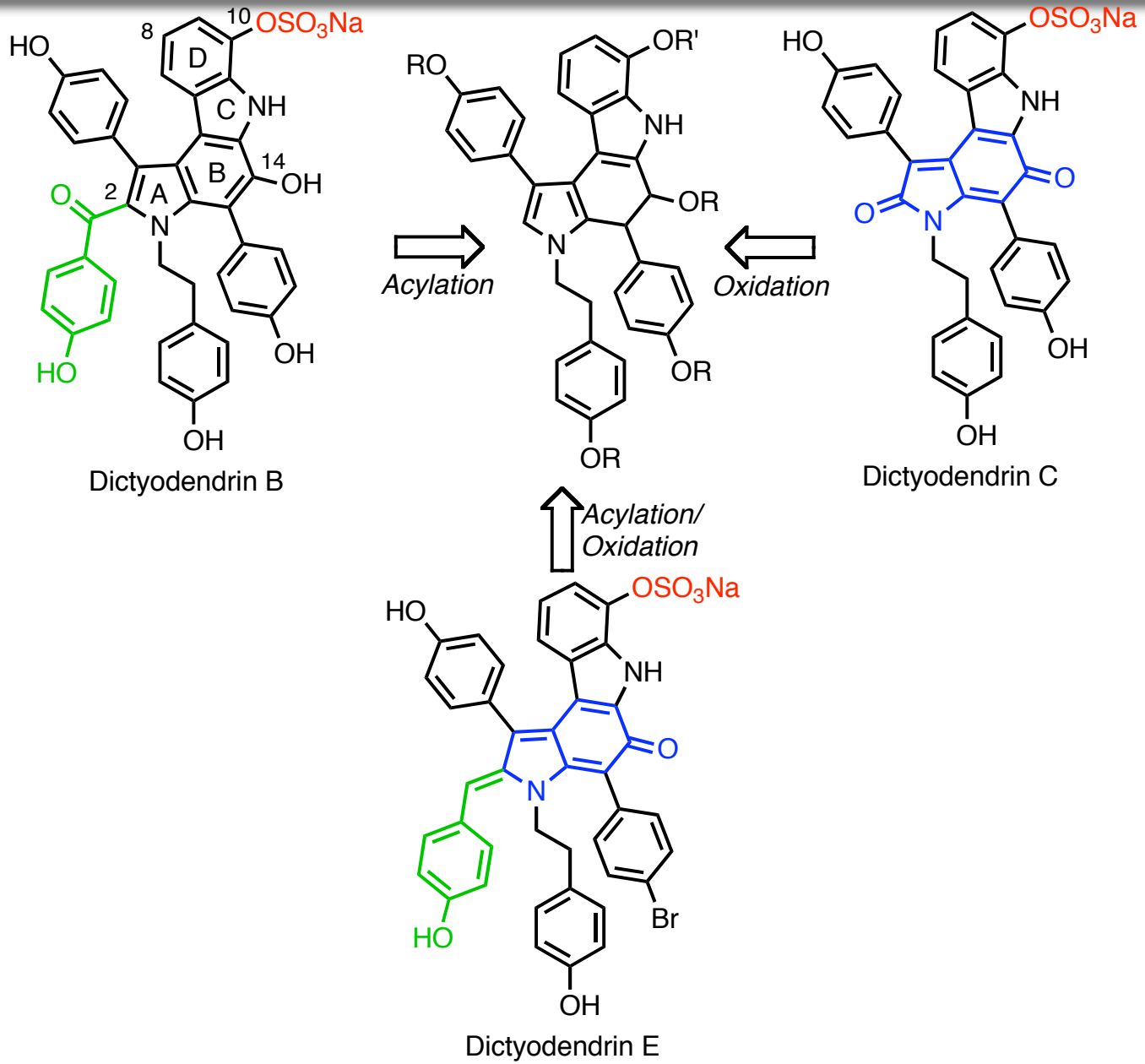


Dictyodendrin E

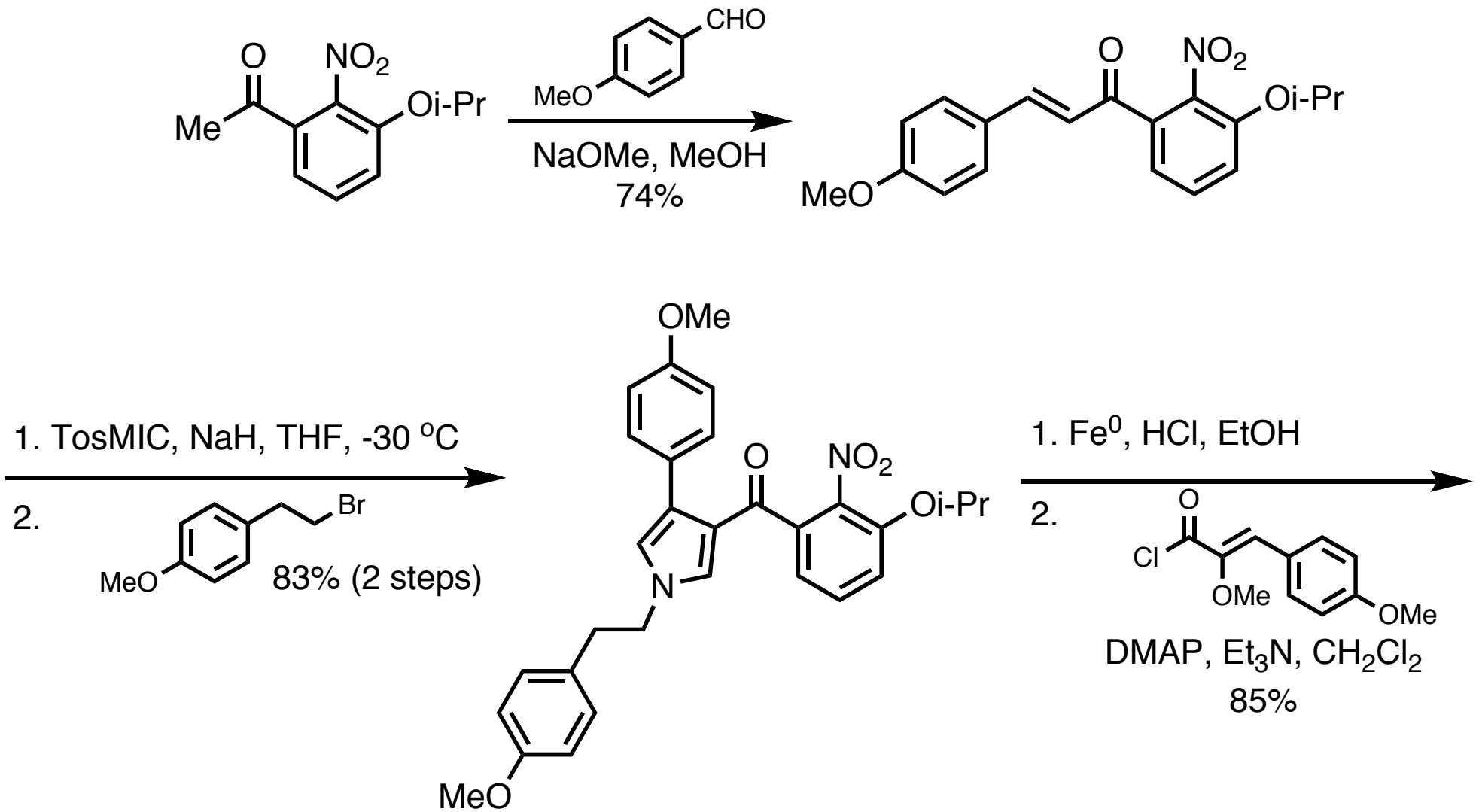
- Collected off the South Japanese coast
- Isolated from the sponge *Dictyodendrilla verongiformis*
- Potent against telomerase (100% @ 50 μg/mL)

J. Am. Chem. Soc. **2005**, *127*, 11620-11621
J. Am. Chem. Soc. **2006**, *128*, 8087-8094

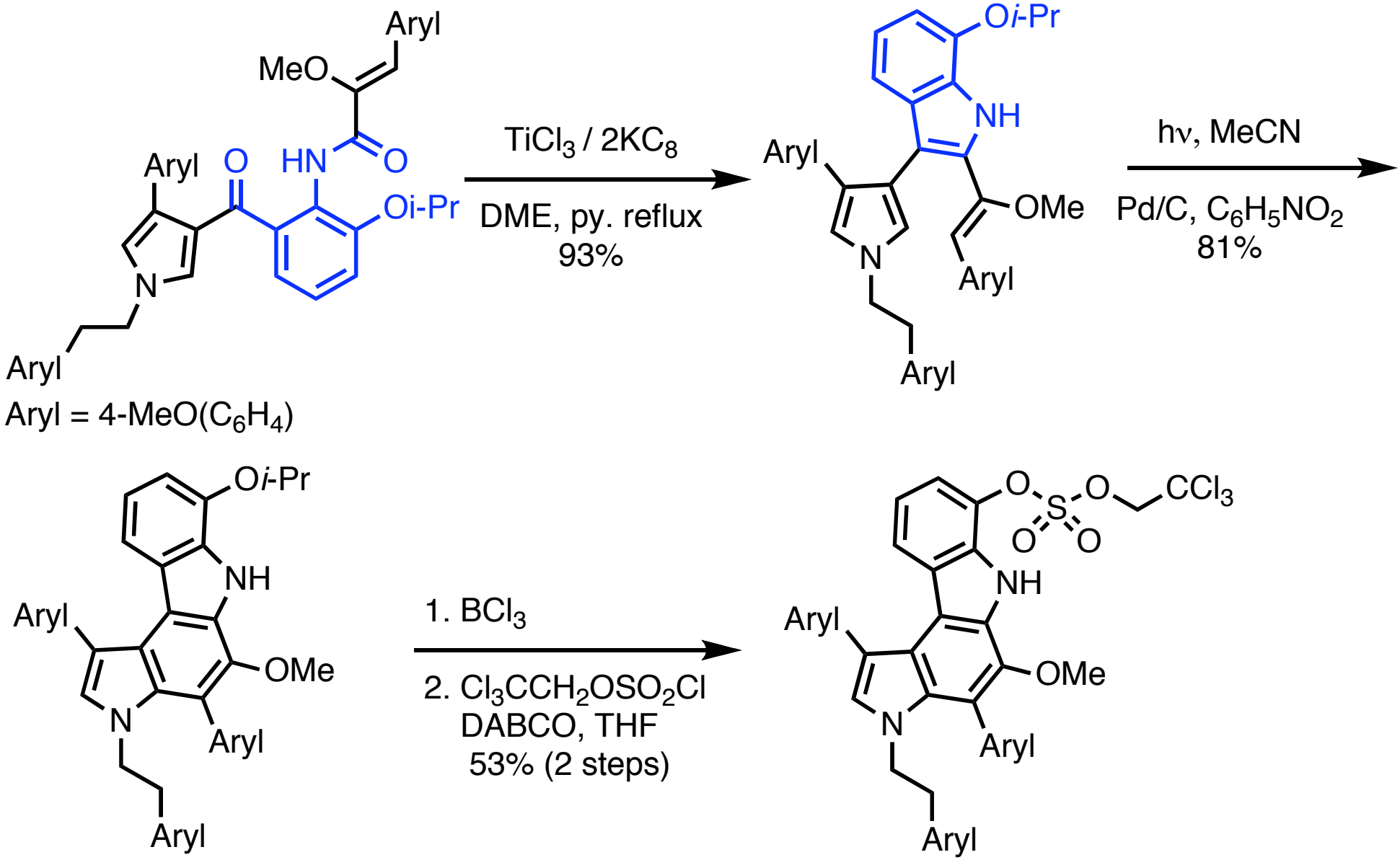
Total Synthesis of Dictyodendrins B, C, E: Analysis



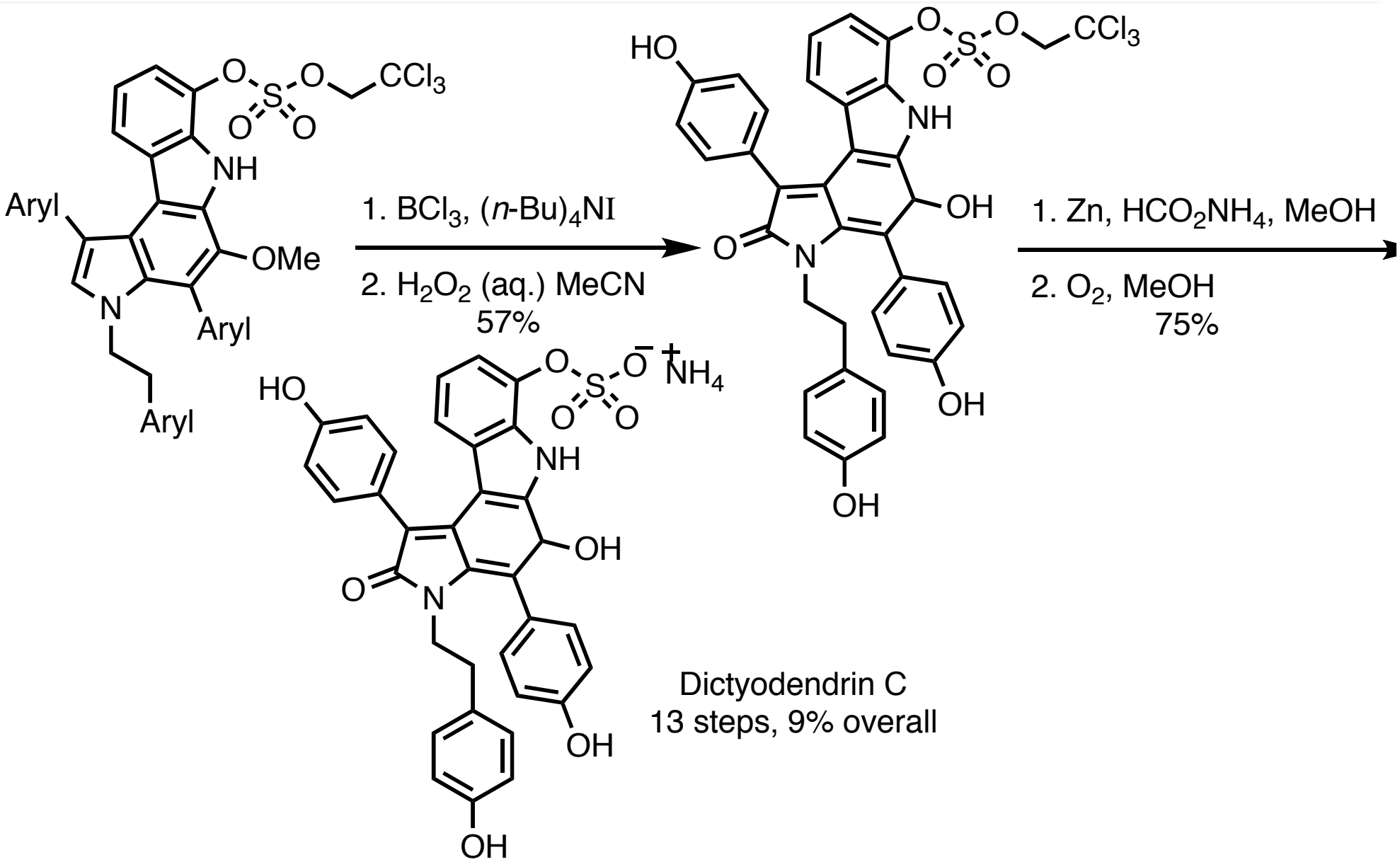
Total Synthesis of Dictyodendrin C: Building the Core



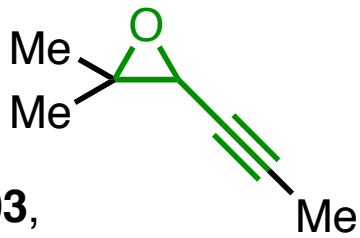
\Total Synthesis of Dictyodendrin C: Completing the Synthesis



Total Synthesis of Dictyodendrin C: Completing the Synthesis

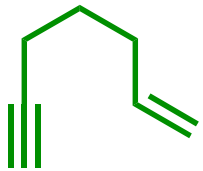


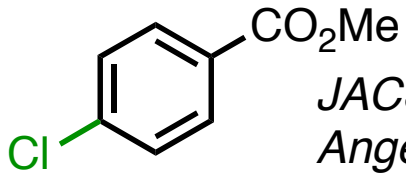
Novel Iron Catalyzed C-C Bond Formations



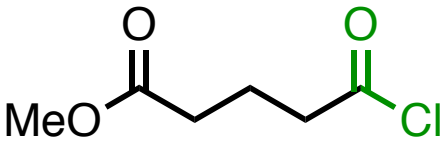
Angew. Chem., **2003**, *115*, 5513

JACS, **2005**, *127*, 12236

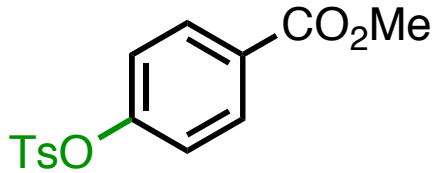


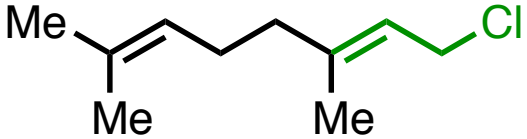


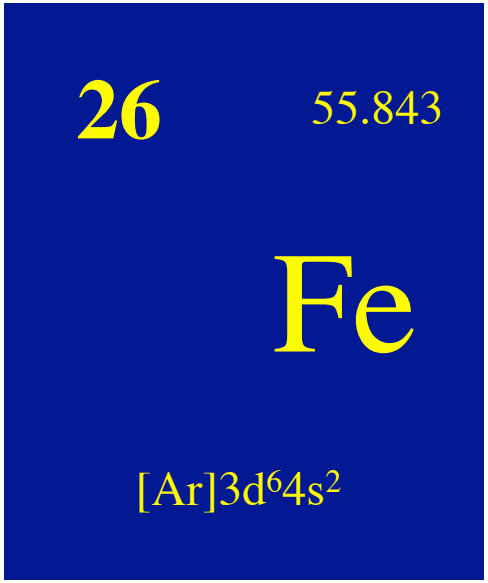
JACS, **2002**, *124*, 3943
Angew. Chem., **2002**, *114*, 632

