Olefination Reactions

Lecture Notes

Key Reviews:

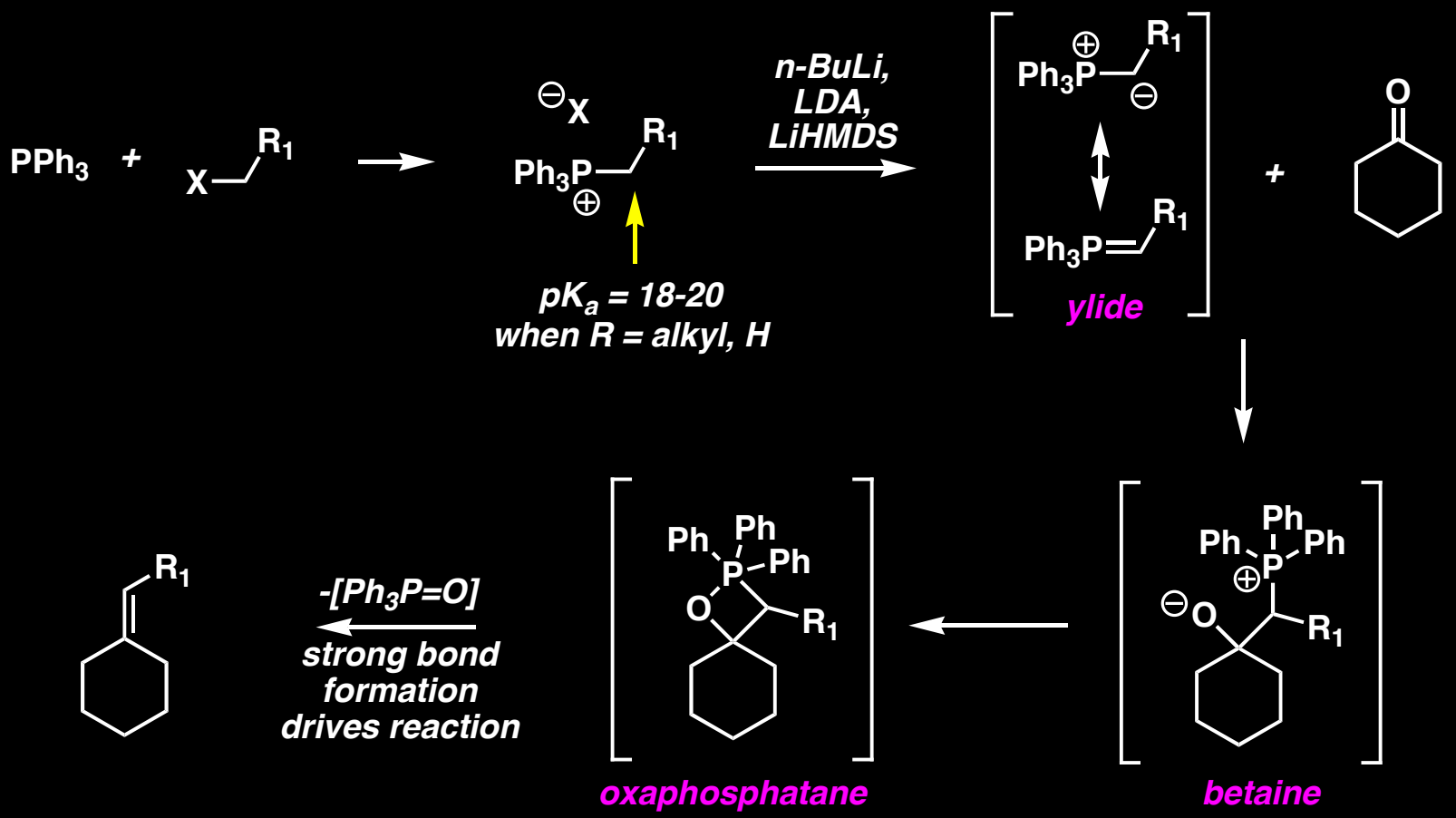
Wittig Reaction
K. C. Nicolaou and co-workers, Ann. 1997, 1283.

Horner-Wadsworth-Emmons and Tebbe Olefinations
S. E. Kelly, Comprehensive Org. Synth. 1991, Vol. 1, 729.

Peterson Olefination
D. J. Ager, Synthesis 1984, 384.

Julia (Julia-Lythgoe) Olefination
B. M. Trost, Bull. Chem. Soc. Jpn. 1988, 61, 107.

Wittig Olefination: Background and Principles



G. Wittig and G. Schollkopf, Chem. Ber. 1954, 87, 1318.

Wittig Olefination: Background and Principles

Stereoselectivity with non-stabilized ylides

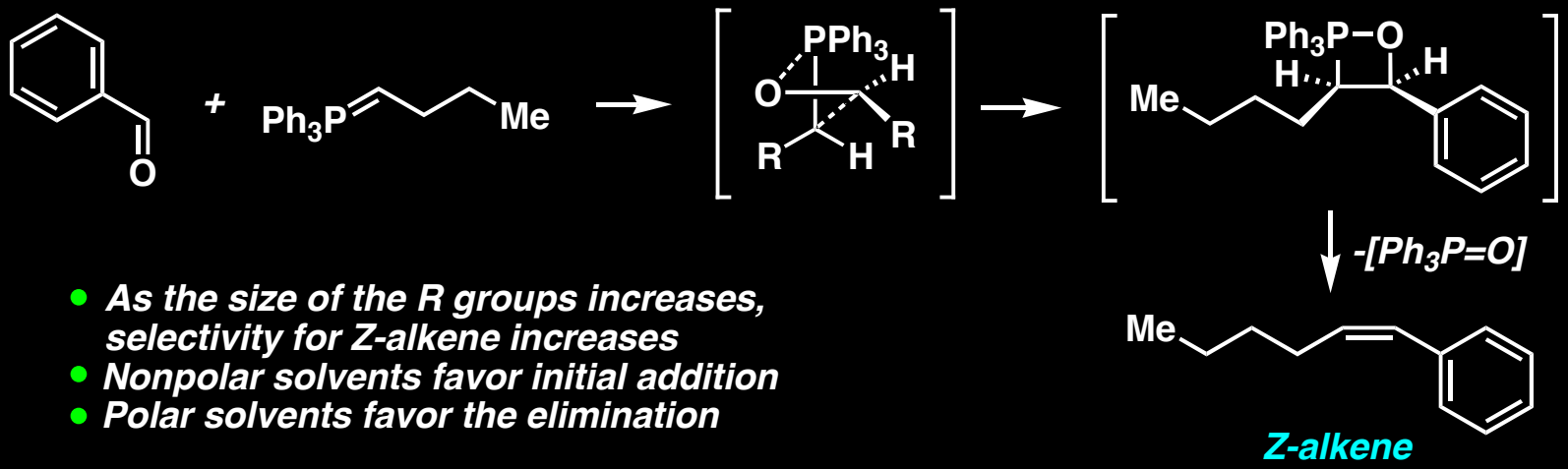
Not stable; must be made in situ and used immediately

Wittig Olefination: Background and Principles

Stereoselectivity with non-stabilized ylides

Not stable; must be made in situ and used immediately

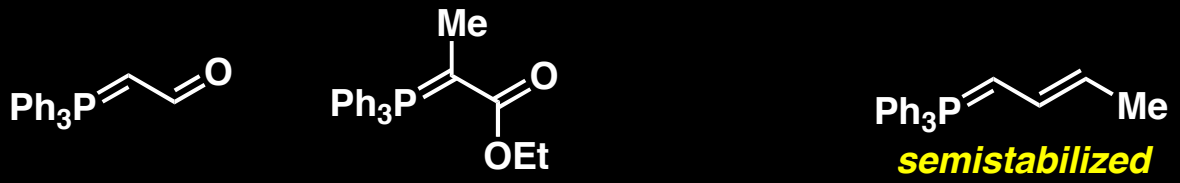
Addition to carbonyl is an irreversible and concerted [2+2] cycloaddition such that the R groups on the aldehyde and the ylide are as far apart as possible



- ***As the size of the R groups increases, selectivity for Z-alkene increases***
- ***Nonpolar solvents favor initial addition***
- ***Polar solvents favor the elimination***

Wittig Olefination: Background and Principles

Stereoselectivity with stabilized ylides

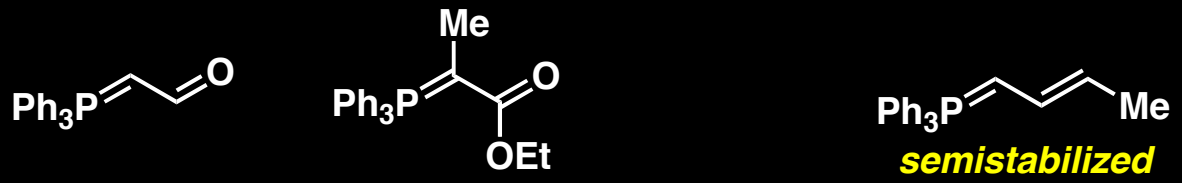


semistabilized

Incredibly stable; not moisture sensitive, can be chromatographed
Price for stability is lower reactivity: reacts well with aldehydes, slowly with ketones

Wittig Olefination: Background and Principles

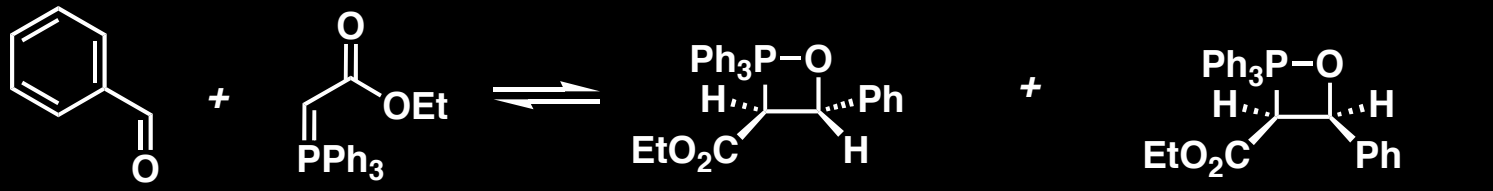
Stereoselectivity with stabilized ylides



semistabilized

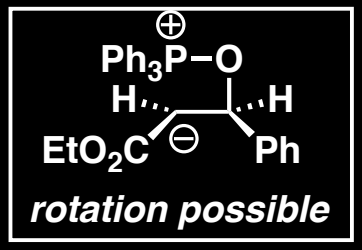
Incredibly stable; not moisture sensitive, can be chromatographed
Price for stability is lower reactivity: reacts well with aldehydes, slowly with ketones

Initial addition to carbonyl is reversible so the thermodynamic elimination product results.



