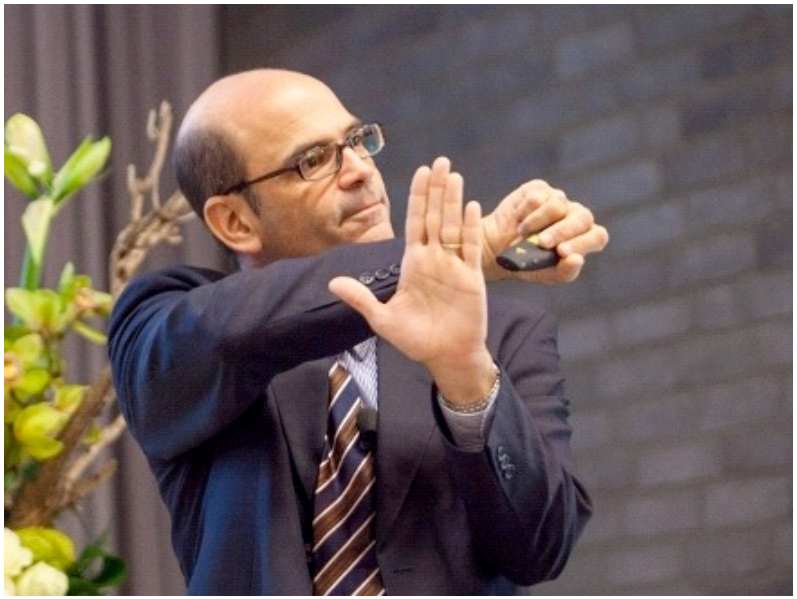
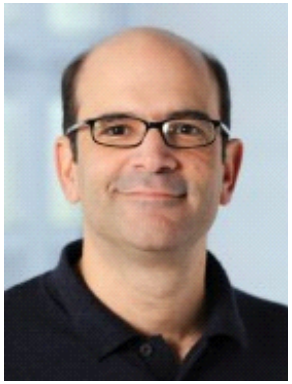
# *The career of Erick M. Carreira*



*Simon Allmendinger*

*MacMIllan Group Meeting*
*April 13, 2017*

# *A Summary*



## Education

| | |
|---|---|
| 1984 | B.S. Chemistry, University of Illinois at Urbana-Champaign<br>Scott E. Denmark |
| 1990 | Ph.D., Harvard University<br>David A. Evans |
| 1990 -1992 | PostDoc, Caltech<br>Peter B. Dervan |

## Academic Career

| | |
|---|---|
| 1992 | Assistant Professor, Caltech |
| 1996 | Associate Professor, Caltech |
| 1997 | Full Professor, Caltech |
| 1998 | Professor, ETH Zürich |
| 2011 | Member of CC-SPMD, ETH Zürich |

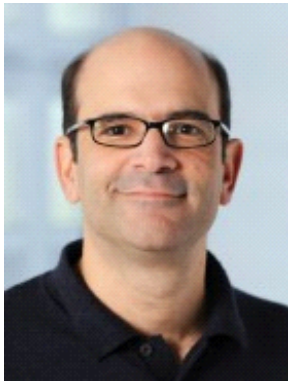
ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

## Famous students

Justin DuBois, Tehshik P. Yoon, Jeffrey W. Bode, Tobias Ritter, Jérôme Waser, Corey C. Stephenson

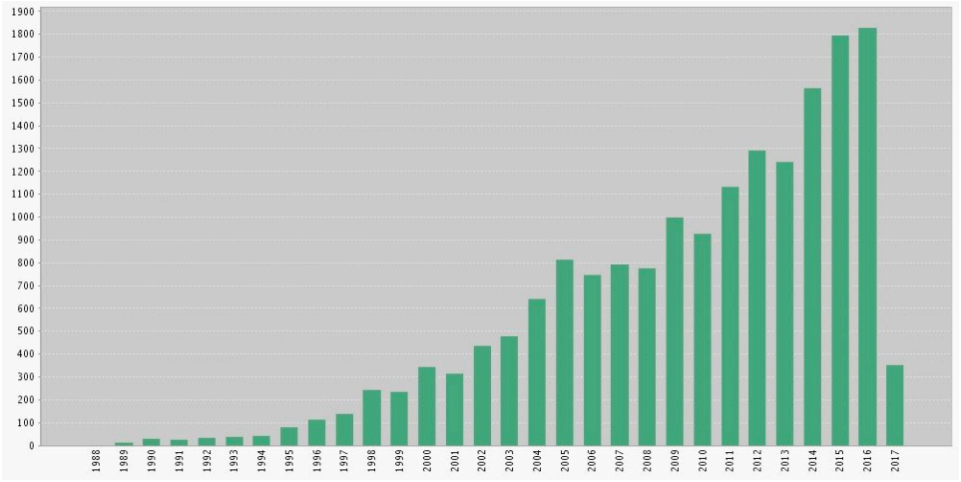
# *A Summary*



- Associate Editor: Org. Lett., Thieme (Synfacts & Synthesis), Org. Synth.

- Awards: ERC commission award, Alfred P. Sloan Fellowship,
  Nobel Laureate Signature Award,
  ACS award for creative work in synthetic organic synthesis,
  ACS award in Pure Chemistry,
  numerous awards sponsored by pharmaceutical companies (DSM, Merck, Eli Lilly, Pfizer)

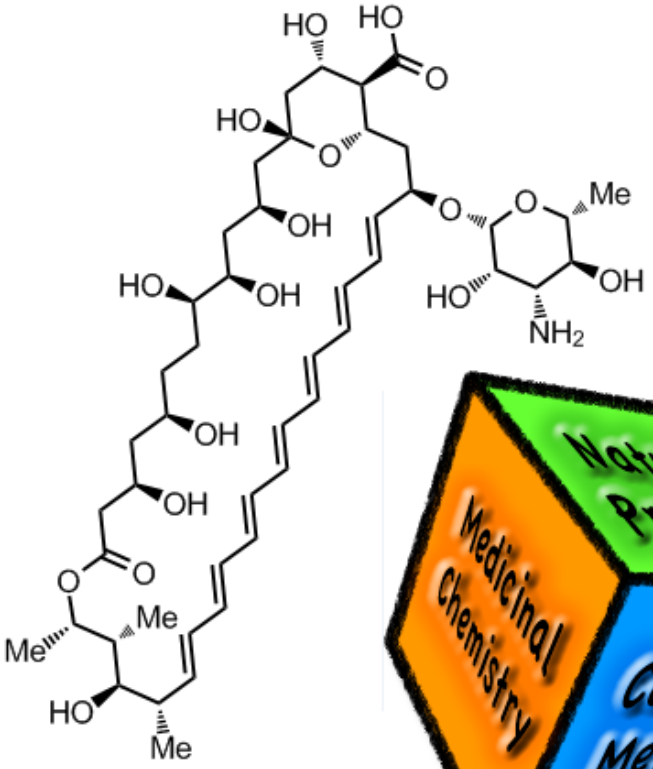
- Papers published: **300**
- citations: **>17´000**
- average citations/paper: **~58**
- h-index: **70**



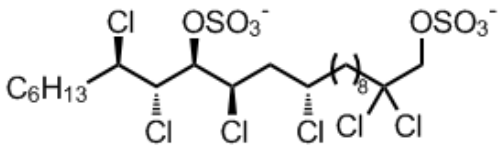

citations/year

- cofounder of three companies: Lipideon, SpiroChem, Glycemicon

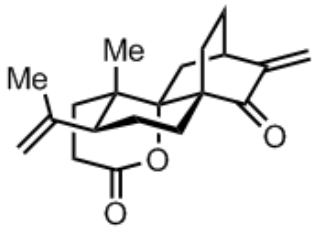
# *Research in the Carreira Lab*



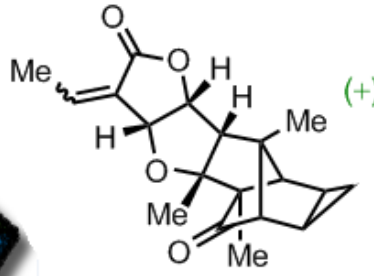
Amphotericin B



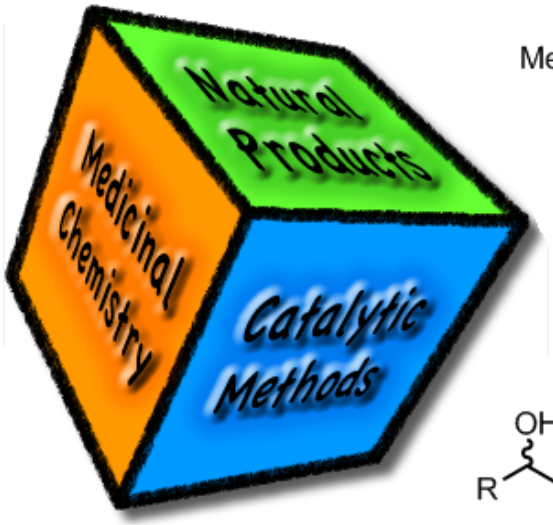
(+)-Danicalipin A

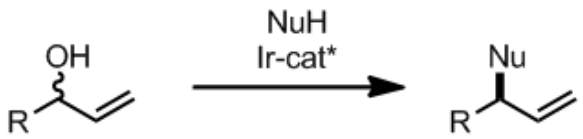


(+)-Crotogoudin

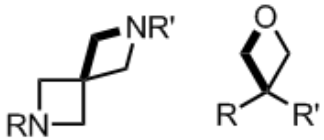


(±)-Pallambin A & B

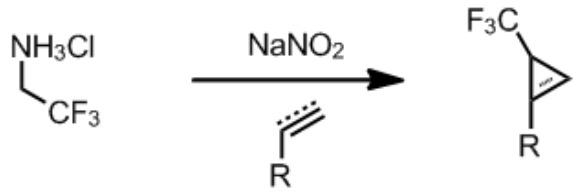



Catalytic Enantioselective Allylic Substitution



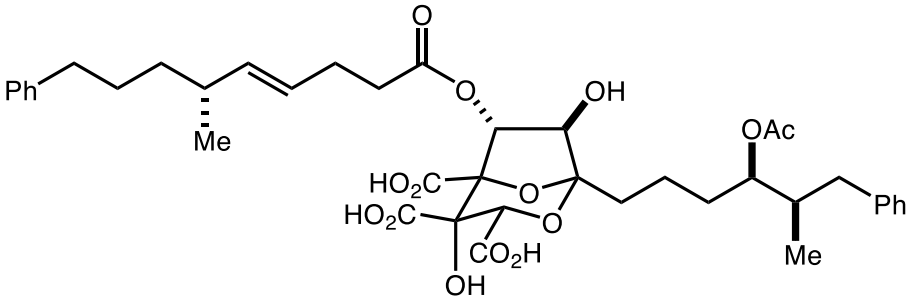
New Heterocyclic Building Blocks



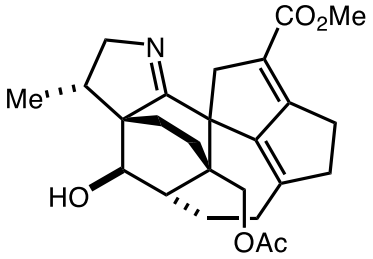

In-situ Generation of Diazomethanes and their Applications

# *Total Synthesis in the Carreira Lab*

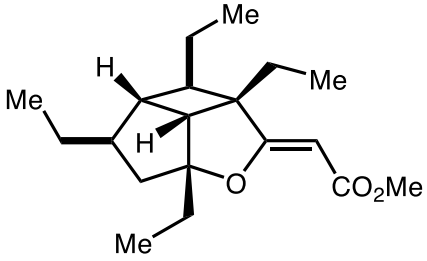
- Polycyclic compounds



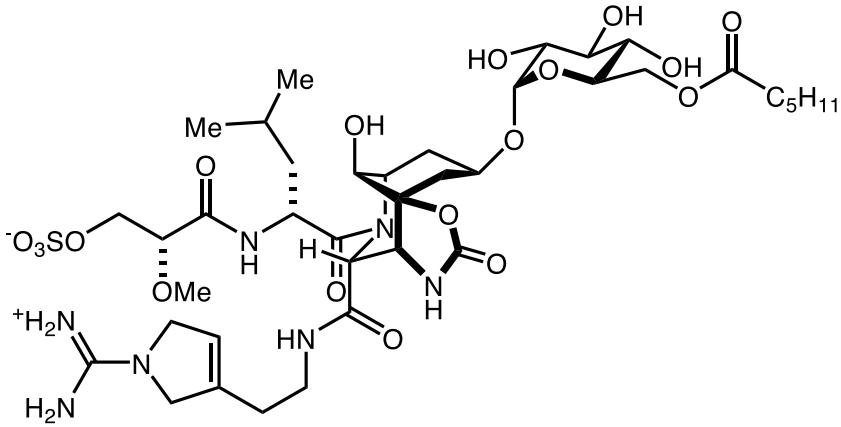

**(+)-Zaragozic Acid C (1994, 1995)**




**(+)-Daphmanidin E (2011)**



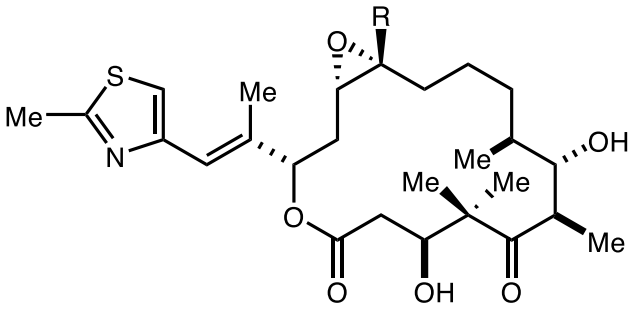

**($^{+}$)-Hippolachnin (2014)**



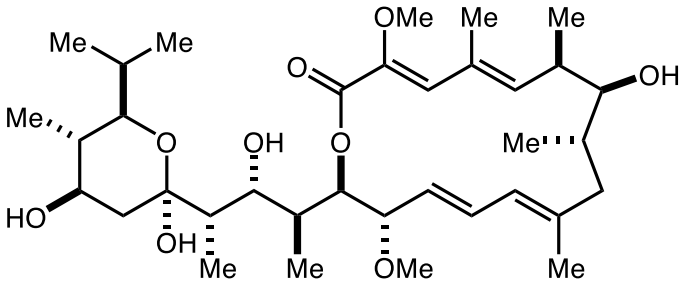

**Banyaside B (2008, 2010 both nominal)**

# *Total Synthesis in the Carreira Lab*

- Macrolides

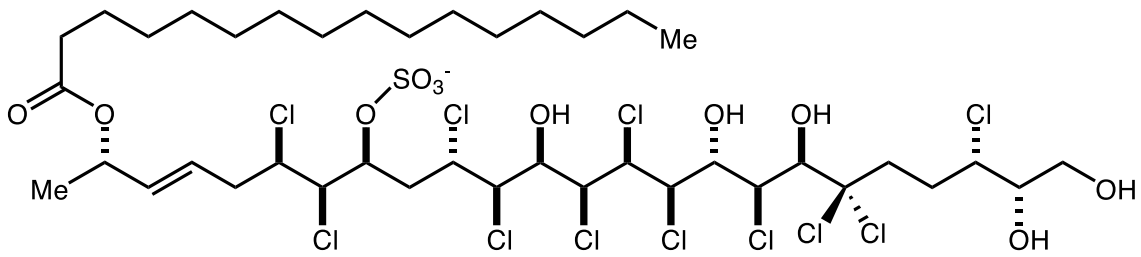



**Epothilone A & B (2001)**



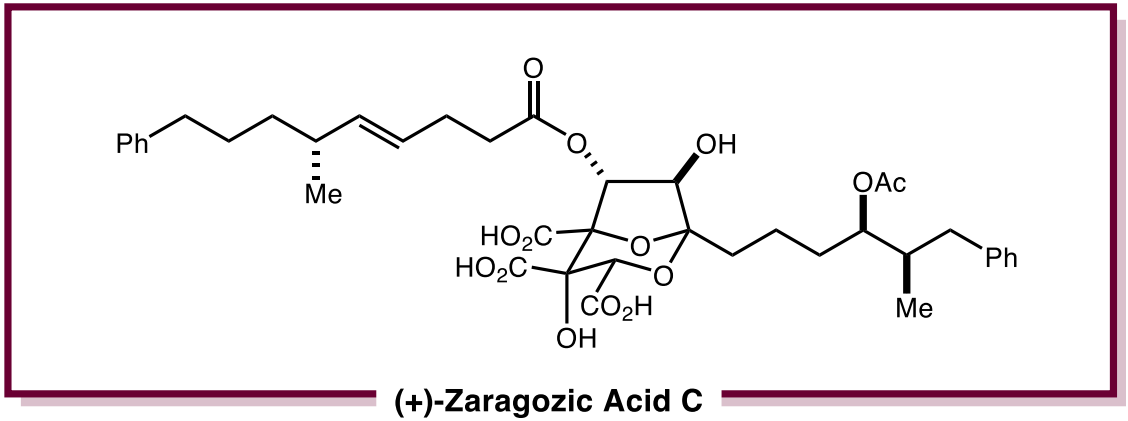

**Bafilomycin $A_1$ (2009)**

- Chlorosulfolipid cytotoxins




**Undecachlorosulfolipid A (2011)**

# *Total Synthesis in the Carreira Lab*



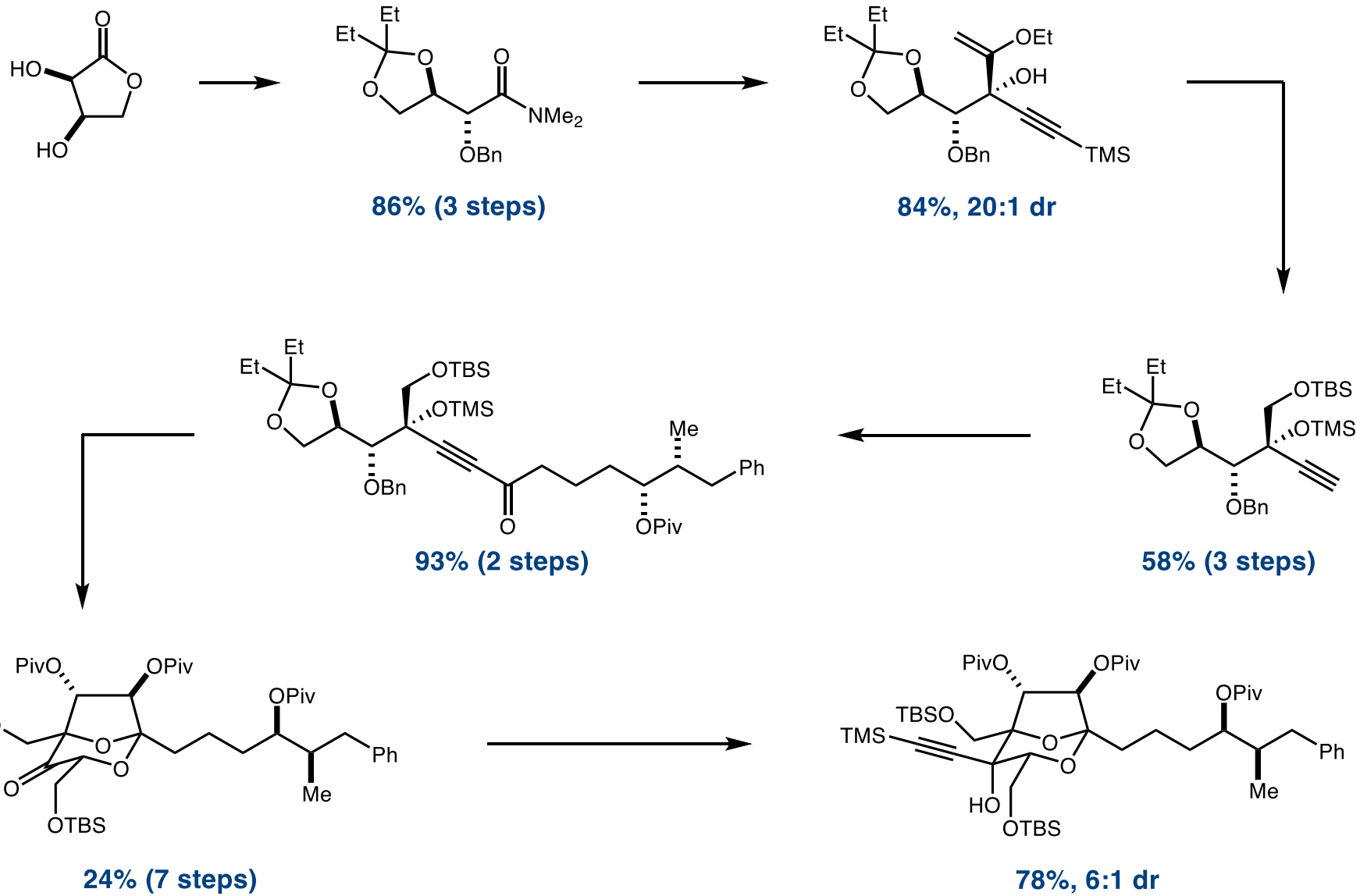

**(+)-Zaragozic Acid C**


Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.