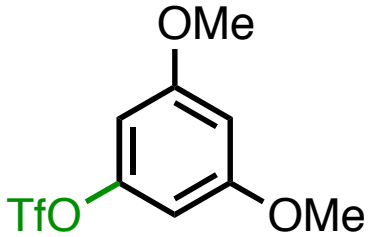


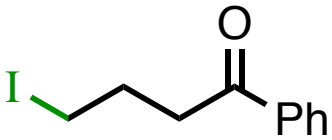
JOC, **2004**, *69*, 3943



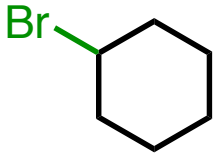


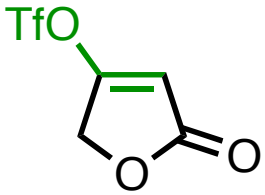






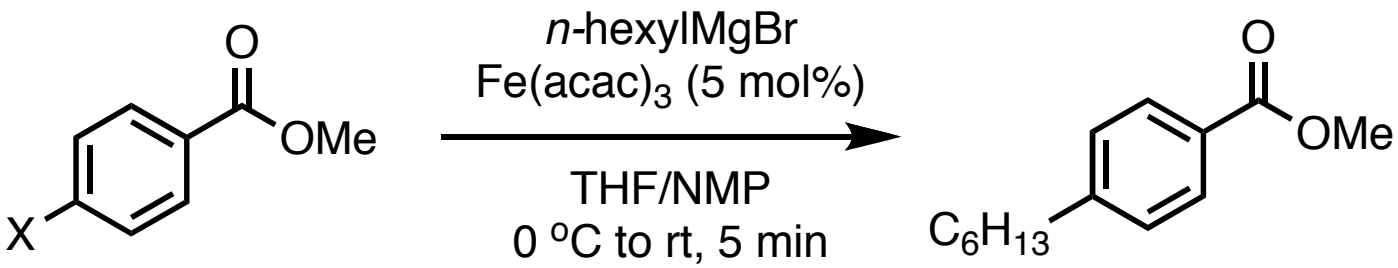
Angew. Chem., **2004**, *116*, 4045





JOC, **2004**, *69*, 3943

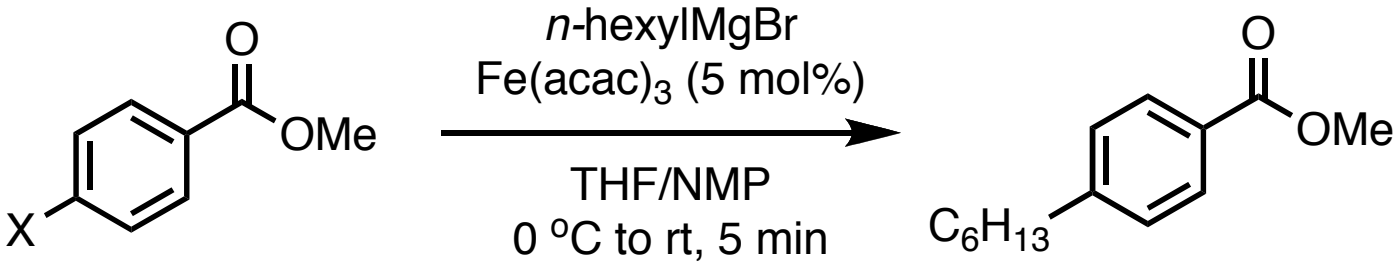
Iron Catalyzed Cross-Coupling Reactions



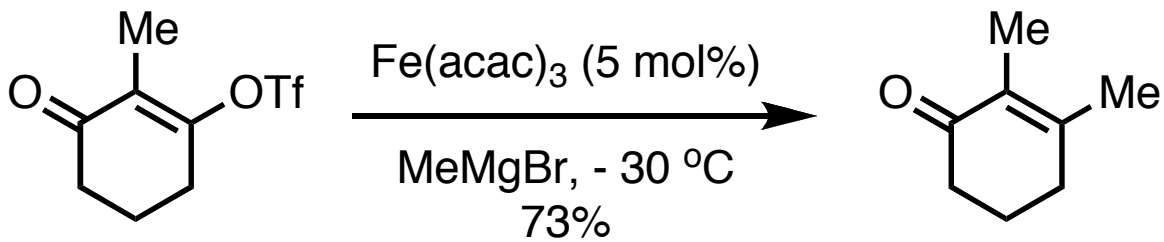
X	yield % (GC)
I	27% (46% reduction)
Br	38% (50 % reduction)
Cl	>95%
OTf	>95%
OTs	>95%

ACIEE, **2002**, *41*, 609
JOC, **2004**, *69*, 3943
JACS, **2002**, *124*, 1385

Iron Catalyzed Cross-Coupling Reactions

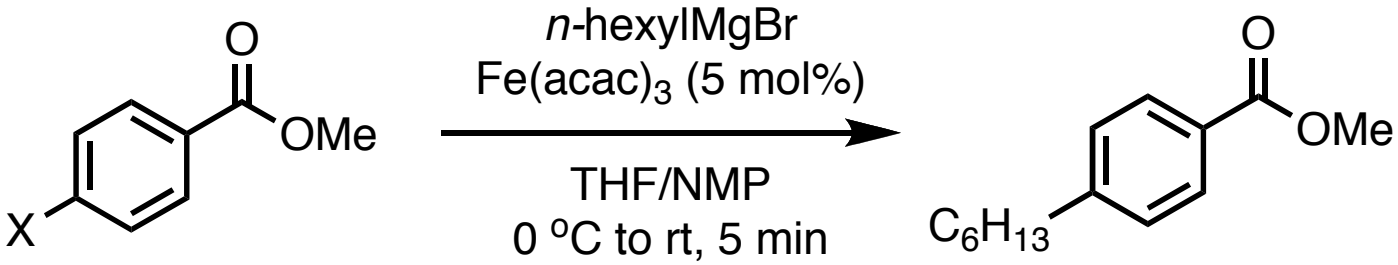


- In this system, alkenyl, aryl, and allyl Grignard reagents gave poor results, perhaps due to oxidative dimerization



ACIEE, **2002**, *41*, 609
JOC, **2004**, *69*, 3943
JACS, **2002**, *124*, 1385

Iron Catalyzed Cross-Coupling Reactions



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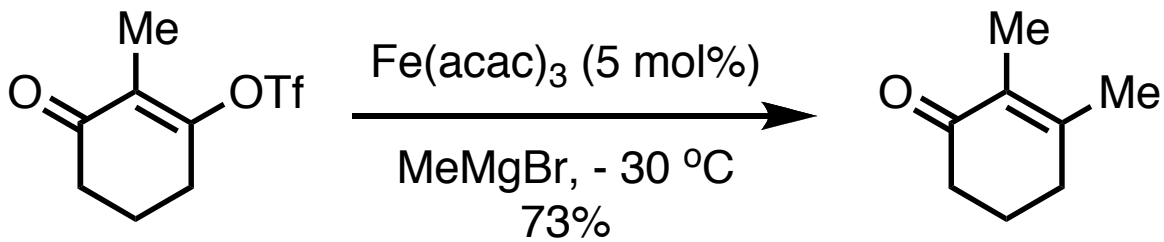
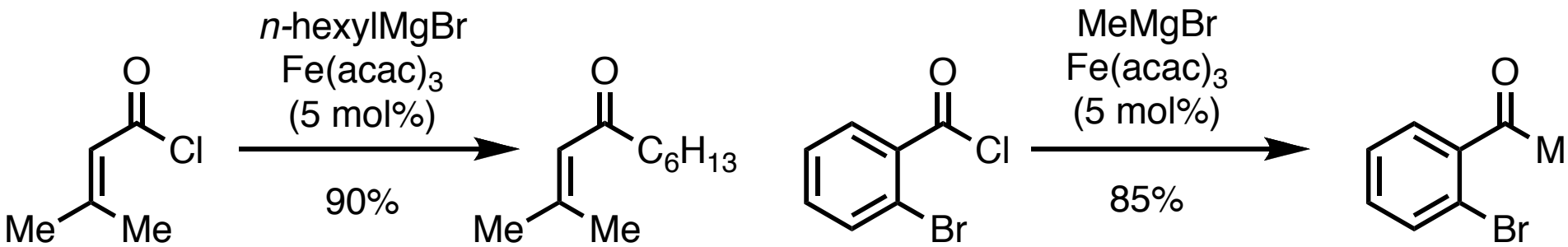
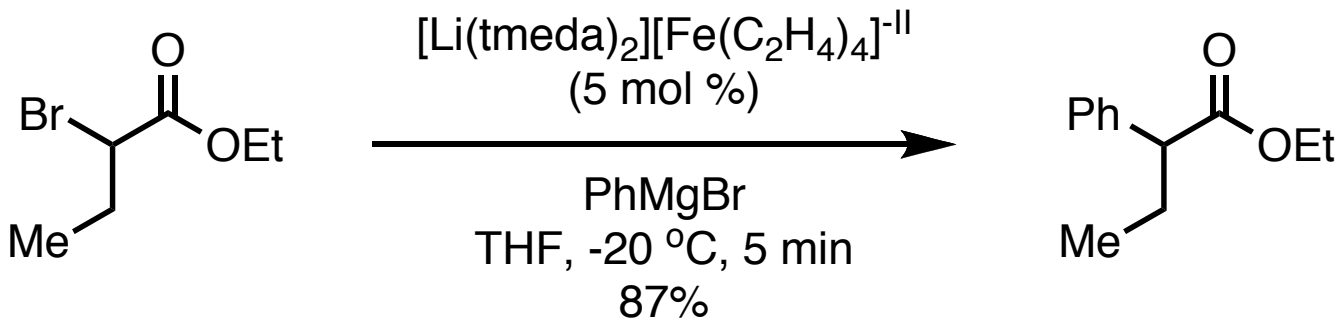
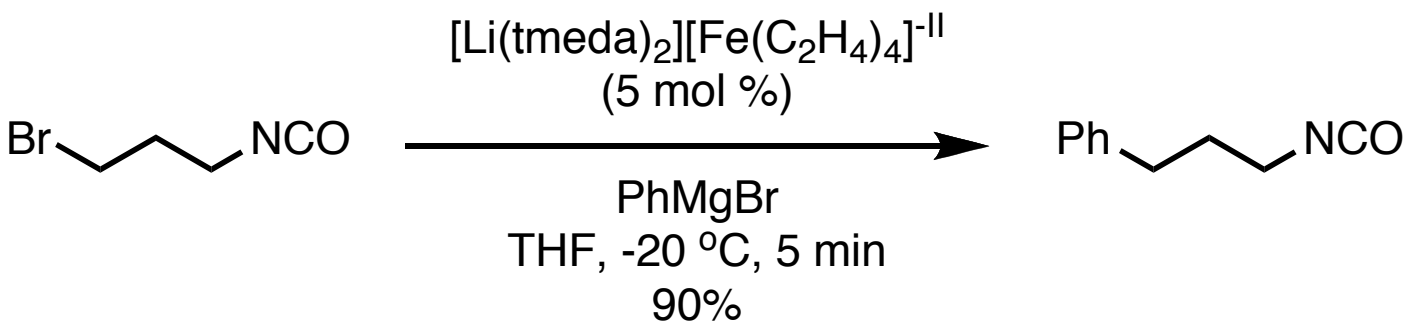


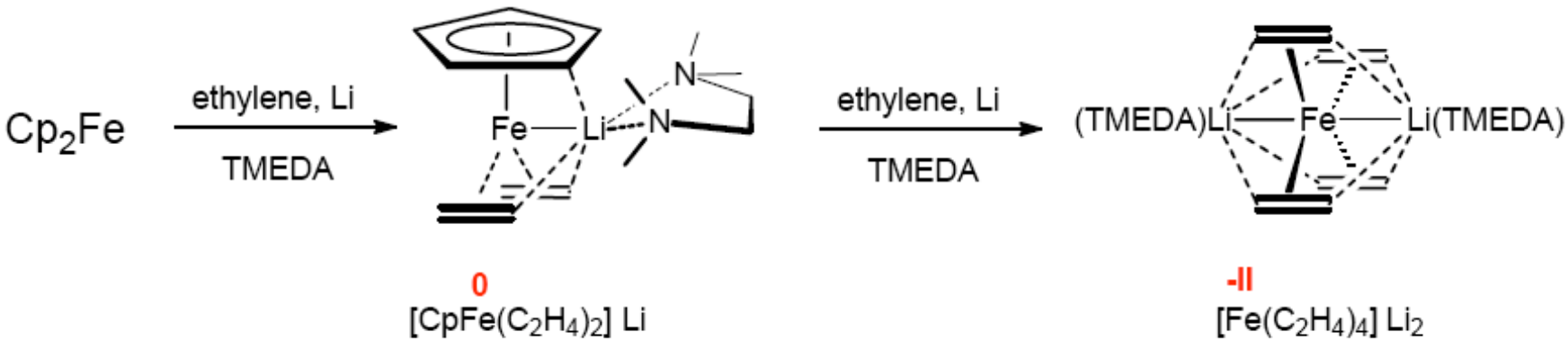


No addition to ketone observed, particularly when the acid chloride was added to the Grignard soli

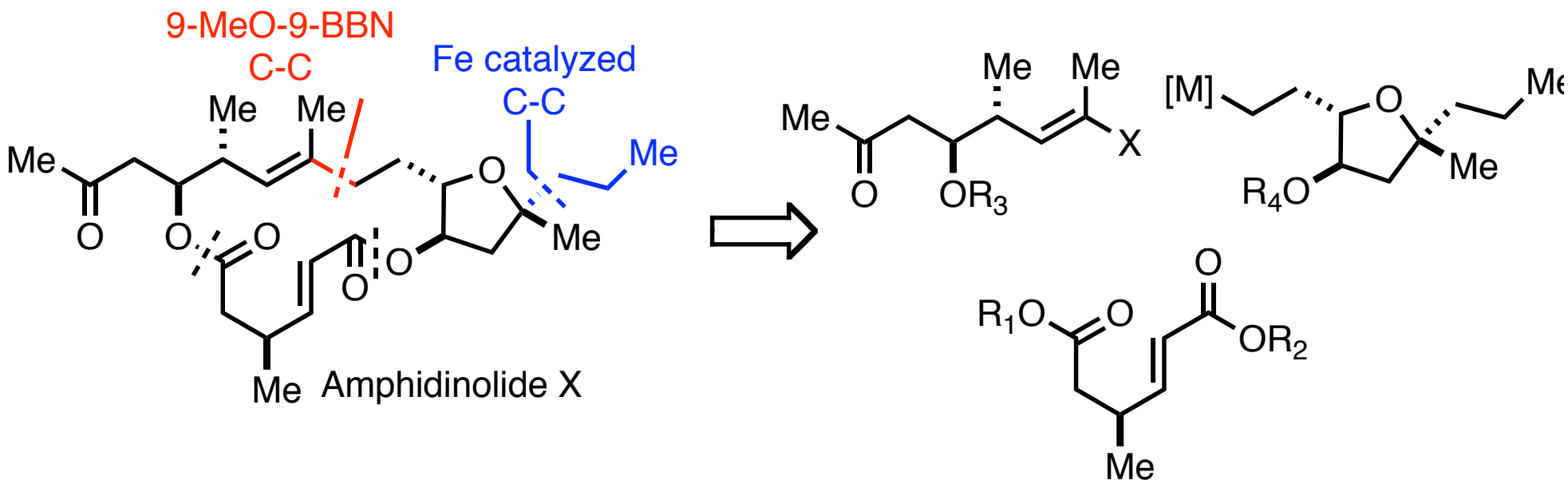
Iron Catalyzed Cross-Coupling of Alkyl Halides