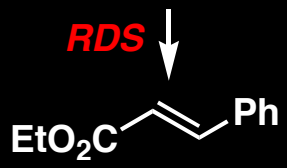
minor kinetic product

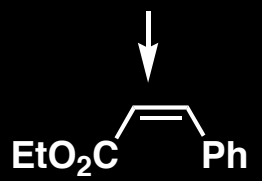
major kinetic product



rotation possible

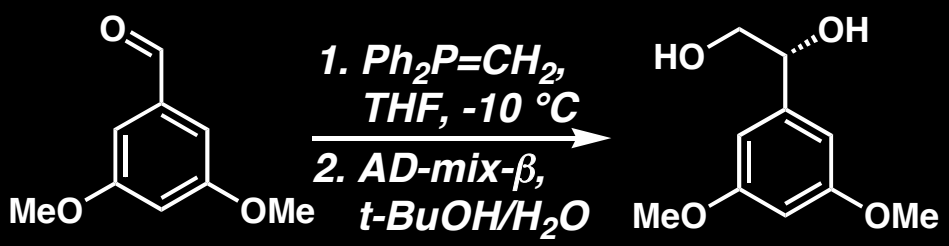
RDS

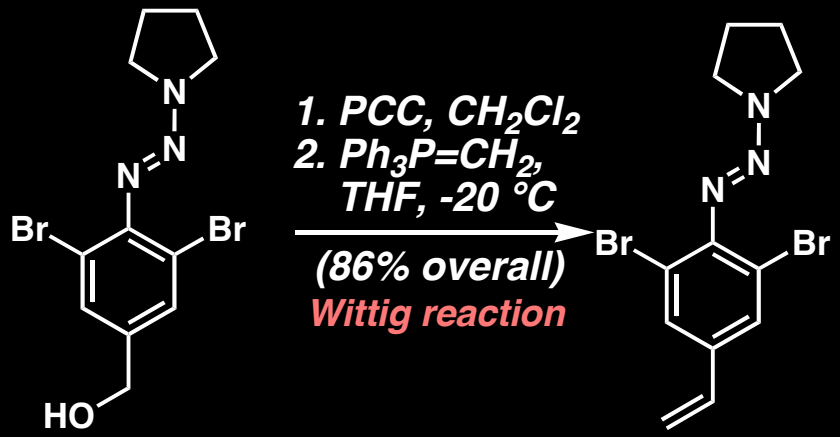


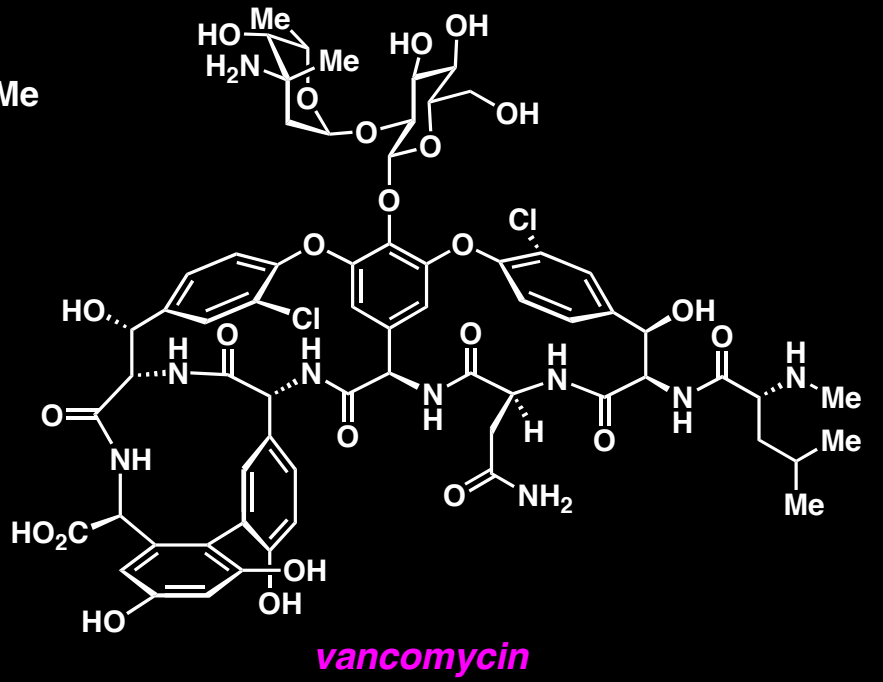


thermodynamically most stable; predominant or only product

Wittig Olefination: Applications in Total Synthesis

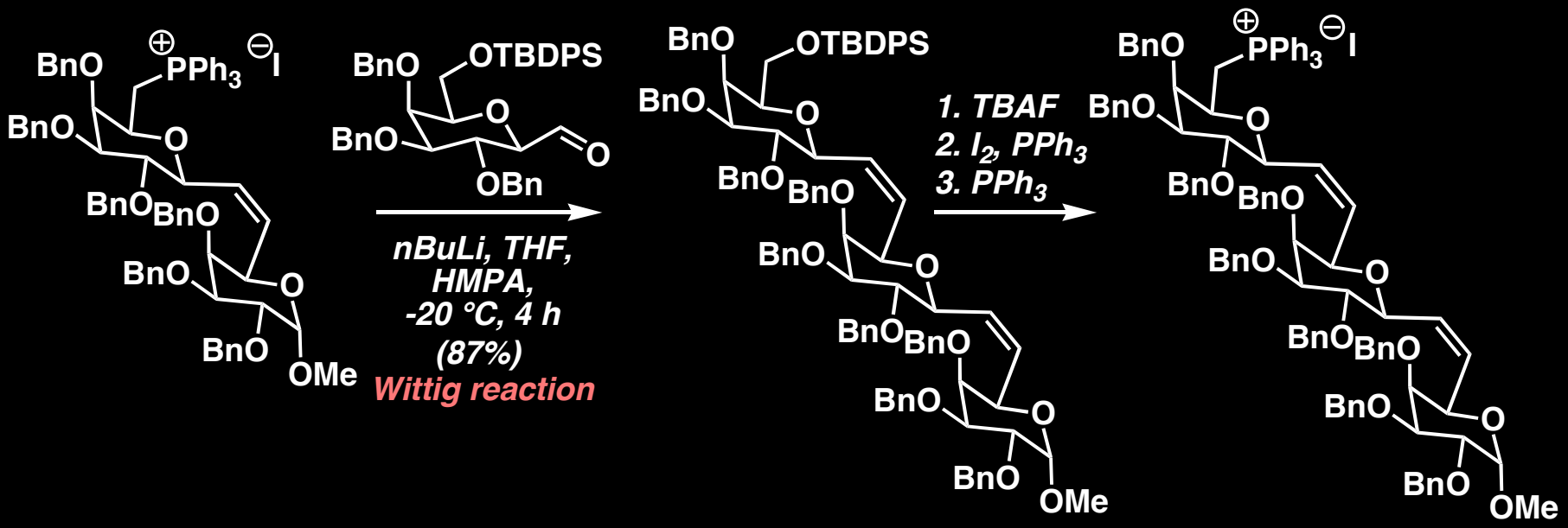






K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 1998, 37, 2708.

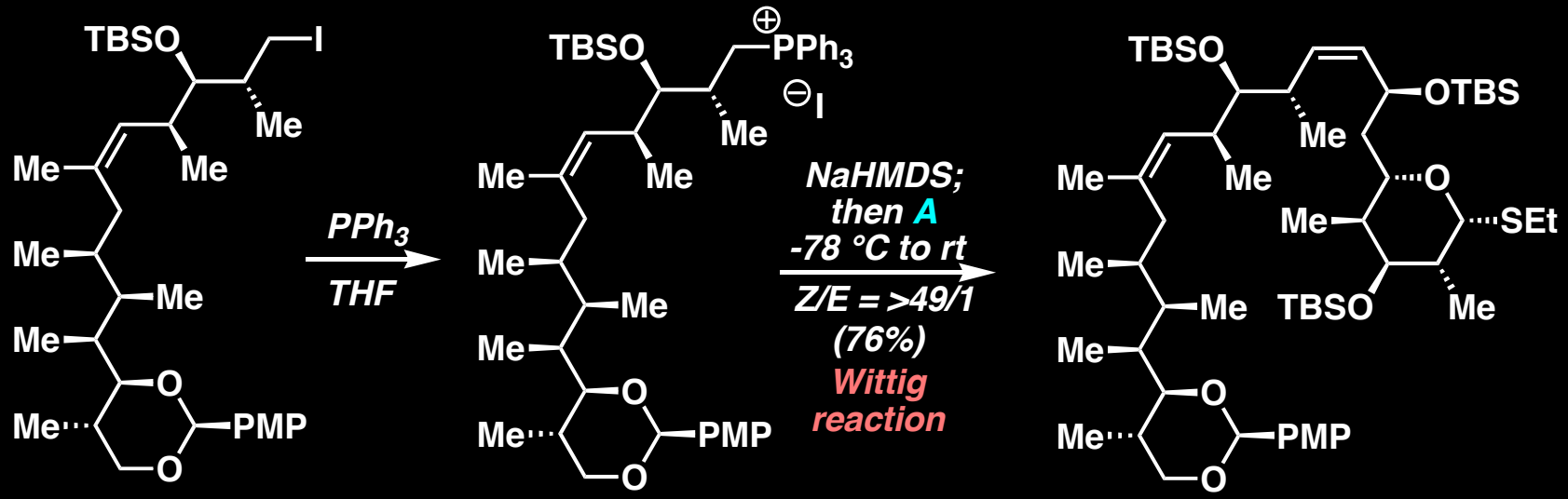
Wittig Olefination: Applications in Total Synthesis



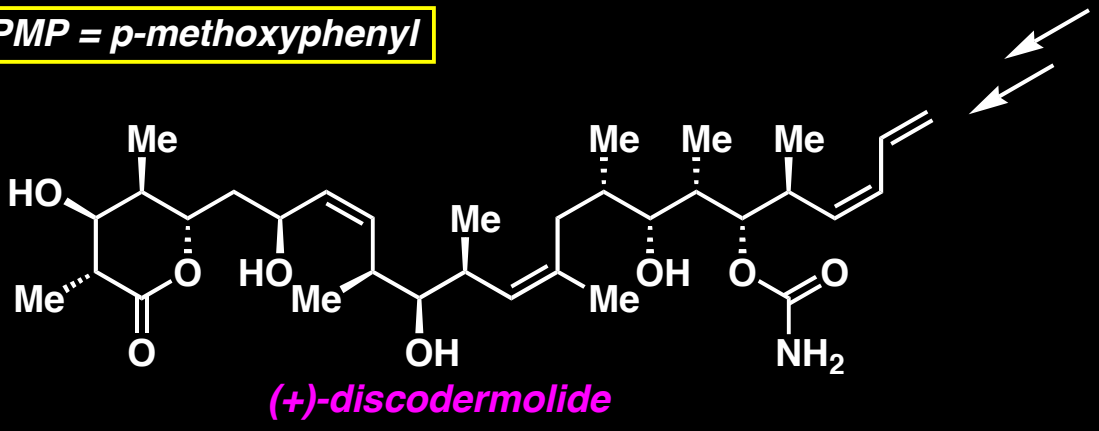
These researchers have made tetraoses and pentaoses via this technology

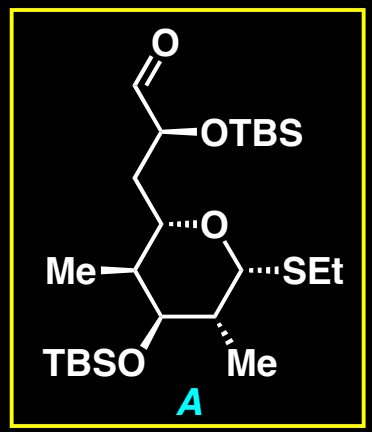
A. Dondoni and co-workers, J. Org. Chem. 2002, 67, 4186.

Wittig Olefination: Applications in Total Synthesis



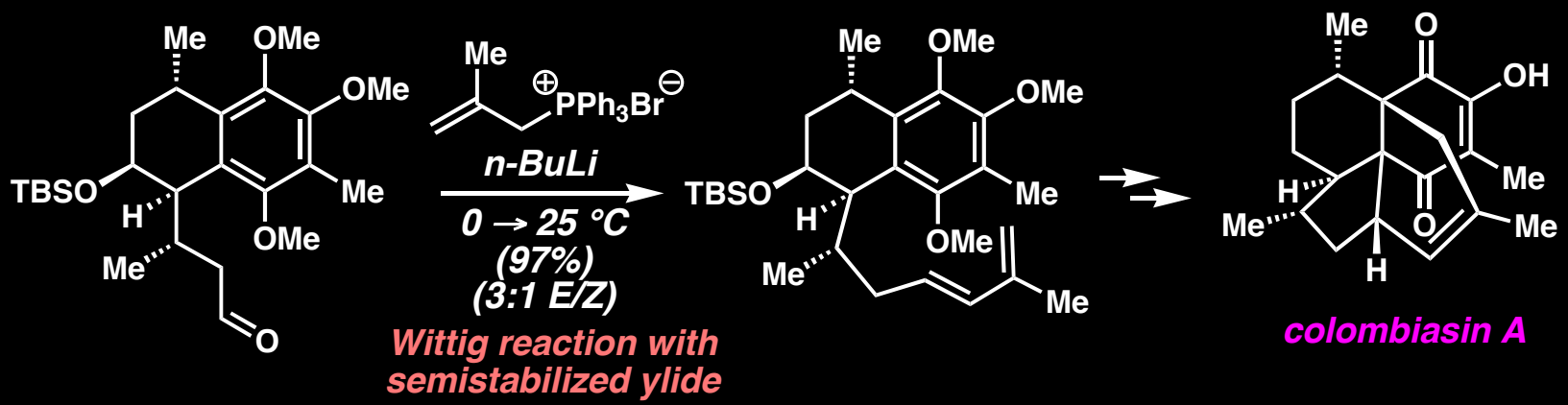
PMP = p-methoxyphenyl





A. B. Smith and co-workers, J. Am. Chem. Soc. 2000, 122, 8654.

Wittig Olefination: Applications in Total Synthesis

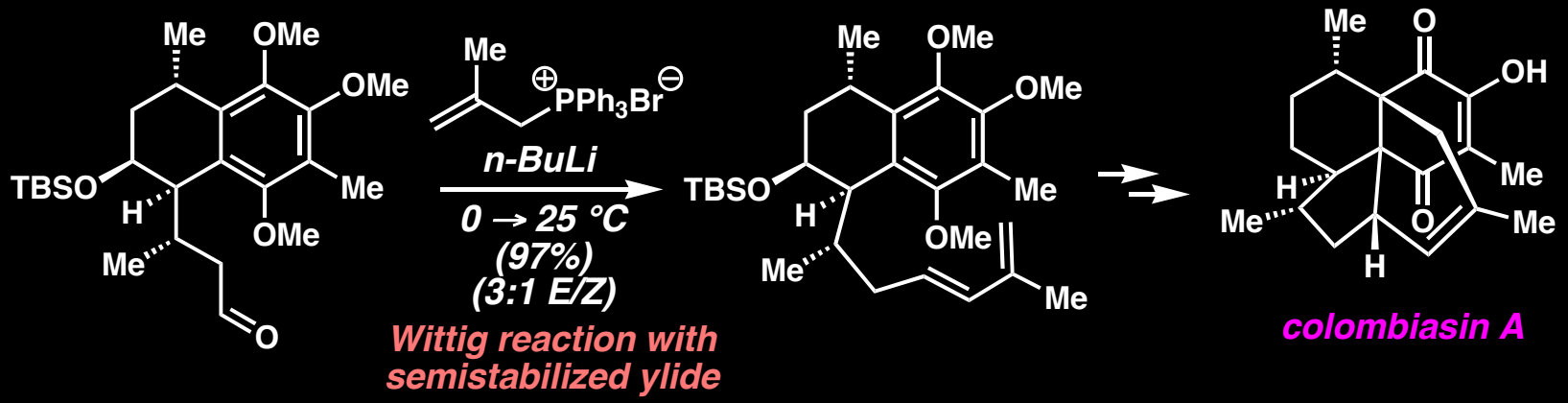


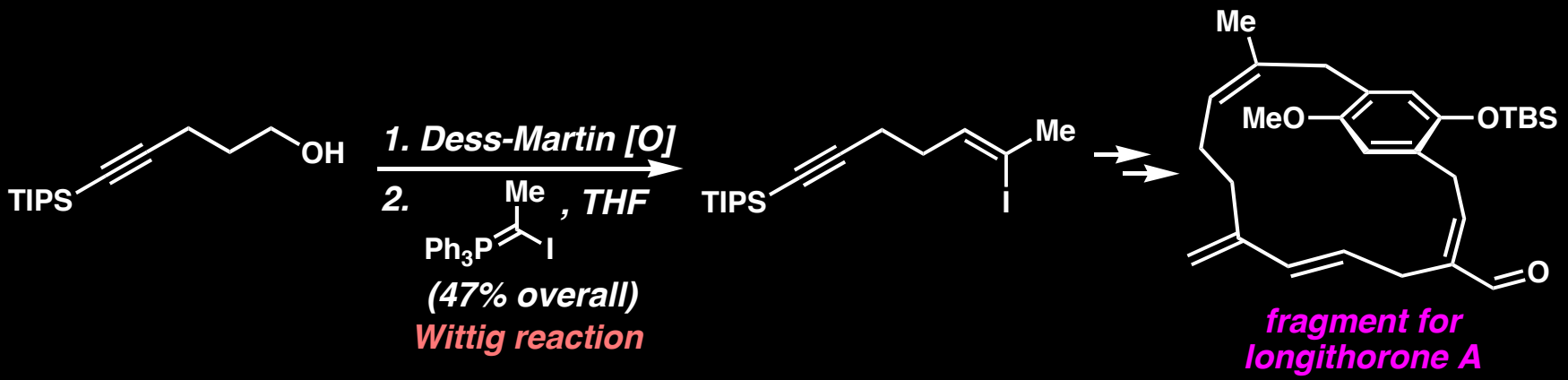
Wittig reaction with semistabilized ylide

colombiasin A

K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 2001, 40, 2482.
M. D. Shair and co-workers, J. Am. Chem. Soc. 2002, 124, 773.