Carreira, E. M.; Du Bois, J.; *Tetrahedron Lett.* **1995**, *36*, 1209.

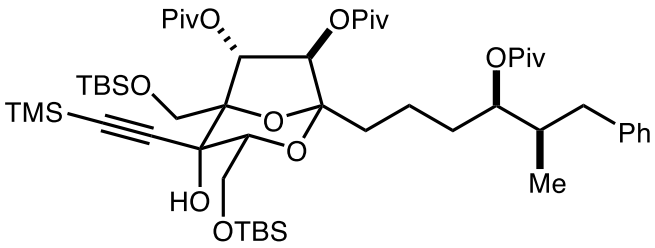
Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1995**, *117,* 8106.

# *(+)-Zaragozic Acid C*

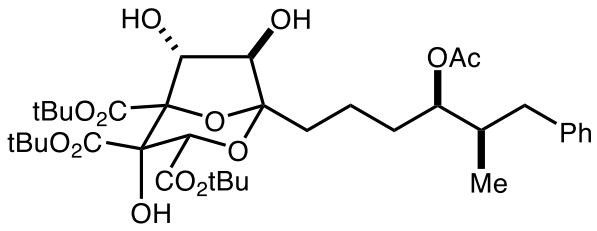



Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.

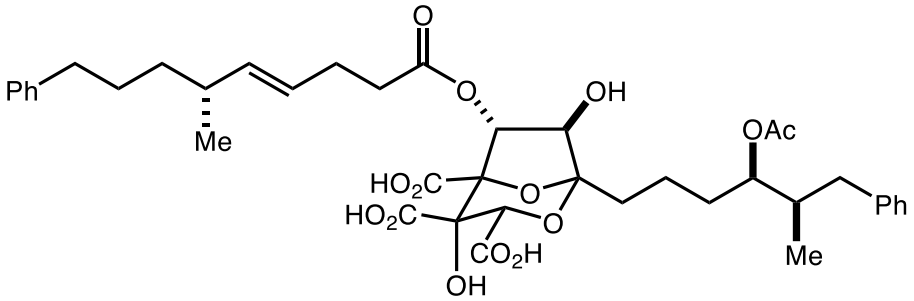
# *(+)-Zaragozic Acid C*






**22% (13 steps)**




**22% (2 steps)**

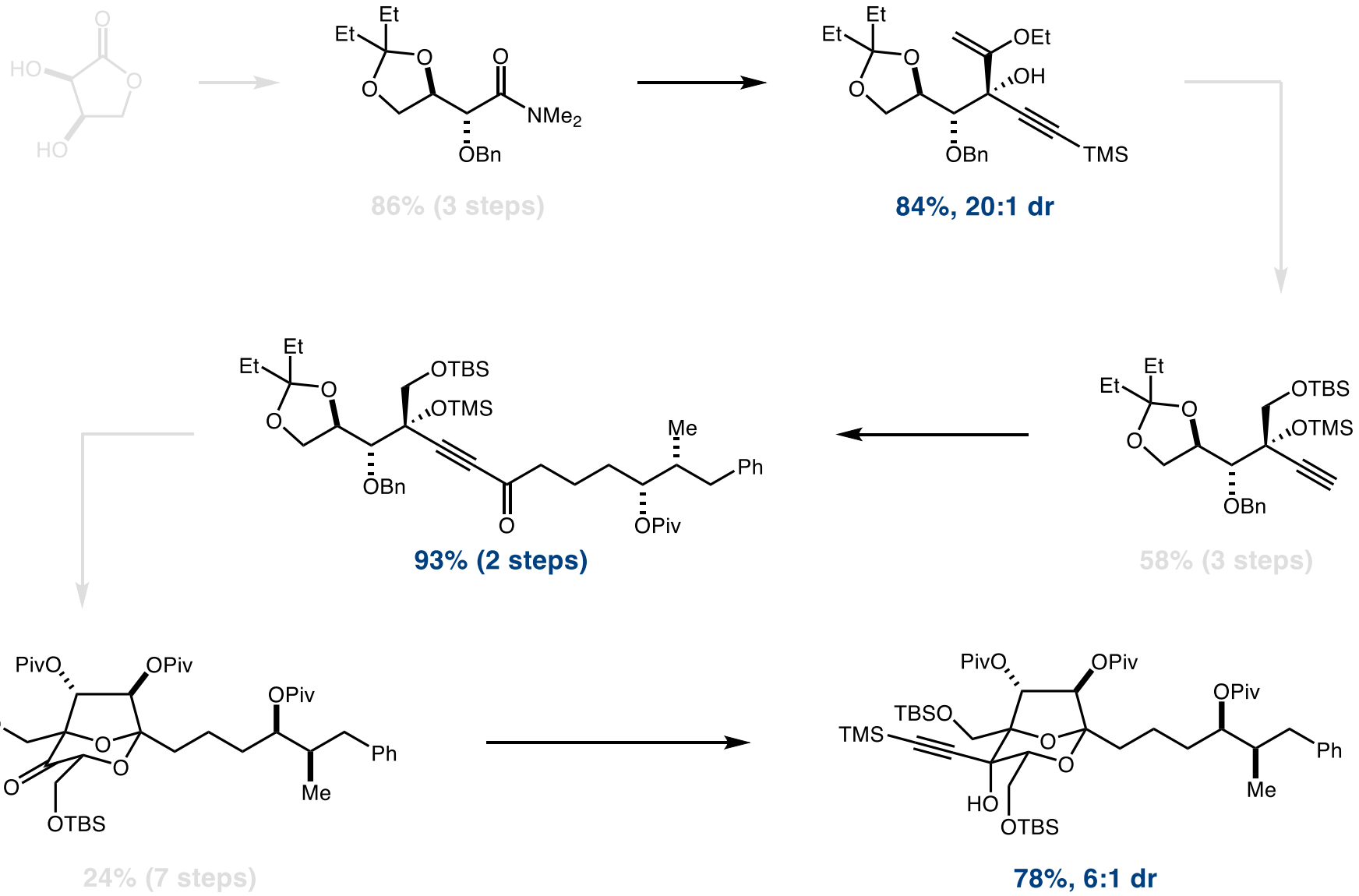
**(+)-Zaragozic Acid C**

44 steps, 28 longest linear

0.4% overall yield

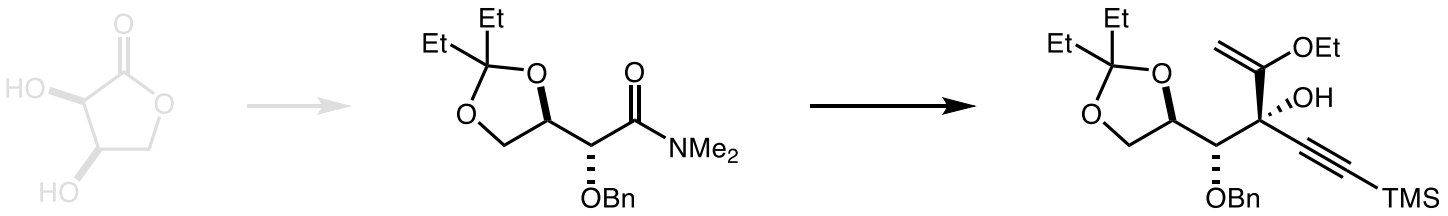
Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.

# *(+)-Zaragozic Acid C*



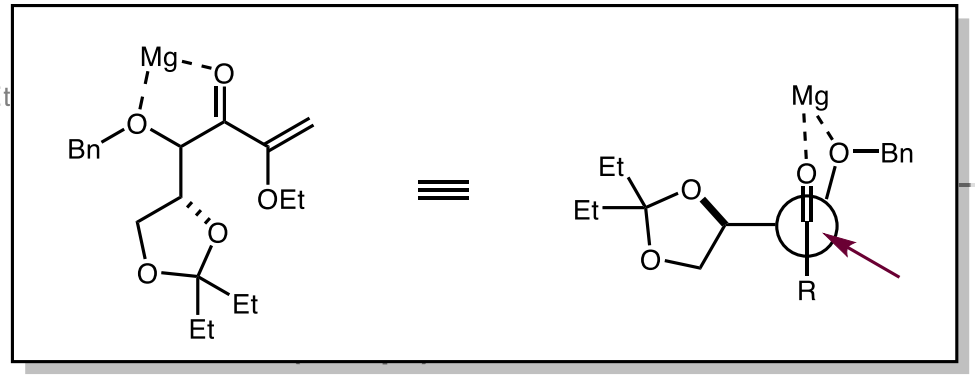

Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.

# (+)-Zaragozic Acid C




86% (3 steps)

84%, 20:1 dr







58% (3 steps)



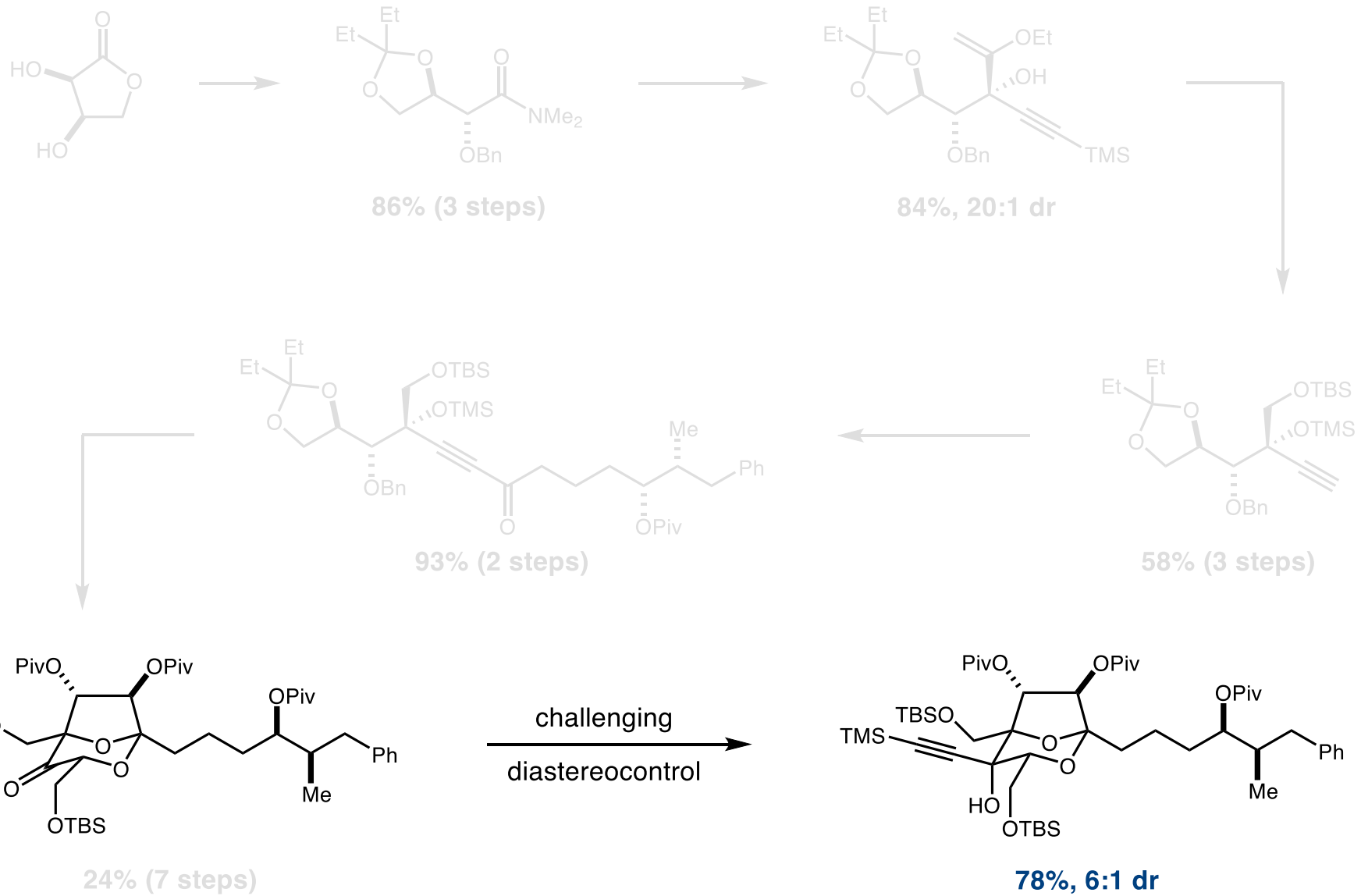

24% (7 steps)




78%, 6:1 dr

Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.

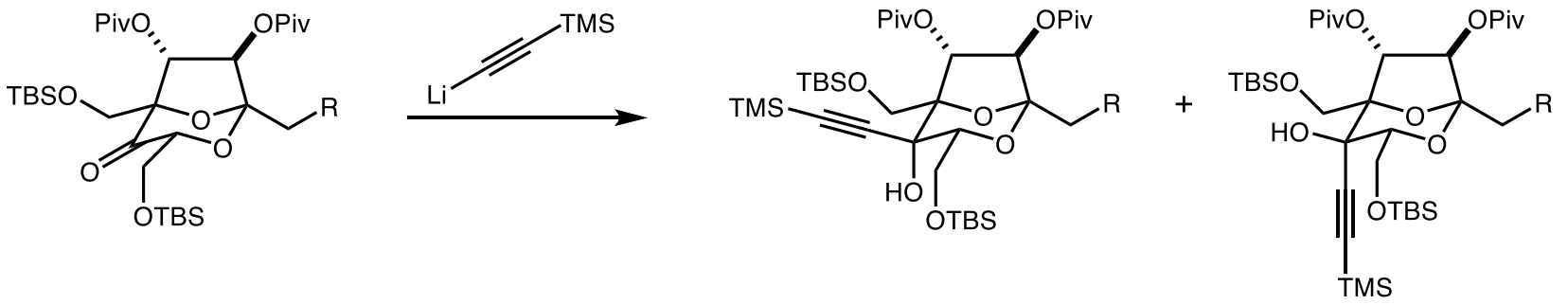
# *(+)-Zaragozic Acid C*




Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.

# *(+)-Zaragozic Acid C*

- Diastereoselectivity in Acetylide addition

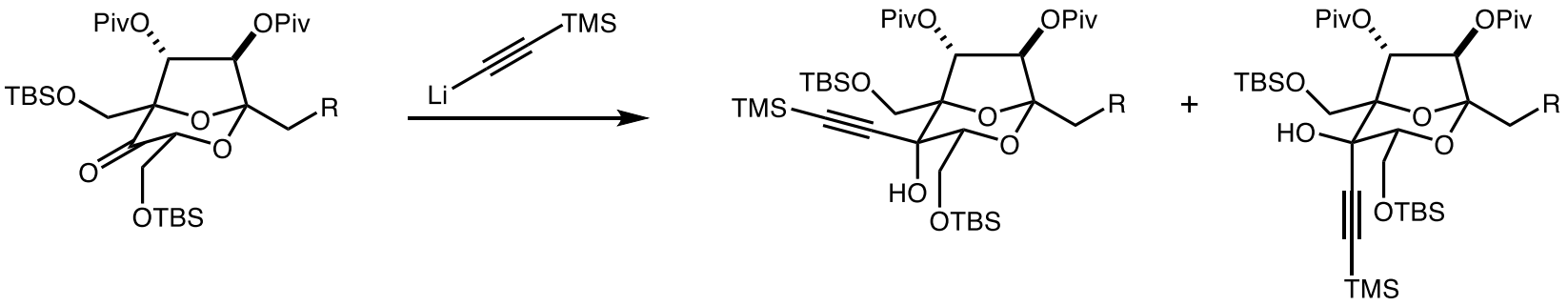


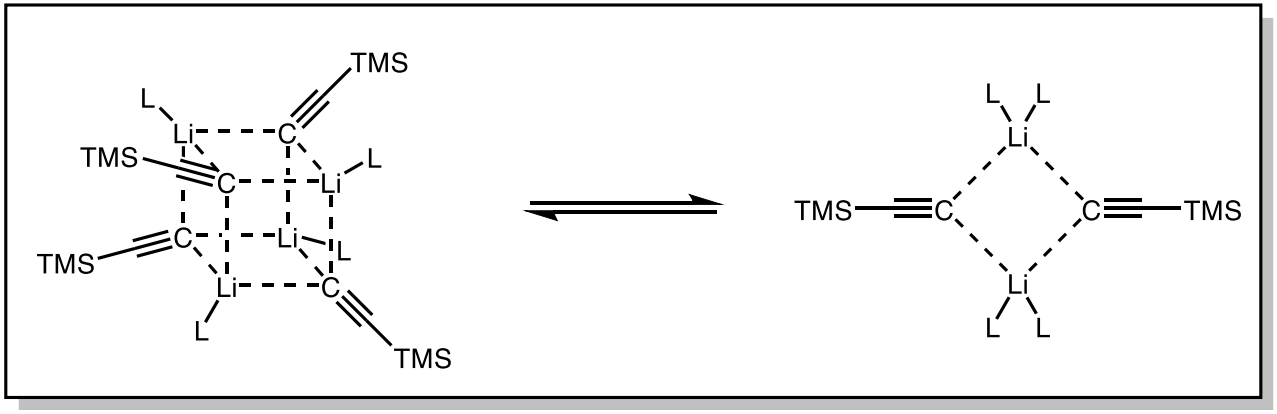

| | | |
|---|---|---|
| THF | 1.5 | 1 |
| THF / TMEDA | 1 | 2 |
| $Et_2O$ | 3.5 | 1 |
| $Et_2O$ / diglyme | 2.2 | 1 |
| $Et_2O$ / 1.0 eq. LiBr | 3.1 | 1 |
| $Et_2O$ / 150 eq. LiBr | 1 | 1.7 |
| **$Et_2O$ / $Me_3N$** | **6.1** | **1** |


Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.
Carreira, E. M.; Du Bois, J.; *Tetrahedron Lett.* **1995**, *36*, 1209.
Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1995**, *117*, 8106.

# *(+)-Zaragozic Acid C*

- Diastereoselectivity in Acetylide addition



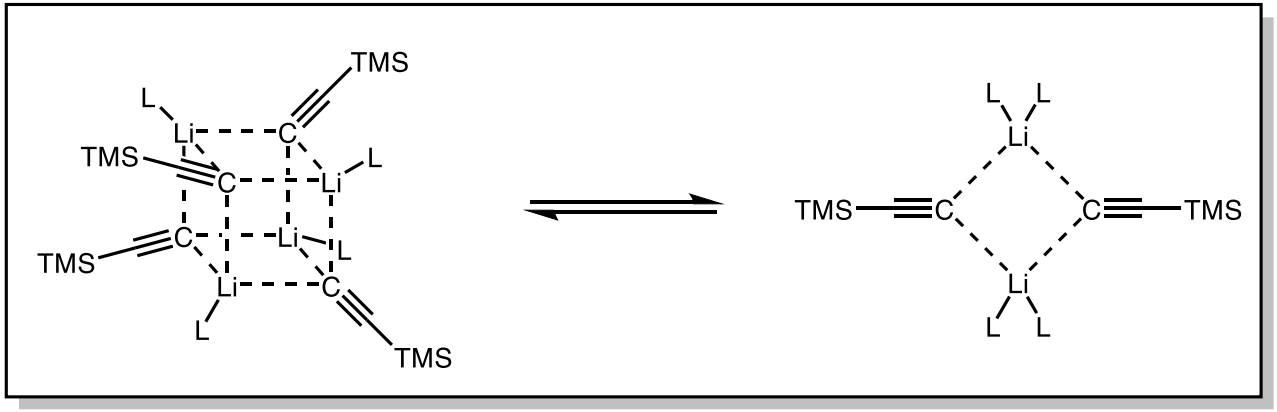





Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.
Carreira, E. M.; Du Bois, J.; *Tetrahedron Lett.* **1995**, *36*, 1209.
Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1995**, *117*, 8106.