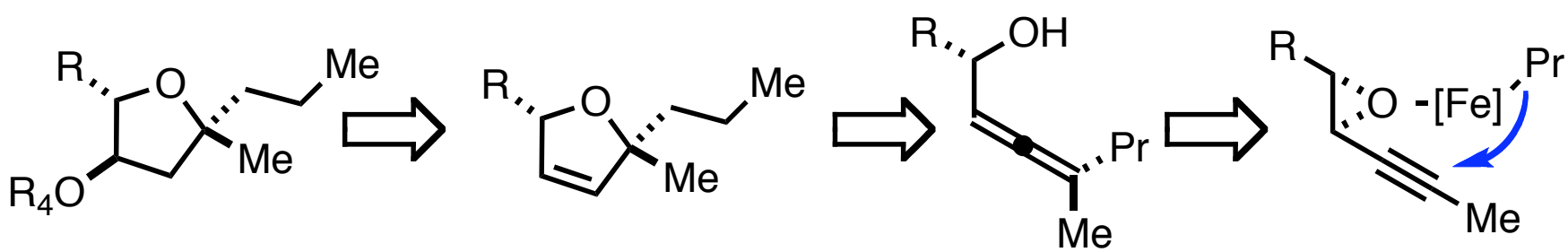






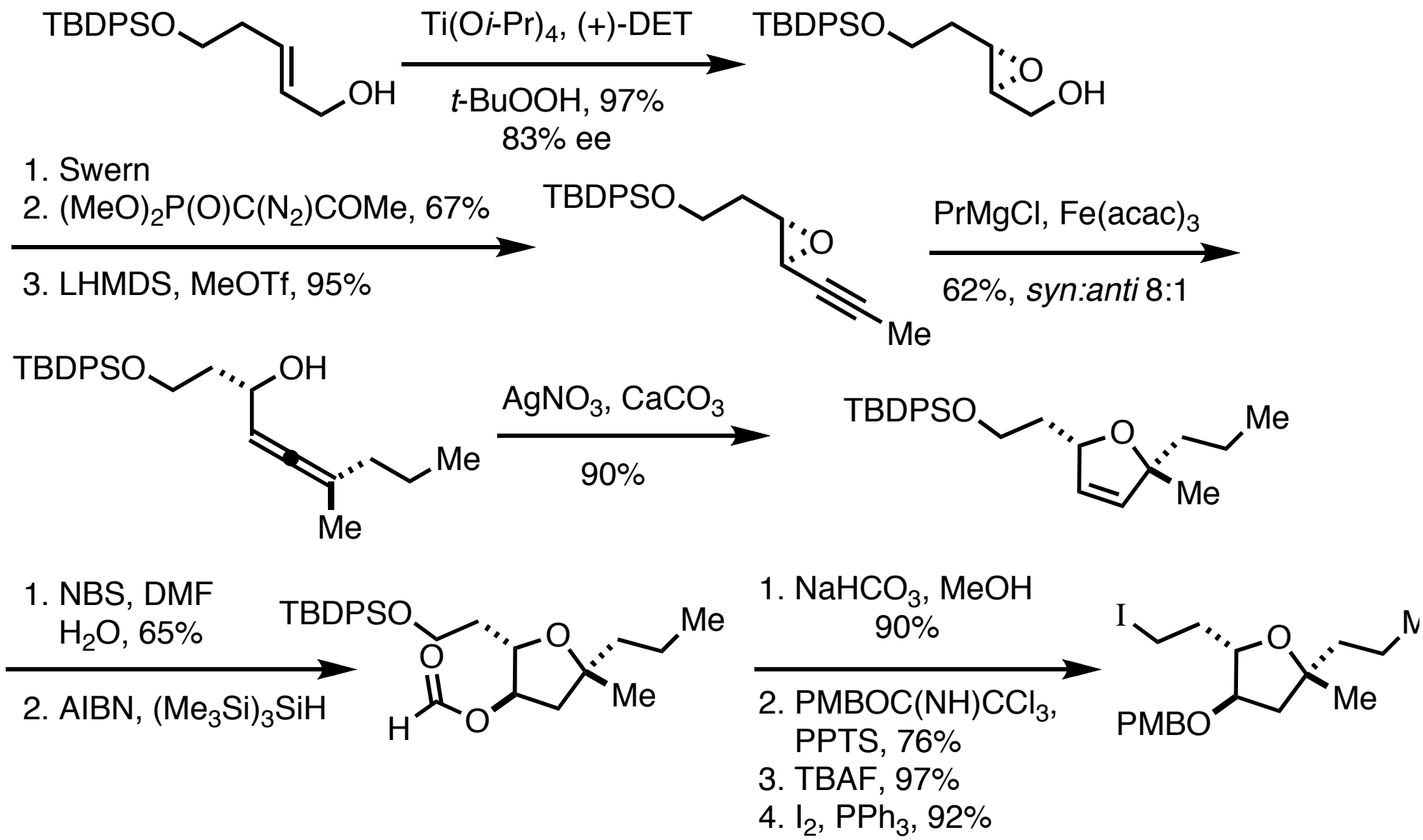
Iron Catalyzed C-C of Propargyl Epoxides in Total Synthesis



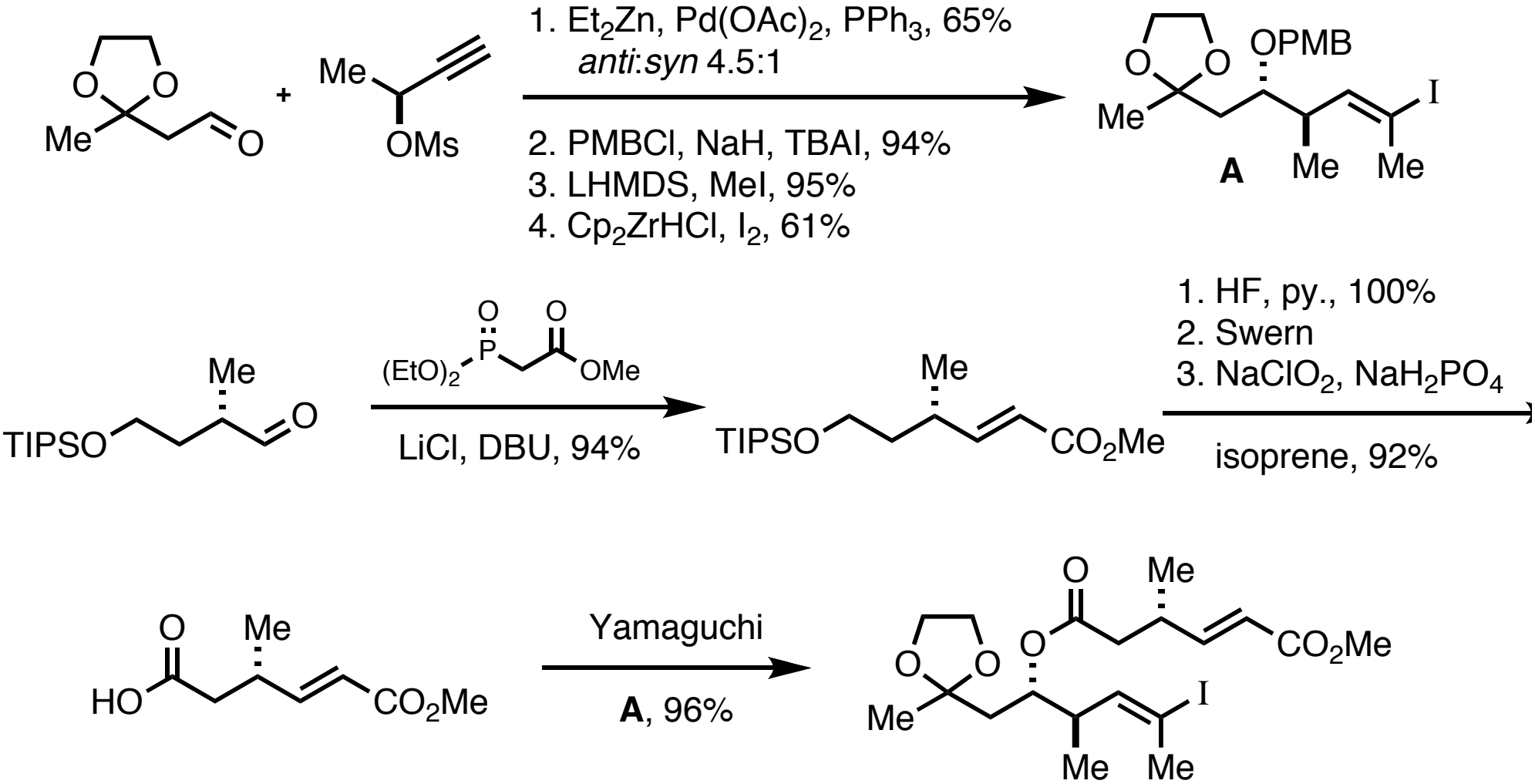


ACIEE, **2003**, *42*, 5355
JACS, **2004**, *126*, 1597
JACS, **2006**, *128*, 9194

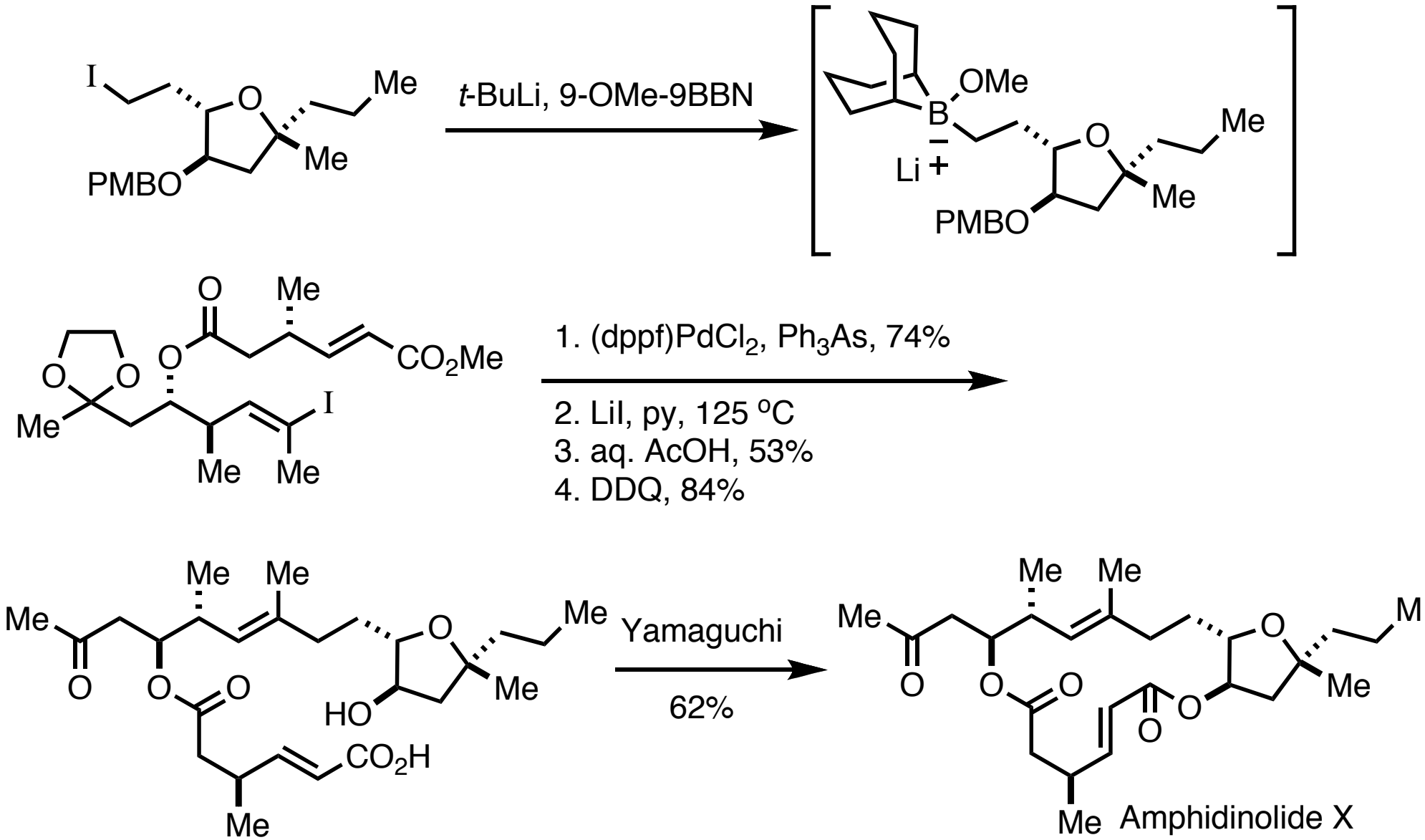
Amphidinolide X: Building the Furan



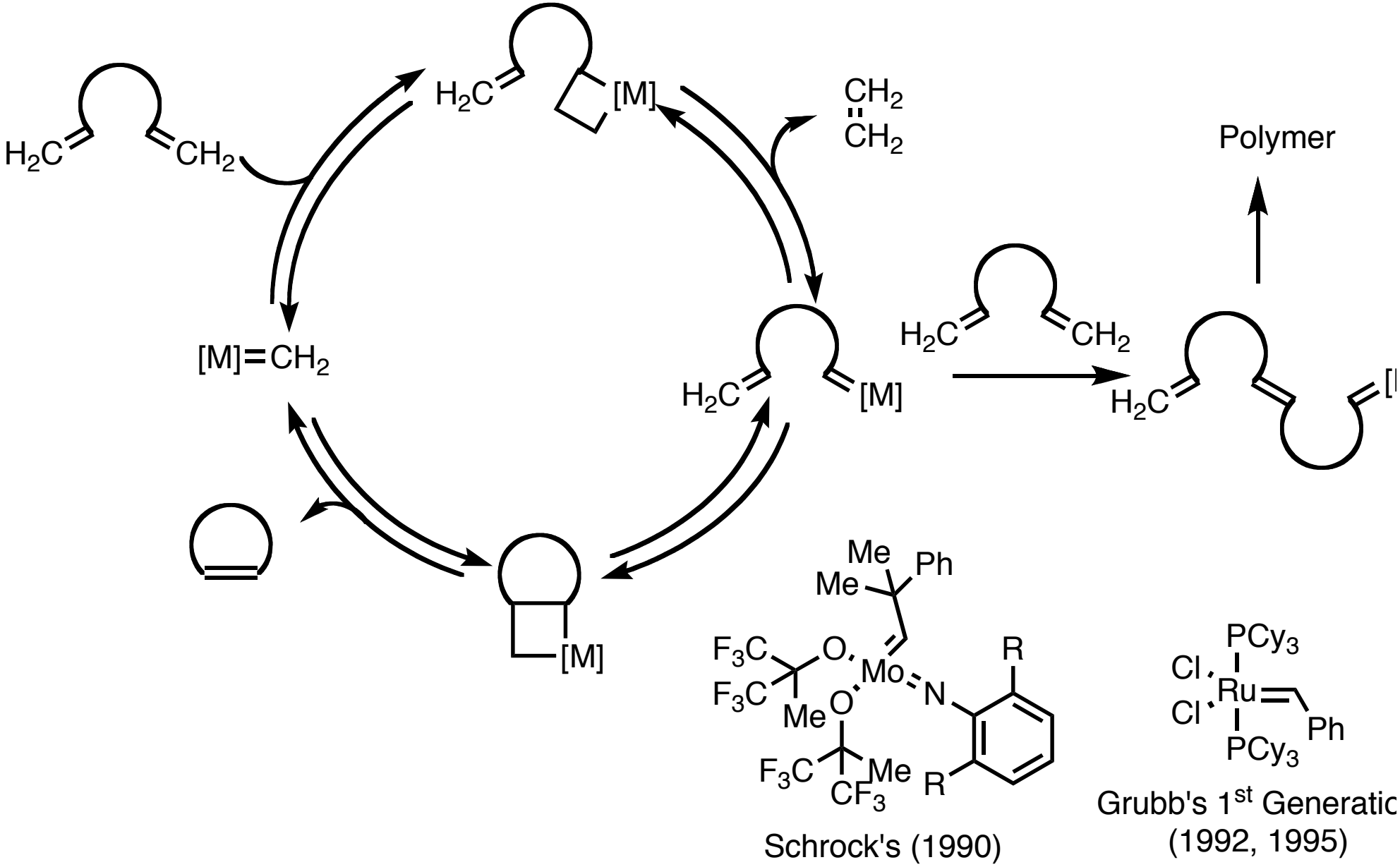
Amphidinolide X: Building the Macrocycle



Amphidinolide X: Completing the Synthesis



Olefin Metathesis: Brief Overview



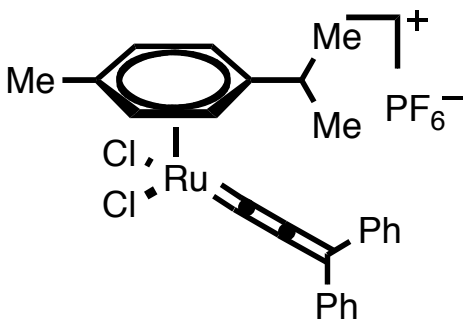
Fürstner's Role in Ring Closing Metathesis (RCM)

- Fuestner's contributions to the field of RCM

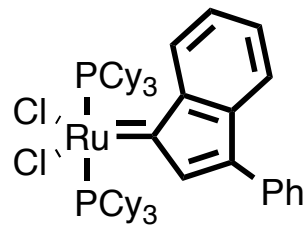
1. Extension to the synthesis of medium and macrocyclic rings

2. Control of product stereochemistry (synthesis of herbarumin I)

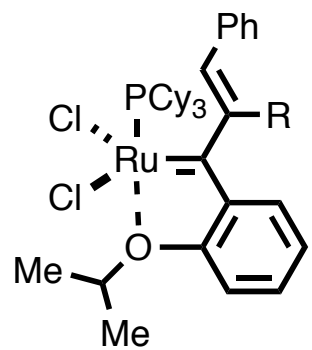
3. Development of new catalyst systems



Chem. Eur. J. **2000**, *6*, 1847



Chem. Eur. J. **2001**, *7*, 74811 sold by Strem



Organometallics, **2005**, *24*, 4065

Fürstner's Role in Ring Closing Metathesis (RCM)

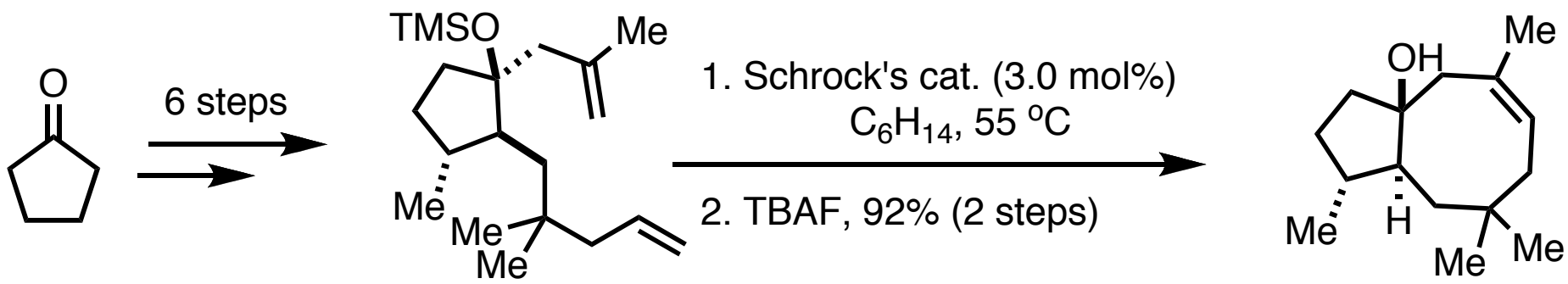
- Fuestner's contributions to the field of RCM

1. Extension to the synthesis of medium and macrocyclic rings
2. Control of product stereochemistry (synthesis of herbarumin I)
3. Development of new catalyst systems
4. Application to the total synthesis of complex molecules
5. Application to nonnatural product synthesis and materials

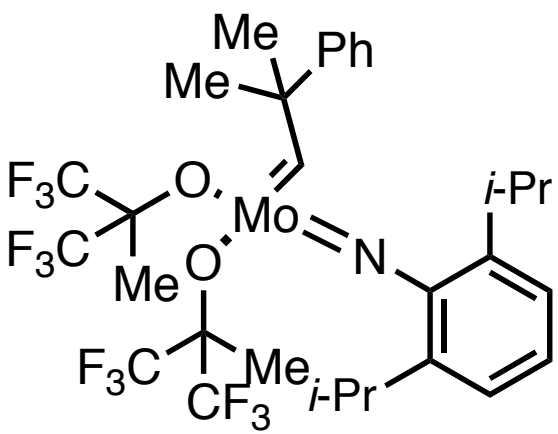
Pioneering (RCM) in the Total Synthesis of Medium and Large Rings

- Fuestner and co-workers used (RCM) in a short synthesis of Dactylol.