Wittig Olefination: Applications in Total Synthesis





K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 2001, 40, 2482.
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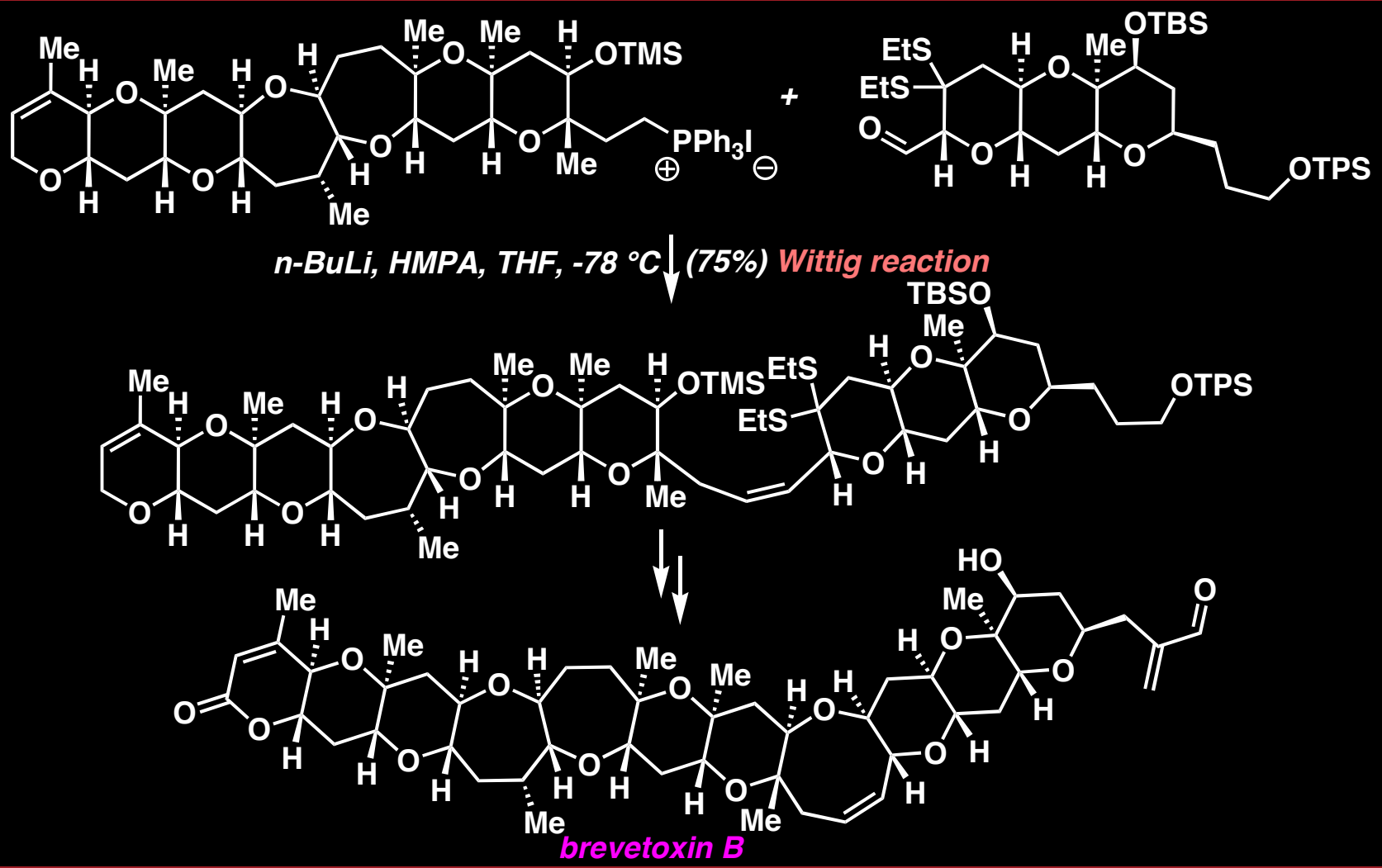
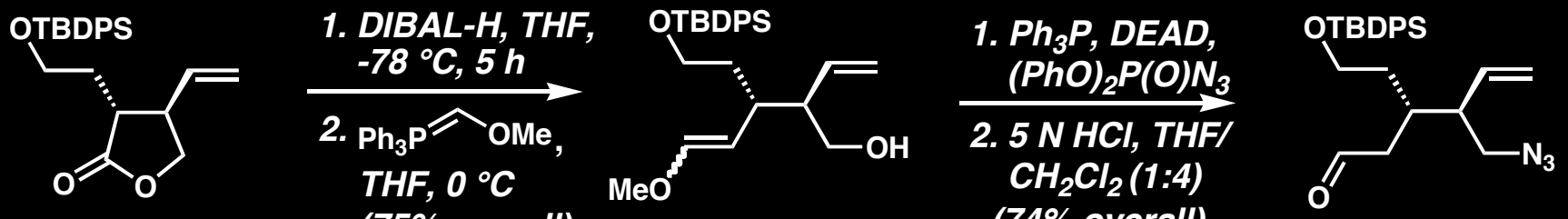
Wittig Olefination: Applications in Total Synthesis

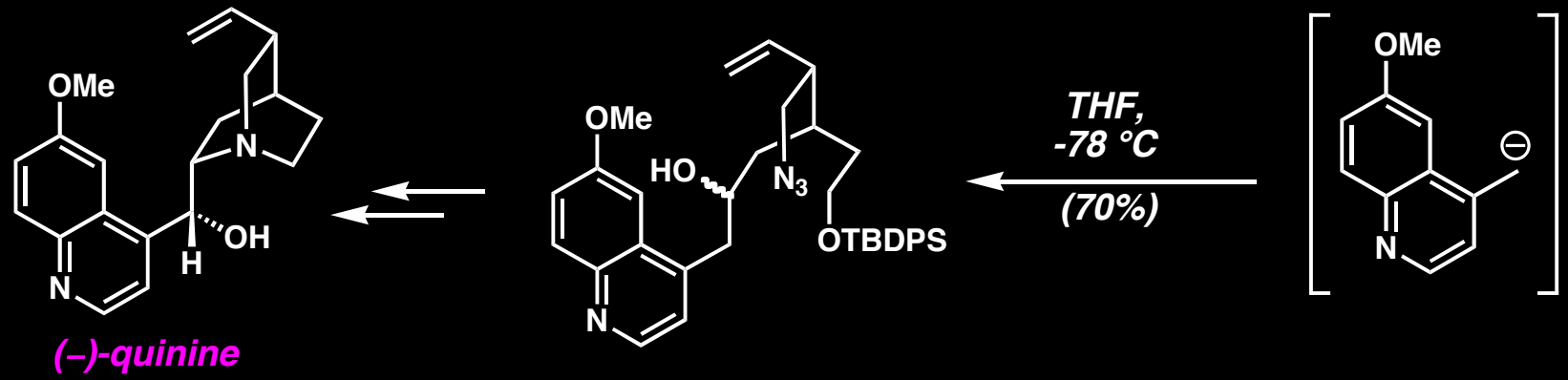


K. C. Nicolaou and co-workers, J. Am. Chem. Soc. 1995, 117, 1171.
For a review, see: Classics in Total Synthesis I, Chapter 37.

Wittig Olefination: Applications in Total Synthesis

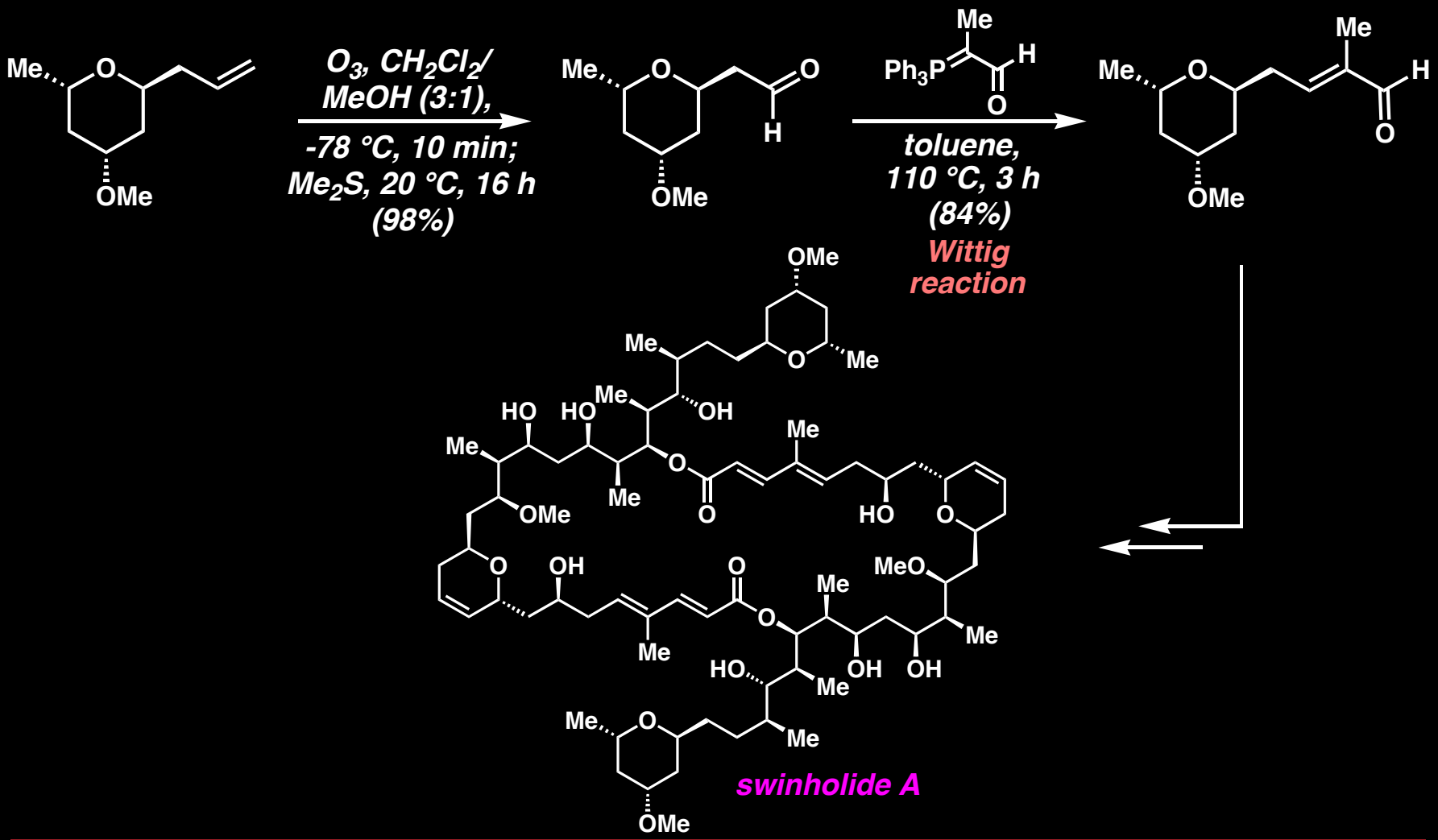


This chain extension technique is usually good yielding as long as the molecule is acid stable



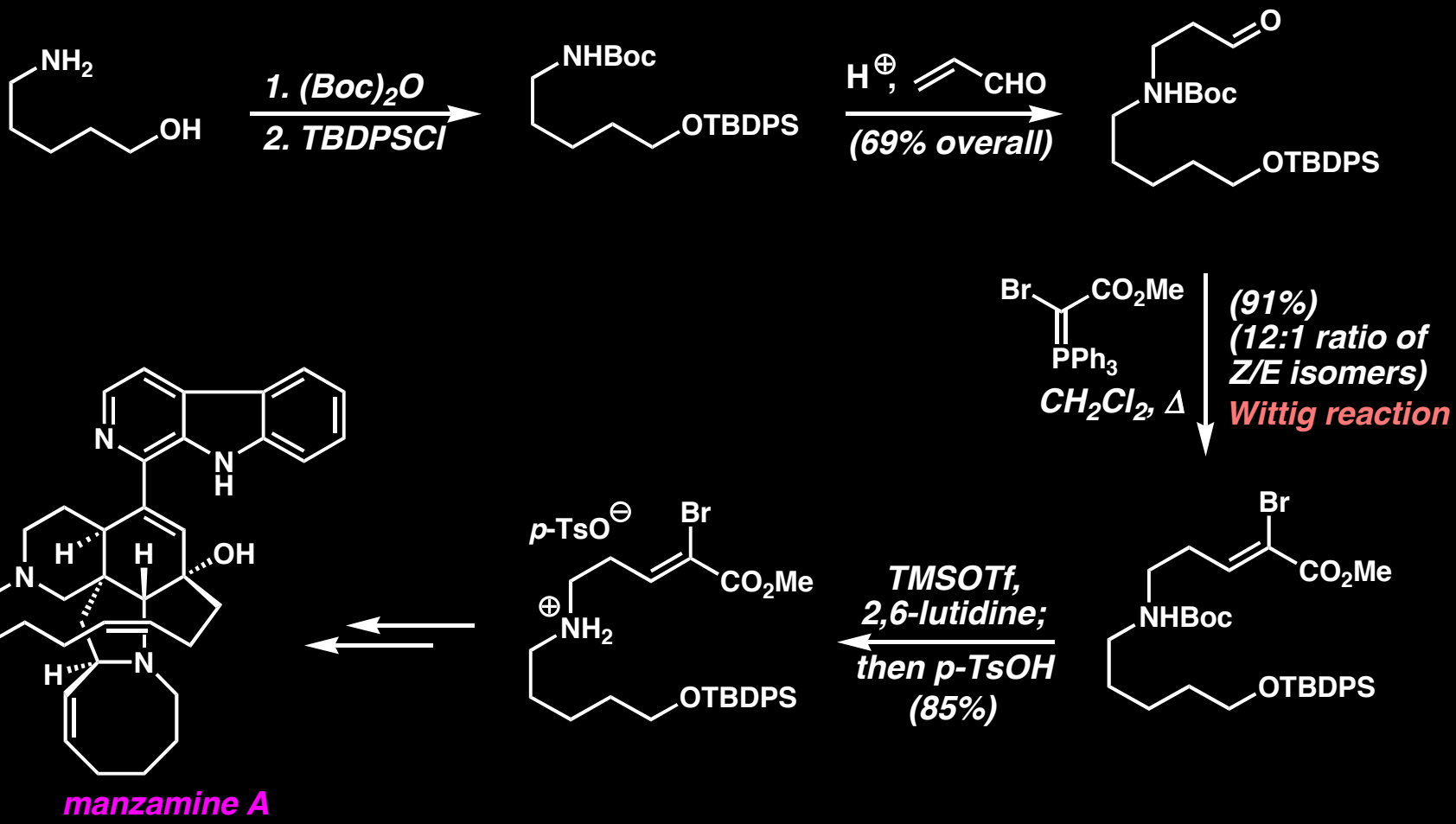
G. Stork and co-workers, J. Am. Chem. Soc. 2001, 123, 3239.