# *(+)-Zaragozic Acid C*

- Diastereoselectivity in Acetylide addition




**Tetramer**

less coordinating solvents
bulky monodentate ligands

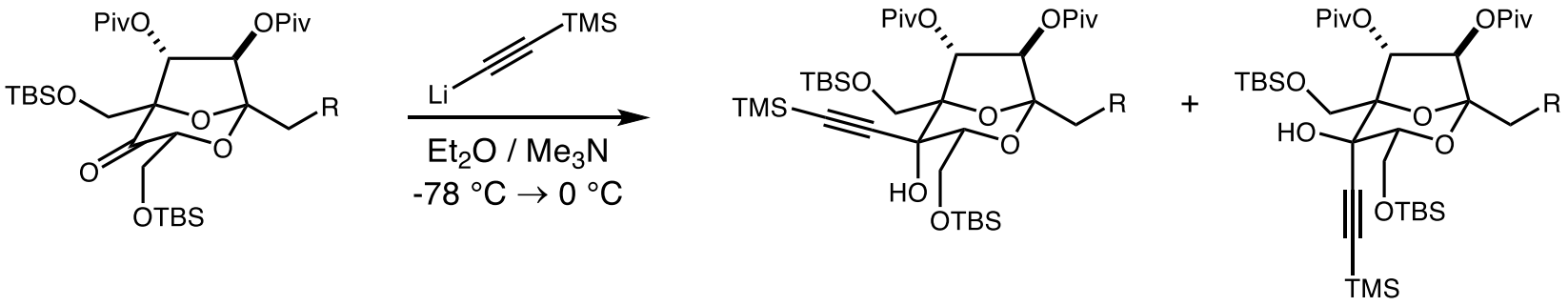
**Dimer**

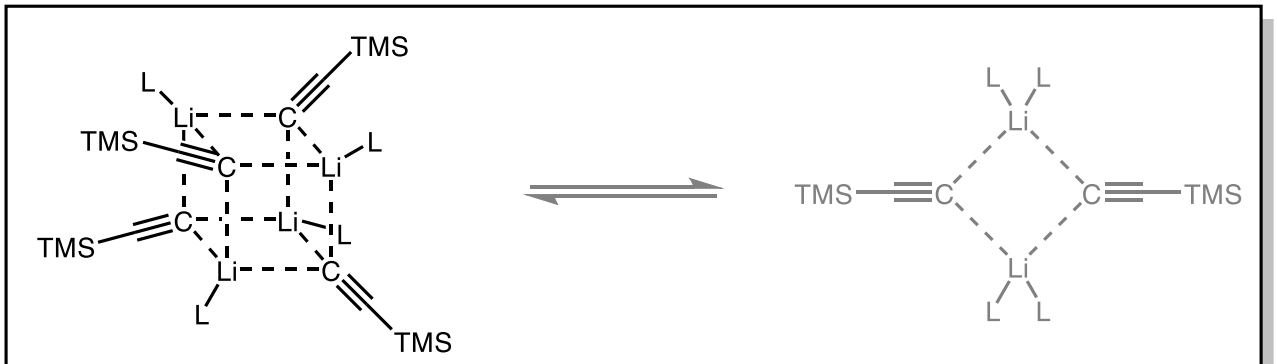
coordinating solvents,
bidentate ligands
large excess of small ligands


Hässig, R.; Seebach, D.; *Helv. Chim. Acta* **1983**, *66*, 2269.
Fraenkel, G.; Pramanik, P.; *J. Chem. Soc., Chem. Commun.* **1983**, 1527.
Bauer, W.; Seebach, D.; *Helv. Chim. Acta* **1984**, *67*, 1972.
Geissler, M.; Kopf, J.; Schubert, B.; Weiss, E.; Neugebauer, W.; von Ragué Schleyer, P.; *Angew. Chem. Int. Ed.* **1987**, *26,* 587.

# *(+)-Zaragozic Acid C*

- Diastereoselectivity in Acetylide addition



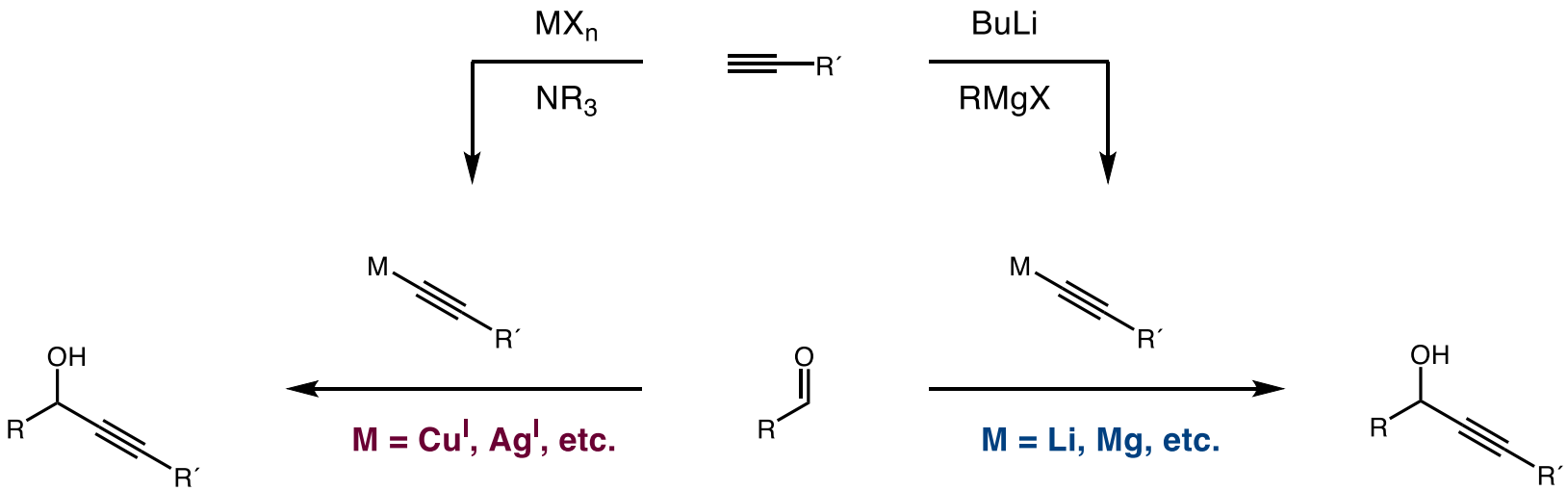




**Aggregation state of acetylide dictates diastereocontrol**


Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1994**, *116*, 10825.
Carreira, E. M.; Du Bois, J.; *Tetrahedron Lett.* **1995**, *36*, 1209.
Carreira, E. M.; Du Bois, J.; *J. Am. Chem. Soc.* **1995**, *117*, 8106.

# *Addition of Acetylides to carbonyl coumpounds*

- Acetylide addition to carbonyl compounds




*easy and mild preparation in-situ*

*but*

*low (no) reactivity*

*high reactivity*

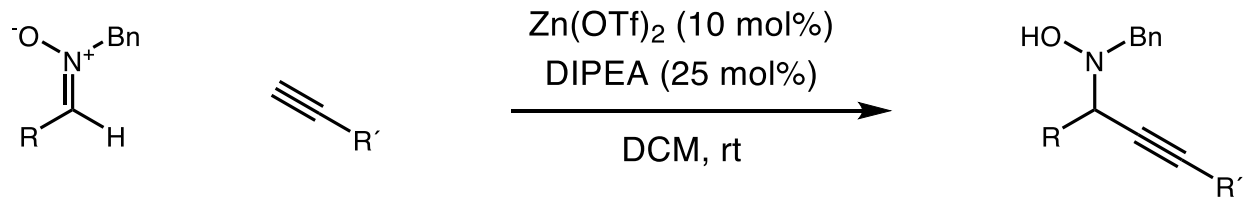
*but*

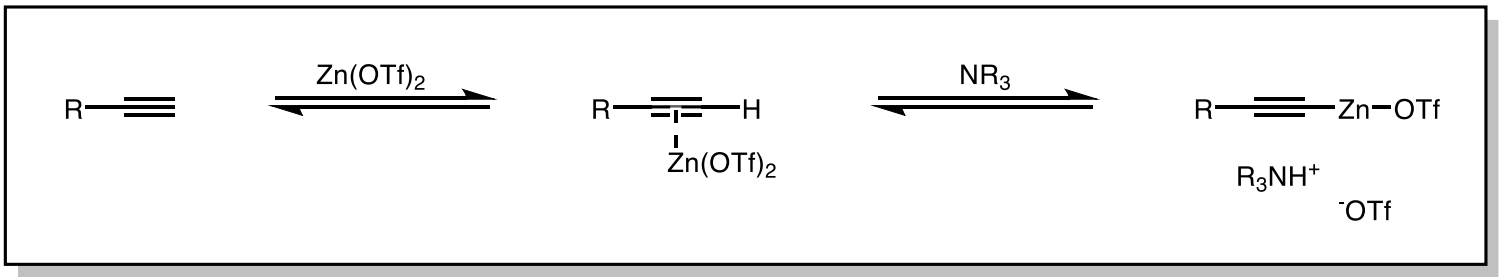
*need for preformation of acetylide*

Frantz, D. E.; Fässler, R.; Carreira, E. M.; *J. Am. Chem. Soc.* **1999**, *121,* 11245.

# *Addition of Acetylides to carbonyl coumpounds*

- $Zn(OTf)_2$ catalyzed addition of terminal alkynes to Nitrones



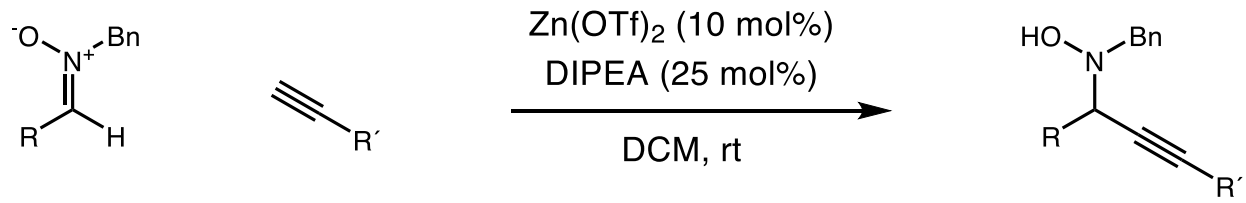


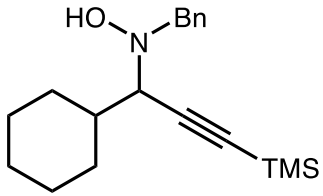
Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M.; *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101, 5843.*

Frantz, D. E.; Fässler, R.; Carreira, E. M.; *J. Am. Chem. Soc.* **1999**, *121,* 11245.

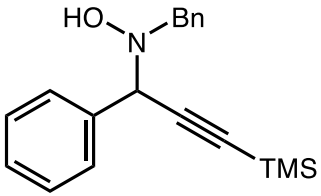
# *Addition of Acetylides to carbonyl coumpounds*

- $Zn(OTf)_2$ catalyzed addition of terminal alkynes to Nitrones

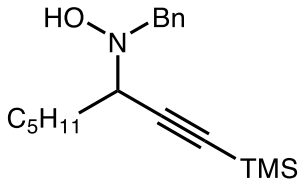


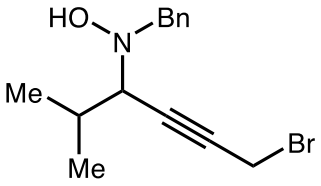

**95% yield**



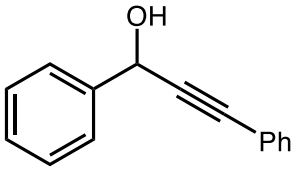

**43% yield**



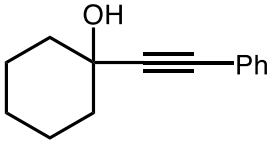

**62% yield**



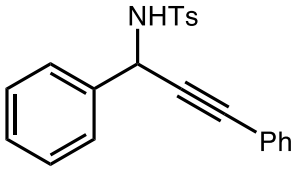

**68% yield**



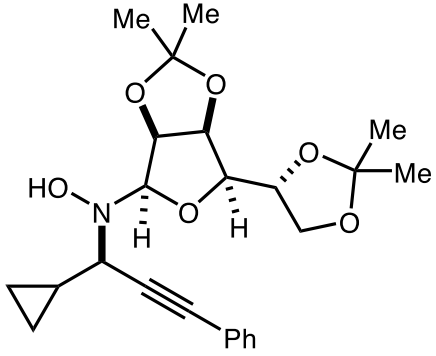

**84% yield**




**80% yield**




**43% yield**

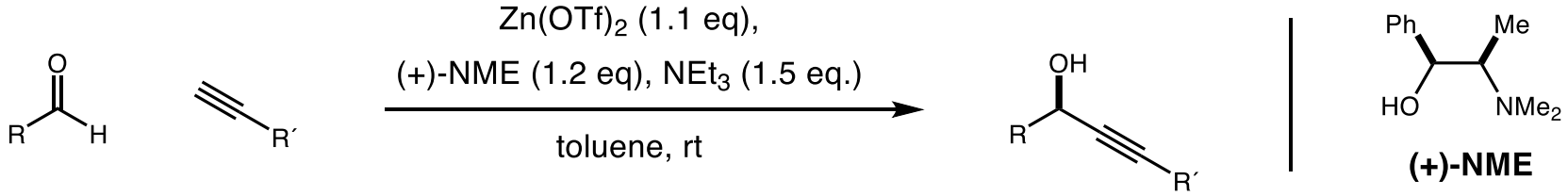


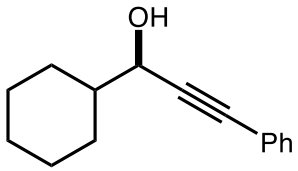

**92% yield, 15:1 dr**


Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2002**, *41*, 3054.
Frantz, D. E.; Fässler, R.; Carreira, E. M.; *J. Am. Chem. Soc.* **1999**, *121*, 11245.

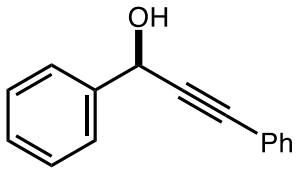
# *Addition of Acetylides to carbonyl coumpounds*

- enantioselective Zn-mediated addition of terminal alkynes to aldehydes

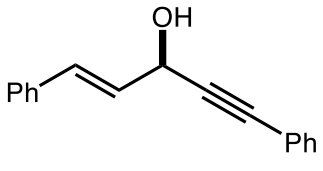


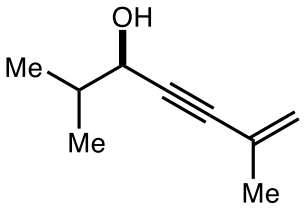

**95%, 96% ee**



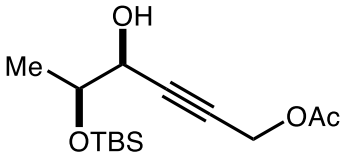

**53%, 94% ee**



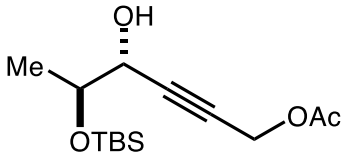

**39%, 80% ee**




**94%, 98% ee**




**70%, 26:1 dr**

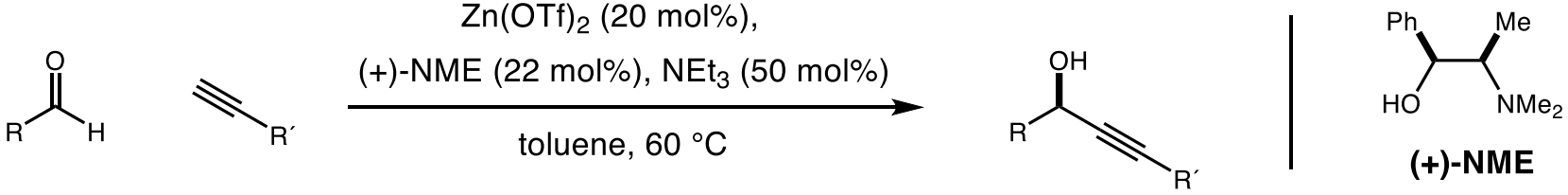


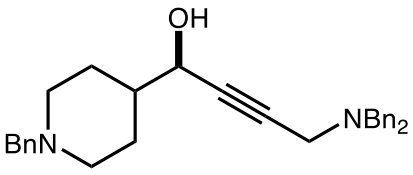

**69%, 1:10 dr**
*with (-)-NME*


Frantz, D. E.; Fässler, R.; Carreira, E. M.; *J. Am. Chem. Soc.* **2000**, *122*, 1806.
El-Sayed, E.; Anand, N. K.; Carreira, E. M.; *Org. Lett.* **2001**, *3*, 3017.

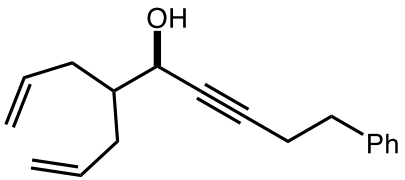
# *Addition of Acetylides to carbonyl coumpounds*

- enantioselective Zn-catalyzed addition of terminal alkynes to aldehydes

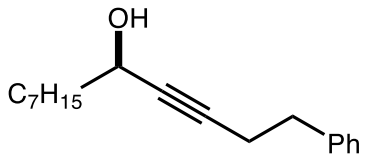


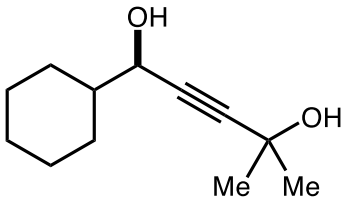

**81%, 94% ee**



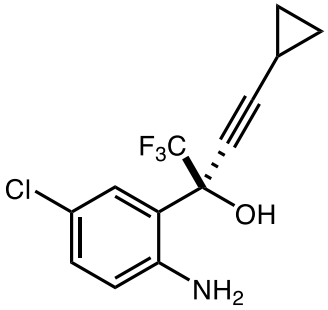

**80%, 93% ee**




**45%, 92% ee**



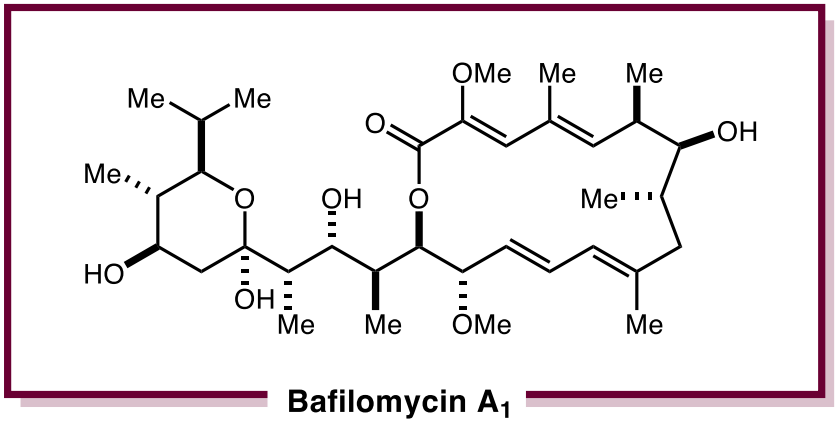

**80%, 99% ee**




**67%, 99% ee**


Anand, N. K.; Carreira, E. M.; *J. Am. Chem. Soc.* **2001**, *123*, 9687.
Chinkov, N.; Warm, A.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2011**, *50*, 2957.