- This was one of the first examples of RCM in synthesis for the Fuestner group.



Dactylol
(17 % overall, 8 steps)

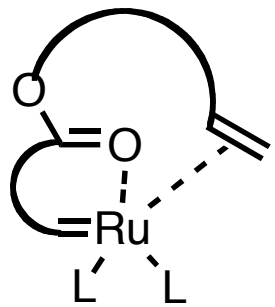


Schrock's catalyst

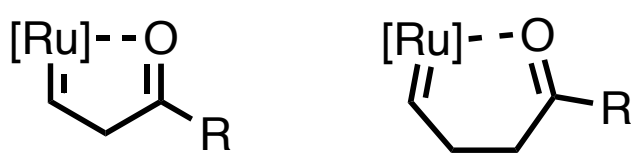
JOC, **1996**, *61*, 874

"Directing Groups" for (RCM)

- Functional groups such as carbonyl and hydroxyl groups greatly assist RCM



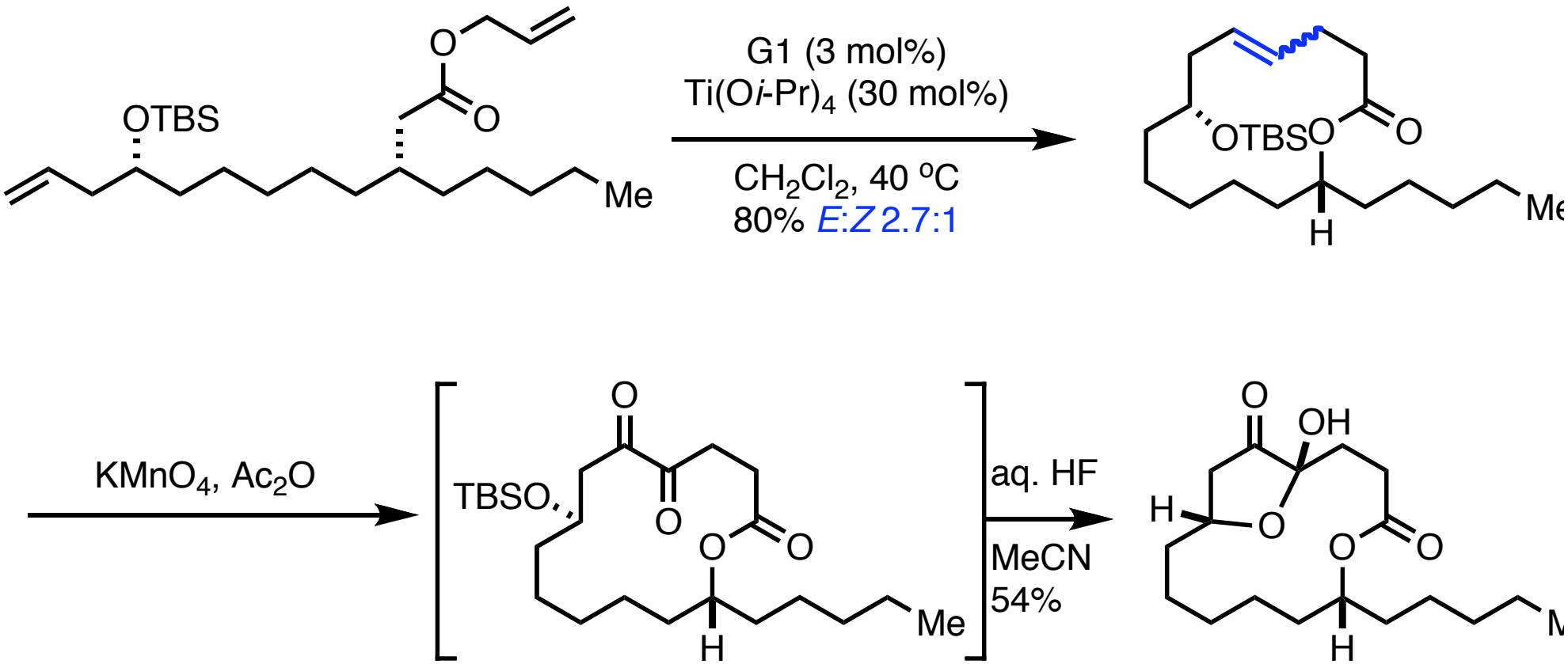
- However, given this assistance such groups can result in stable chelates that sequester the G 1



- Fuestner found that the use of mild Lewis acids ex. Ti(O*i*-Pr)$_4$) could overcome such chelation

JOC, **1996**, *61*, 3942
Organometallics, **2002**, *21*, 3

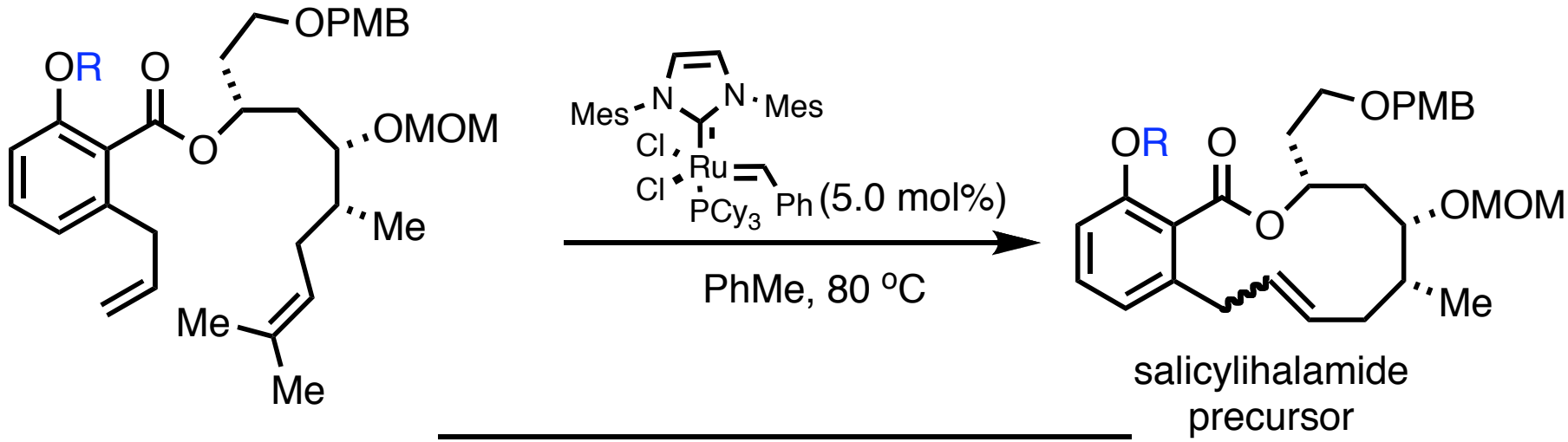
Synthesis of (–)-Gloeosporone: Key Step



(-)-Gleosporone
8 steps, 18% overall

JACS, **1997**, *119*, 9130

The Influence of Remote Functionality Pt. 2



R	yield	time, h	*E* : *Z*
H	69%	20	0 : 100
Me	93%	1.5	66 : 34
MOM	91%	3	68 : 32
TBS	91%	1	40 : 60

Org. Lett. **2000**, *2*, 373

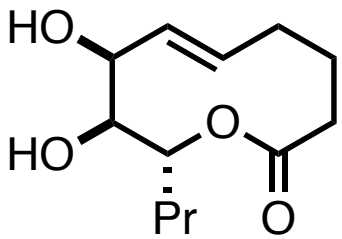
Controlling Olefin Geometry *via* Catalyst Tuning

- Alkene metathesis is inherintly a reversible process, make the synthesis of med. rings difficul

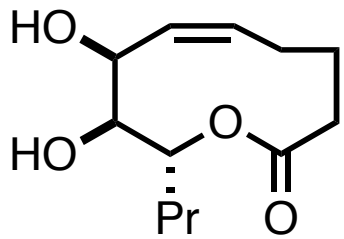
Solutions for Ring Closure:

1. Removal of volatile byproducts (i.e. ethylene)

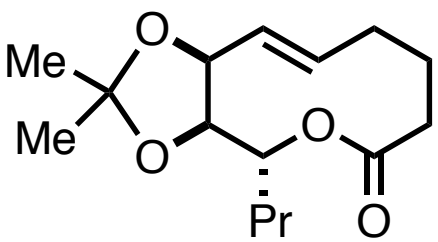
2. Increase product olefin substitution

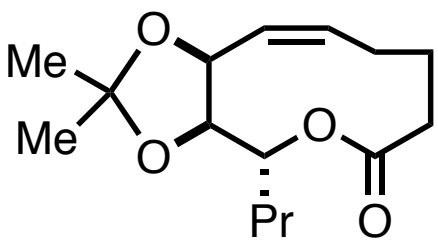


Herbarumin I



(*Z*)-isomer is ca. 1.5 kcal/mol more stabl

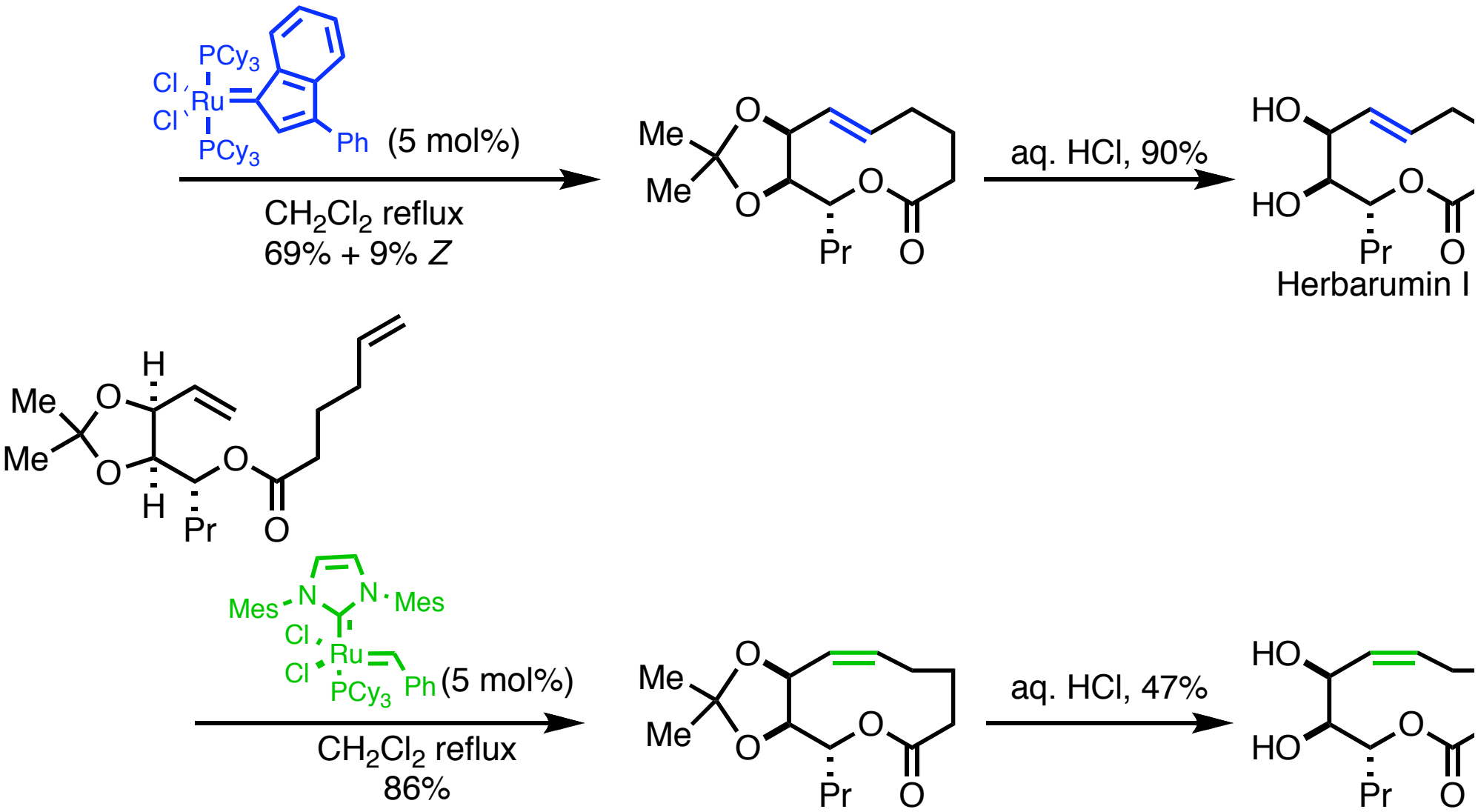




(*Z*)-isomer is ca. 3.5 kcal/mol more stabl

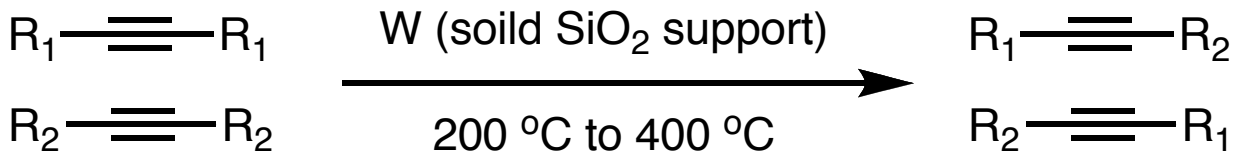
JACS, **2002**, *124*, 7061
concept of catalyst 'tuning'
see *Adv. Synth. Catal.* **2002**, *344*, 65

Synthesis of Herbarumin I: Favoring Olefin Geometry *via* Catalyst Tunir

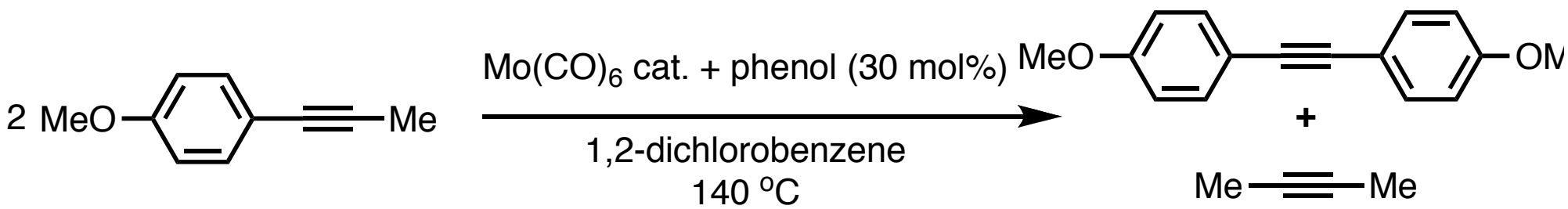


- This is the first example of the selective synthesis of both isomers of a target by catalyst choice

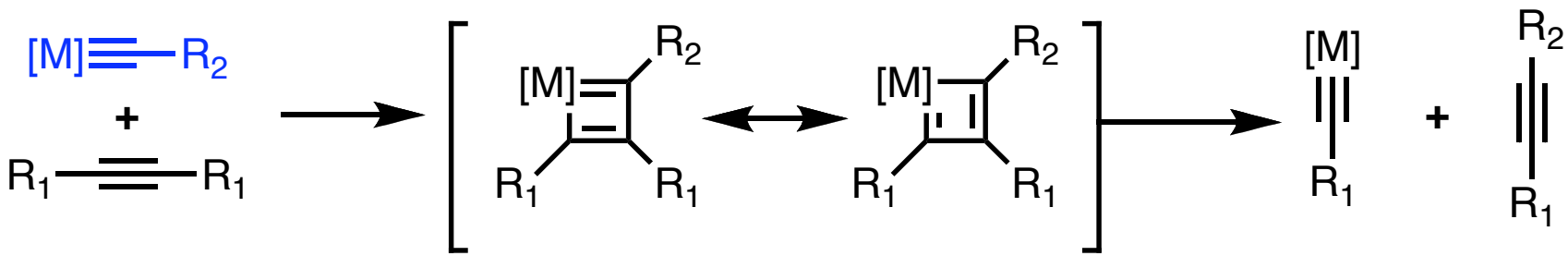
Alkyne Metathesis: Brief Overview



Review:
Fuestner, A., Davies, P. *Chem. Commun.* **2005**, 2307
Fuestner, A. in *Handbook of Metathesis*, Wiley-VCH, **2003**, Vol. 2, p. 432



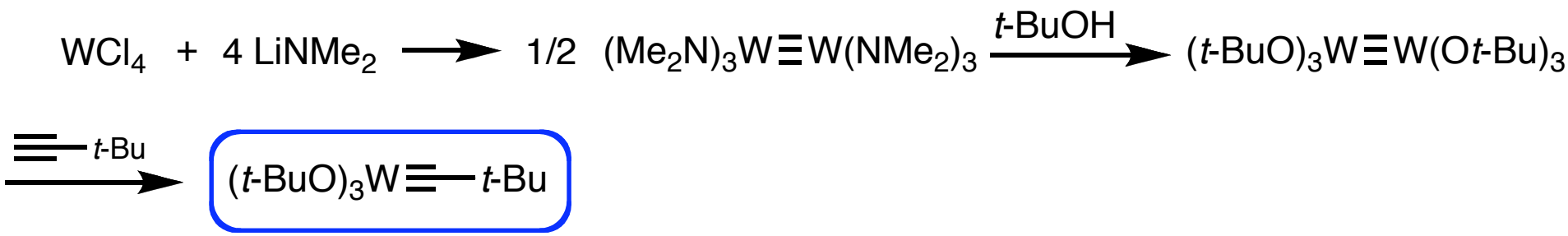
Mortreux, *et. al.*, *Chem. Commun.* **1974**, 786



Active complex: Metal Alkylidene?