Wittig Olefination: Applications in Total Synthesis



I. Paterson and co-workers, Tetrahedron 1995, 51, 9393.

Wittig Olefination: Applications in Total Synthesis



S. F. Martin and co-workers, J. Am. Chem. Soc. 1999, 121, 866.

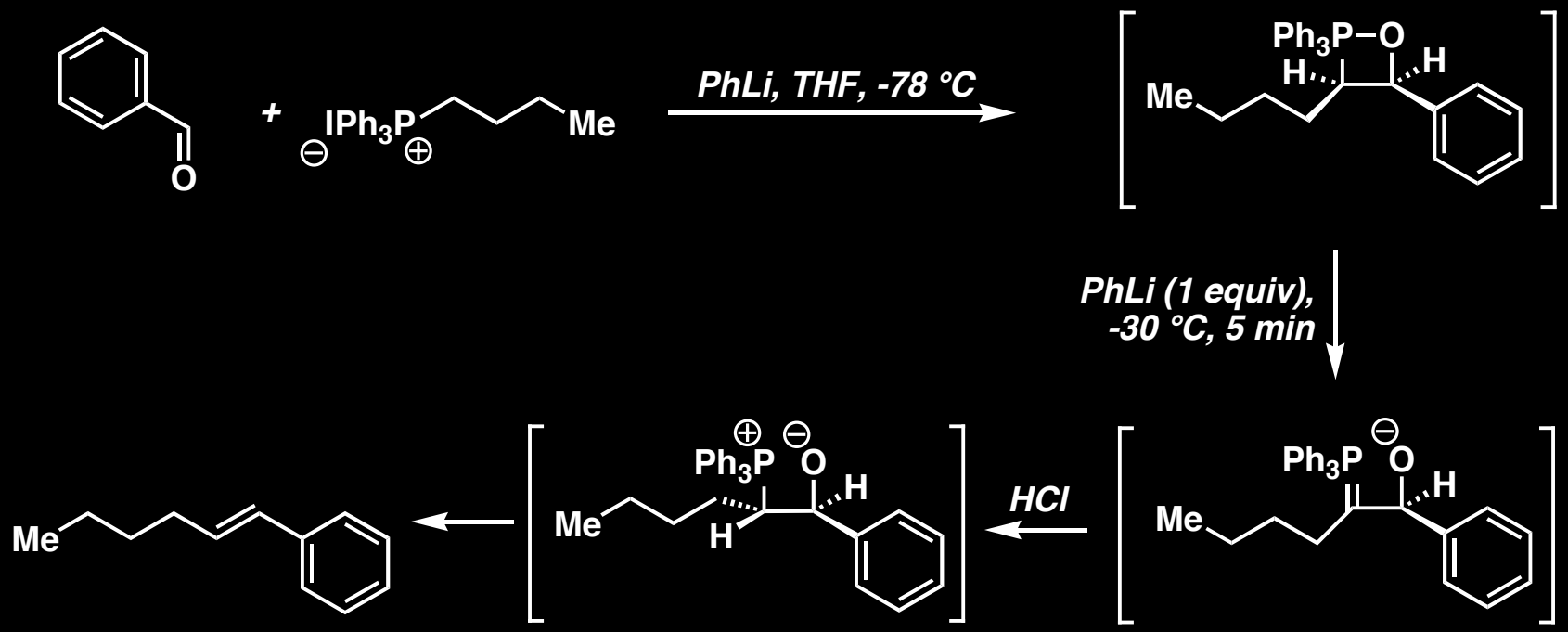
Wittig Olefination: Background and Principles

Schlösser-modified Wittig Reaction: How to Get E-products with Non-stabilized Ylides

M. Schlösser, Angew. Chem. Int. Ed. Engl. 1966, 5, 126.

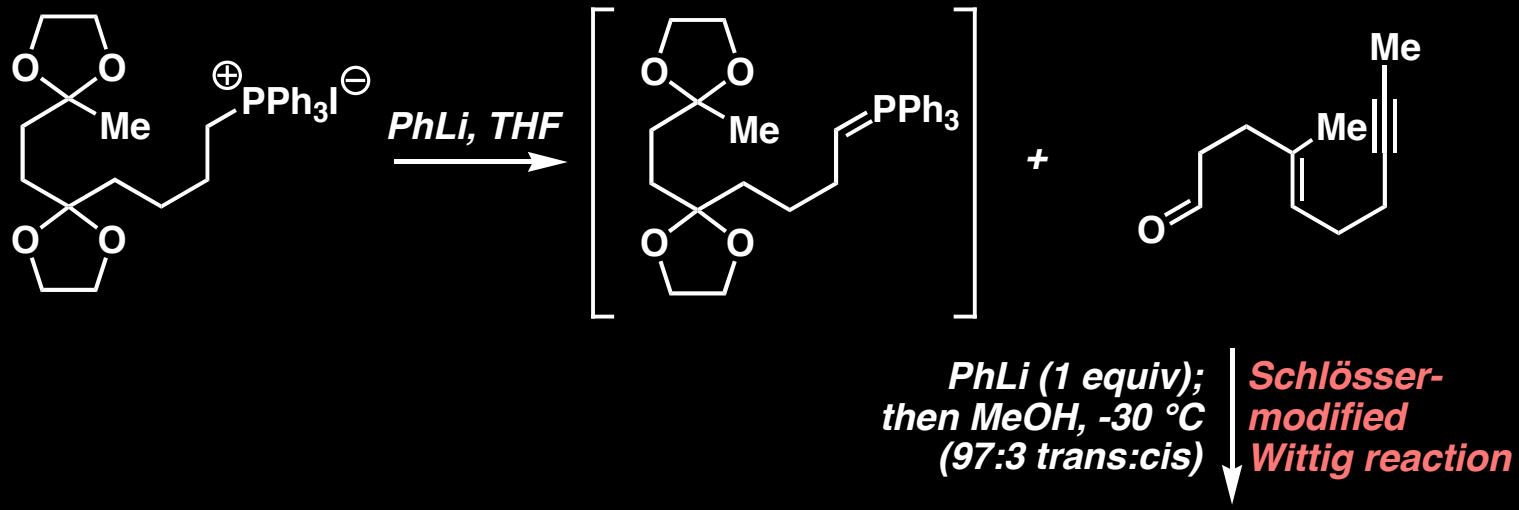
Wittig Olefination: Background and Principles

Schlösser-modified Wittig Reaction: How to Get E-products with Non-stabilized Ylides



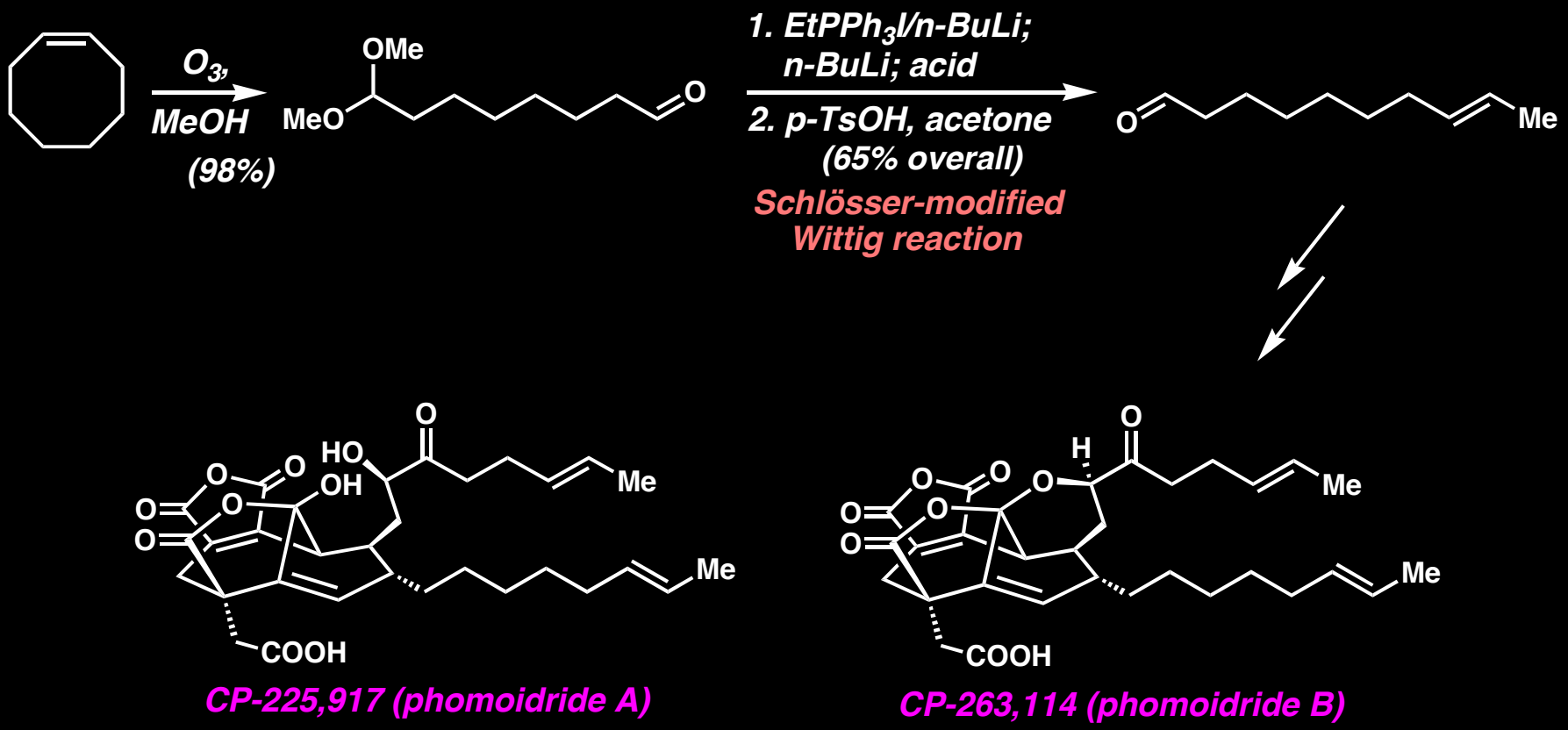
M. Schlösser, Angew. Chem. Int. Ed. Engl. 1966, 5, 126.

Wittig Olefination: Applications in Total Synthesis



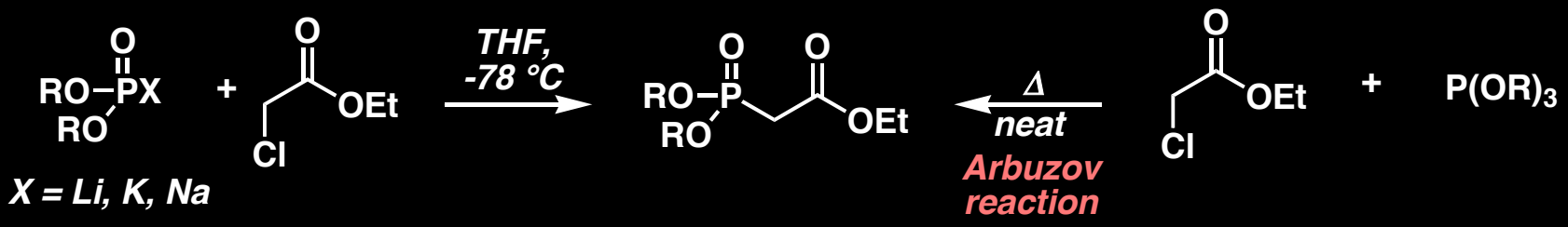
W. S. Johnson and co-workers, J. Am. Chem. Soc. 1970, 92, 741.
For a review, see: Classics in Total Synthesis I, Chapter 6.

Wittig Olefination: Applications in Total Synthesis

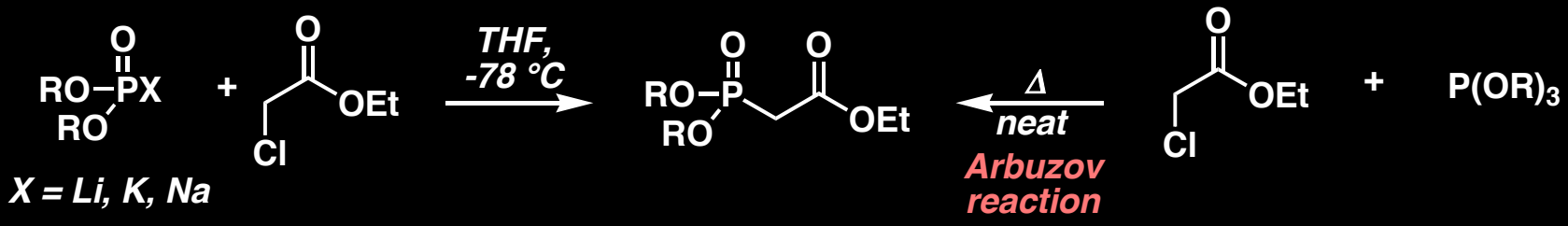


K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 1999, 38, 1669.

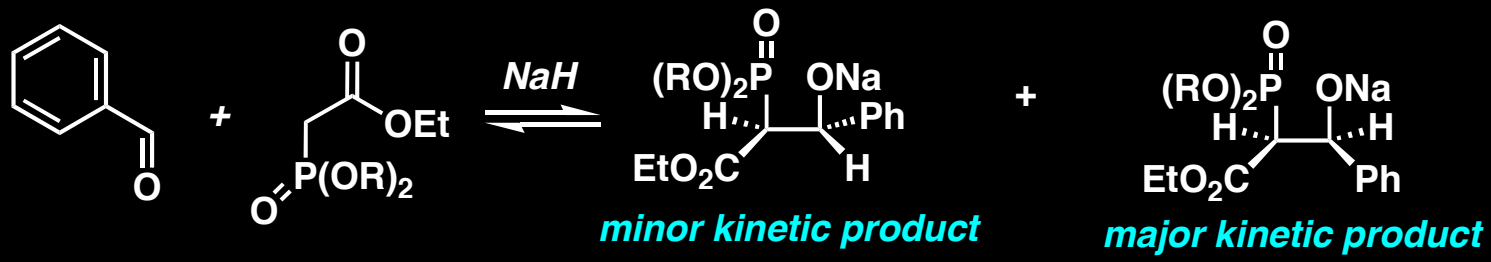
Horner-Wadsworth-Emmons Olefination: Background and Principles

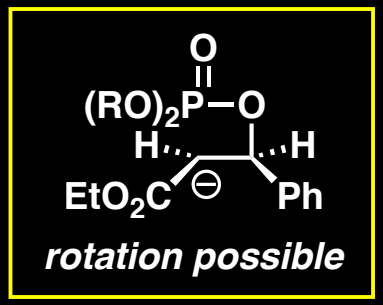


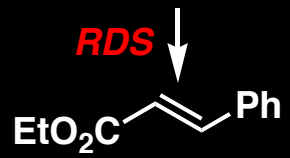
Horner-Wadsworth-Emmons Olefination: Background and Principles



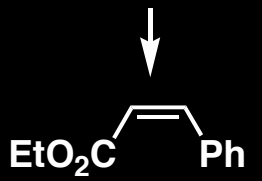
Stereoselectivity Principles: Follows general rules of stabilized ylides