# *Addition of Acetylides to carbonyl coumpounds*

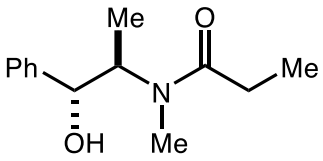


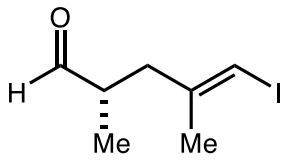

**Bafilomycin $A_1$**


Kleinbeck, F.; Carreira, E. M..; *Angew. Chem. Int. Ed.* **2009**, *48*, 578.

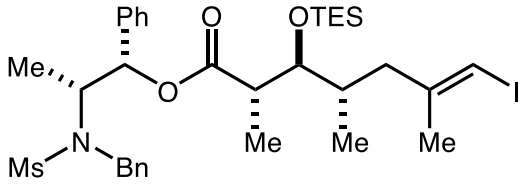
Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M.; *Chem. Eur. J.* **2012**, *18,* 3598.

# *Bafilomycin $A_1$*

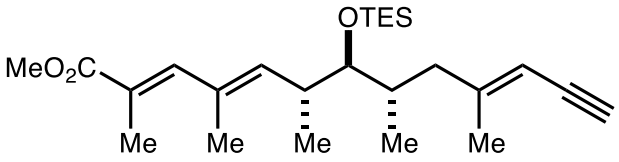



**75% (3 steps)**
**97:3 dr**

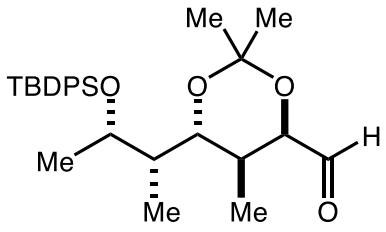


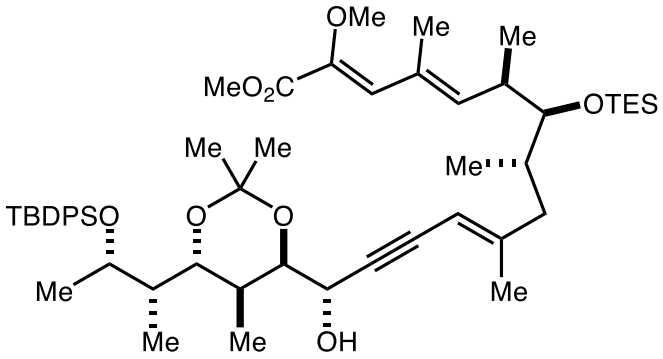

**88% (2 steps)**
**>95:5 dr**




**70% (8 steps)**

$Zn(OTf)_2$
(+)-NME
DIPEA

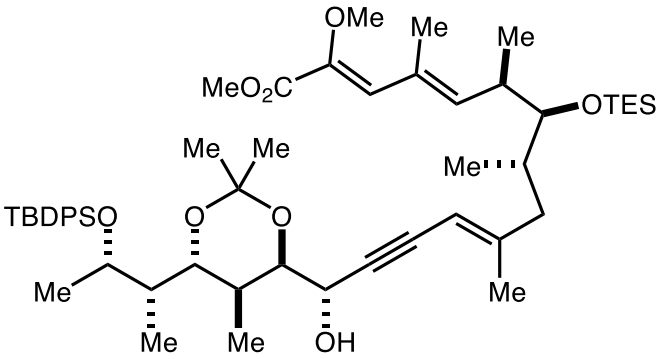


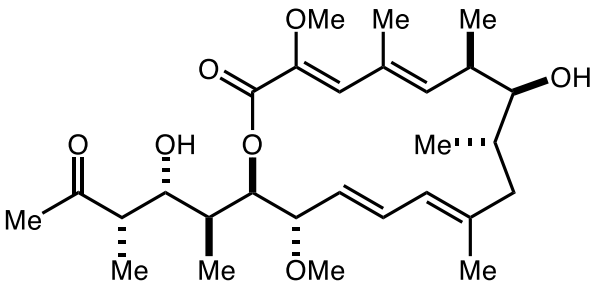




**91%, >95:5 dr**

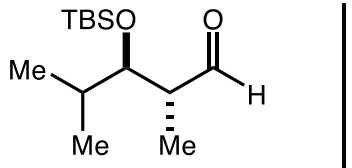

Kleinbeck, F.; Carreira, E. M..; *Angew. Chem. Int. Ed.* **2009**, *48*, 578.
Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M.; *Chem. Eur. J.* **2012**, *18,* 3598.

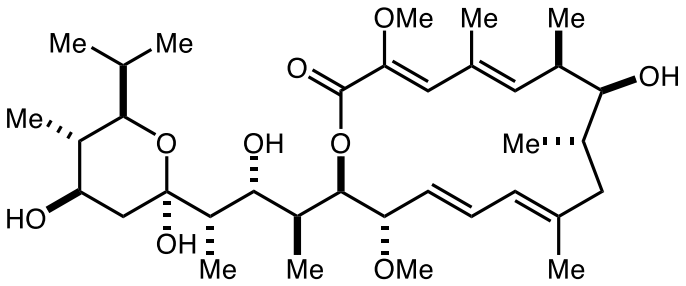
# *Bafilomycin $A_1$*




**15% (10 steps)**



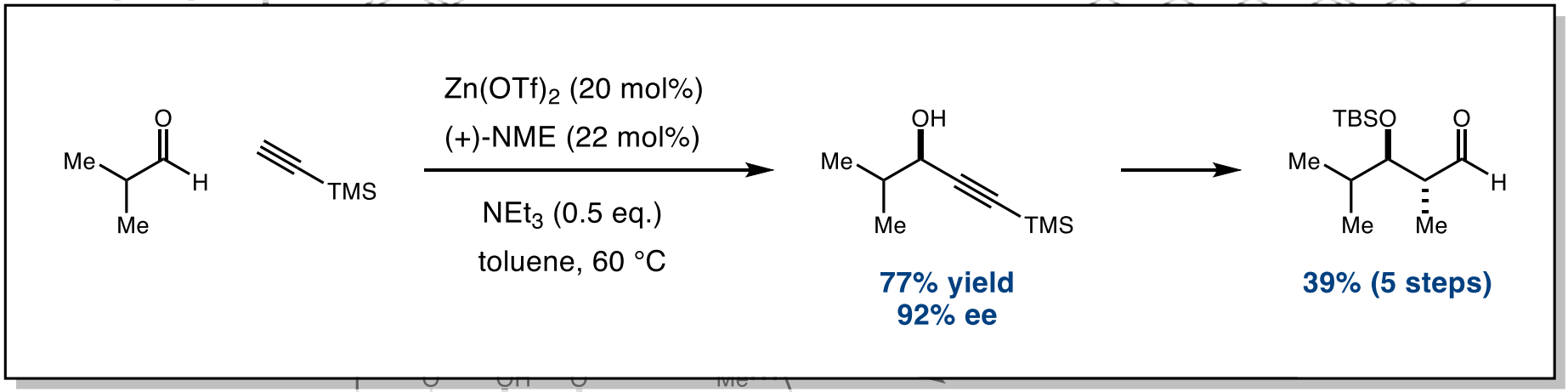




**36%, 76% brsm (3 steps)**

**Bafilomycin $A_1$**
41 steps, 28 longest linear
1.2% overall yield


Kleinbeck, F.; Carreira, E. M..; *Angew. Chem. Int. Ed.* **2009**, *48*, 578.
Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M.; *Chem. Eur. J.* **2012**, *18,* 3598.

# *Bafilomycin $A_1$*



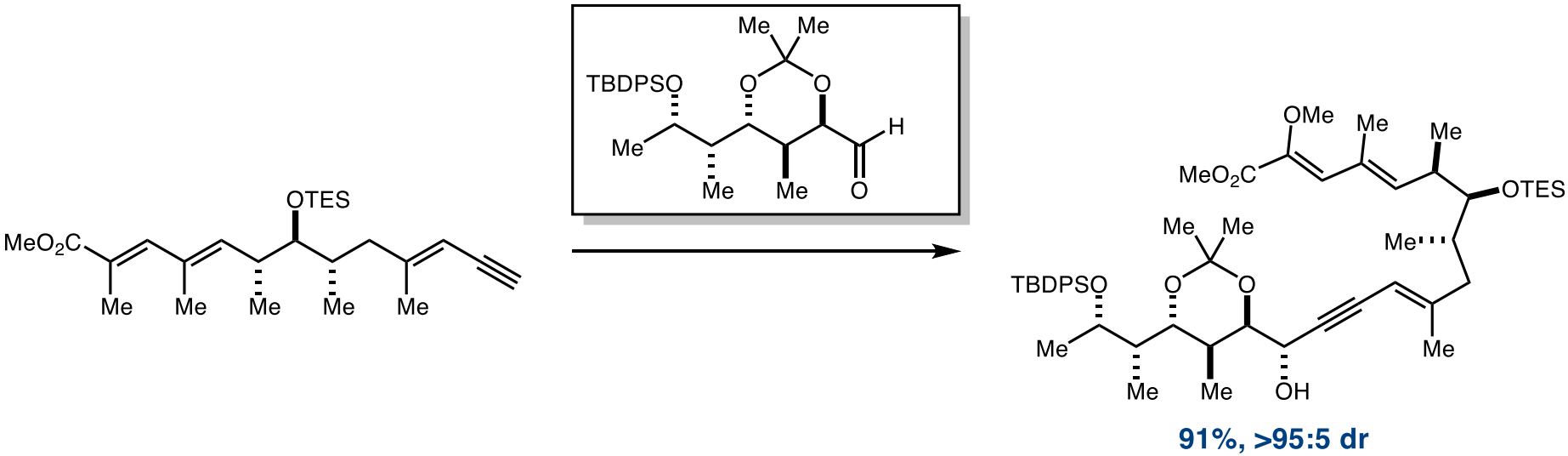

36%, 76% brsm (3 steps)

**Bafilomycin $A_1$**
41 steps, 28 longest linear
1.2% overall yield


Kleinbeck, F.; Carreira, E. M..; *Angew. Chem. Int. Ed.* **2009**, *48*, 578.
Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M.; *Chem. Eur. J.* **2012**, *18,* 3598.

# *Bafilomycin $A_1$*

- The C14-C20 fragment



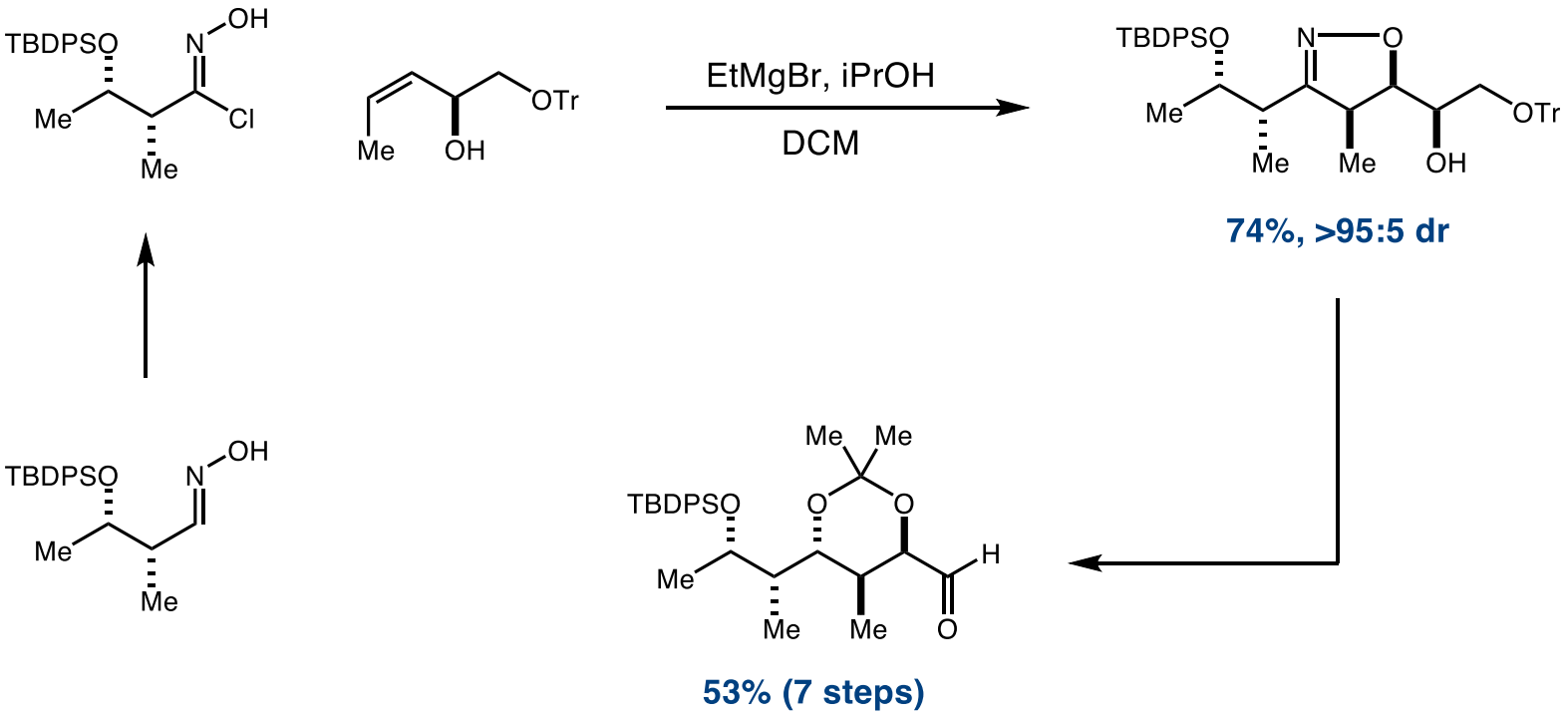

**91%, >95:5 dr**


Kleinbeck, F.; Carreira, E. M..; *Angew. Chem. Int. Ed.* **2009**, *48*, 578.

Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M.; *Chem. Eur. J.* **2012**, *18,* 3598.

# *Bafilomycin $A_1$*

- the Kanemasa Nitrile Oxide [3+2]-cycloaddition



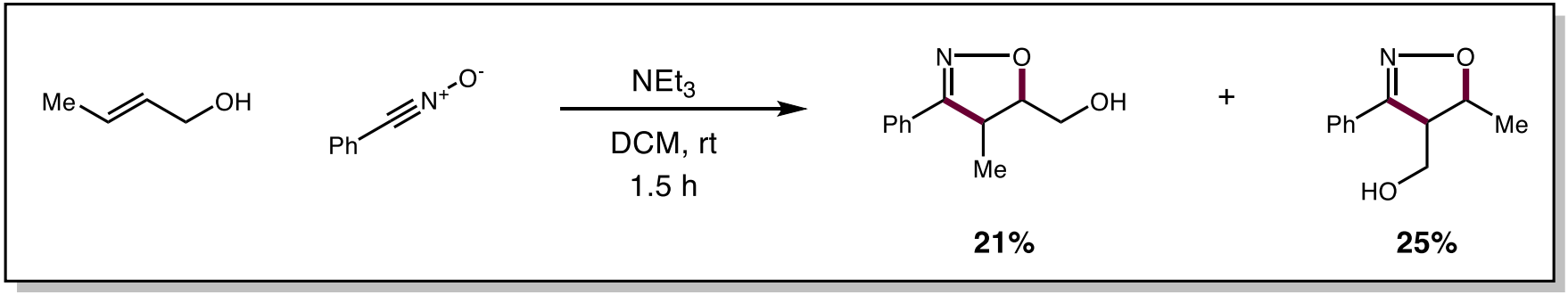


Kleinbeck, F.; Carreira, E. M..; *Angew. Chem. Int. Ed.* **2009**, *48*, 578.

Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M.; *Chem. Eur. J.* **2012**, *18,* 3598.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

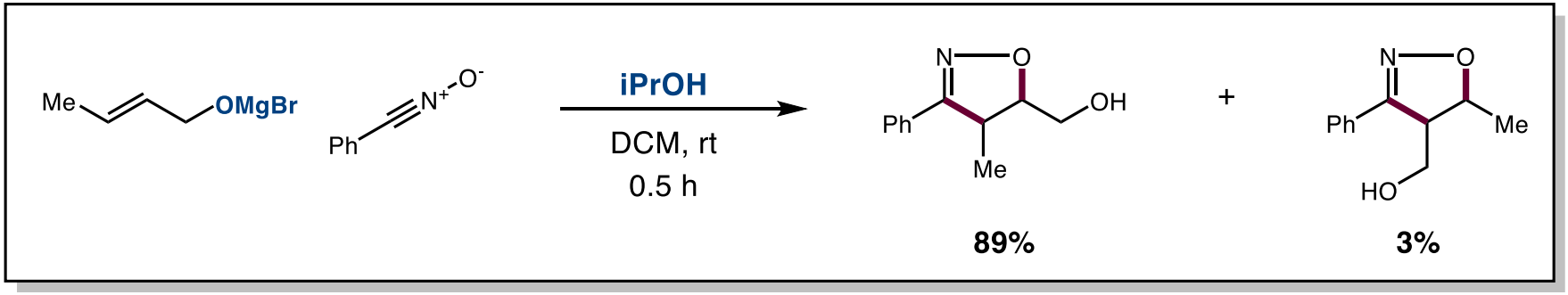
- Kanemasa´s unnoted report

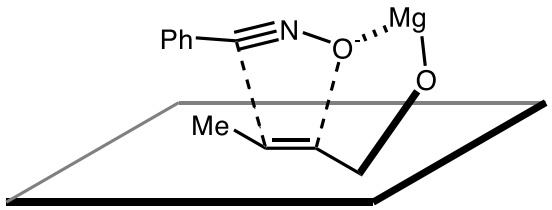



Kanemasa, S.; Nishiuchi, M.; Wada, E.; *Tetrahedron Lett.* **1992**, *33,* 1357.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

- Kanemasa´s unnoted report

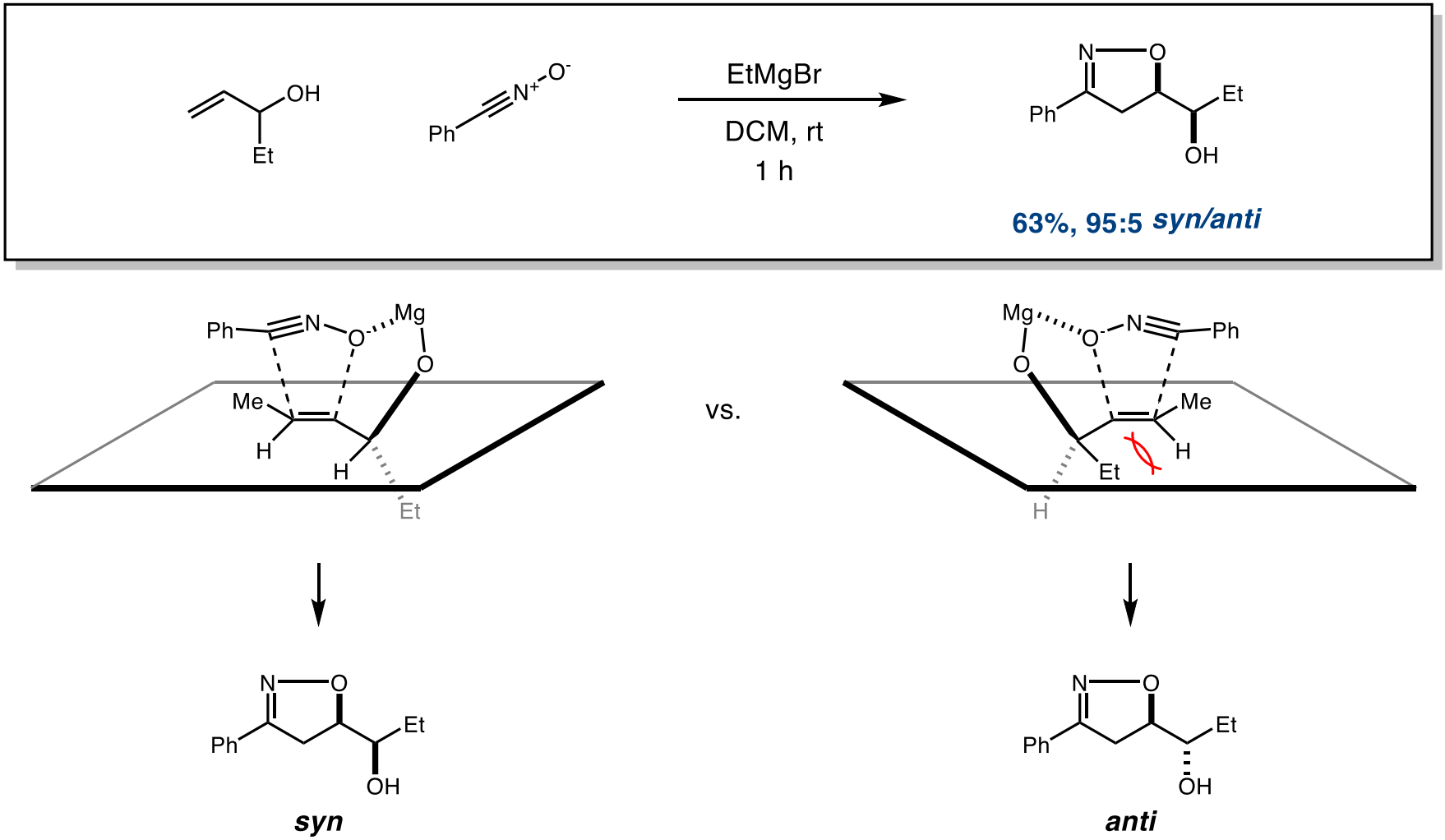



Kanemasa, S.; Nishiuchi, M.; Wada, E.; *Tetrahedron Lett.* **1992**, *33,* 1357.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