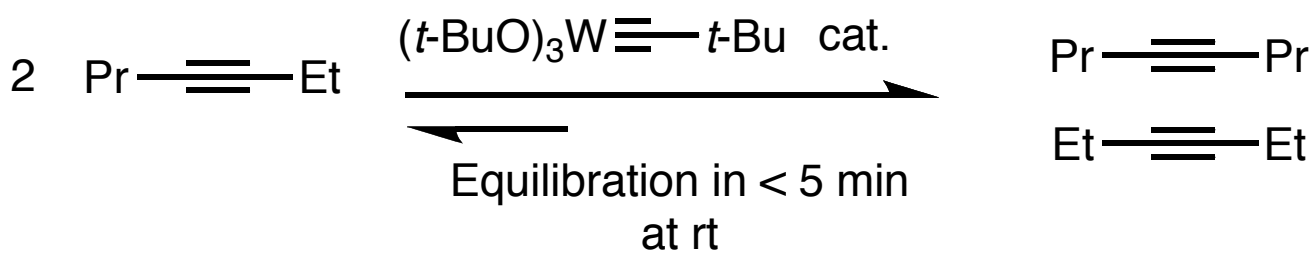
Katz, *et. al.*, *JACS*, **1975**, *97*, 1592.

Application of the "Schrock" Tungsten Carbyne



- Scrock was able to prepare and structurally characterize the first tungsten alkylidyne

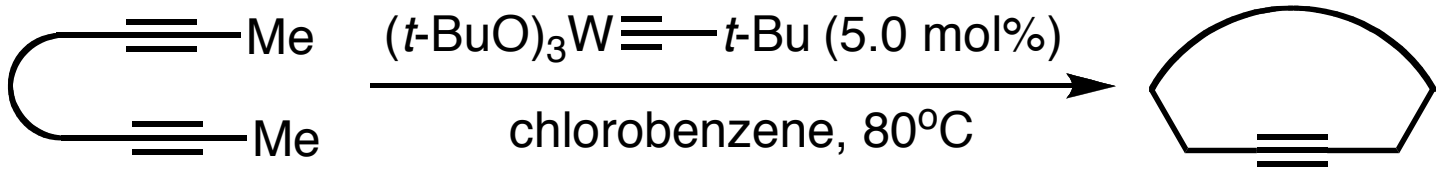
Schrock, R.R. *et. al., Organometallics*, **1982**, *1*, 1645

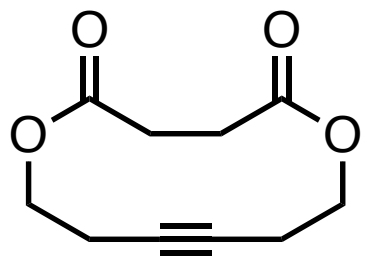
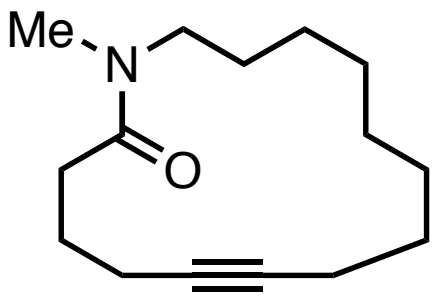
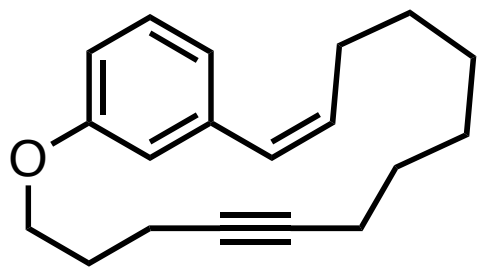


Given these results alkyne metathesis was still only limited to macromolecular chemistry and the metathesis of simple phenyl acetylenes

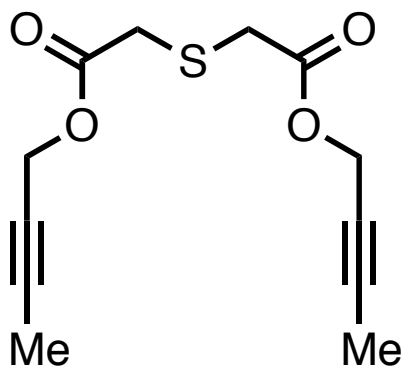
Schrock, R.R. *Chem. Rev.* **2002**, *102*, 145.

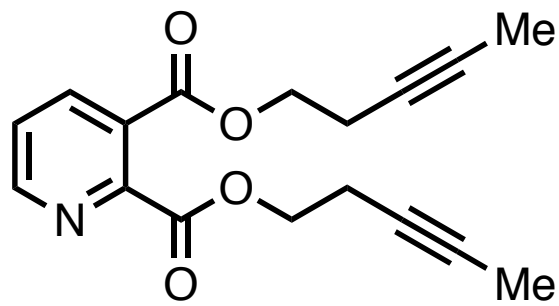
Ring Colsing Alkyne Metathesis (RCAM): Early Model Studies

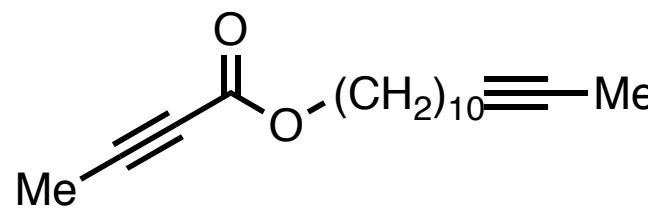


Entry	Product	Isolated yield, %
1		73
2		72
3		79

Ring Colsing Alkyne Metathesis (RCAM): Early Limitations







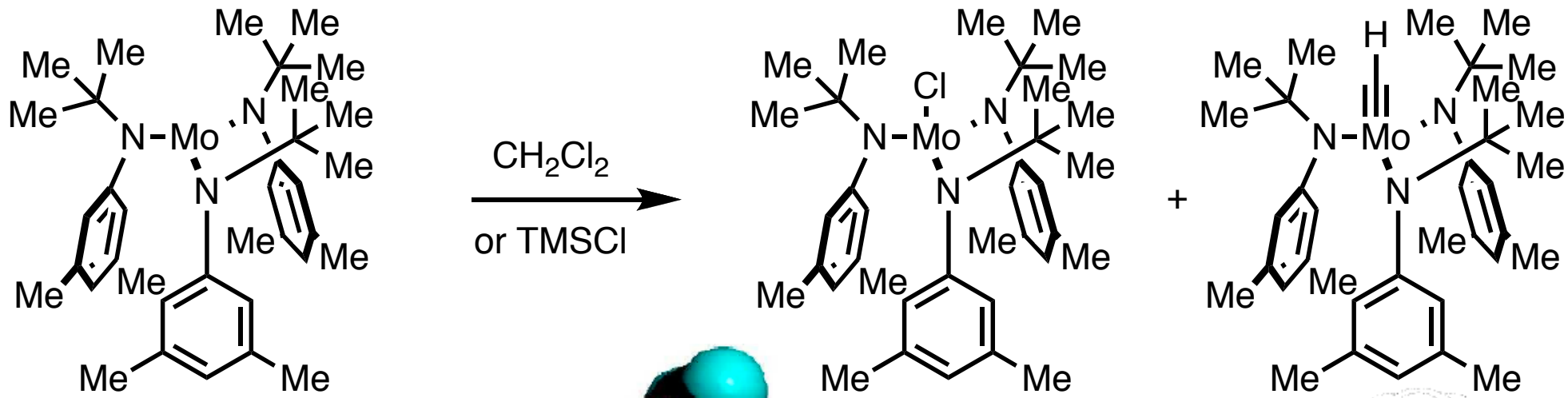
- The (RCAM) works well with functional groups such as ethers, esters, enoates, amides, silyl ether sulfonamides, carbamates, and sulfones, metal centers, alkenes, furans, ketone, acetal, etc.

- The (RCAM) can also be run in THF, toluene, chlorobenzene, 1,2,4-trichlorobenzene

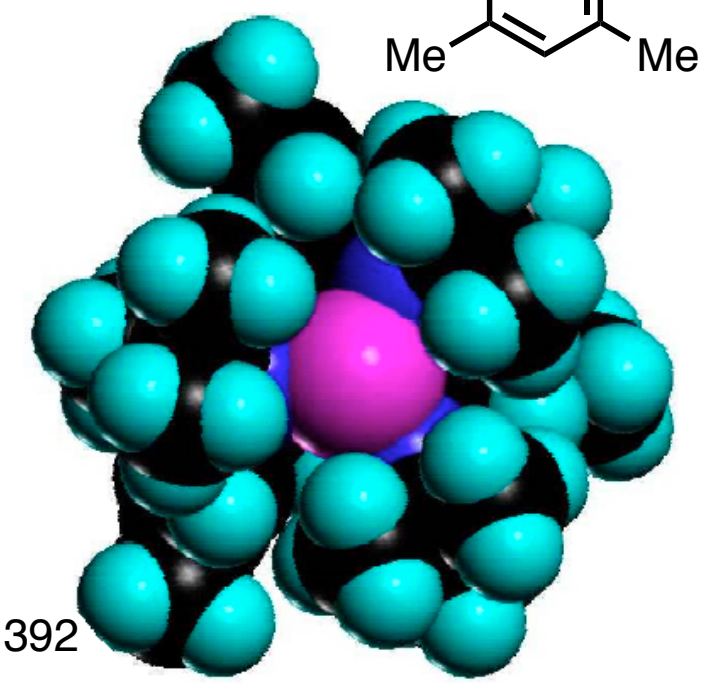
- Functional groups that have a high affinity for the Lewis acidic [W] center were unreactive: (i.e. thioethers, basic nitrogen groups, also butyonates were unreactive)

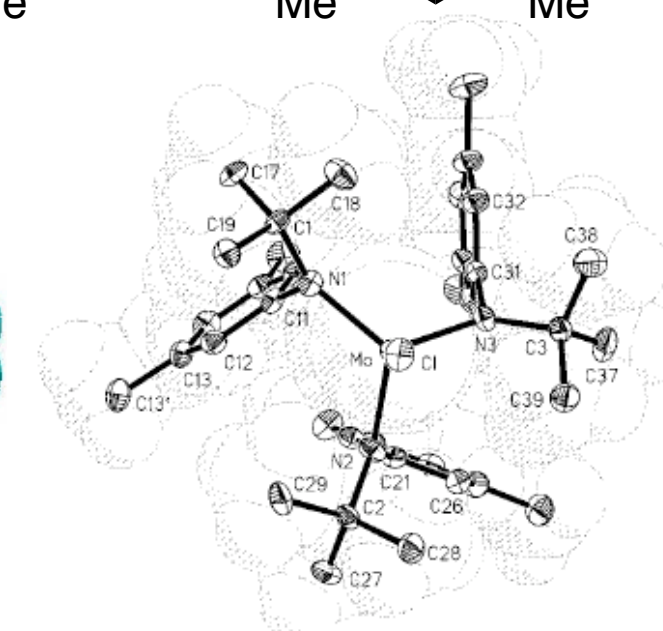
Fuerstner, A.; *et. al. JACS*, **1999**, *121*, 11108

(RCAM): Development of a New Catalyst



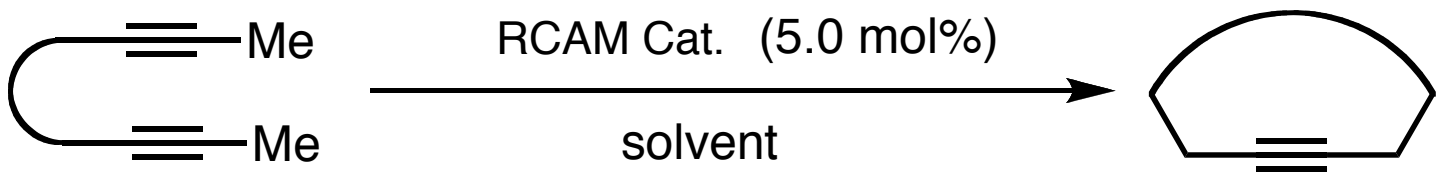
Inspired by the work of Cummins
for the activation of N_2
Chem. Commun. **1998**, 1777

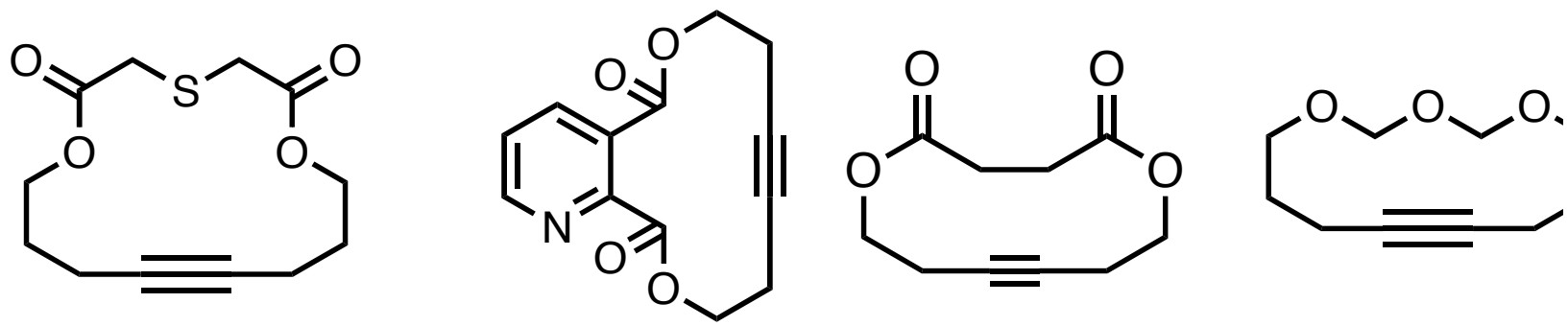




JACS. **1999**, *121*, 9453
Chem. Eur. J. **2001**, *7*, 5299
Moore, *et. al. JACS,* **2004**, *126*, 392

(RCAM): Comparison of Catalysts

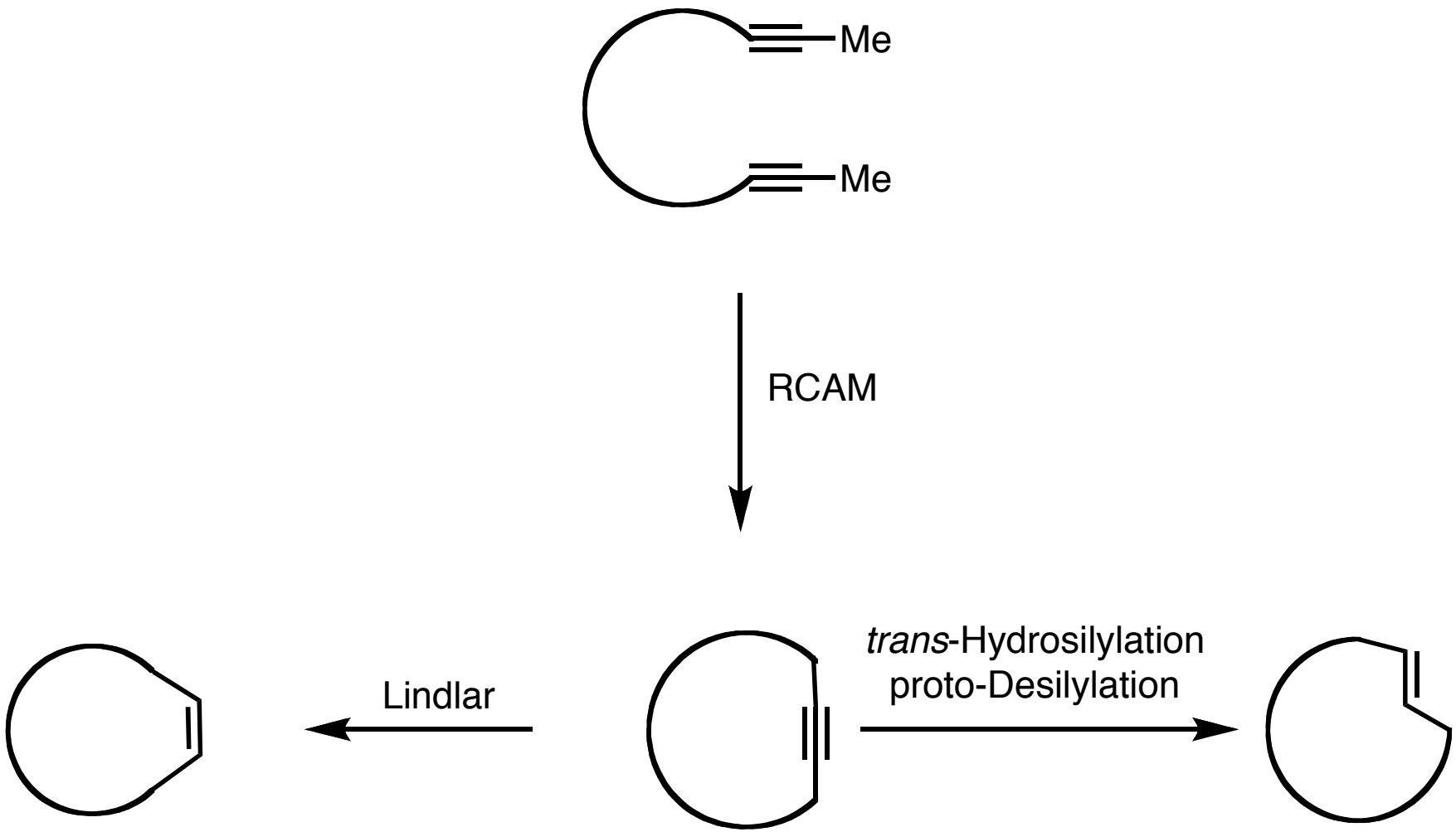




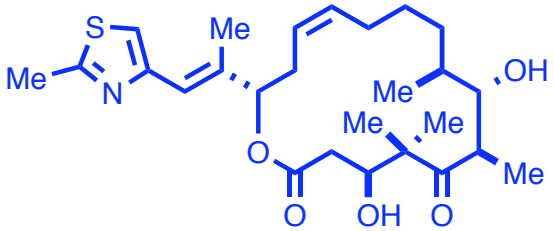
[(*t*-Bu)(Aryl)N]$_3$Mo	**91%**	**84%**	**88%**	**60%**
(*t*-BuO)$_3$W≡—*t*-Bu	73%	0%	0%	0%