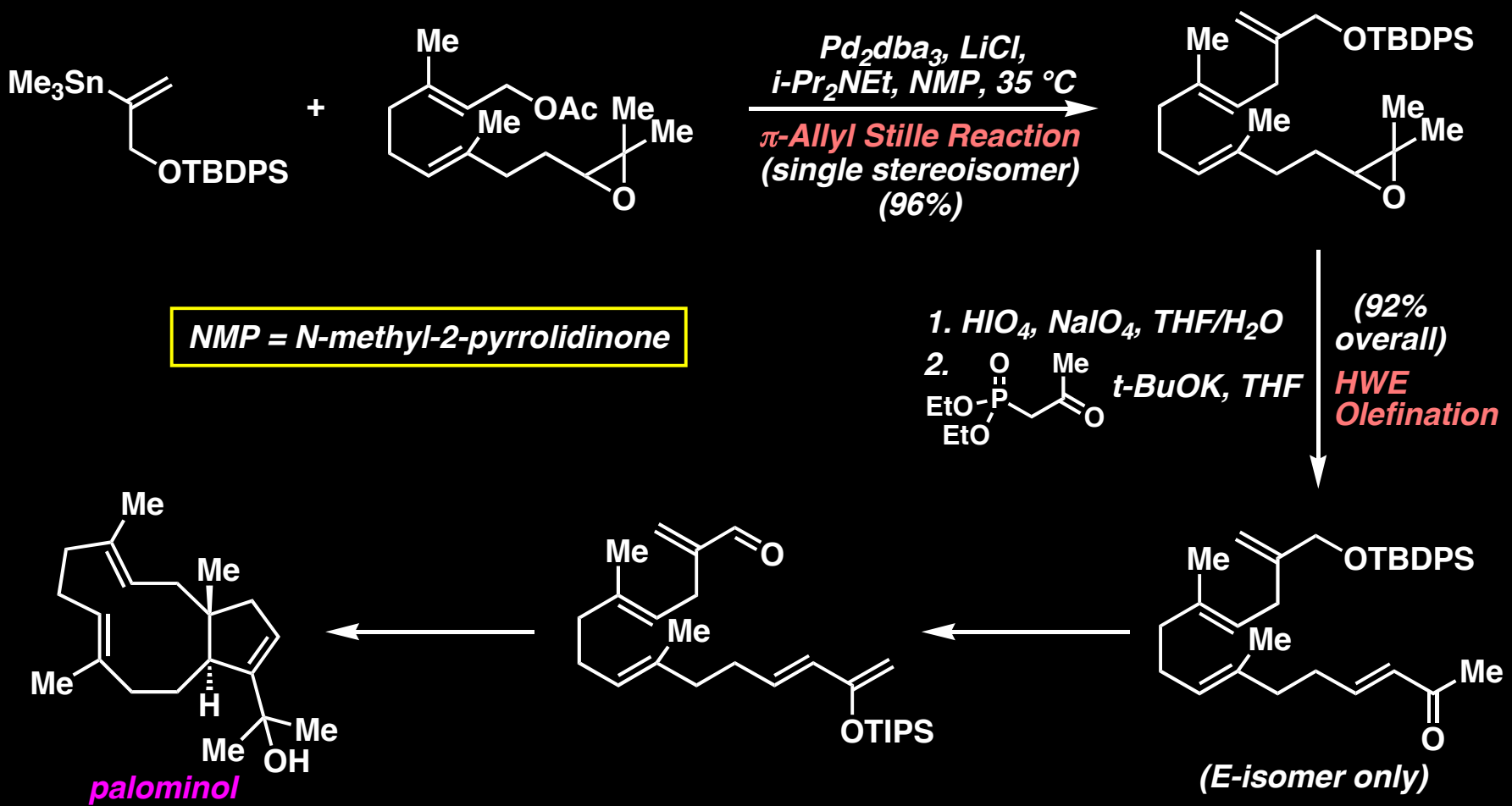




thermodynamically most stable; predominant or only product

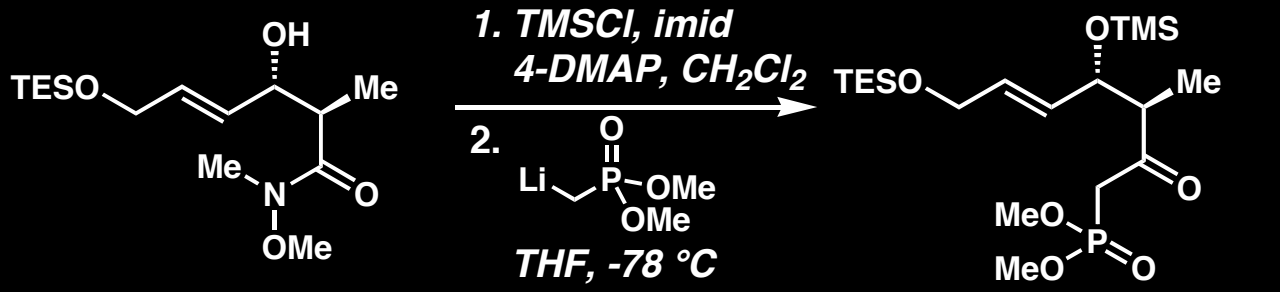


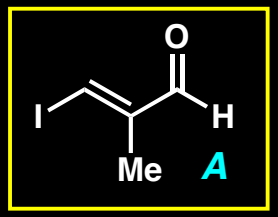
Horner-Wadsworth-Emmons Olefination: Applications in Total Synthesis

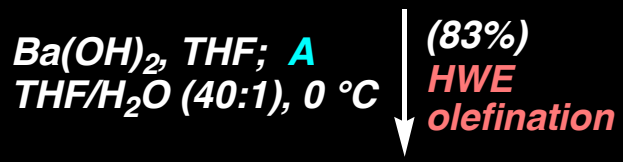


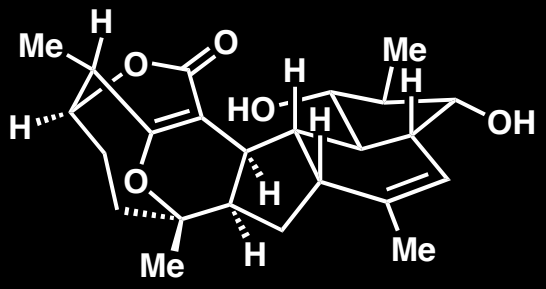
S. A. Snyder, E. J. Corey, J. Am. Chem. Soc. 2006, 128, 740.

Horner-Wadsworth-Emmons Olefination: Applications in Total Synthesis









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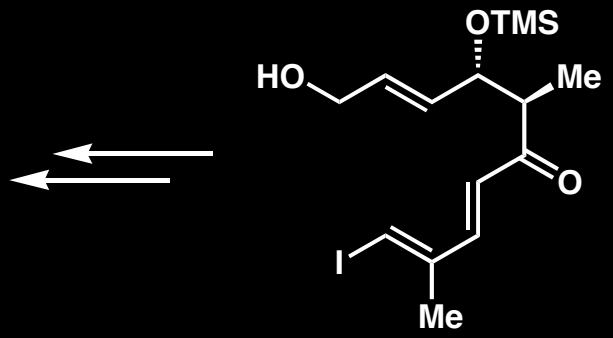
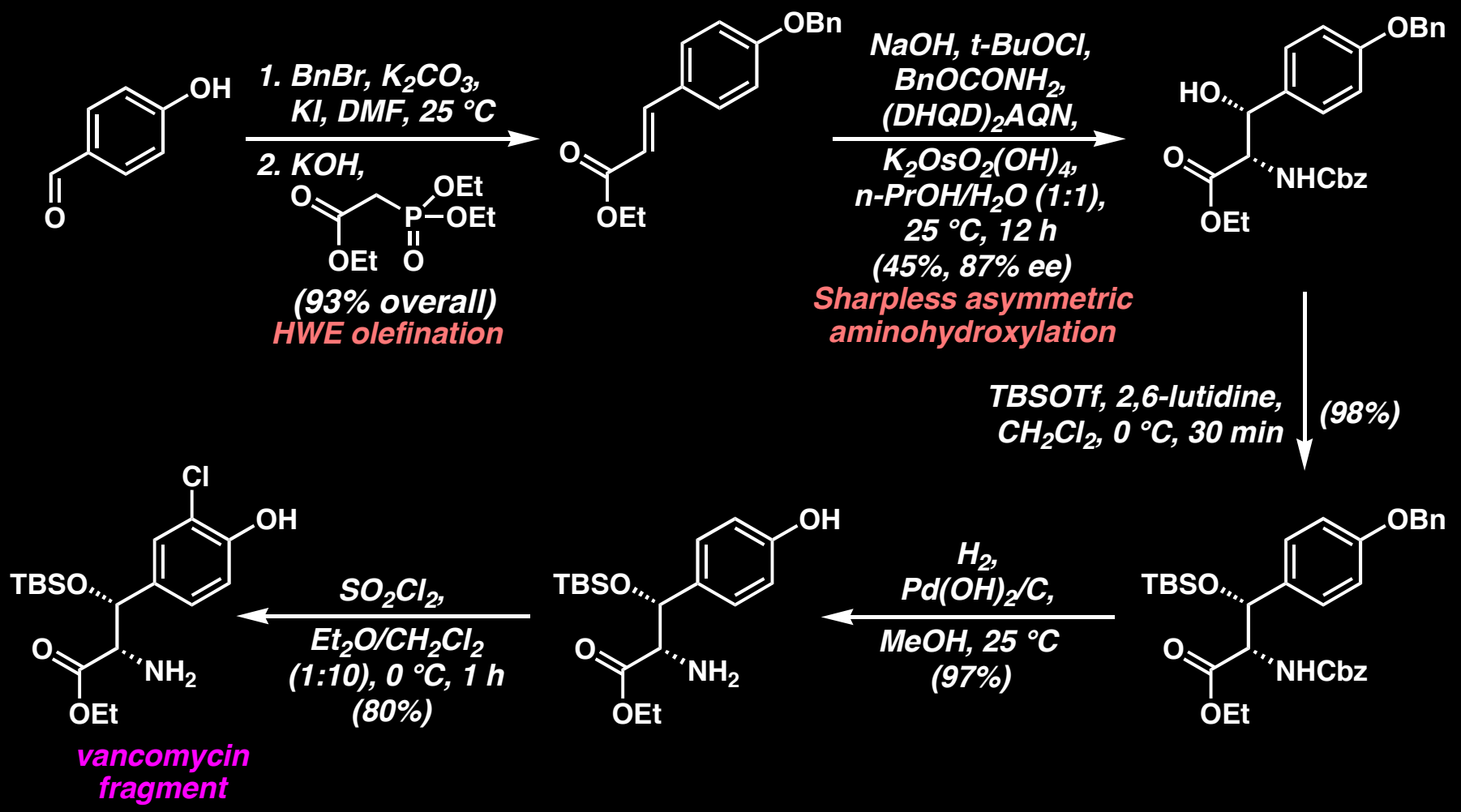


E. J. Sorensen and co-workers, J. Am. Chem. Soc. 2003, 125, 5393.

Horner-Wadsworth-Emmons Olefination: Applications in Total Synthesis



K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 1998, 37, 2708.

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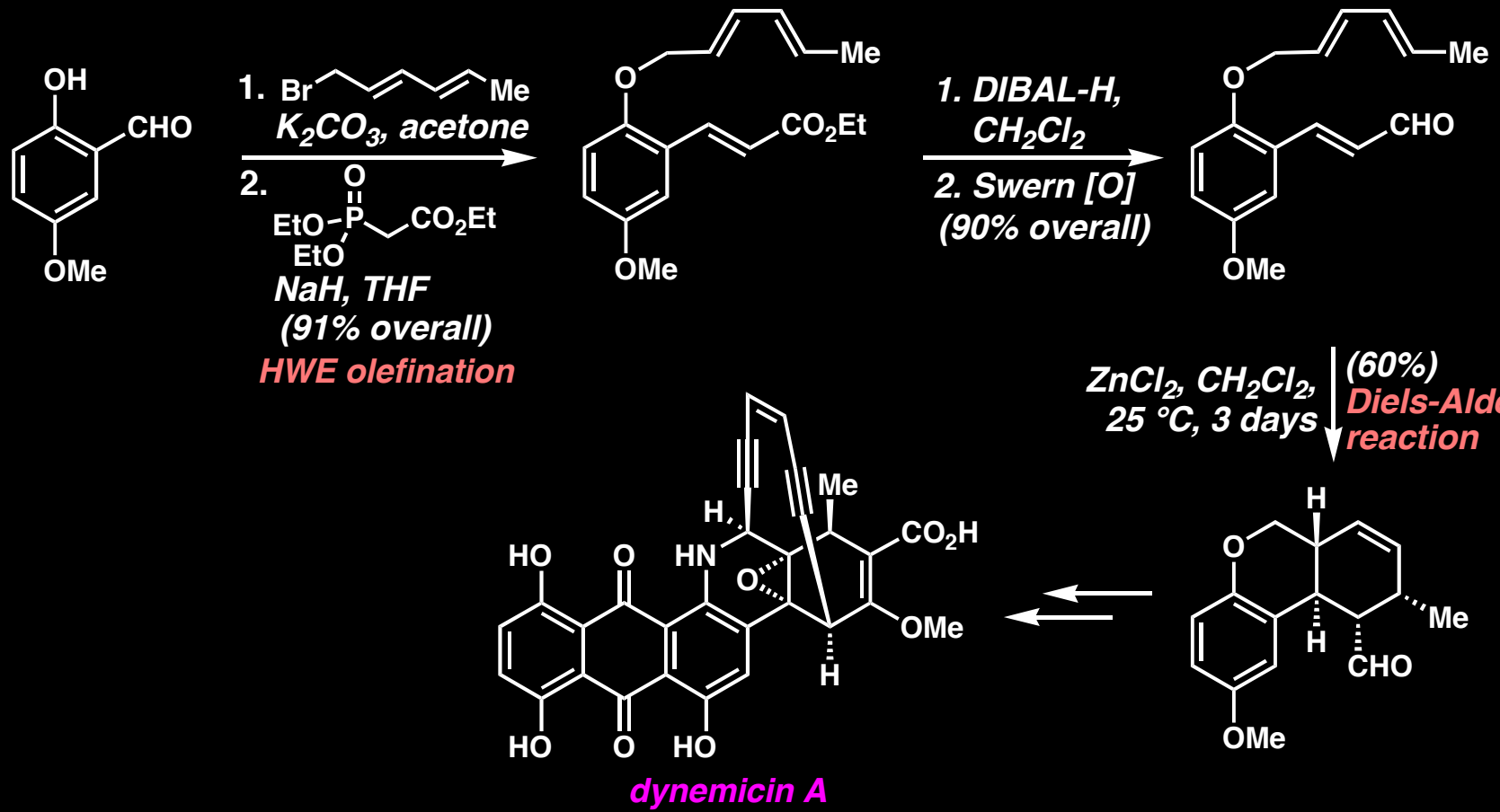
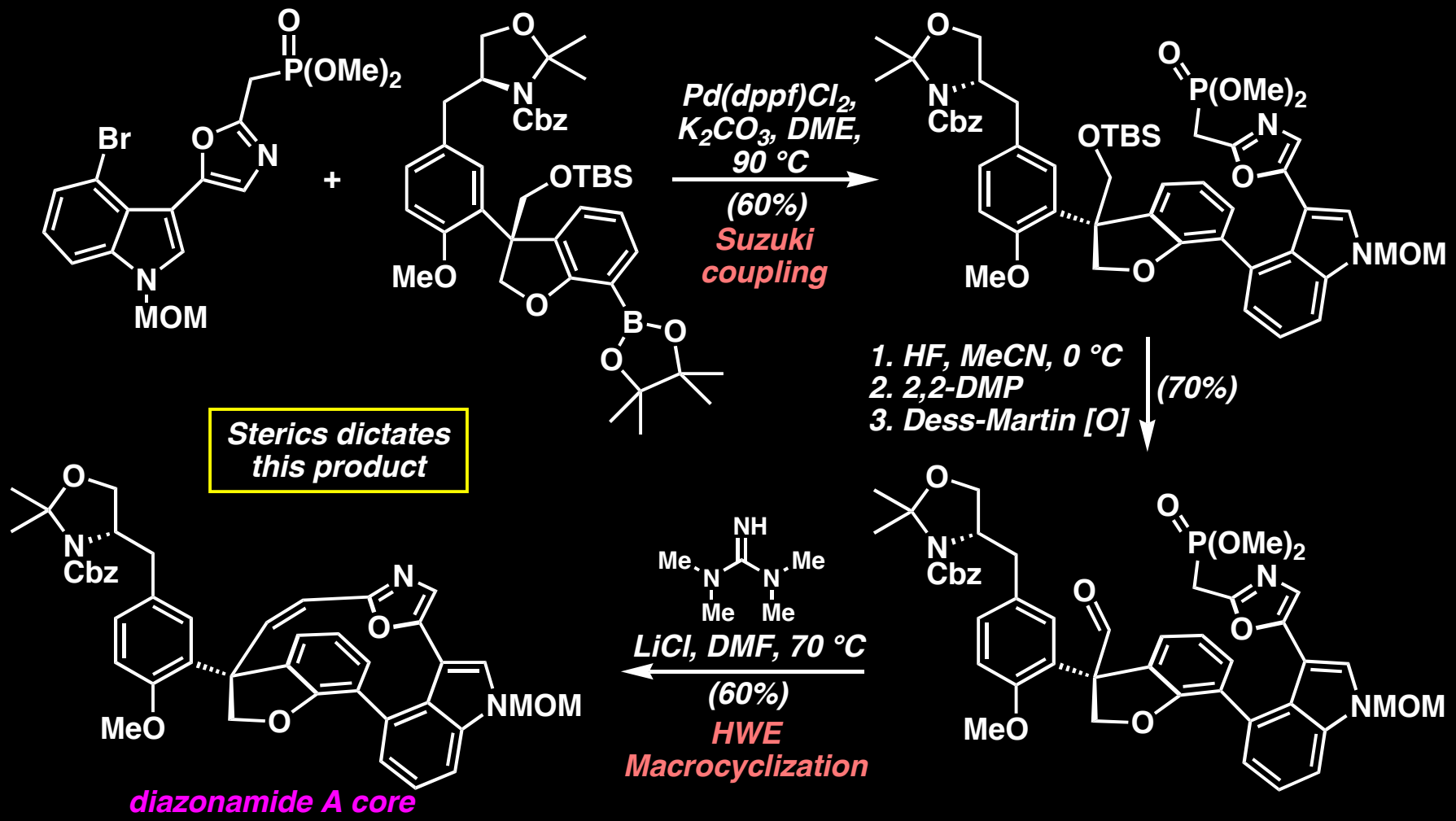


S. J. Danishefsky and co-workers, J. Am. Chem. Soc. 1996, 118, 9509.

Horner-Wadsworth-Emmons Olefination: Applications in Total Synthesis



K. C. Nicolaou and co-workers, J. Am. Chem. Soc. 2002, 126, 10162.
For a related use of 1,1,3,3-TMG, see: S.J. Danishefsky, et al. J. Am. Chem. Soc. 2001, 123, 1890.