- Kanemasa´s unnoted report

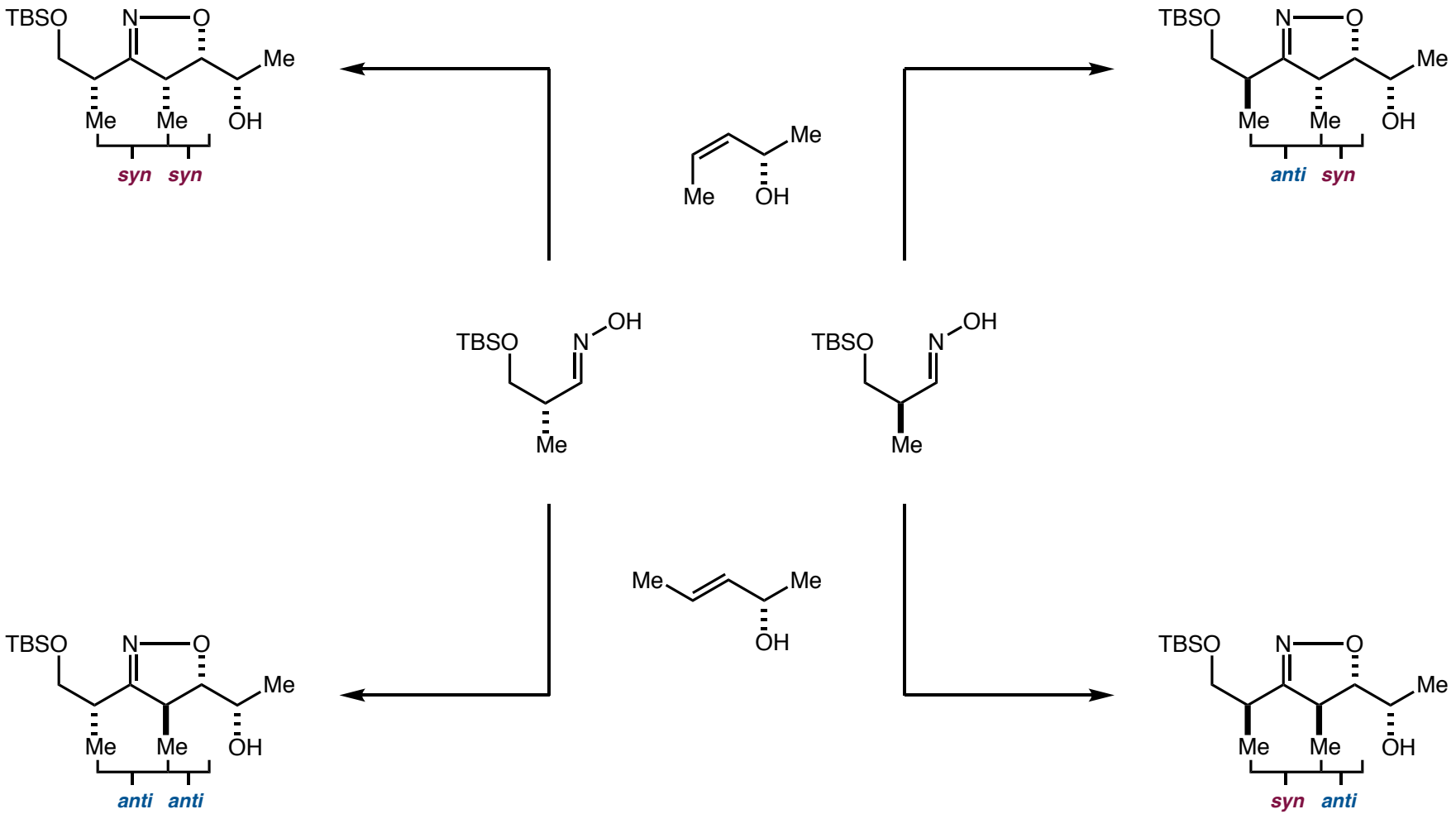




Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E.; *Tetrahedron Lett.* **1991**, *32,* 6367.
Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K.; *J. Am. Chem. Soc.* **1994**, *116,* 2324.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

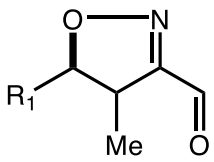
- Access to all possible diastereomers

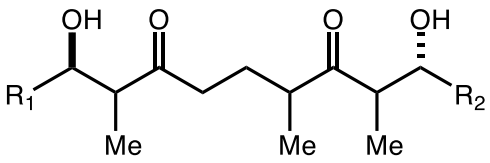


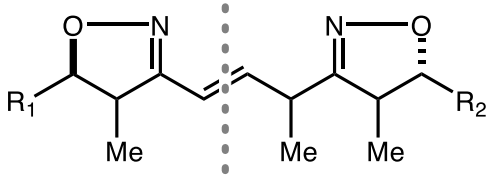

Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2001**, *40,* 2082.

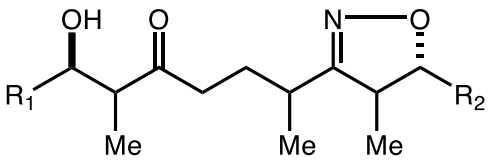
# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

- the Bis(isoxazoline) approach



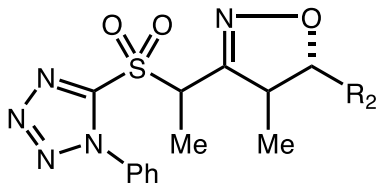




**conditions:**

1. $H_2$, Pd/C
   EtOH
2. $H_2$, Raney-Ni, $B(OH)_3$
   $MeOH/H_2O$

**conditions:**

$SmI_2$, $THF/H_2O$

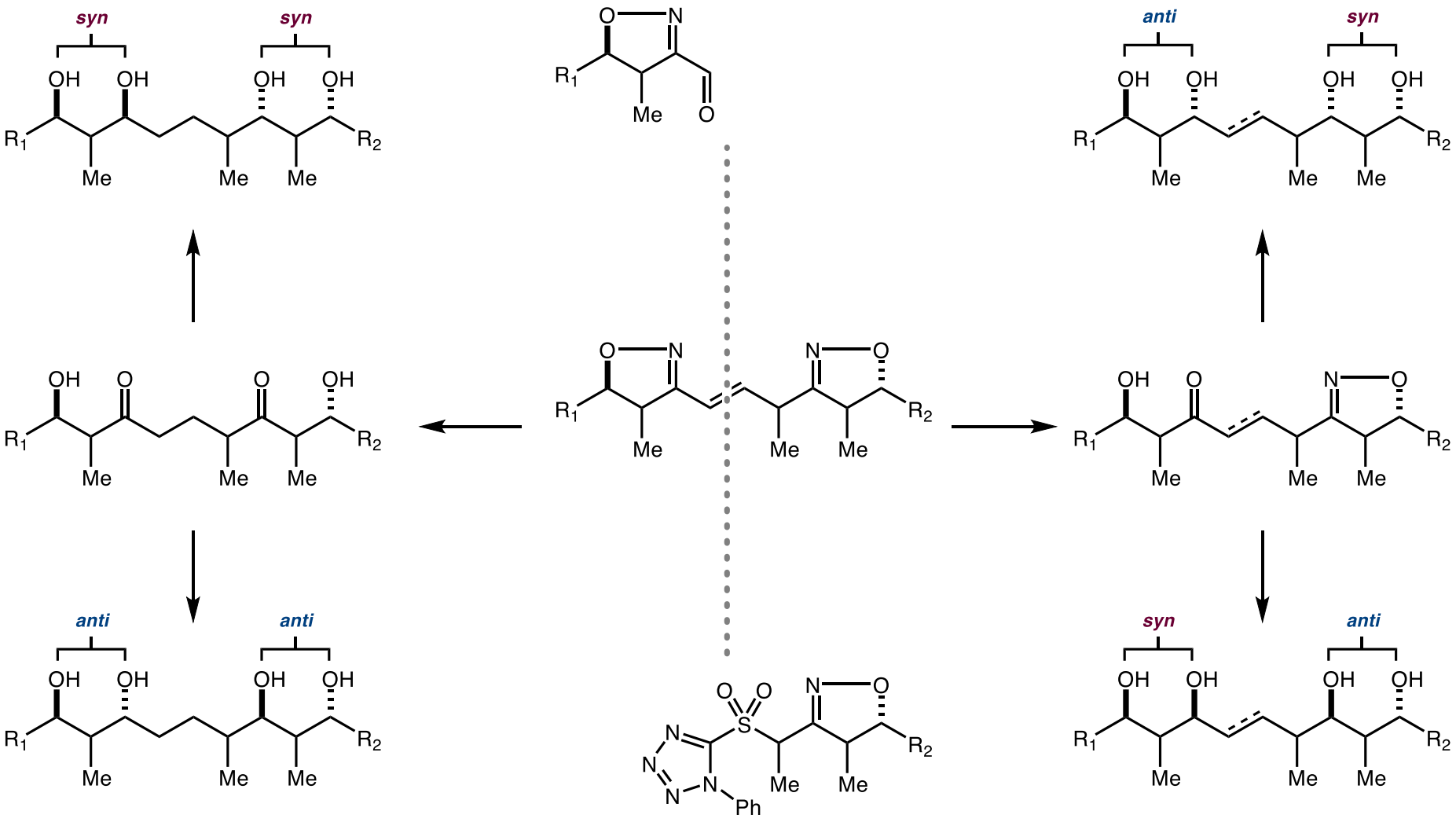




Bode, J. W.; Carreira, E. M.; *Org. Lett.* **2001**, *3,* 1587.
Fader, L. D.; Carreira, E. M.; *Org. Lett.* **2004**, *6,* 2485.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

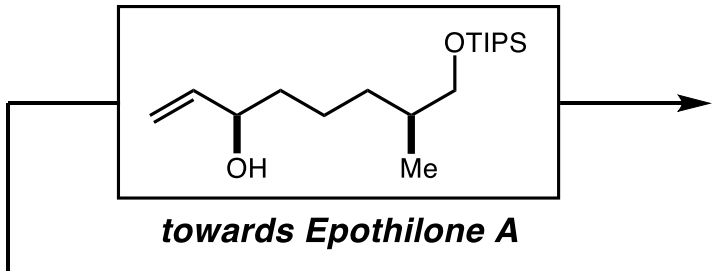
- the Bis(isoxazoline) approach



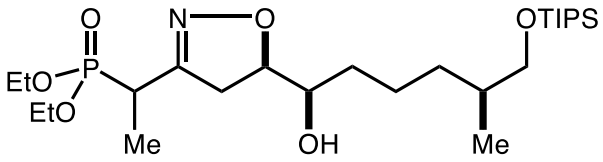

Fader, L. D.; Carreira, E. M.; *Org. Lett.* **2004**, *6,* 2485.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

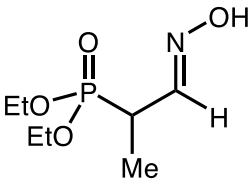
- Epothilone A & B



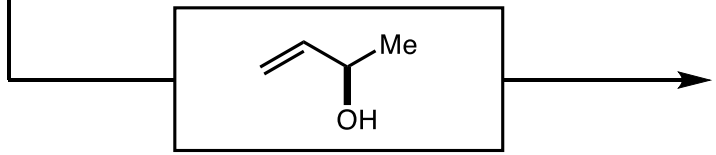

***towards Epothilone A***

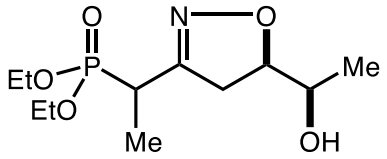



**56% (94% brsm), >95:5 dr**




***towards Epothilone B***



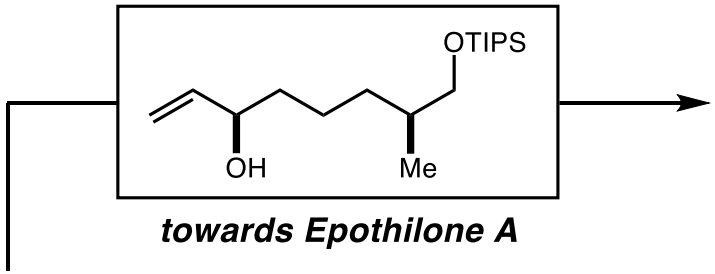




**79%, >95:5 dr**

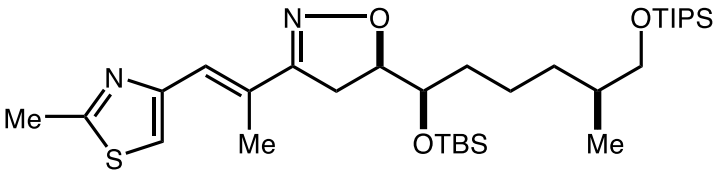

Bode, J. W.; Carreira, E. M.; *J. Am. Chem. Soc.* **2001**, *123,* 3611.
Bode, J. W.; Carreira, E. M.; *J. Org. Chem.* **2001**, *66,* 6410.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

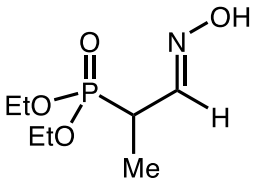
## ■ Epothilone A & B



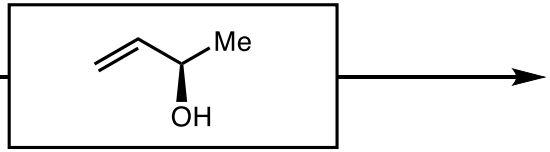

***towards Epothilone A***

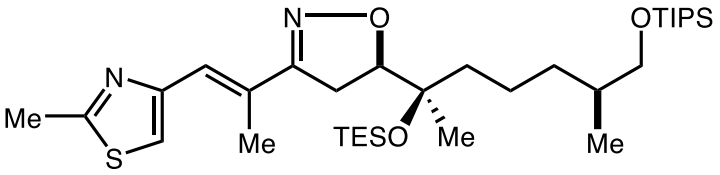



**39% (3 steps)**
**66% brsm (3 steps)**




***towards Epothilone B***



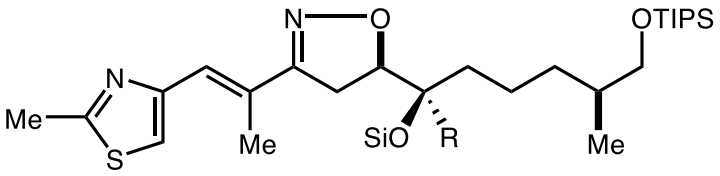



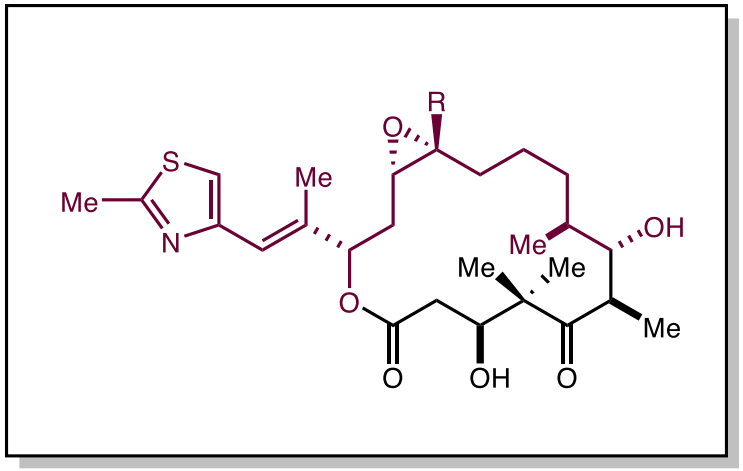

**50% (5 steps)**


Bode, J. W.; Carreira, E. M.; *J. Am. Chem. Soc.* **2001**, *123,* 3611.
Bode, J. W.; Carreira, E. M.; *J. Org. Chem.* **2001**, *66,* 6410.

# *Nitrile Oxide [3+2]-cycloaddition for Polyketide Synthesis*

- Epothilone A & B

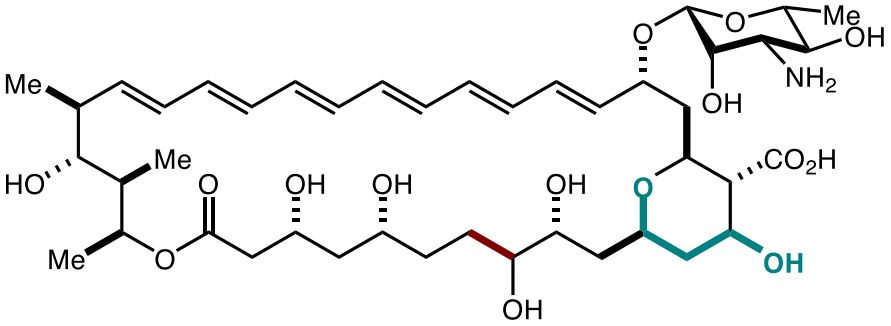


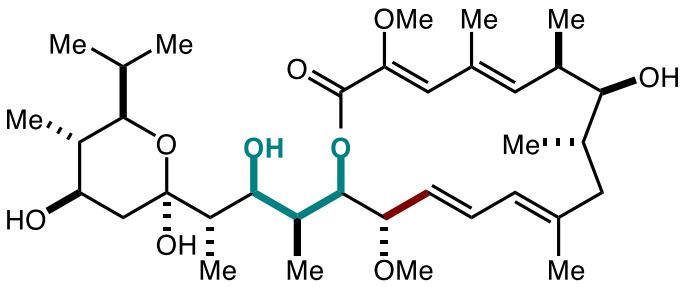

**R = H** **Epothilone A**
**R = Me** **Epothilone B**

Bode, J. W.; Carreira, E. M.; *J. Am. Chem. Soc.* **2001**, *123,* 3611.
Bode, J. W.; Carreira, E. M.; *J. Org. Chem.* **2001**, *66,* 6410.