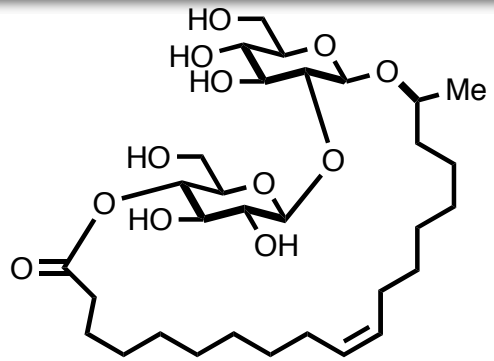
JACS, **1999**, *121*, 9453
Chem. Eur. J. **2001**, *7*, 5299

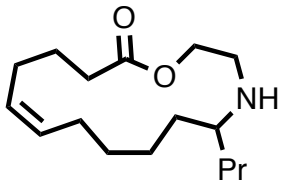
(RCAM): Concept

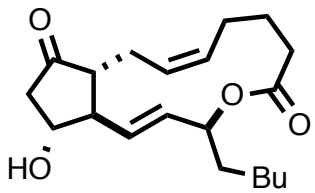


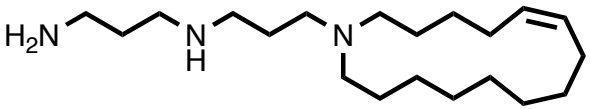
Examples of Total Syntheses Completed *via* RCAM

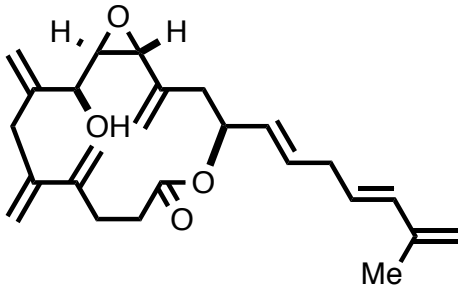


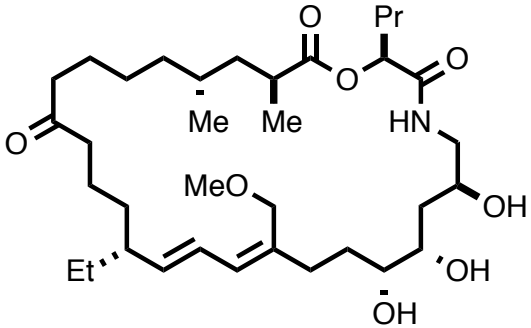


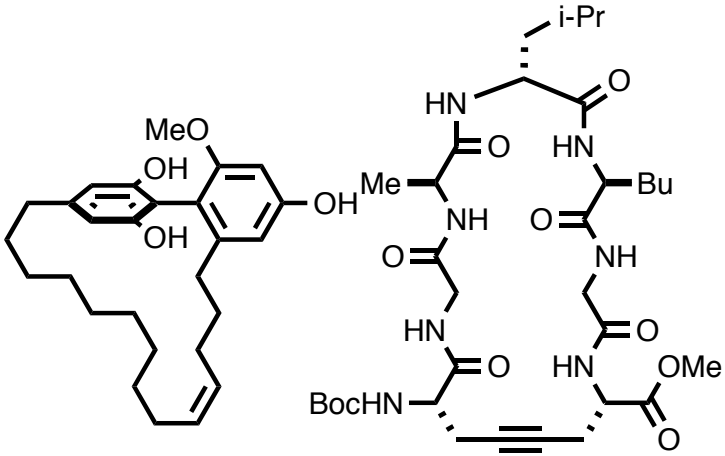


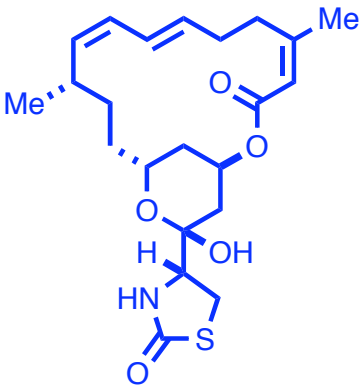


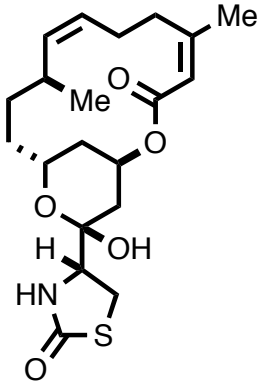


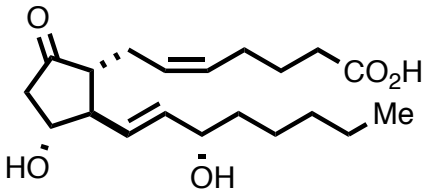


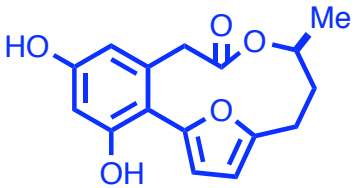


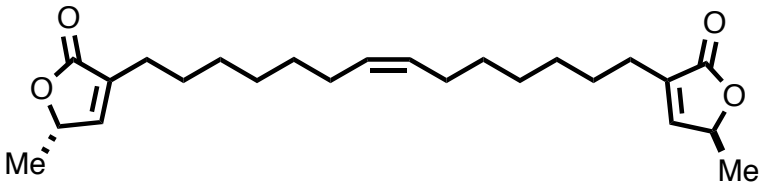




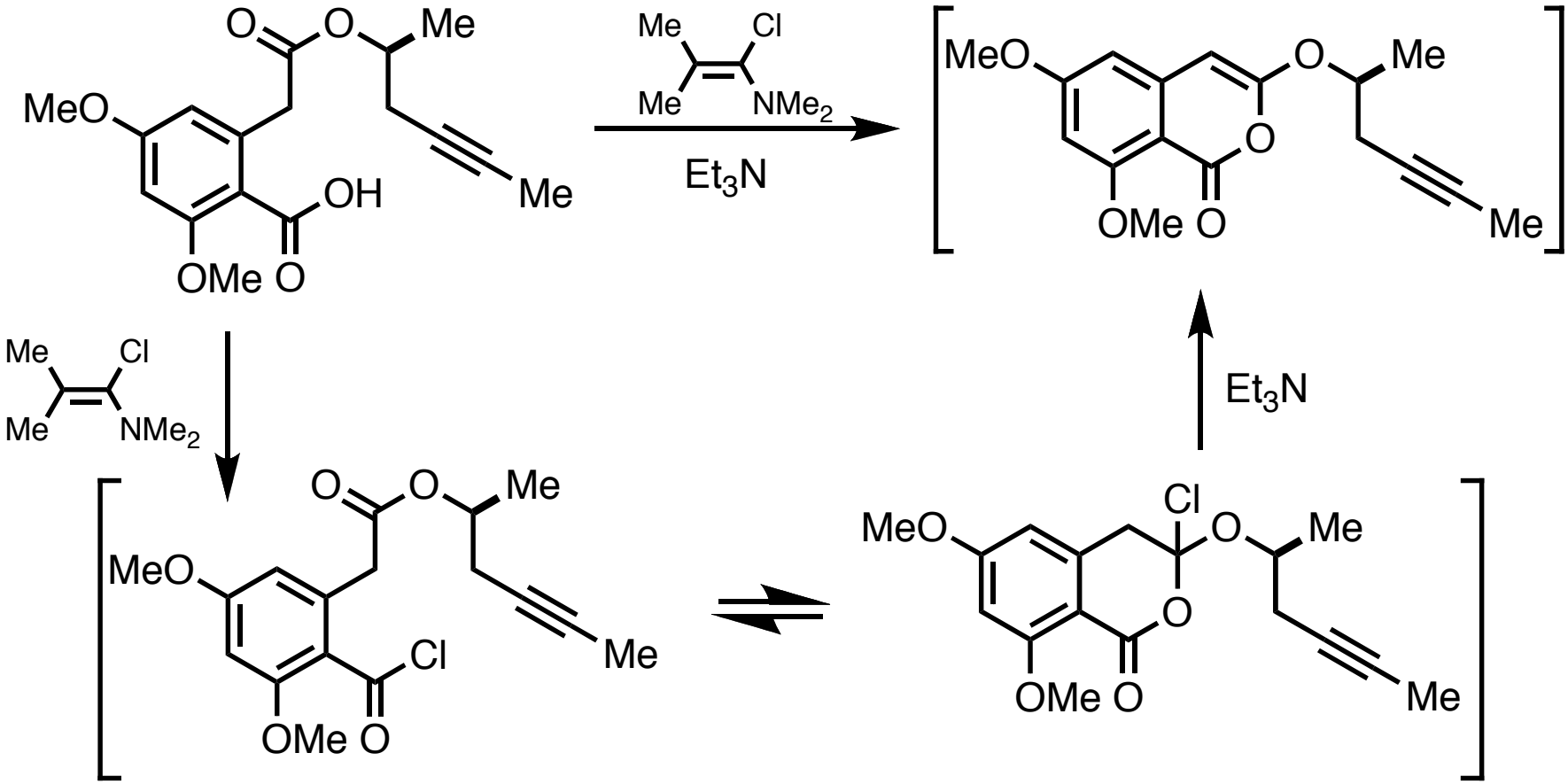




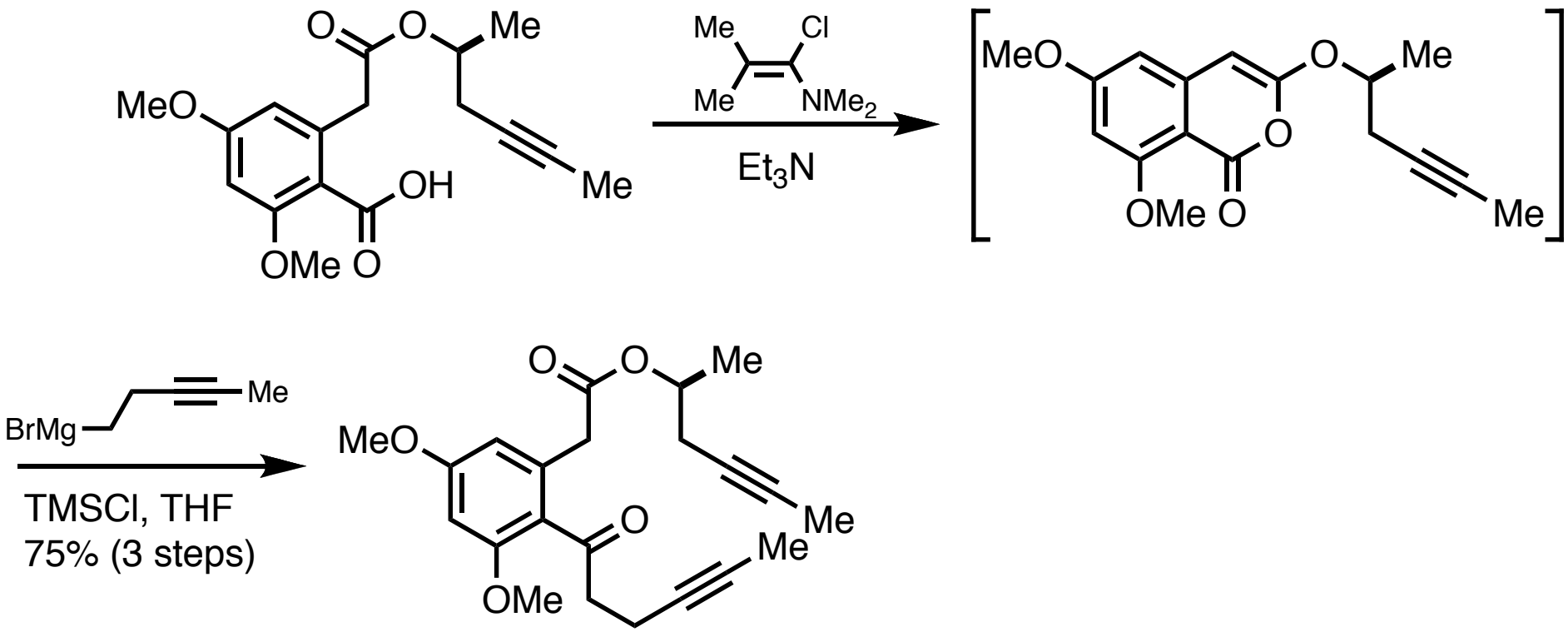




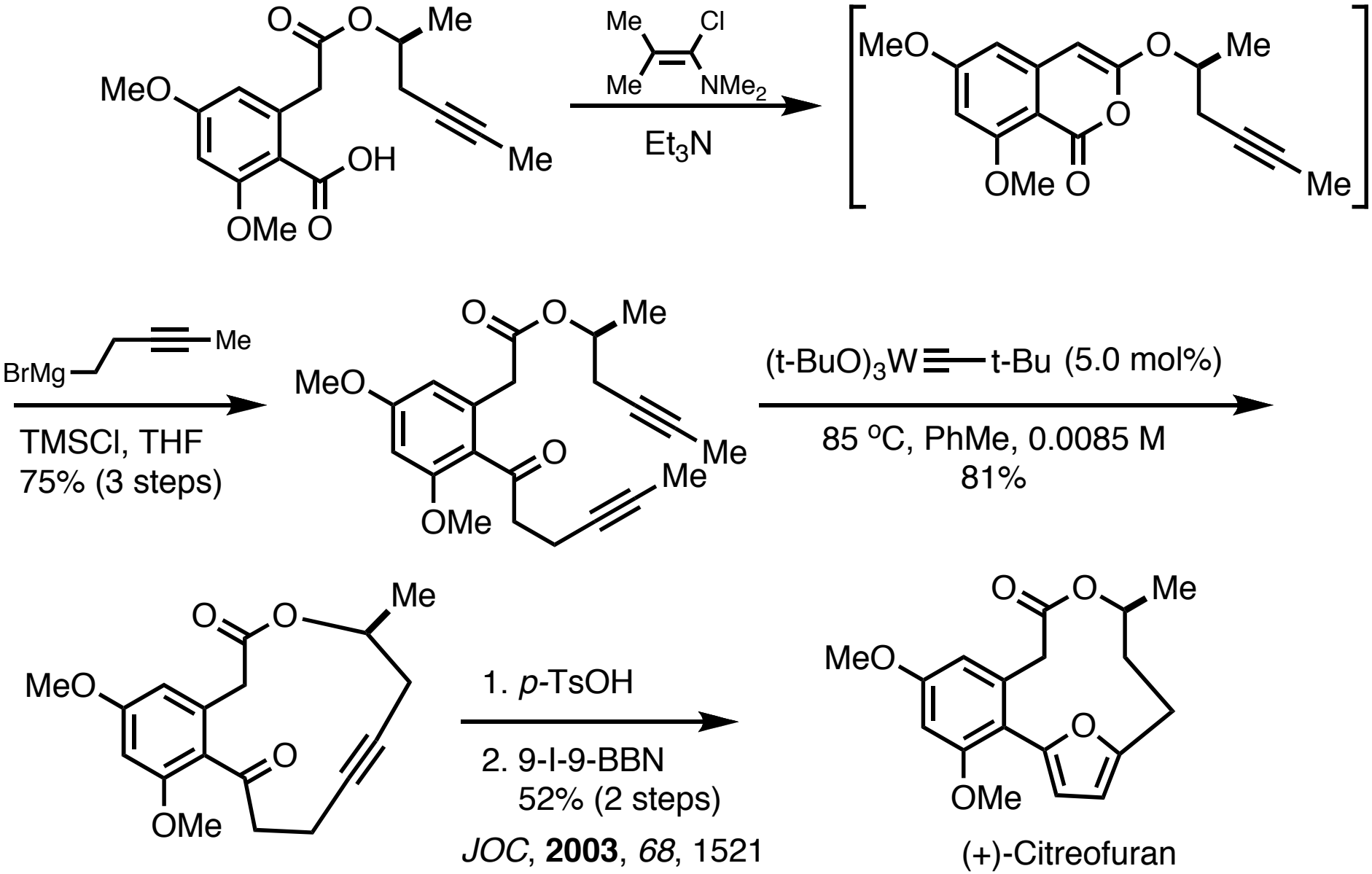
RCAM in Total Synthesis: (S)-(+)-Citreofuran