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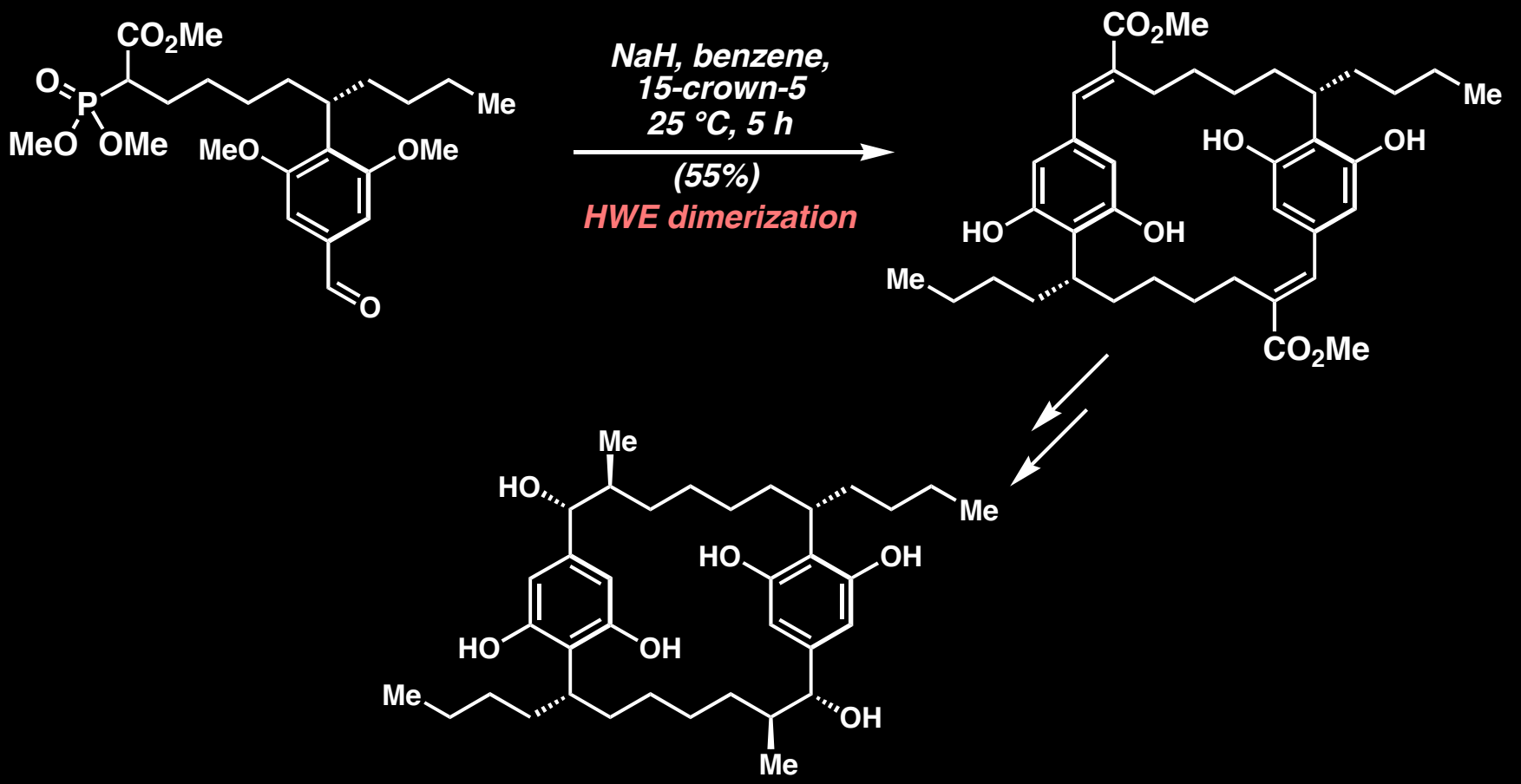
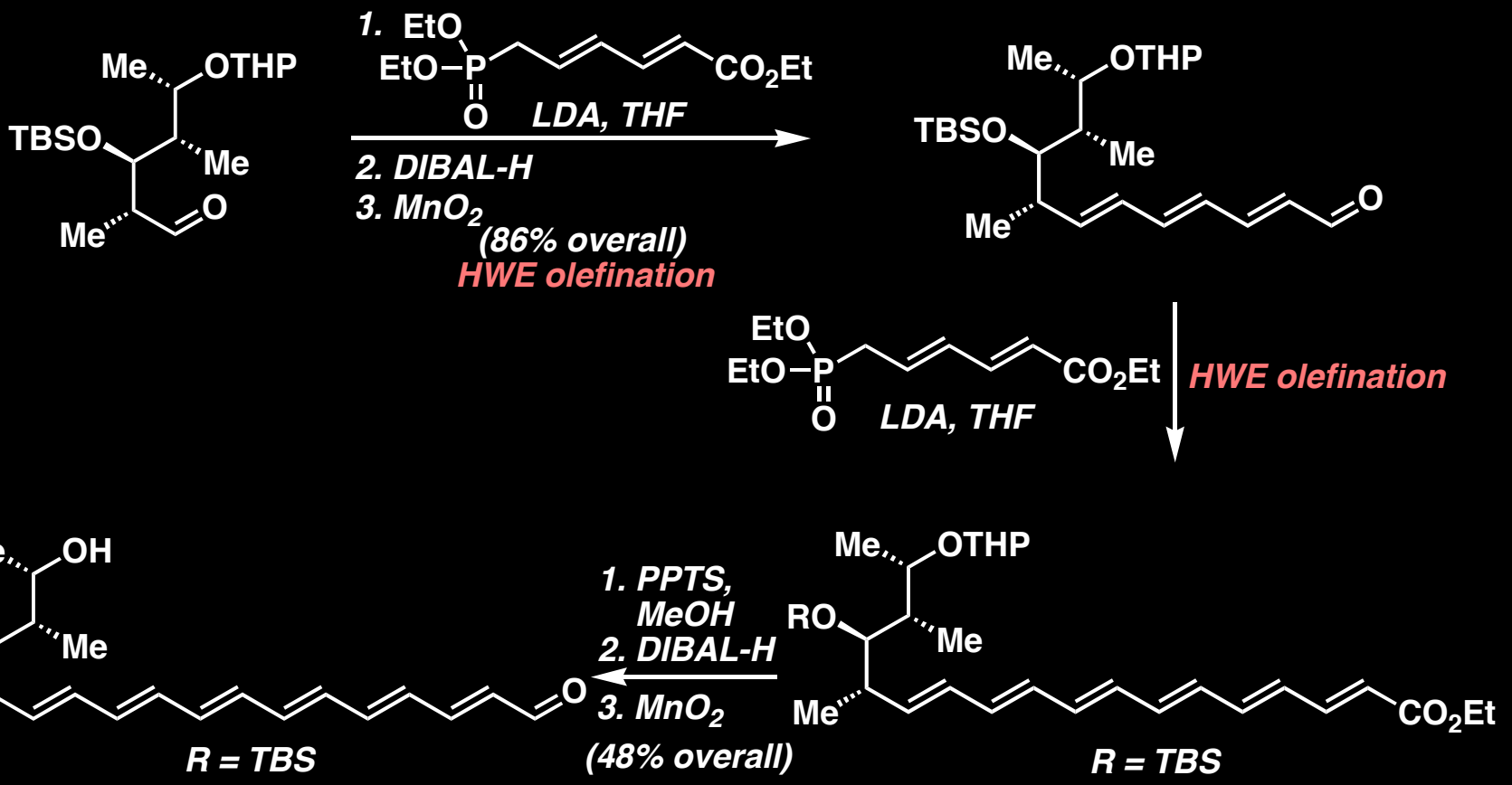


(–)-cylindrocyclophane A

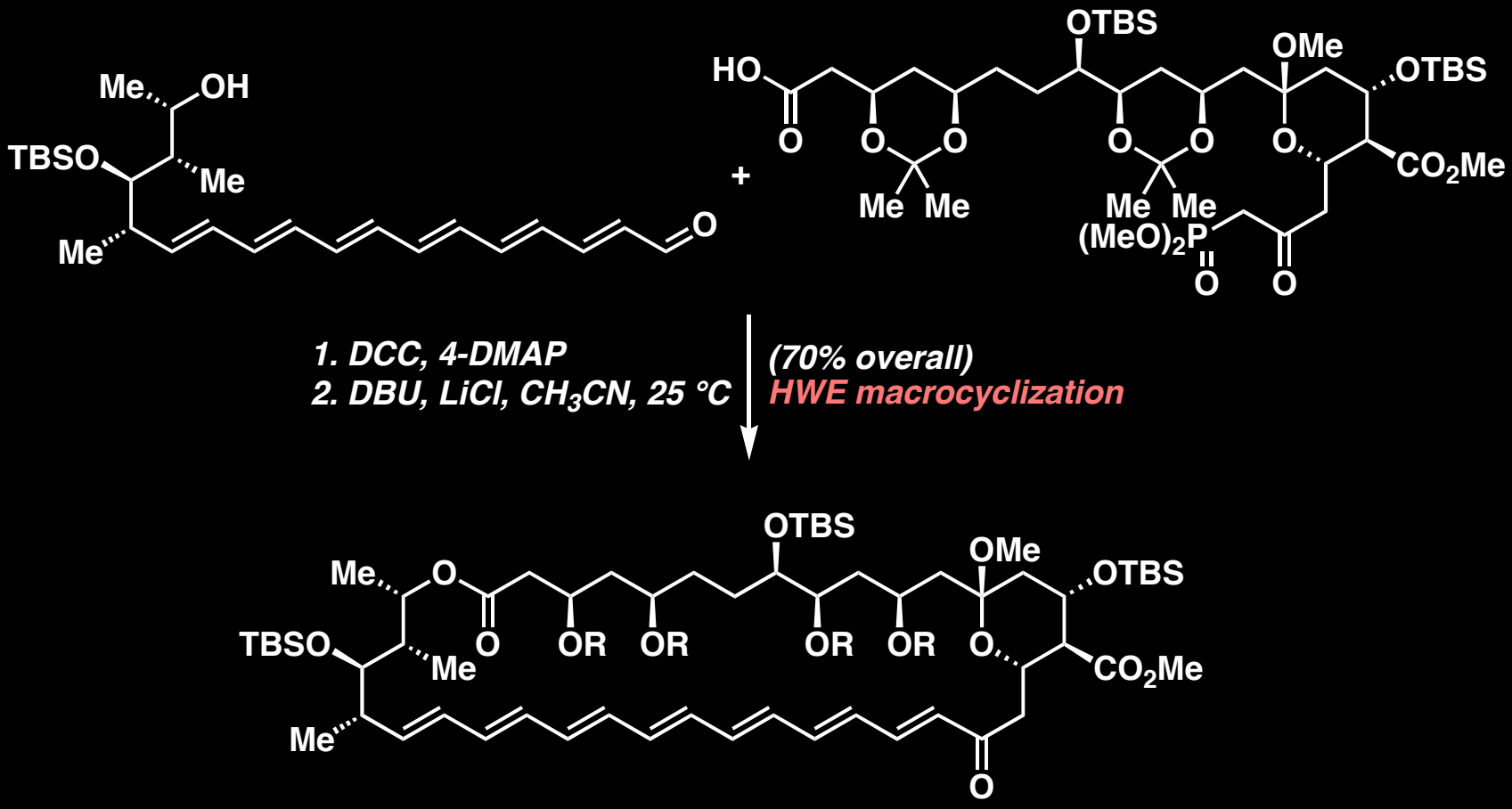
T. R. Hoye and co-workers, J. Am. Chem. Soc. 2000, 122, 4982.

Horner-Wadsworth-Emmons Olefination: Applications in Total Synthesis



K. C. Nicolaou and co-workers, J. Am. Chem. Soc. 1988, 110, 4672.
For a review, see: Classics in Total Synthesis I, Chapter 24.