# *Total Synthesis in the Carreira Lab*



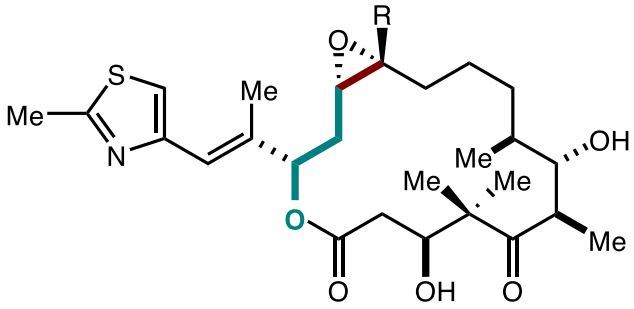
**Amphotericine B**



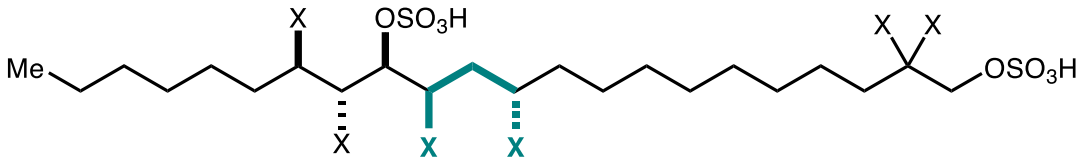
**Bafilomycin $A_1$**

**Alkyne addition**

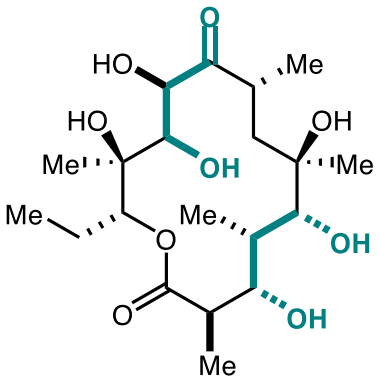
**Nitrile oxide [3+2]**



**Epothilone A & B**

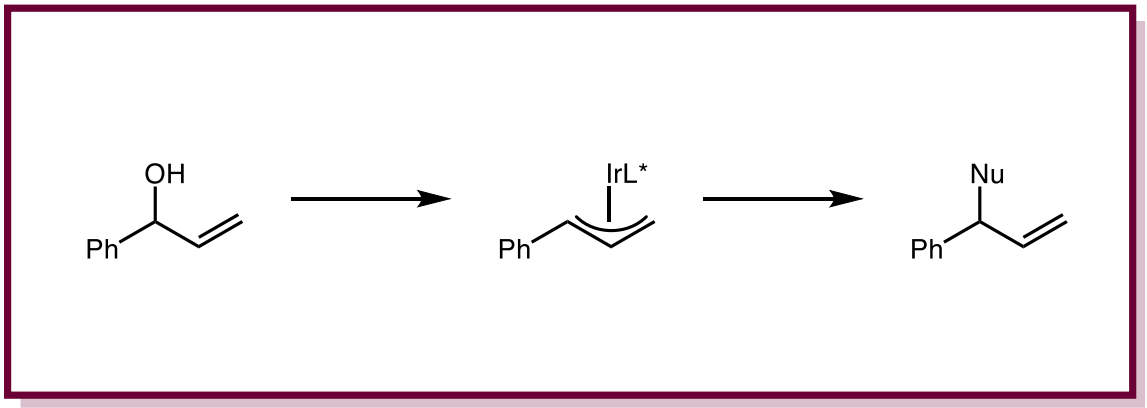


**X = F** **Fluorodanicalipin A**
**X = Br** **Bromodanicalipin A**

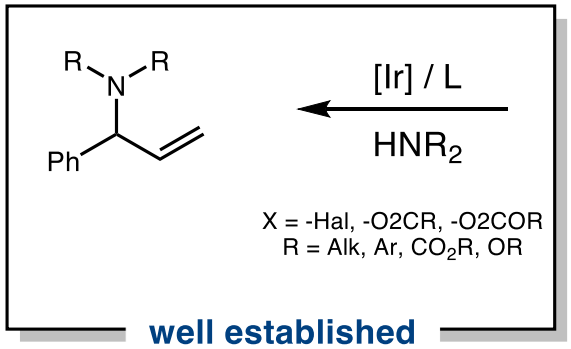


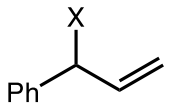
**Erythronolide A**

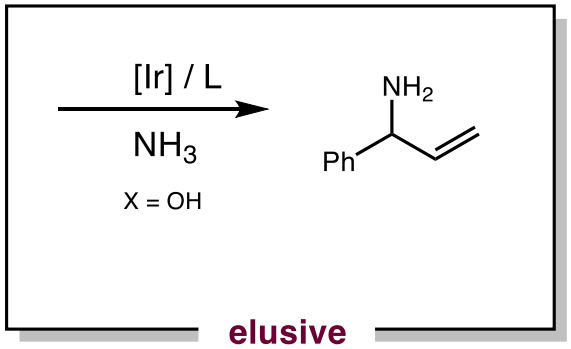
# *The Ir-catalyzed Allylic Substitution*



# *The Ir-catalyzed Allylic Substitution*



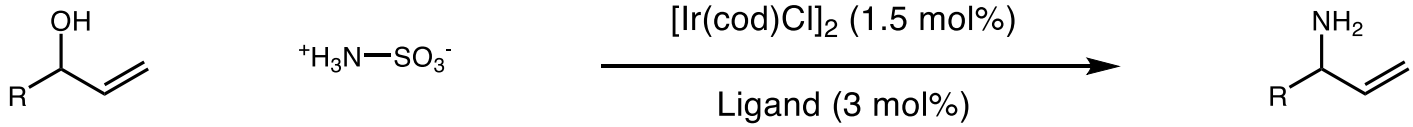



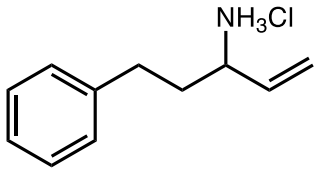

Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2007**, *46,* 3139.

# *The Ir-catalyzed Allylic Substitution*

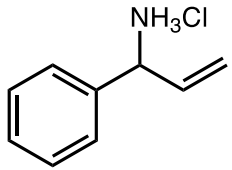
- The Synthesis of primary allylic amines from allylic alcohols



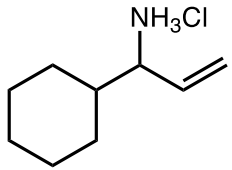

---



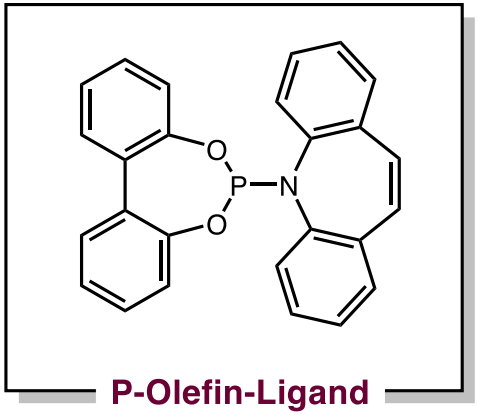

**82% yield**

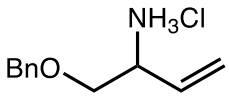



**78% yield**

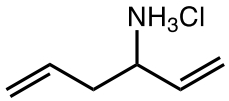



**75% yield**




**71% yield**

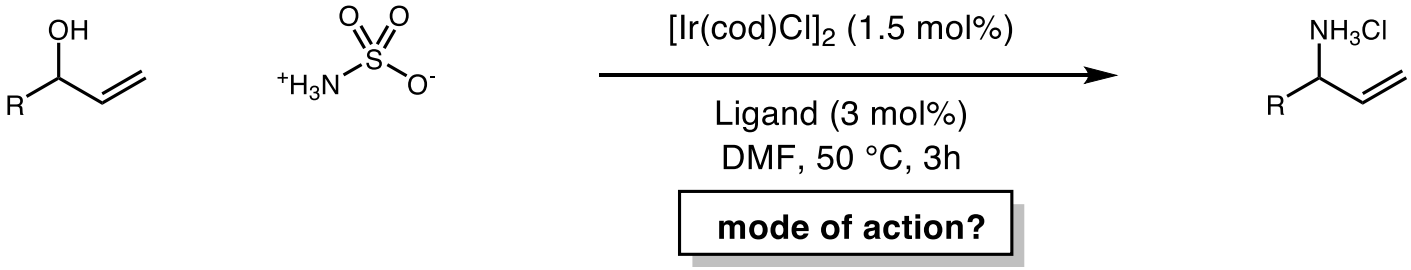



**75% yield**

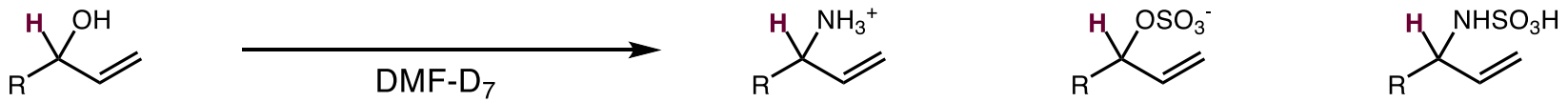
Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2007**, *46,* 3139.

# *The Ir-catalyzed Allylic Substitution*

- Sulfamic acid - a masked ammonia equivalent




in situ-NMR studies

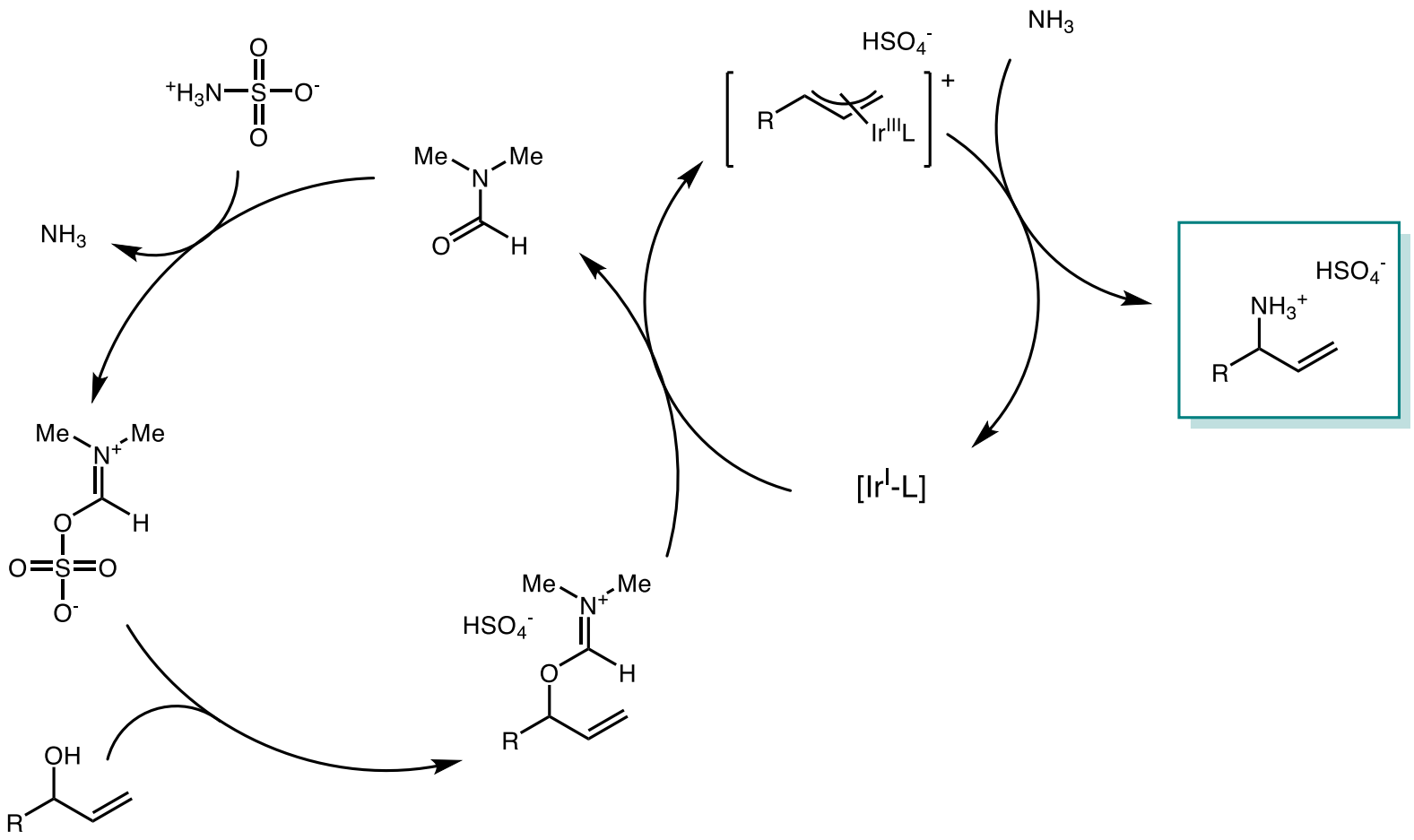



| | | | |
|---|---|---|---|
| standard conditions, 4h | ✓ | ✗ | ✗ |
| 2 eq. $NH_3SO_3$, 2h | ✓ | ✗ | ✗ |
| 2 eq. $NH_3SO_3$, 8h | ✓ | ✗ | ✓ |
| allylic amine + $NH_3SO_3$, 9h | ✓ | ✗ | ✓ |
| 2 eq. $NH_3SO_3$, w/o catalyst | ✗ | ✓ | ✗ |

Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2007**, *46,* 3139.

# *The Ir-catalyzed Allylic Substitution*

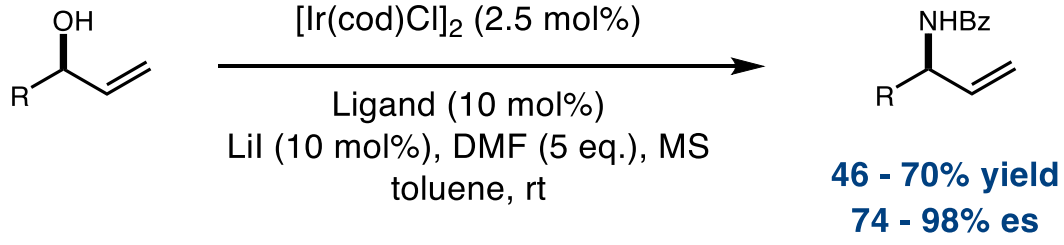
- proposed mechanism of the allylic amination



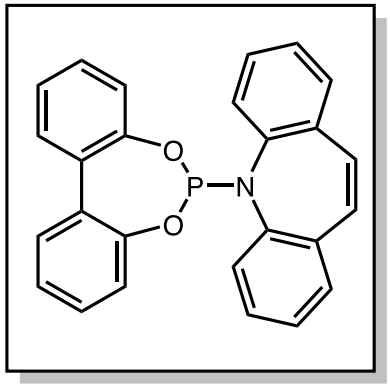

Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2007**, *46,* 3139.