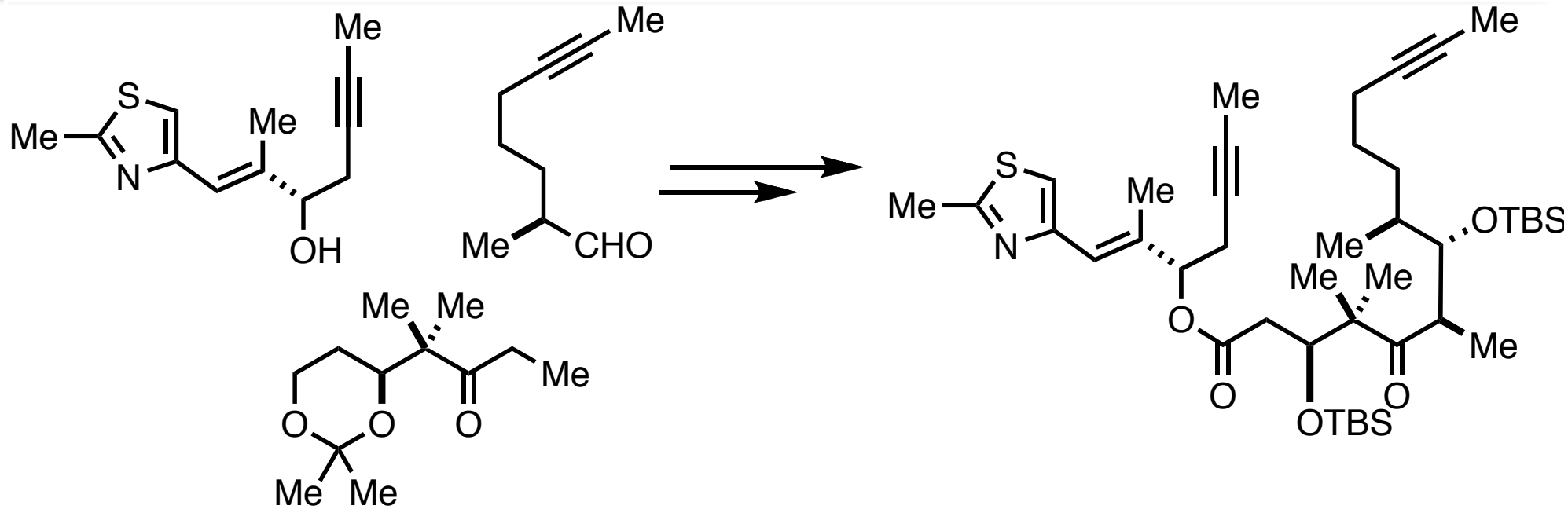
RCAM in Total Synthesis: (S)-(+)-Citreofuran

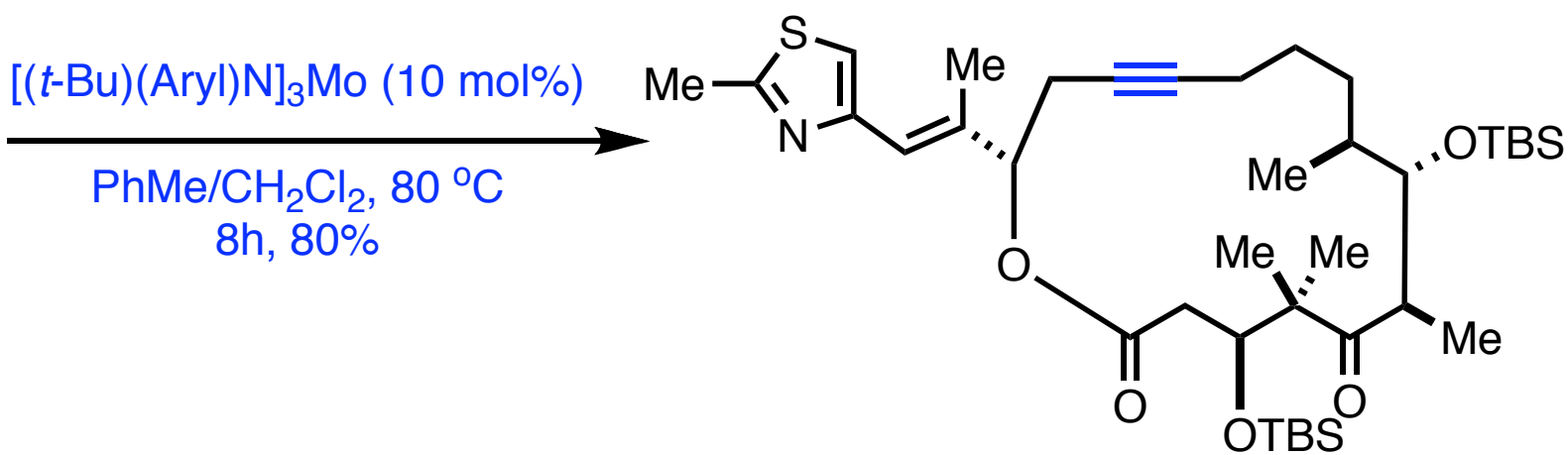


(S)-(+)-Citreofuran: Completing the Synthesis

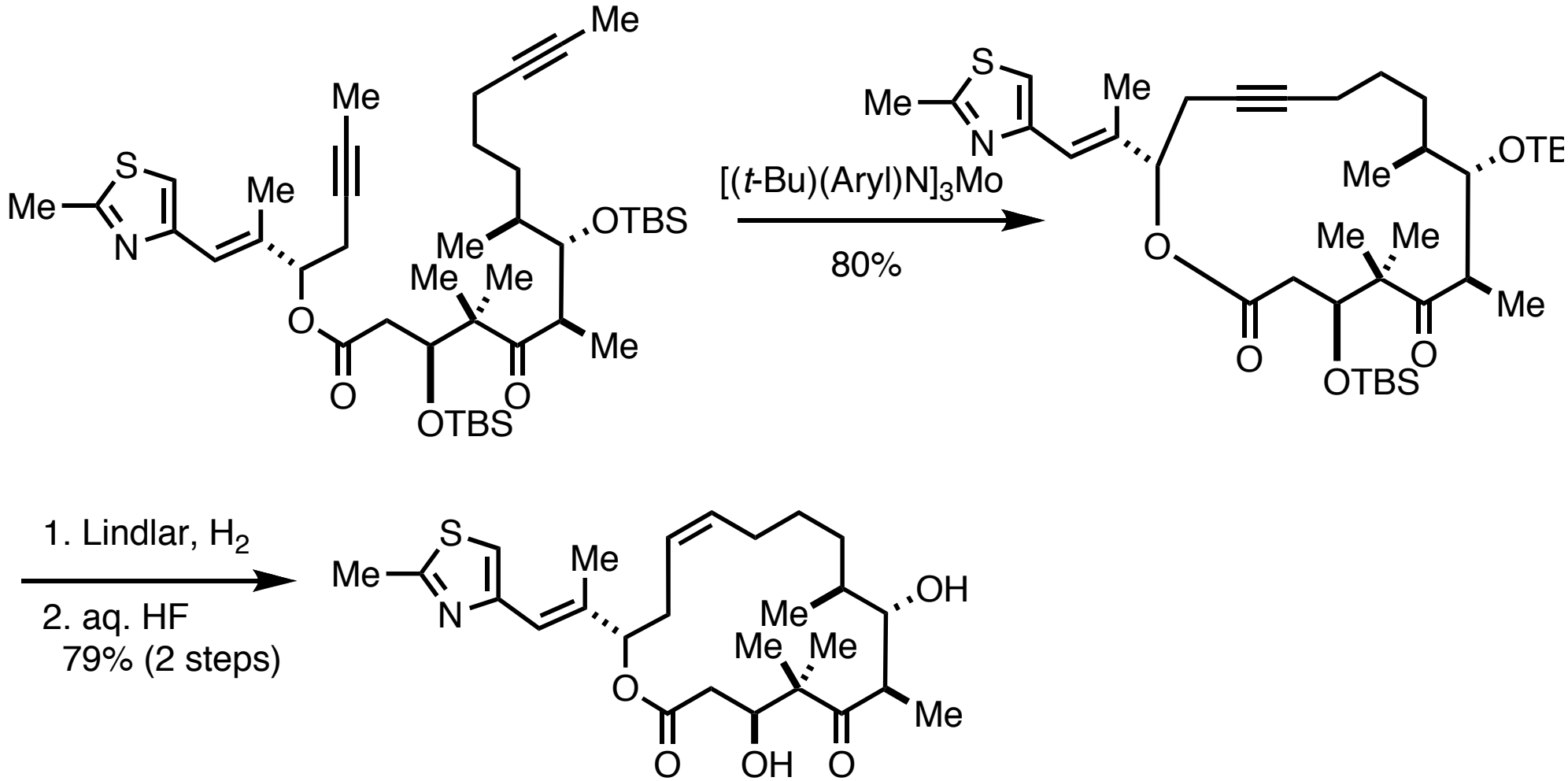


RCAM in Total Synthesis: Epothilone C





RCAM in Total Synthesis: Completing the Synthesis of Epothilone C

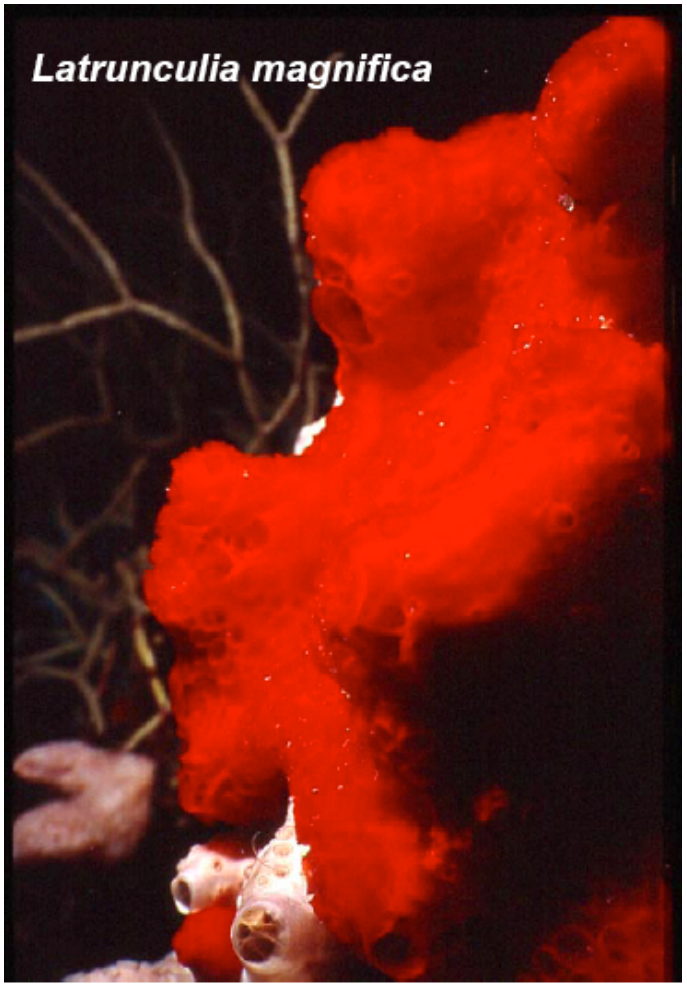


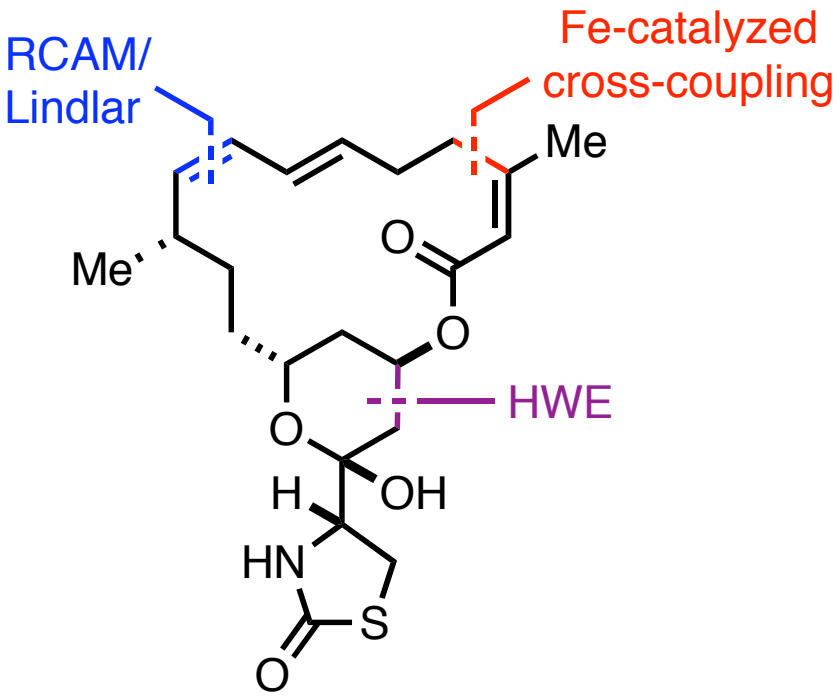
Epothilone C: 14 steps, 5.1% from 3-hydroxypropionitrile

Chem. Commun. **2001**, 1057
Chem. Eur. J. **2001**, *7*, 5299

- Best result in previous syntheses using RCM (alkene metathesis, G1)were 86% yield, 1.7:1 *E*:*Z*

Synthesis of Latrunculin A *via* Enyne-yne Metathesis



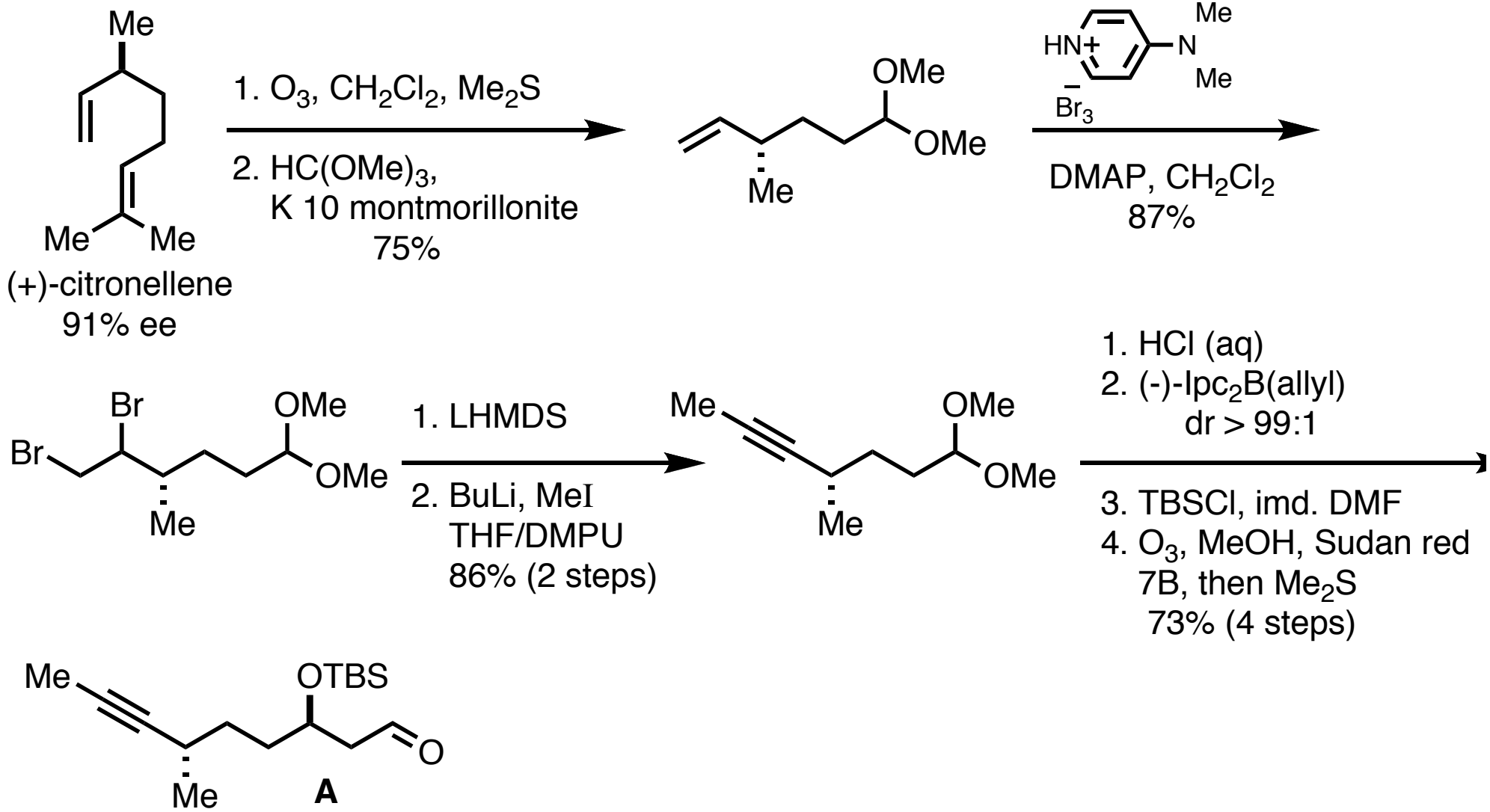


Latrunculin A

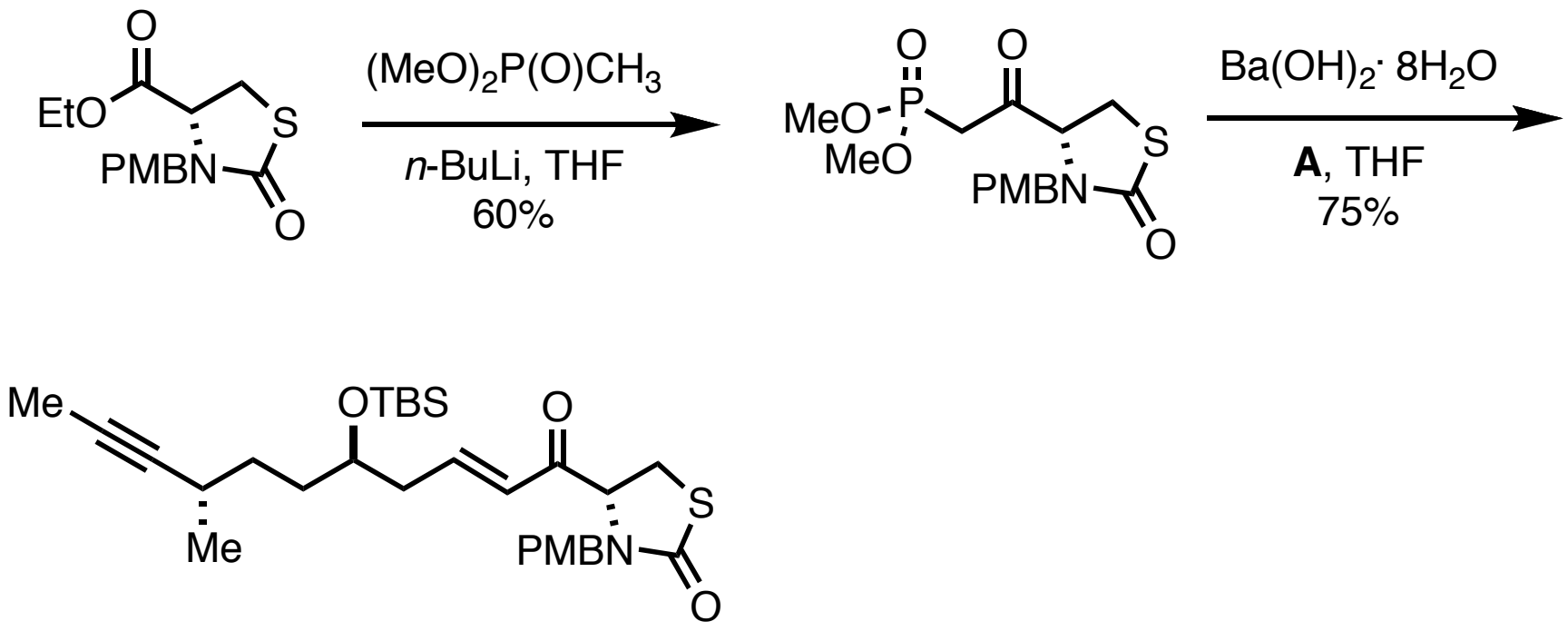
ACIEE, **2003**, *42*, 5358
ACIEE, **2005**, *44*, 3462
Chem. Eur. J. **2007**, *13*, 115