Horner-Wadsworth-Emmons Olefination: Applications in Total Synthesis



core architecture of amphotericin B

K. C. Nicolaou and co-workers, J. Am. Chem. Soc. 1988, 110, 4672.
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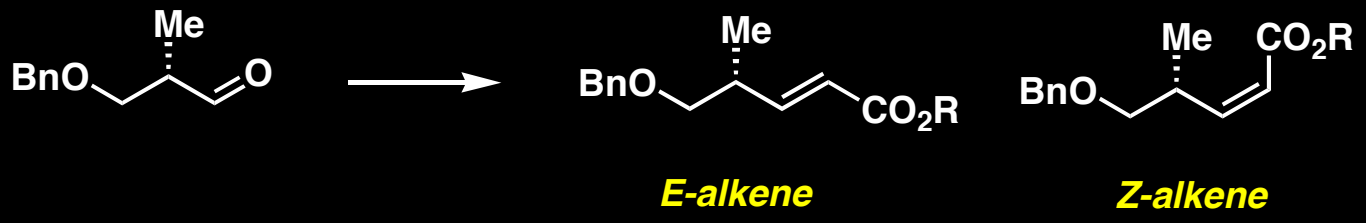
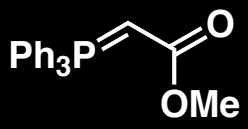
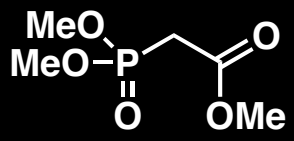
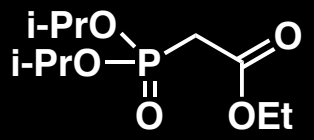
Horner-Wadsworth-Emmons Olefination: Background and Principles

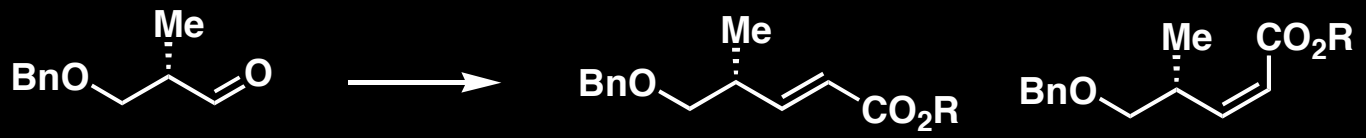


E-alkene *Z-alkene*

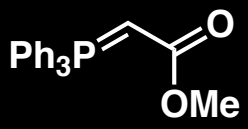
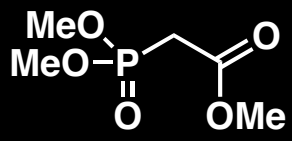
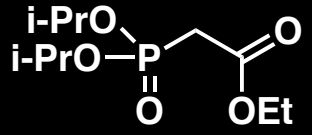
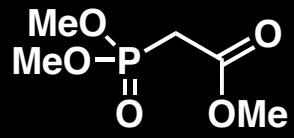
	*CH_2Cl_2, 0 °C*	*7*	*1*
	*LiHMDS, THF, -78 °C*	*3*	*1*
	*LiHMDS, THF, -78 °C*	*19*	*1*

Y. Kishi and co-workers, Tetrahedron 1981, 37, 3873.

Horner-Wadsworth-Emmons Olefination: Background and Principles

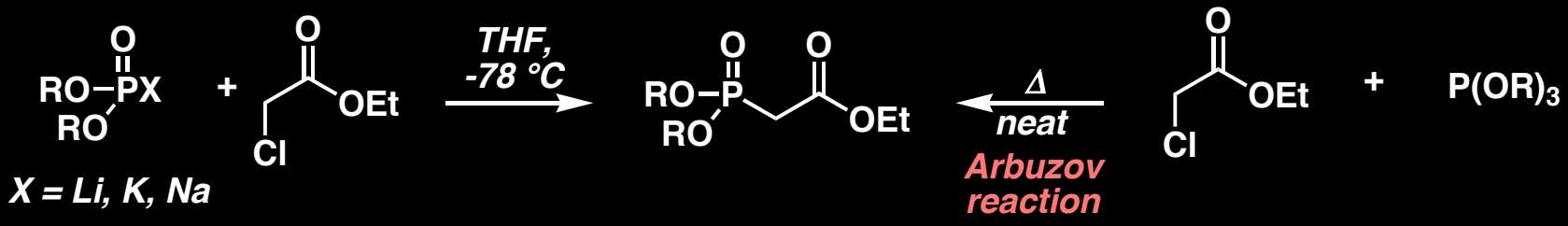


E-alkene *Z-alkene*

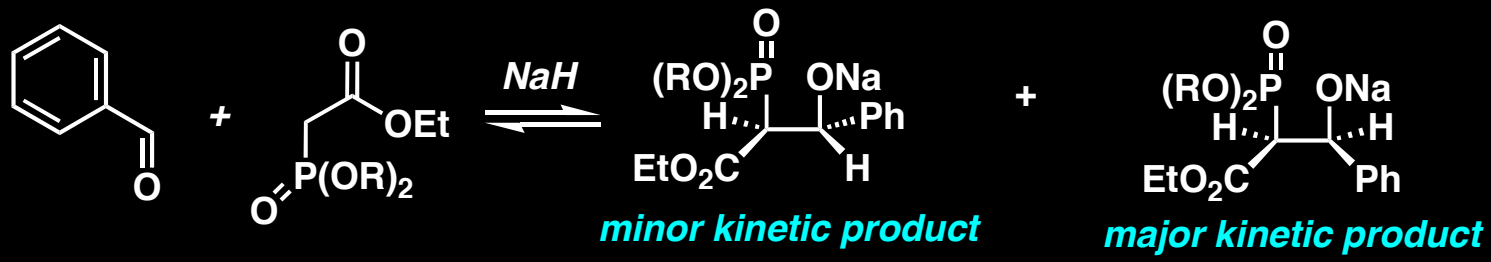
	*CH_2Cl_2, 0 °C*	*7*	*1*	
	*LiHMDS, THF, -78 °C*	*3*	*1*	
	*LiHMDS, THF, -78 °C*	*19*	*1*	*Use of non-hindered phosphonate, low temp., and KOt-Bu can favor Z-olefin*
	*KOt-Bu, THF, -78 °C*	*1*	*3*	*Enhances rate of elimination relative to equilibration*

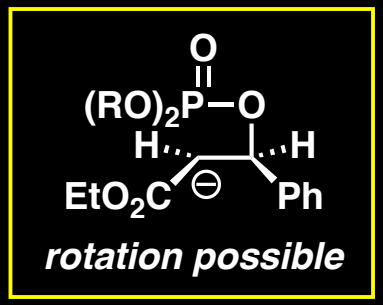
Y. Kishi and co-workers, Tetrahedron 1981, 37, 3873.

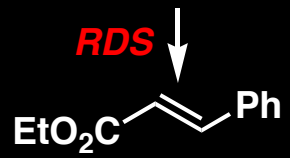
Horner-Wadsworth-Emmons Olefination: Background and Principles



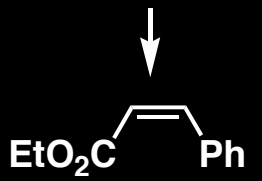
Stereoselectivity Principles: Follows general rules of stabilized ylides





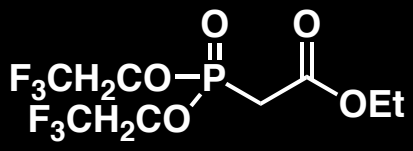


thermodynamically most stable; predominant or only product



Horner-Wadsworth-Emmons Olefination: Still-Gennari Modification

First Method to Use Phosphonates and Get E-Alkenes

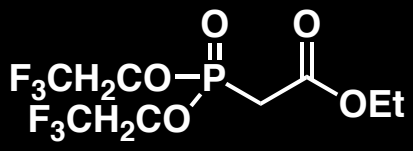


KHMDS, KOt-Bu, KH, or K_2CO_3 with 18-Crown-6

W. C. Still, C. Gennari, Tetrahedron Lett. 1983, 24, 4405.

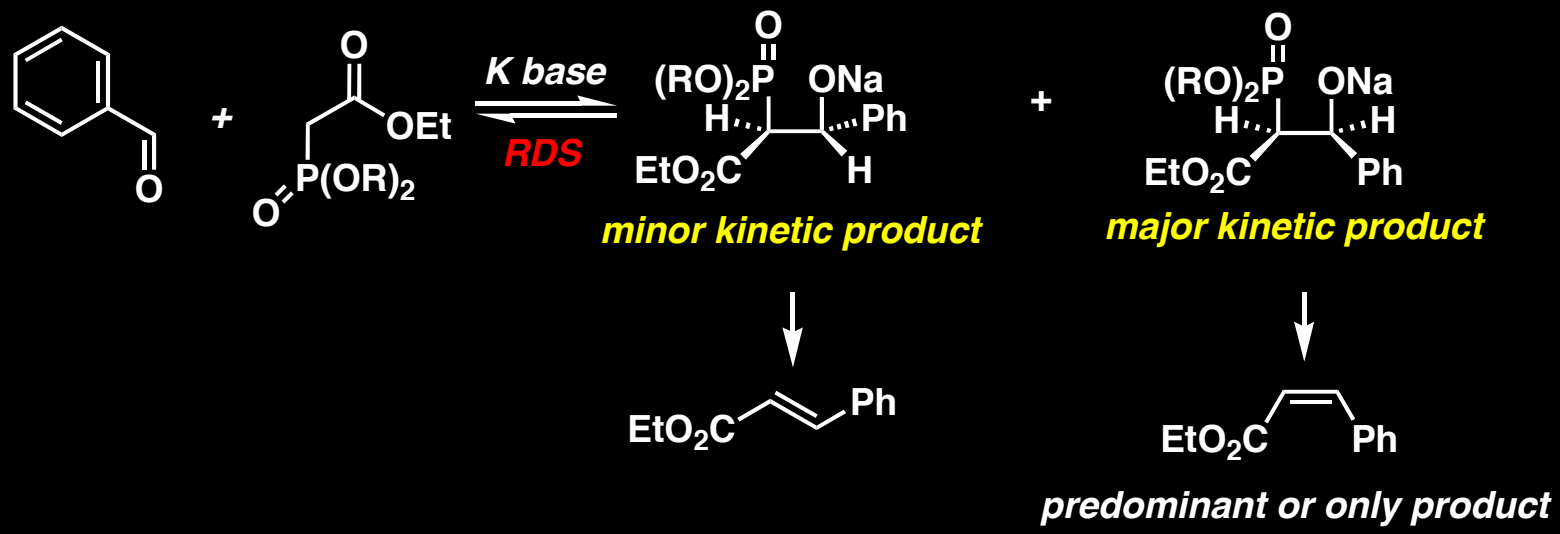
Horner-Wadsworth-Emmons Olefination: Still-Gennari Modification

First Method to Use Phosphonates and Get E-Alkenes



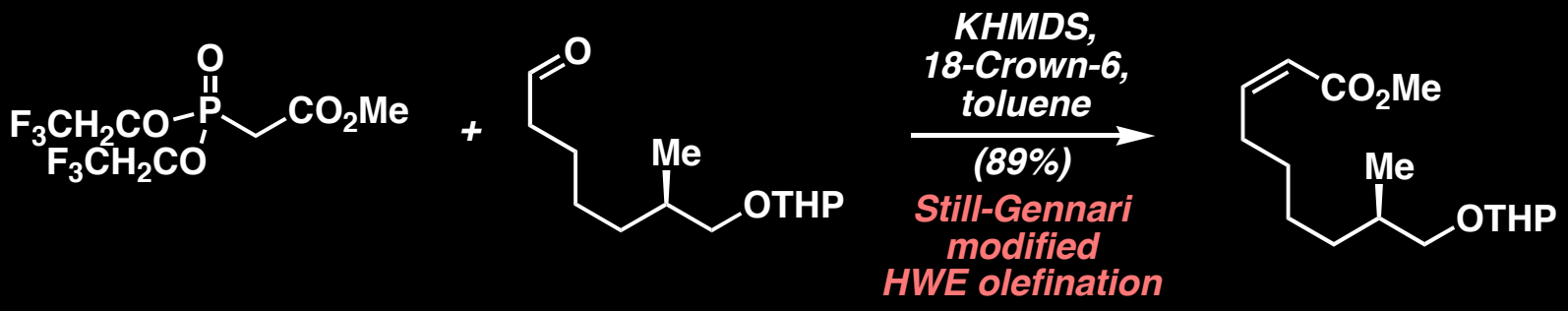
KHMDS, KOt-Bu, KH, or K_2CO_3 with 18-Crown-6

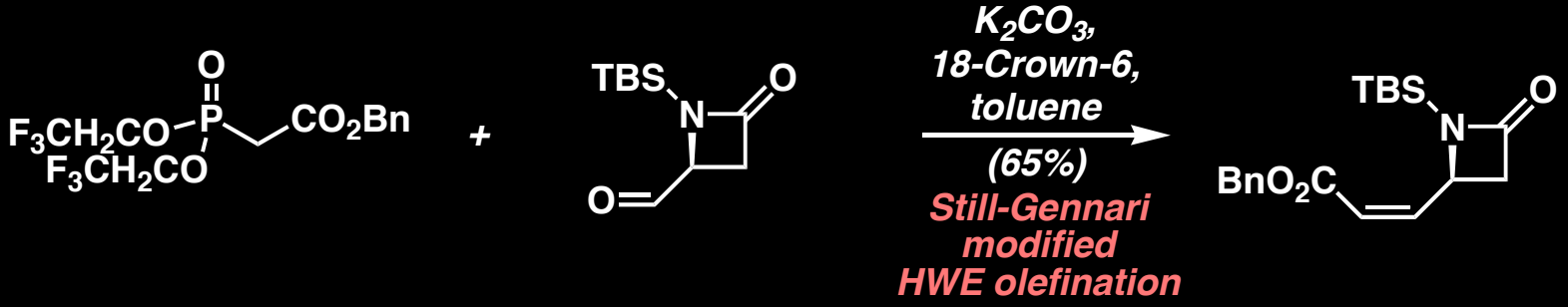
Stereoselectivity Principles: Changes the RDS from the elimination to the initial addition



W. C. Still, C. Gennari, Tetrahedron Lett. 1983, 24, 4405.

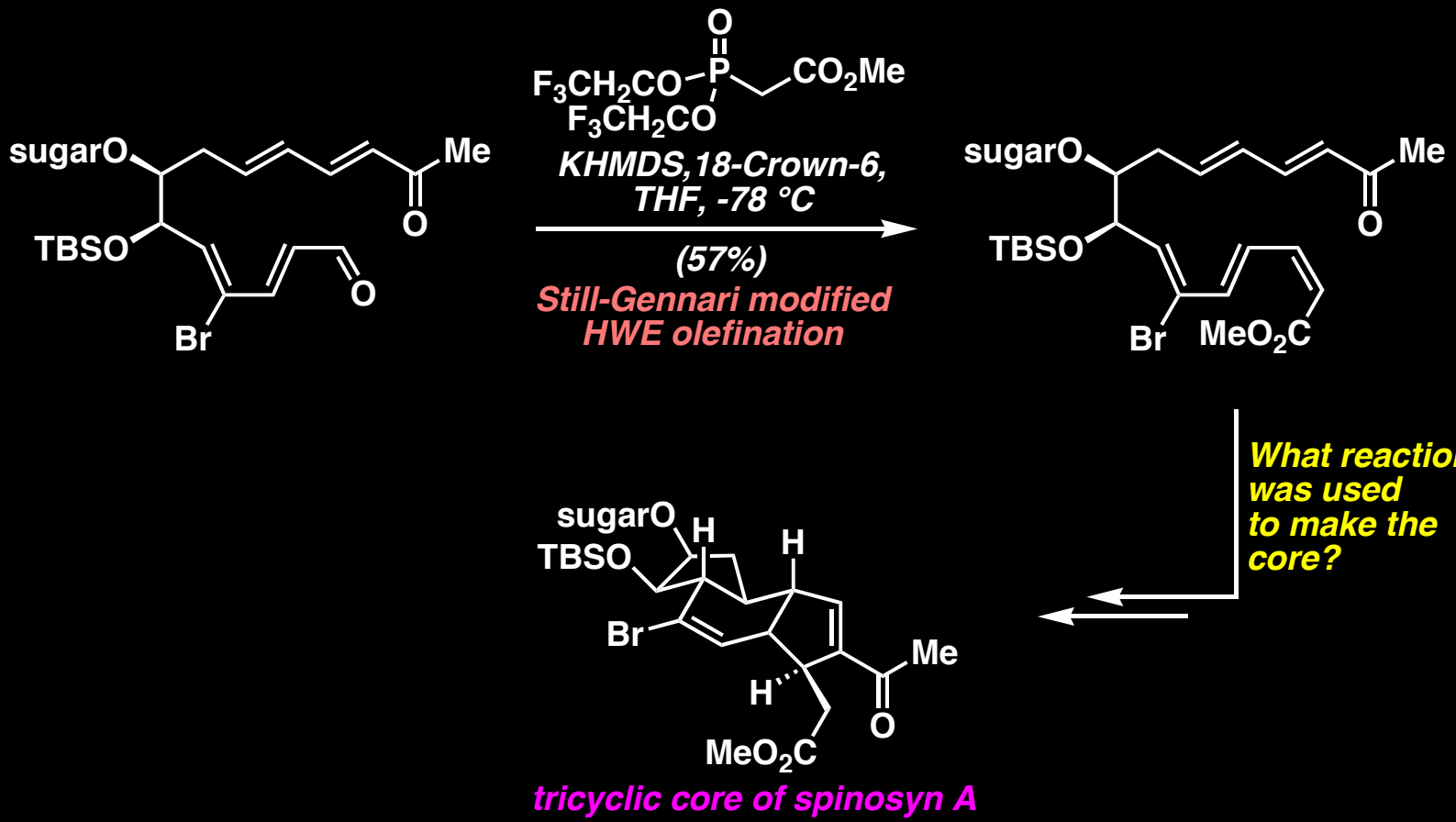
Still-Gennari Modified HWE Olefination: Applications in Total Synthesis