# *The Ir-catalyzed Allylic Substitution*

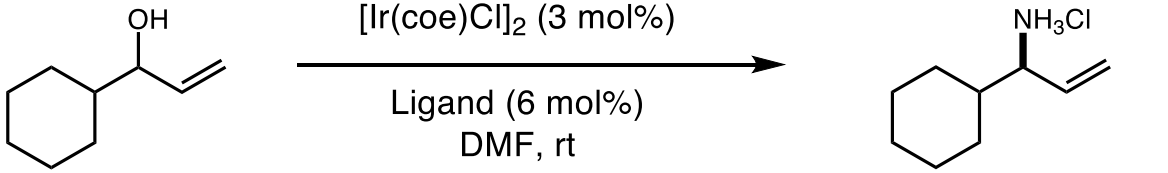
## ■ stereospecific allylic amination



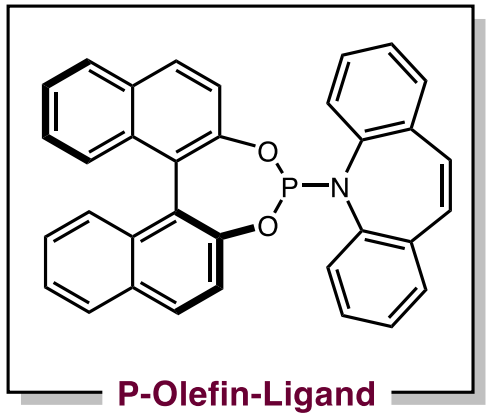

**46 - 70% yield**
**74 - 98% es**




## ■ enantioselective allylic amination



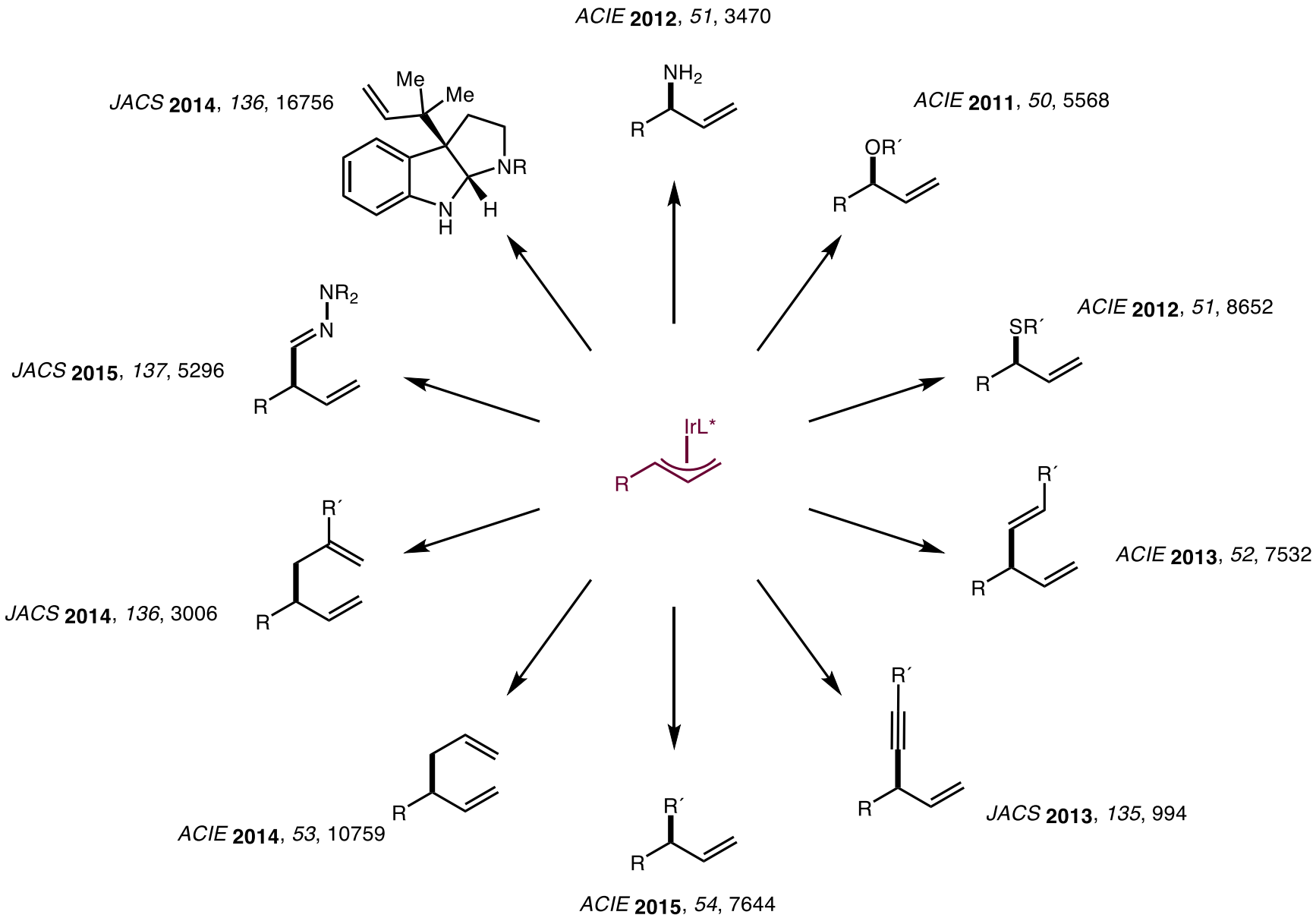

**70% yield**
**70% ee** **93% ee** after trituration



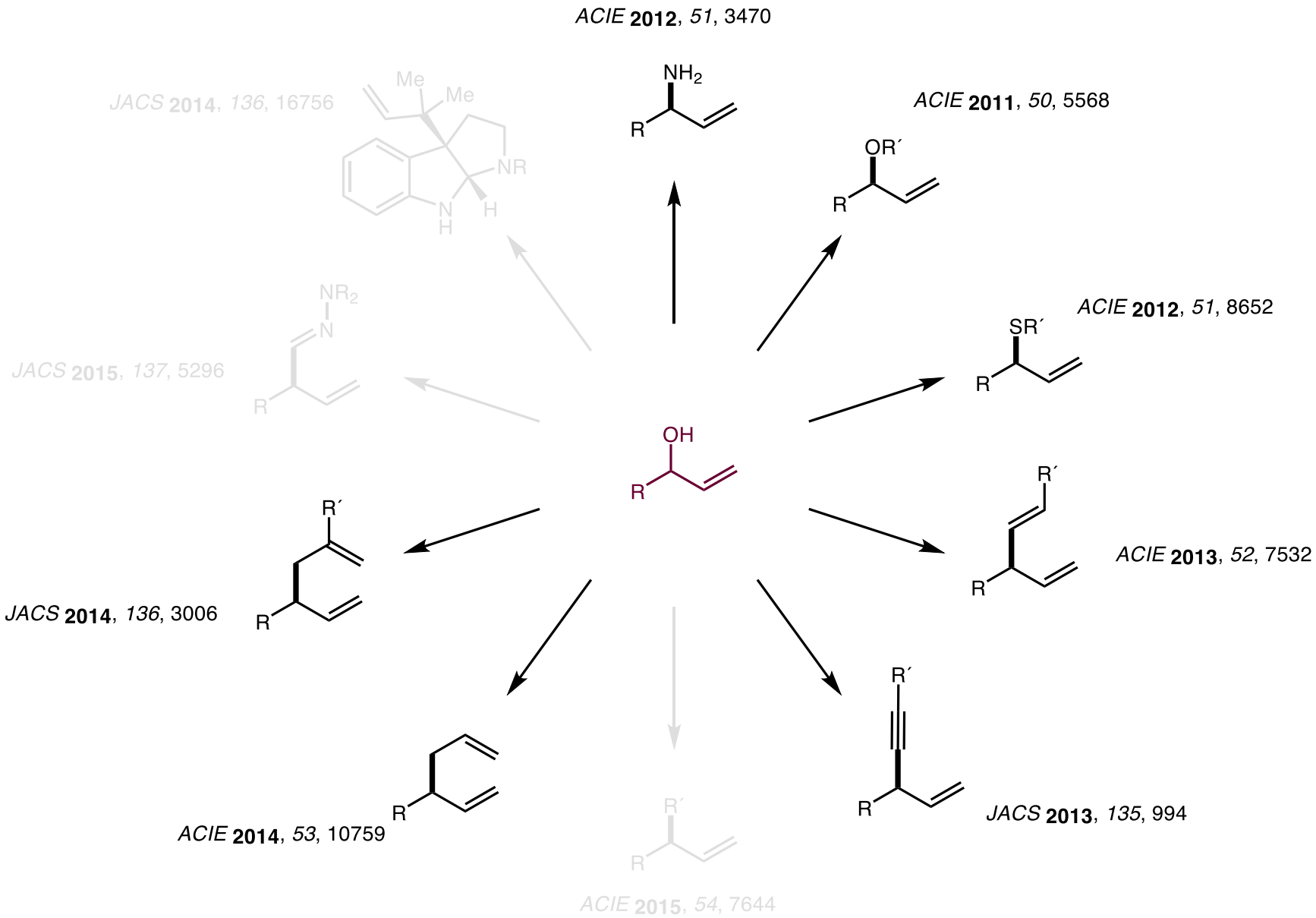


Roggen, M.; Carreira, E. M.; *J. Am. Chem. Soc.* **2010**, *132,* 11917.
Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2007**, *46,* 3139.

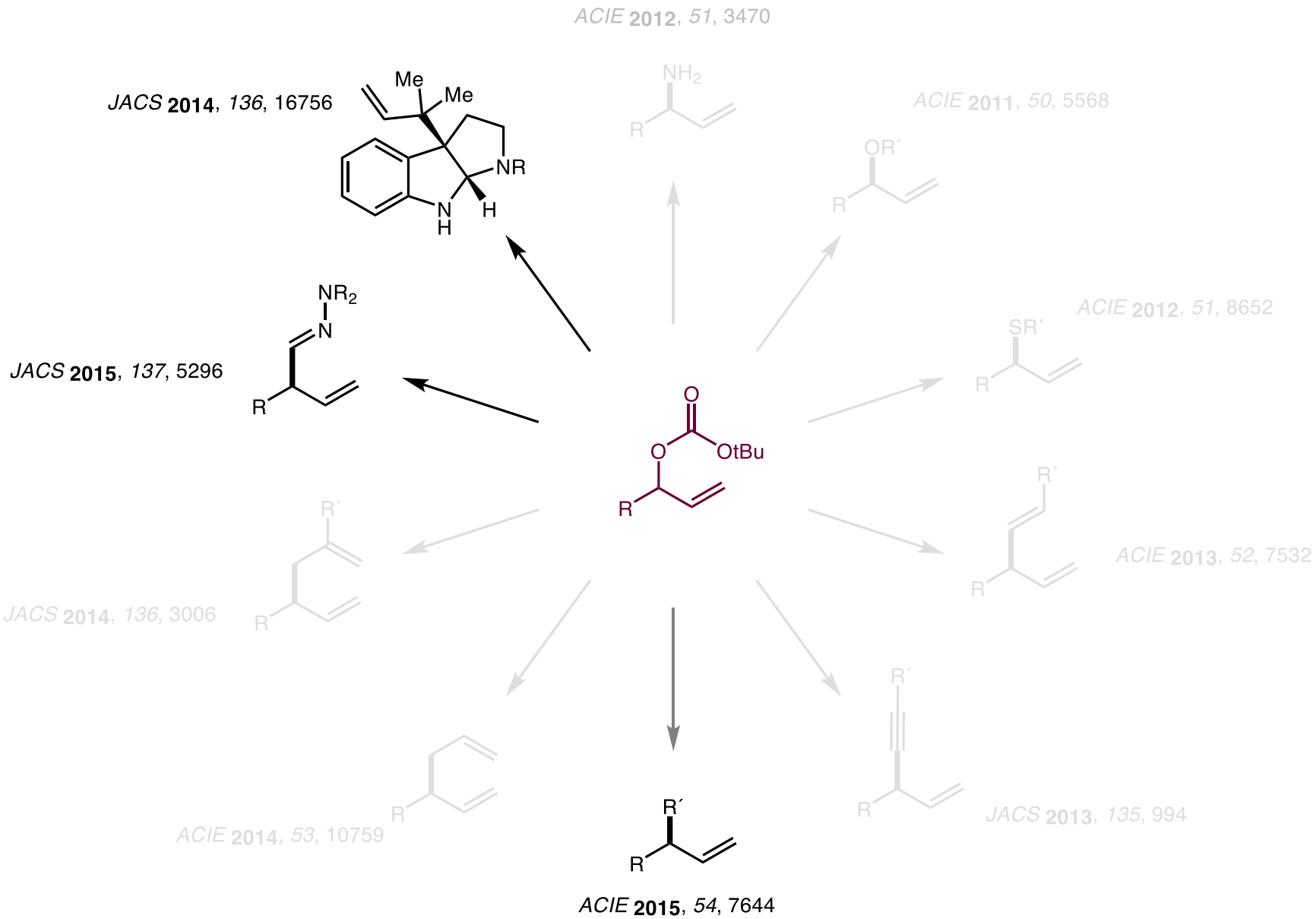
# *The Ir-catalyzed Allylic Substitution*



# *The Ir-catalyzed Allylic Substitution*

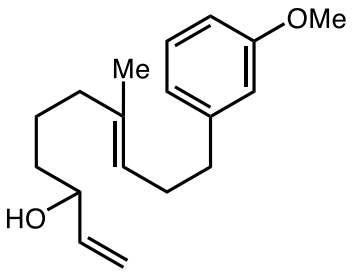


# *The Ir-catalyzed Allylic Substitution*



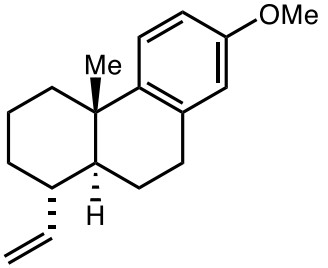
# *The Ir-catalyzed Allylic Substitution*

- enantioselective Polyene cyclization



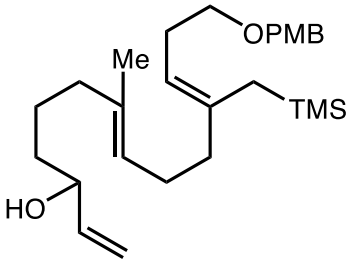

$[Ir(cod)Cl]_2$ (4 mol%)
Ligand (16 mol%)

$Zn(OTf)_2$ (20 mol%)
DCE, rt



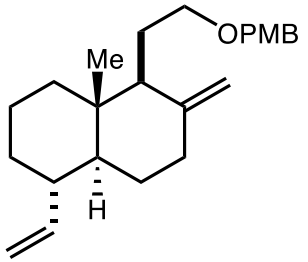

**69% yield**
**>20:1 dr, >99% ee**

---




$[Ir(cod)Cl]_2$ (3.2 mol%)
Ligand (12.8 mol%)

$Zn(OTf)_2$ (16 mol%)
DCE, rt

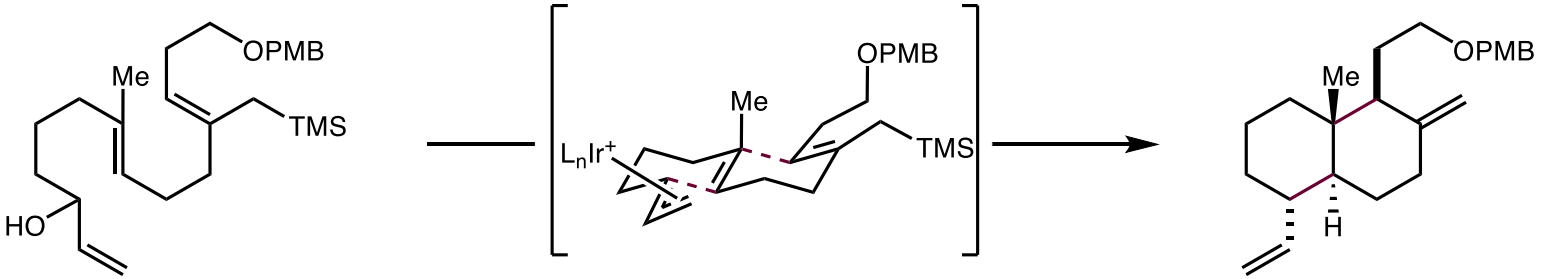



**73% yield**
**9:1 dr, 96% ee**

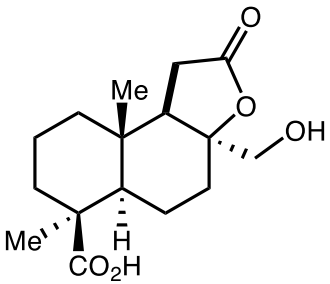
Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M.; *J. Am. Chem. Soc.* **2012**, *134,* 20276.
Jeker, O. F.; Kravina, A. G.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2013**, *52,* 12166.

# *The Ir-catalyzed Allylic Substitution*

- intramolecular allyl-allyl coupling towards (+)-Asperolide




**73% yield**
**9:1 dr, 96% ee**

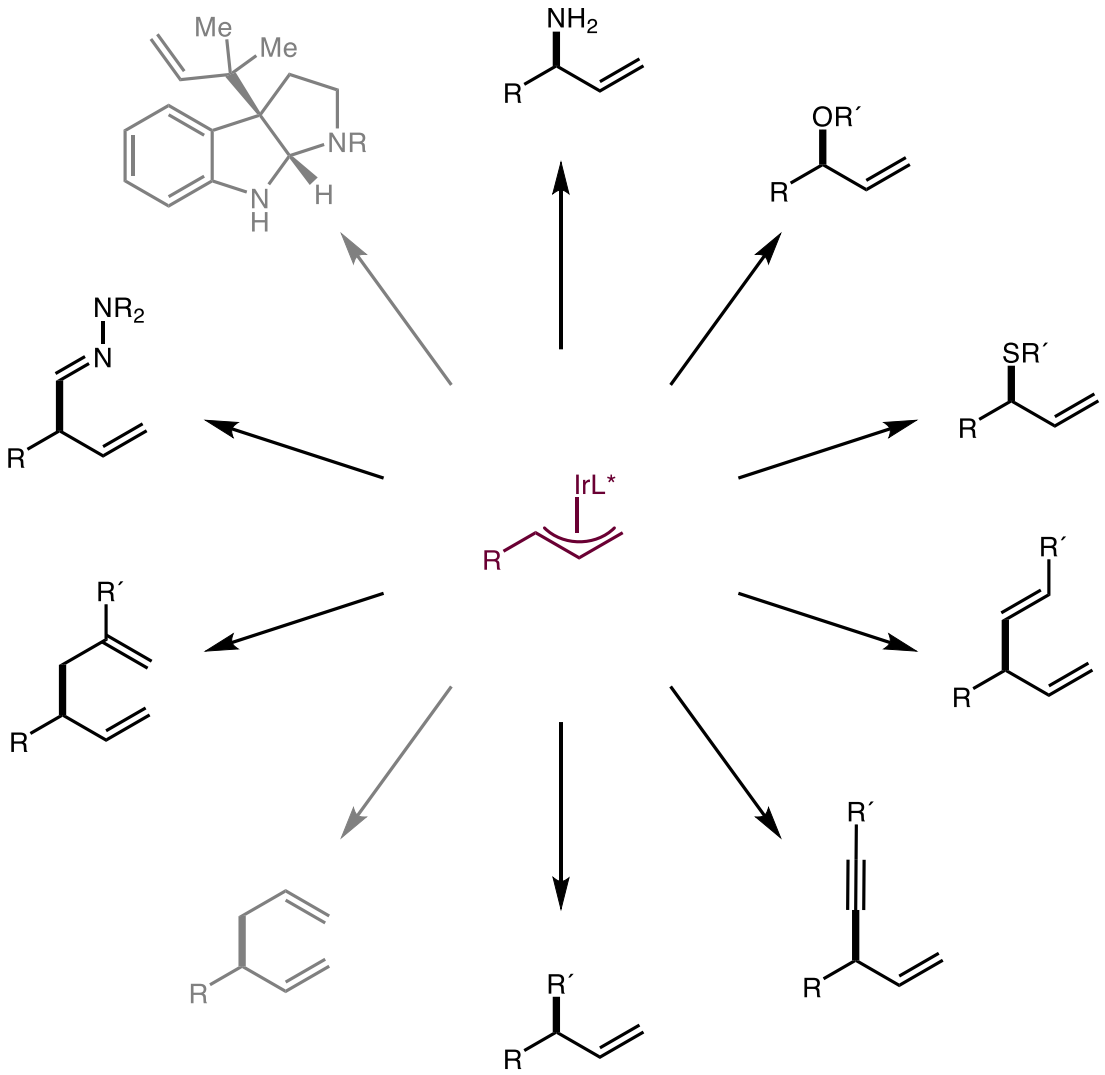



**2.8% (10 steps)**

**(+)-Asperolide**
23 steps, 19 longest linear
0.25% overall yield

Jeker, O. F.; Kravina, A. G.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2013**, *52,* 12166.

# *The Ir-catalyzed Allylic Substitution*




**Mono Catalysis**

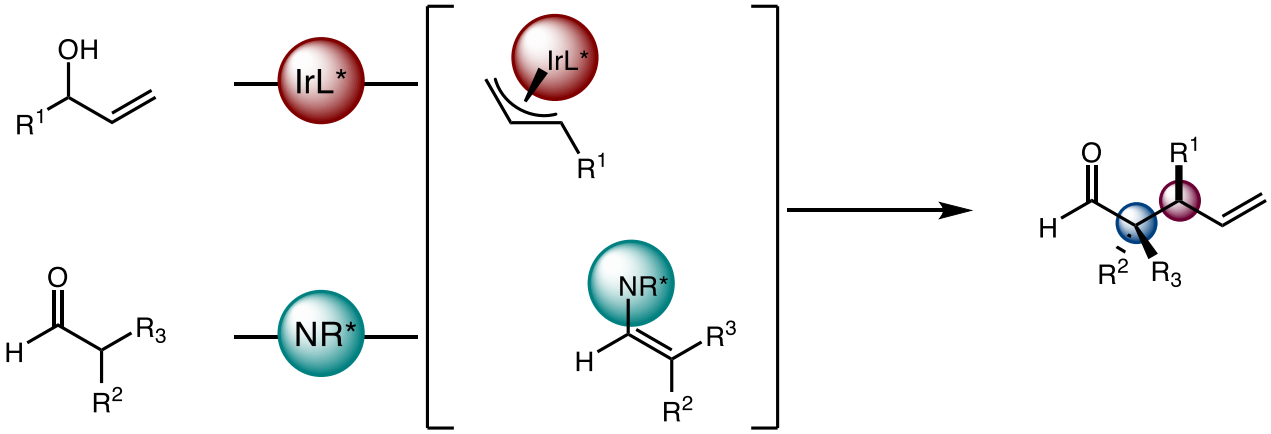
**efficient control of <u>one</u> stereocenter**

**Dual Catalysis**

**enantio- and diastereodivergent?**

# *The Ir-catalyzed Allylic Substitution*

- α-allylation of aldehydes

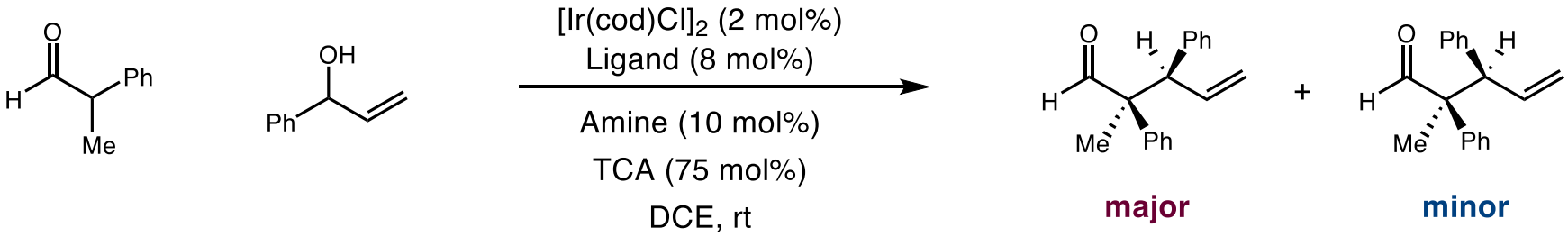


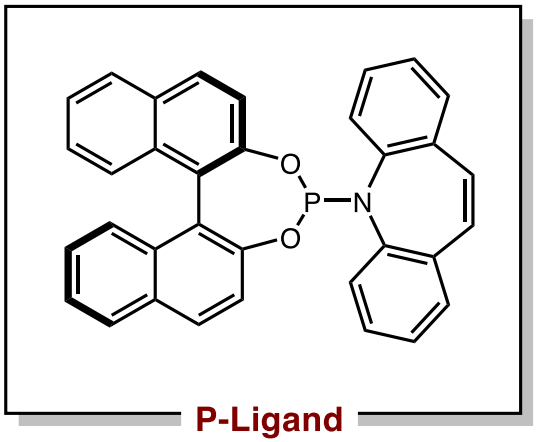

**Dual Catalysis**

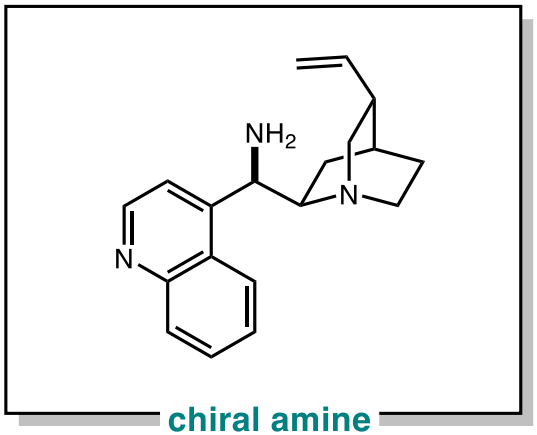
**enantio- and diastereodivergent?**


Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M.; *Science* **2013**, *340,* 1065.
Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M.; *J. Am. Chem. Soc.* **2014**, *136,* 3020.
Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2015**, *54,* 14363.