- Potent actin mirofilament disrupting agent
- Isolated from various marine organisms

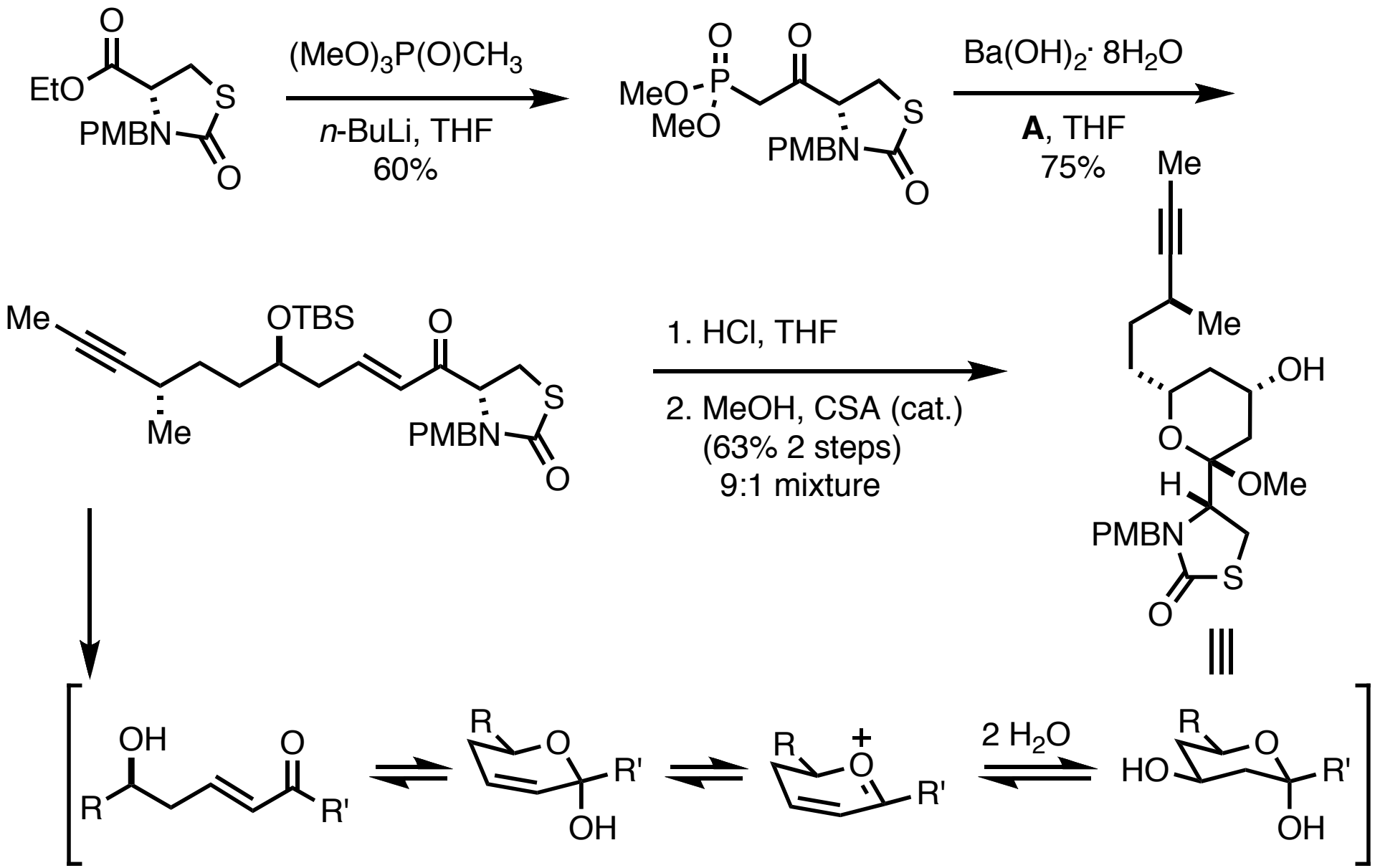
Synthesis of Latrunculin A: Building the Pyran



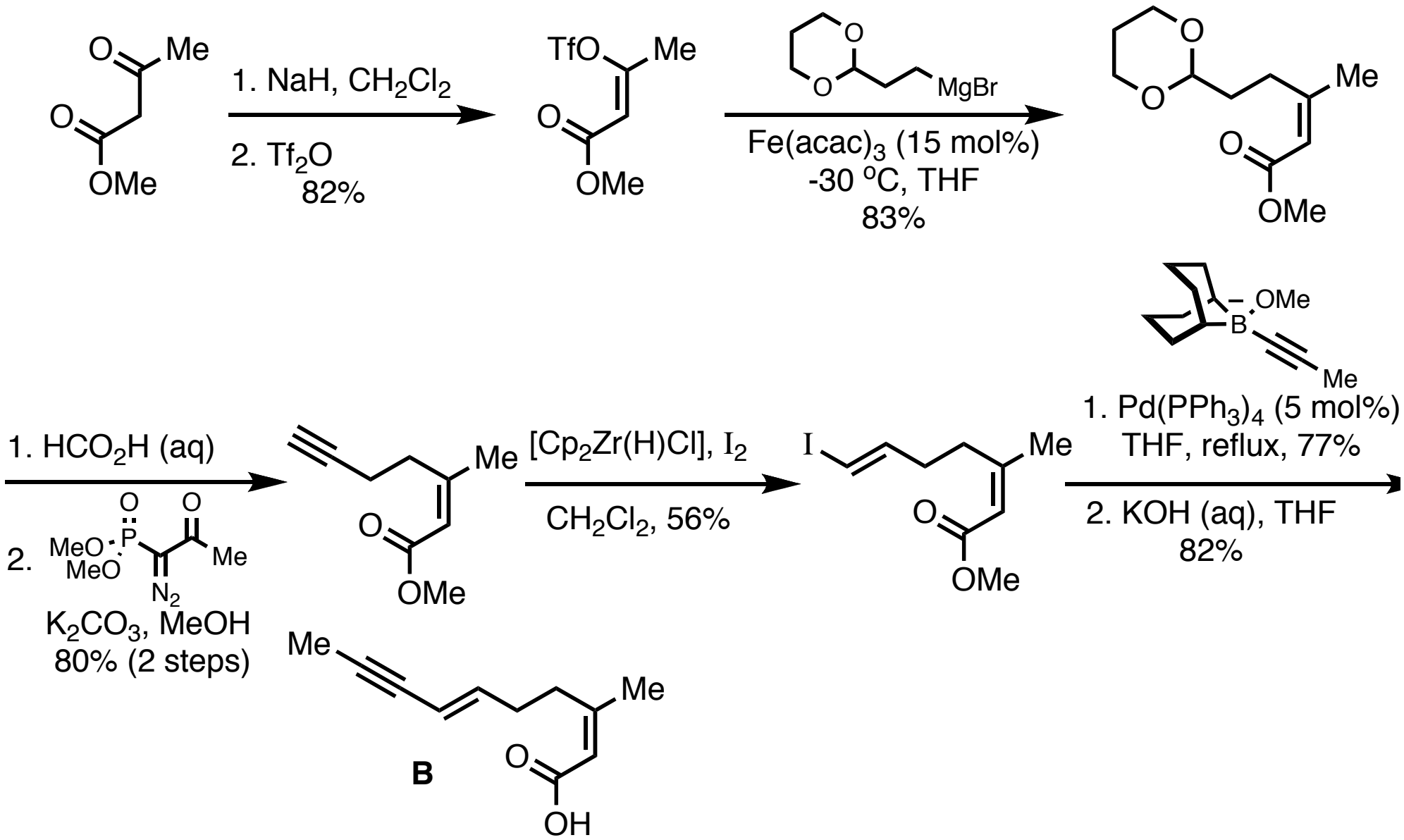
Synthesis of Latrunculin A: Building the Pyran



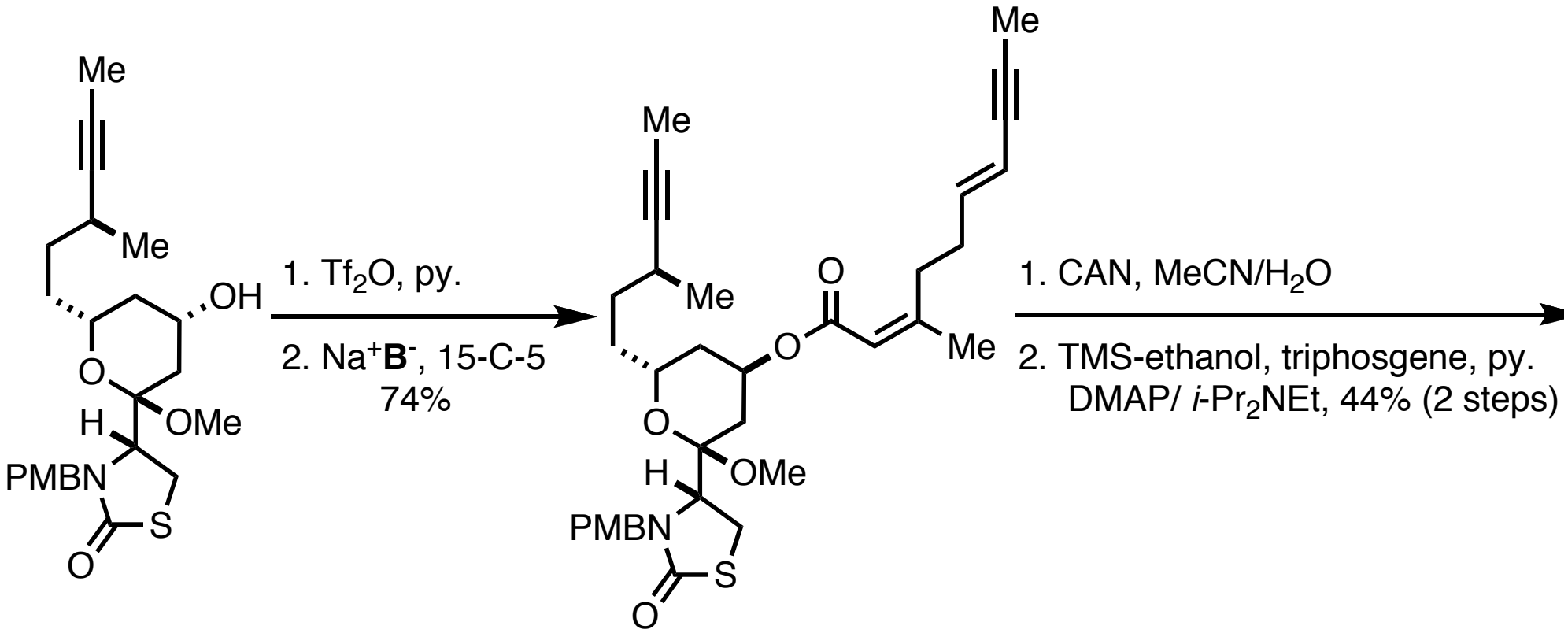
Synthesis of Latrunculin A: Building the Pyran



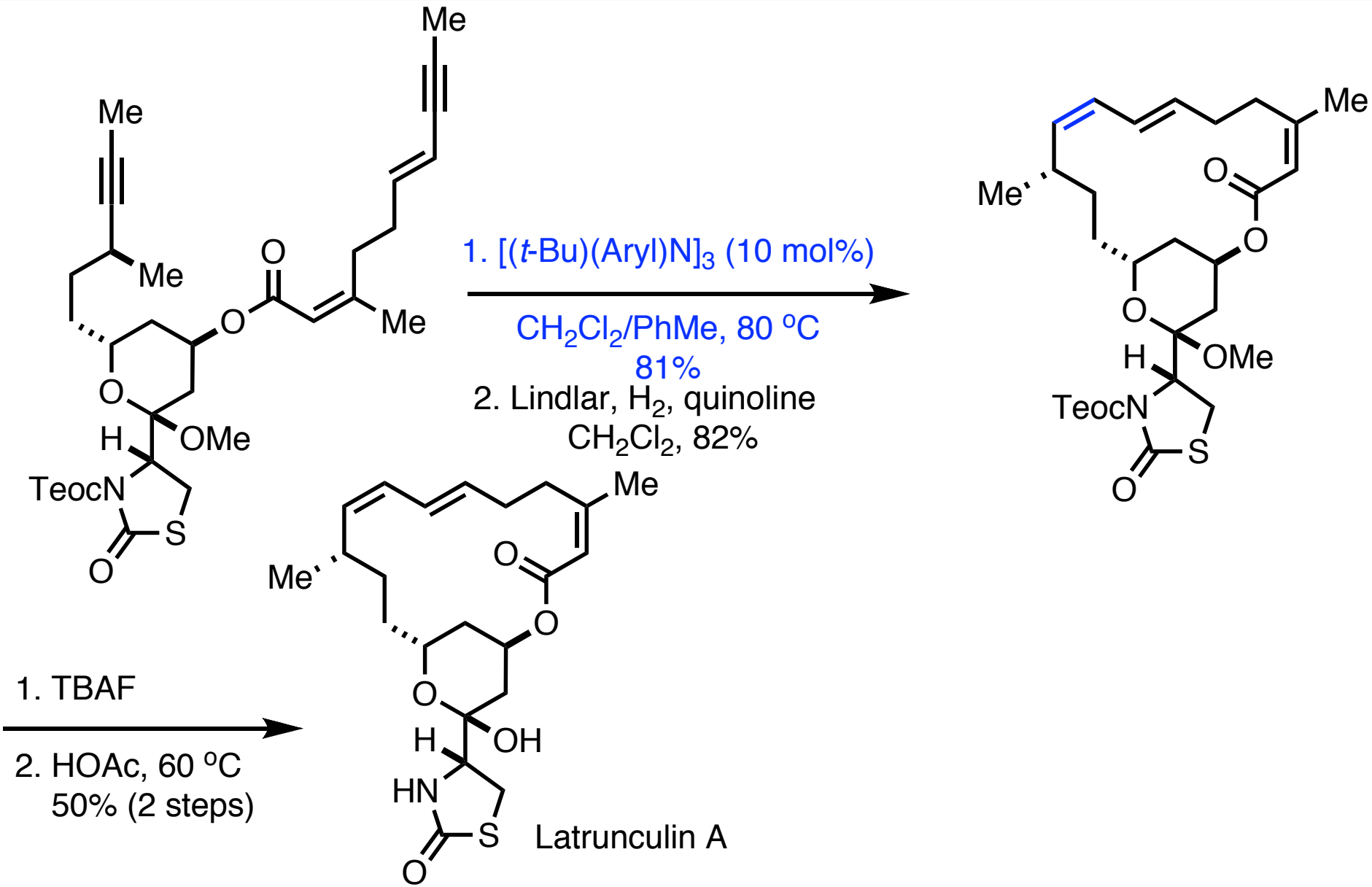
Synthesis of Latrunculin A: Building the Enyne



Synthesis of Latrunculin A: Setting the Stage for Enyne-yne Metathesis



Synthesis of Latrunculin A: End Game



Alois Fürstner Research Interests

New Synthetic Methods and Concepts for Catalysis

-Catalytic Nozaki-Hiyama-Kishi Reaction

-Titanium-induced Heterocycle Synthesis (McMurry)

-Boron Chemistry- 9-Methoxy-9-BBN Variant of the Suzuki Reaction

-*N*-Heterocyclic Carbenes and Silylenes

-Iron Catalyzed Cross-Coupling

-Platinum and Gold Cycloisomerizations

Alkene Metathesis

-Ring Closing Metathesis (RCM)

-Application of RCM in Total Synthesis

-Metathesis in $scCO_2$

-Development of Alternative RCM Catalysts

Alkyne Metathesis

-Ring Closing Metathesis (RCAM)

-Application of RCAM in Total Synthesis

-Synthesis of Metalla-Macrocycles

-Application of RCAM in the Synthesis of Materia

-Catalyst Development