# *The Ir-catalyzed Allylic Substitution*

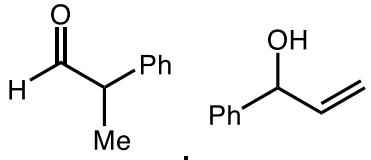


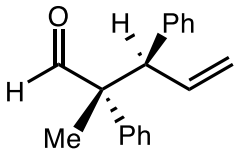
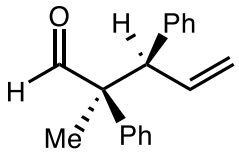
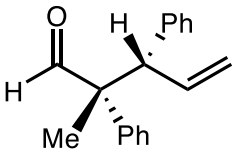
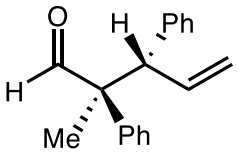



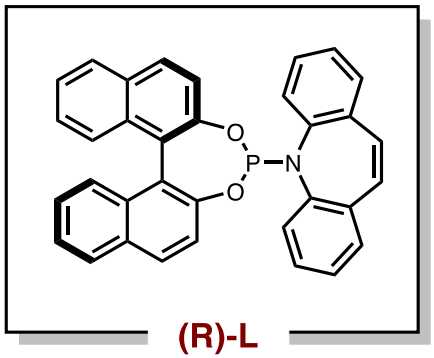



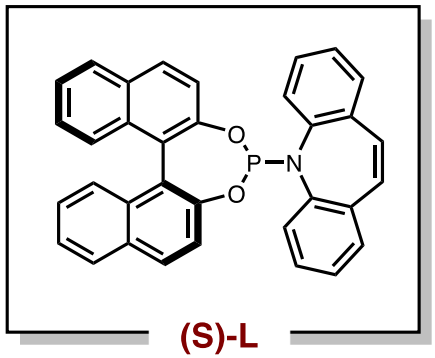

Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M.; *Science* **2013**, *340,* 1065.

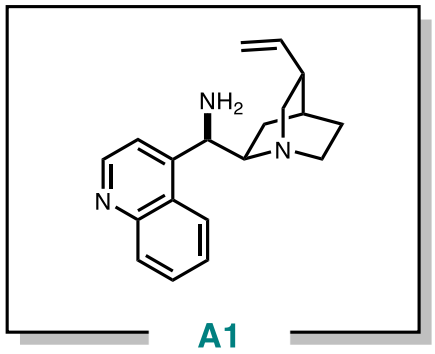
# *The Ir-catalyzed Allylic Substitution*

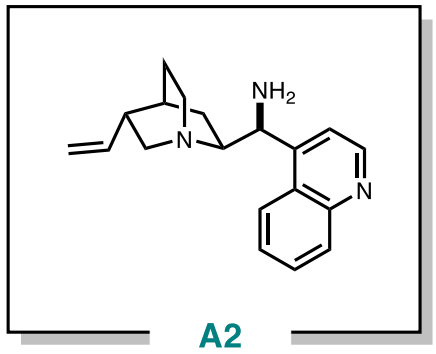



| (R)-L A1 | (R)-L A2 | (S)-L A1 | (S)-L A2 |
|---|---|---|---|
|  |  |  |  |
| *(R,R)* | *(S,R)* | *(R,S)* | *(S,S)* |
| **77% yield** | **80% yield** | **78% yield** | **71% yield** |
| **>20:1 dr, >99% ee** | **20:1 dr, >99% ee** | **15:1 dr, >99% ee** | **>20:1 dr, >99% ee** |



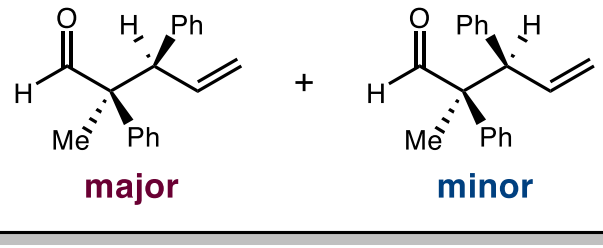





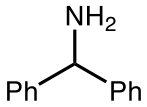
Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M.; *Science* **2013**, *340,* 1065.
Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M.; *J. Am. Chem. Soc.* **2014**, *136,* 3020.
Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2015**, *54,* 14363.

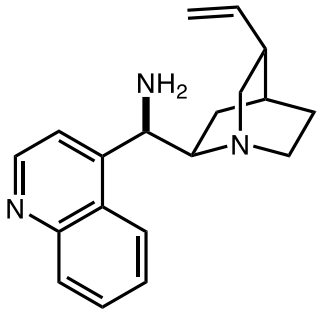
# *The Ir-catalyzed Allylic Substitution*




**Amine**

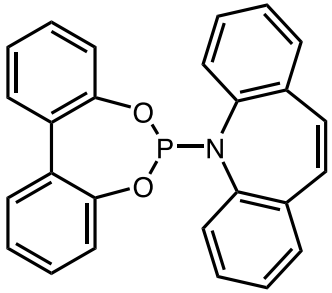
**control of carbon**

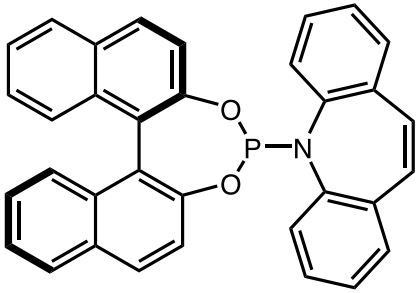




**P-Ligand**

**control of carbon**

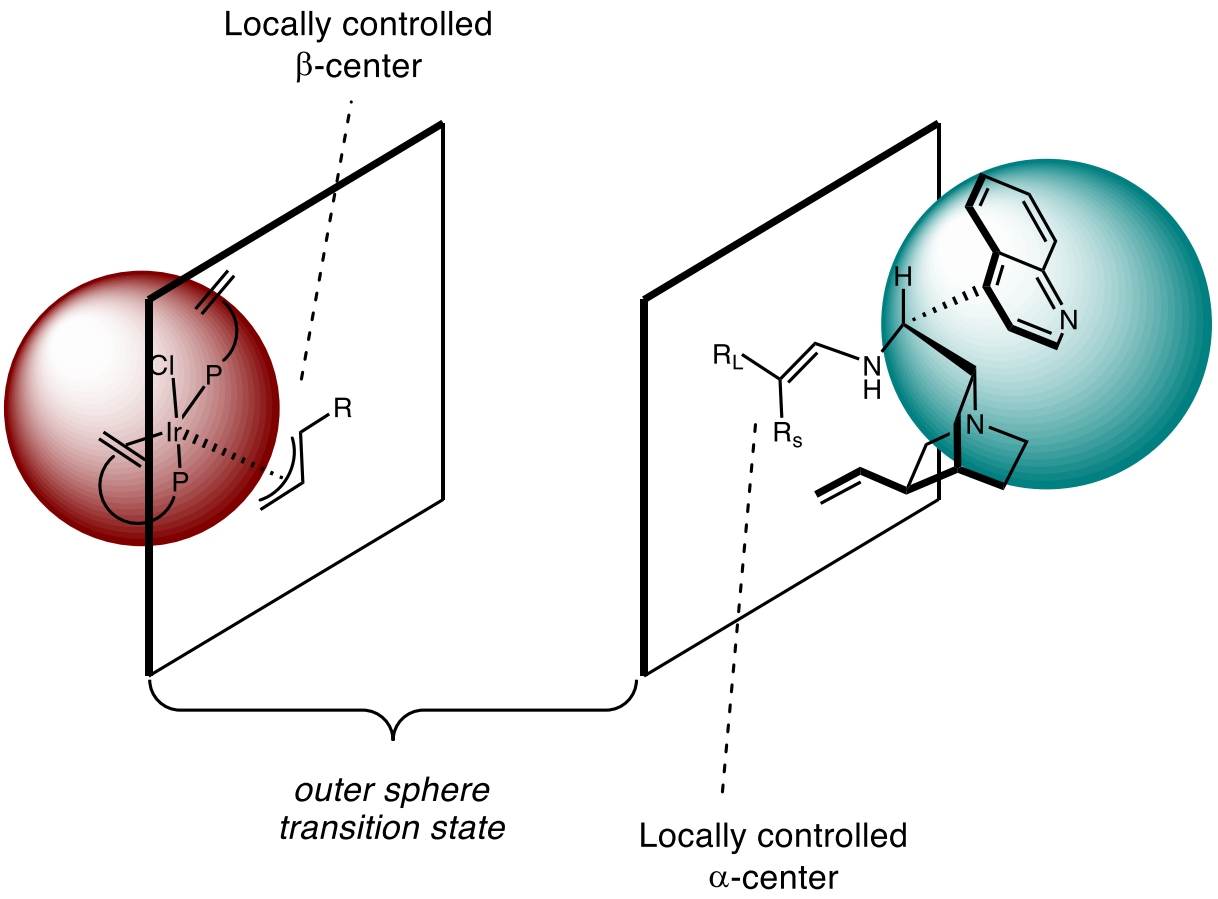




| | |
|---|---|
| **71% yield**<br>**3:1 dr** | **69% yield**<br>**1.3:1 dr**<br>**68% ee, 92%ee** |
| **69% yield**<br>**3:1 dr**<br>**99%ee** | **77% yield**<br>**>20:1 dr**<br>**99%ee** |

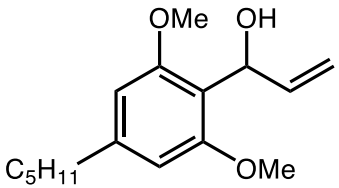
Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M.; *Science* **2013**, *340,* 1065.

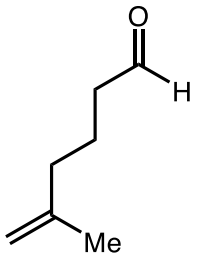
# *The Ir-catalyzed Allylic Substitution*

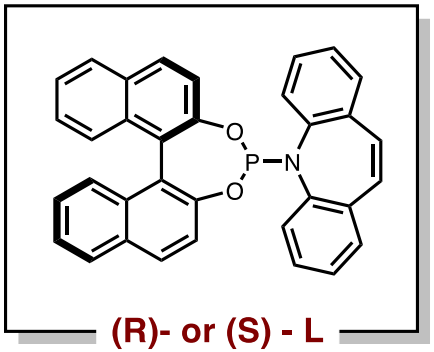



Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M.; *Science* **2013**, *340,* 1065.

# *The Ir-catalyzed Allylic Substitution*



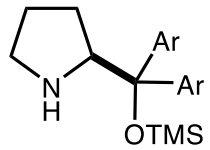




**(R)- or (S) - L**

$[Ir(cod)Cl]_2$ (3 mol%)
Ligand (12 mol%)

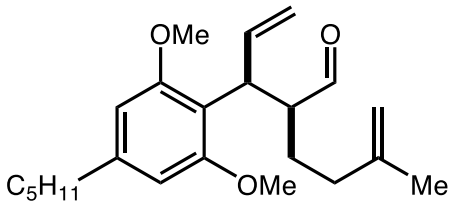
Amine (15 mol%)
$Zn(OTf)_2$ (5 mol%)
DCE, rt




Ar = 3,5-$(CF_3)_2$Ph

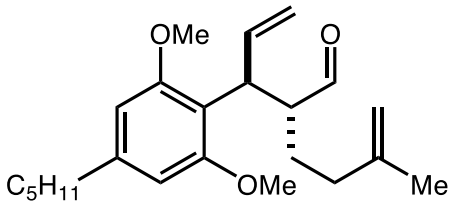
**(R)- or (S) - A**

**(R)-L**
**(R)-A** →



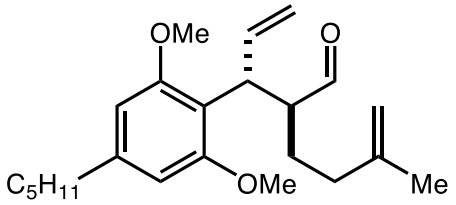

*(S,S)*
**60% yield**
**15:1 dr, 98%ee**

**(R)-L**
**(S)-A** →



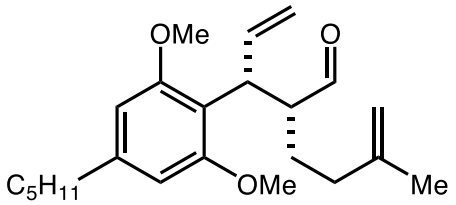

*(R,S)*
**55% yield**
**20:1 dr, 98%ee**

**(S)-L**
**(R)-A** →




*(S,R)*
**54% yield**
**20:1 dr, 98%ee**

**(S)-L**
**(S)-A** →



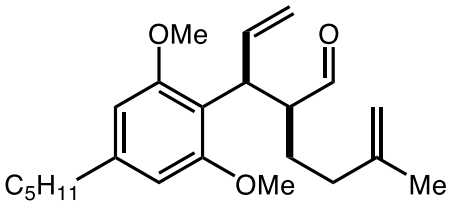

*(R,R)*
**62% yield**
**15:1 dr, 98%ee**

Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2014**, *53,* 13898.

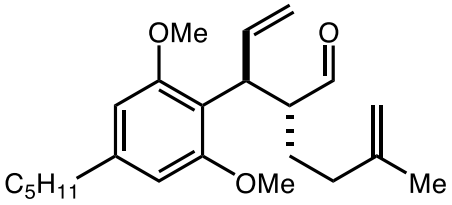
# *The Ir-catalyzed Allylic Substitution*

- stereodivergent synthesis of $\Delta^9$-Tetrahydrocannabinols

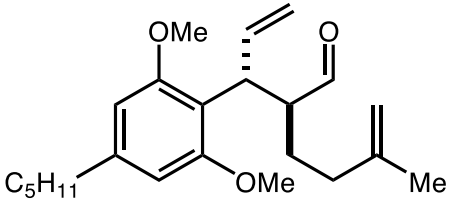
*(S,S)*



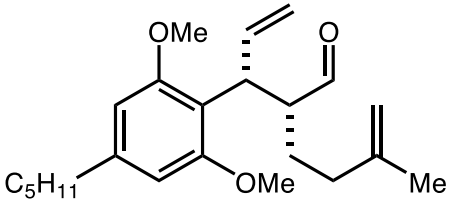

*(R,S)*

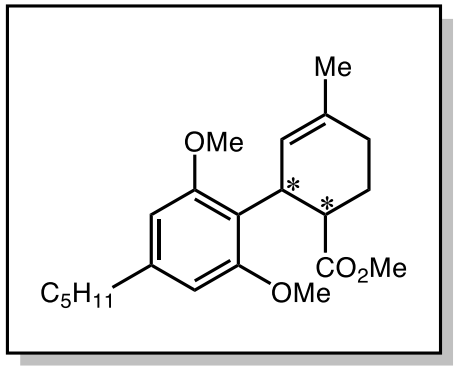



*(S,R)*




*(R,R)*



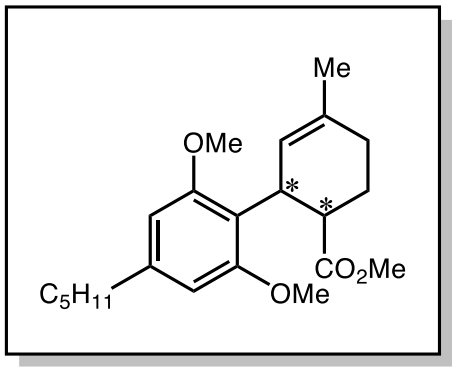



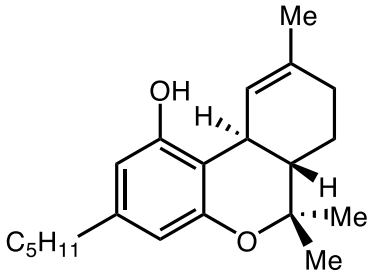

**56% (3 steps)**
on average

Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2014**, *53,* 13898.

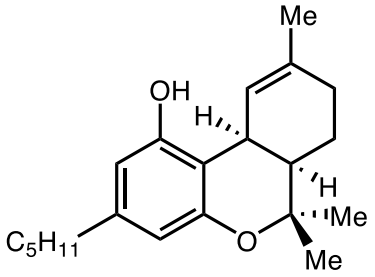
# *The Ir-catalyzed Allylic Substitution*

- stereodivergent synthesis of $\Delta^9$-Tetrahydrocannabinols

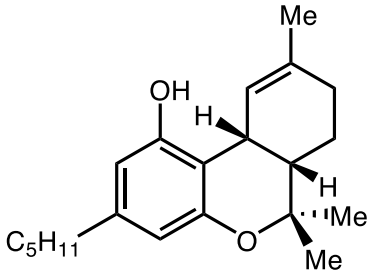


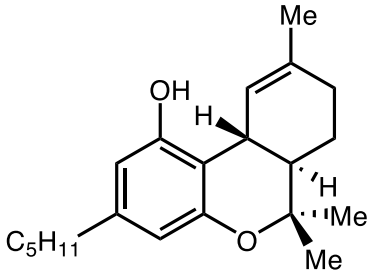

*(S,S)*




*(R,S)*




*(S,R)*
**(+)-$\Delta^9$-cis-THC**



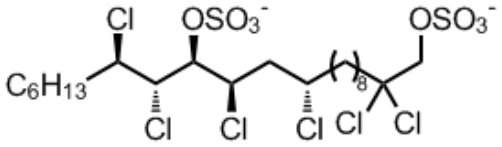

*(R,R)*
**(-)-$\Delta^9$-trans-THC**

Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2014**, *53,* 13898.

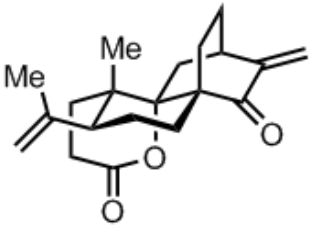
# *Research in the Carreira Lab*

**~ 50 syntheses completed (including nominal)**

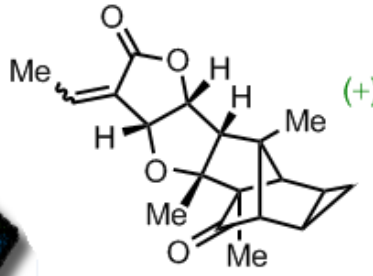
Epothilones A & B
Undecachlorosulfolipid
Zaragozic Acid C
Amphotericine
...among others



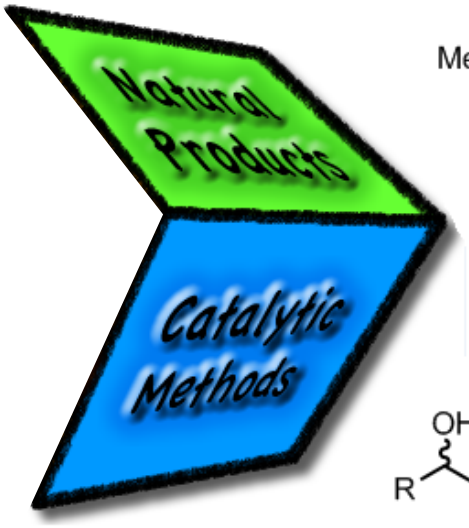

(+)-Danicalipin A




(+)-Crotogoudin

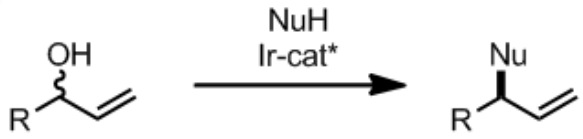



(±)-Pallambin A & B

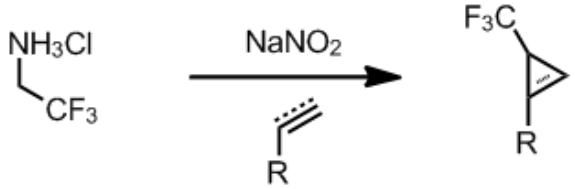



**numerous synthetic methods developed**

alkyne addition to carbonyl compunds,
Nitrile Oxide [3+2] cycloadditions
Ir-catalyzed allylic substitutions
in-situ generation of Diazocompounds
Olefin functionalization




Catalytic Enantioselective Allylic Substitution




In-situ Generation of Diazomethanes
and their Applications