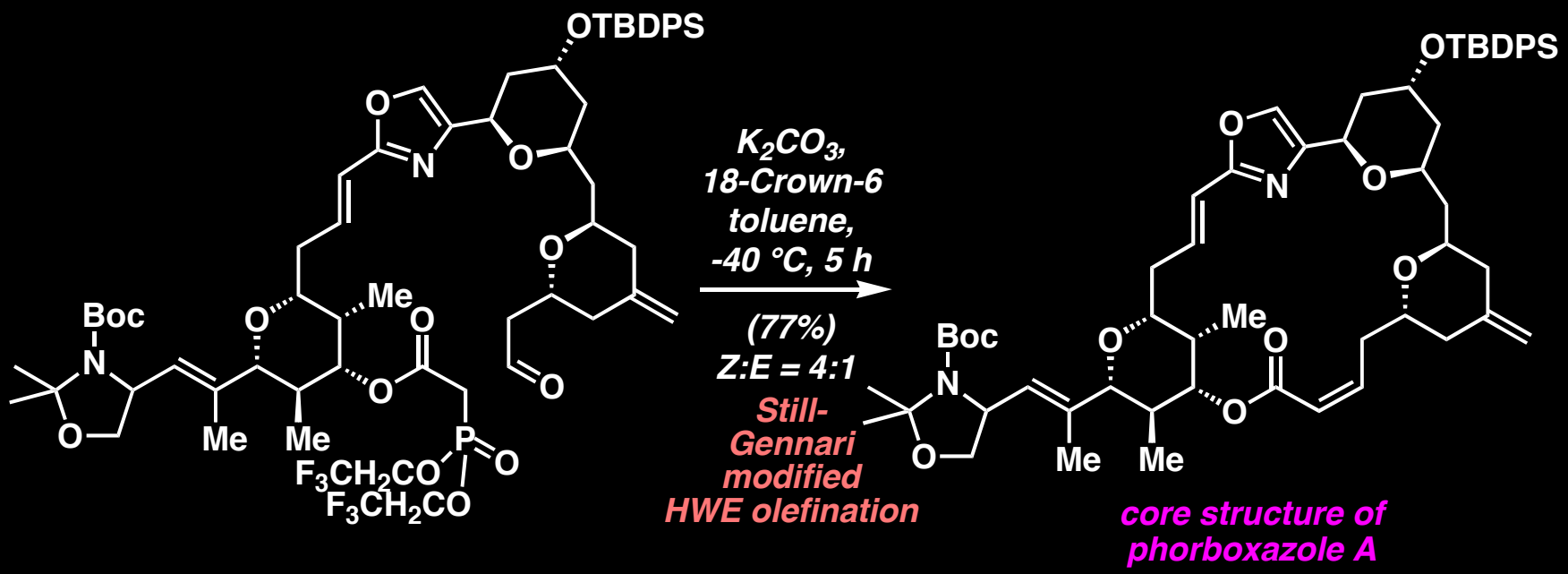
S. V. Ley and co-workers, J. Chem. Soc., PT 1 1999, 1917.
E. J. Thomas and co-workers, J. Chem. Soc., PT 1 1999, 1083.

Still-Gennari Modified HWE Olefination: Applications in Total Synthesis



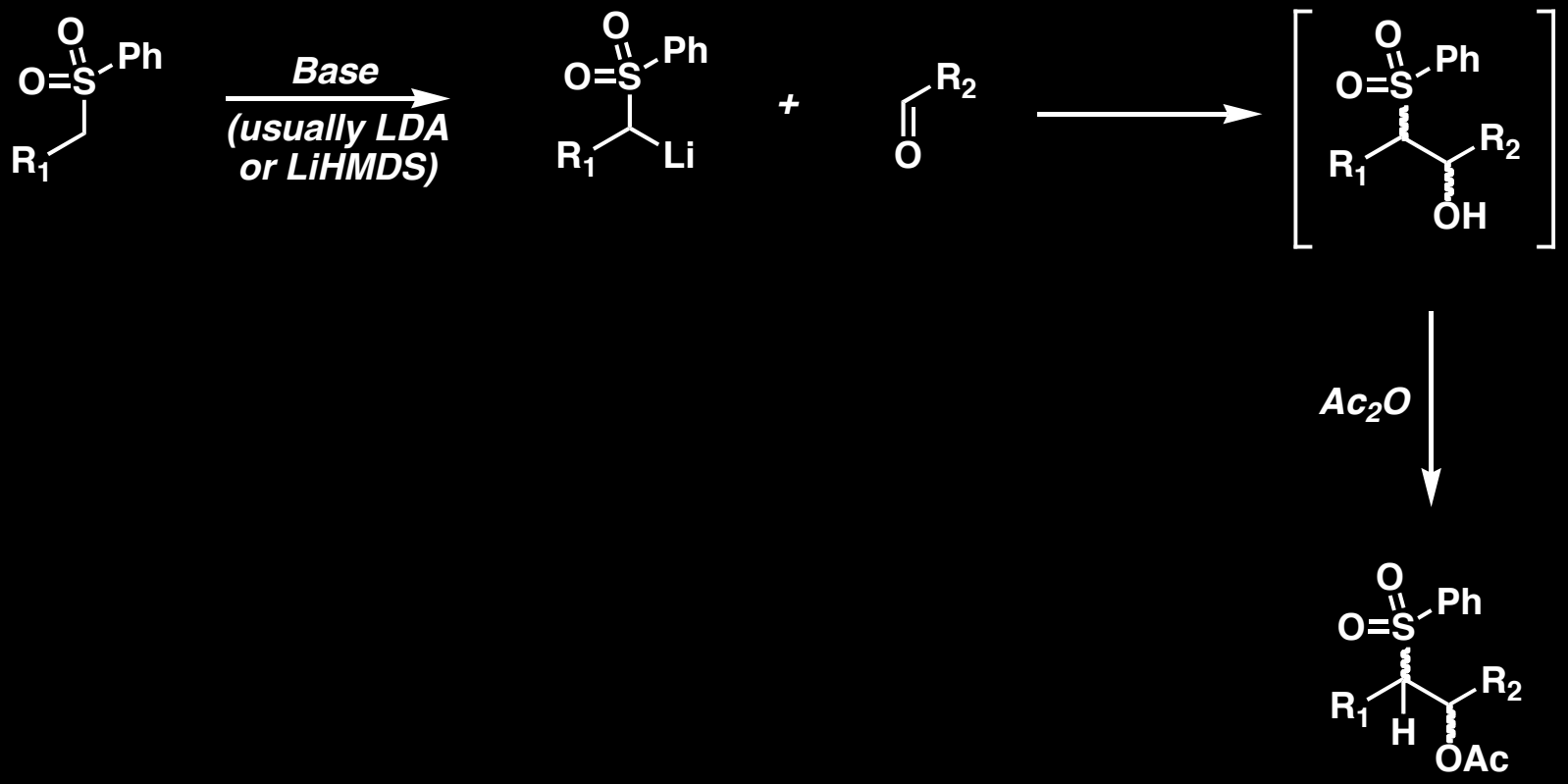
W. R. Roush and co-workers, Org. Lett. 2002, 4, 3157.

Still-Gennari Modified HWE Olefination: Applications in Total Synthesis



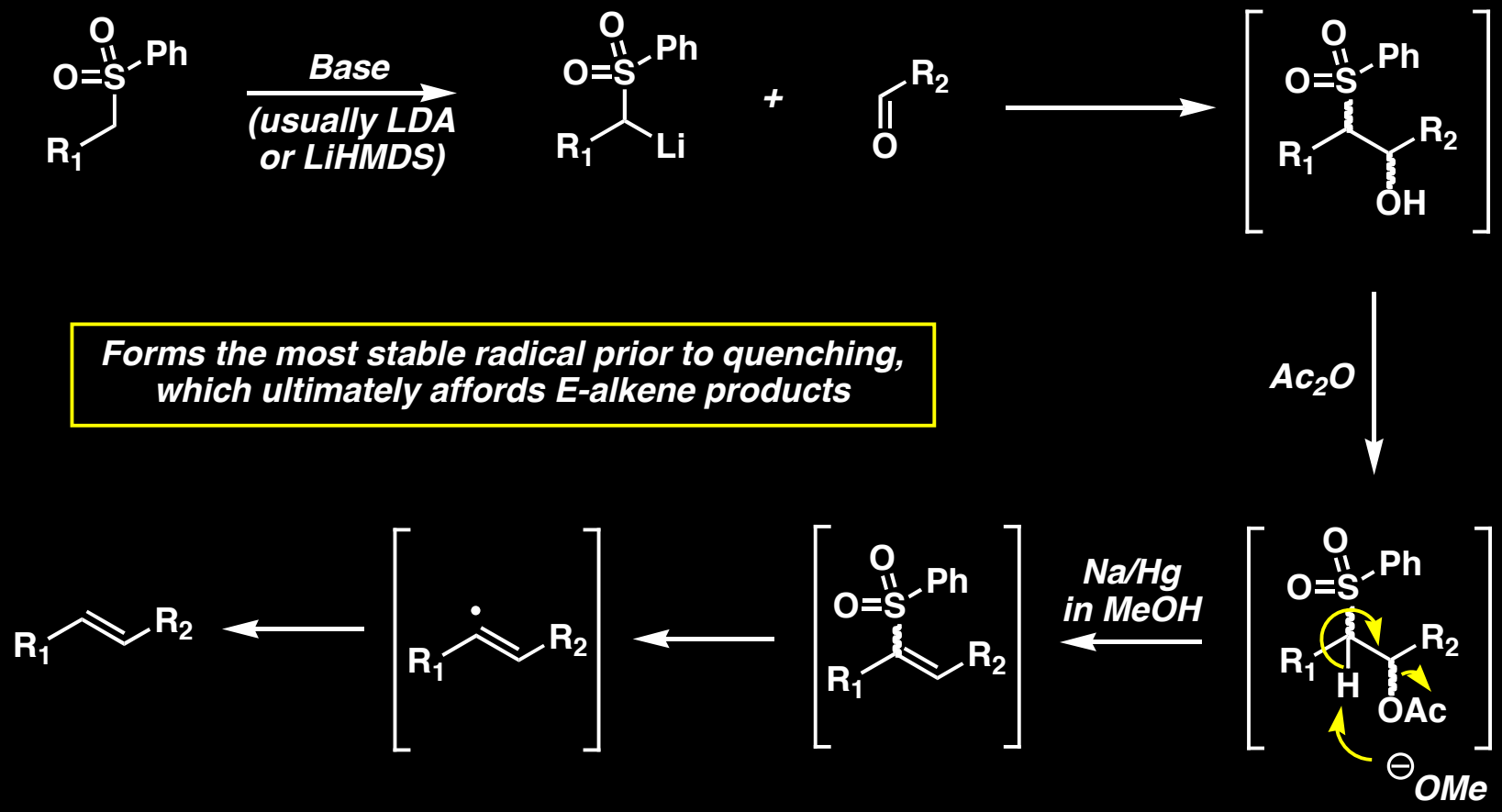
C. J. Forsyth and co-workers, J. Am. Chem. Soc. 1998, 120, 5597.

Julia-Lythgoe Olefination: A Versatile Method for Forming E-Alkenes



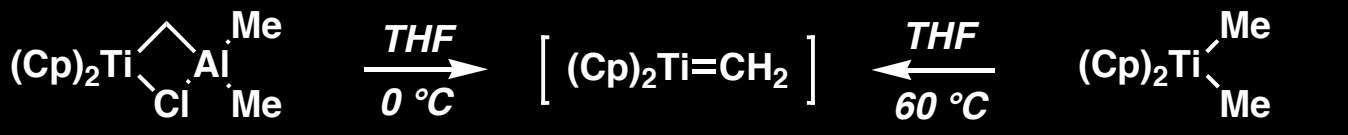
M. Julia, J.-M. Paris, Tetrahedron Lett. 1973, 4833.

Julia-Lythgoe Olefination: A Versatile Method for Forming E-Alkenes



M. Julia, J.-M. Paris, Tetrahedron Lett. 1973, 4833.

Tebbe Olefination: Background and Principles



Tebbe Reagent ***Petasis Reagent***

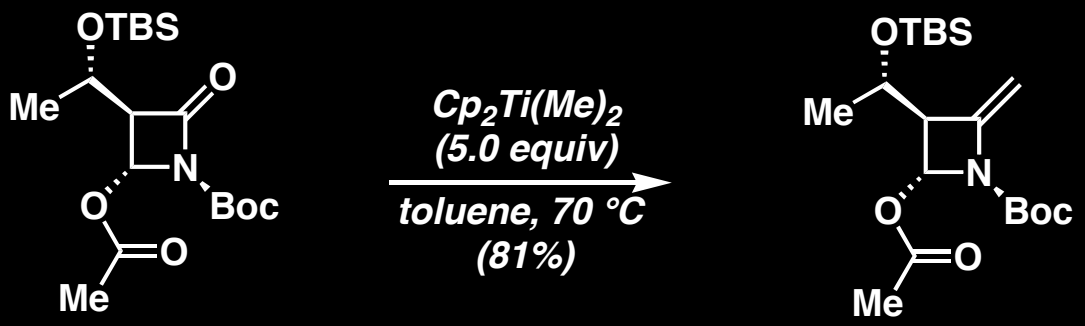
- *Tebbe reagent is commercially available ($454.50 for 100 mL of a 0.5 M solution in toluene)*

  By contrast, simple ylide sells for pennies per gram

- *Reacts with virtually every carbonyl (which other methods do not do at all).*

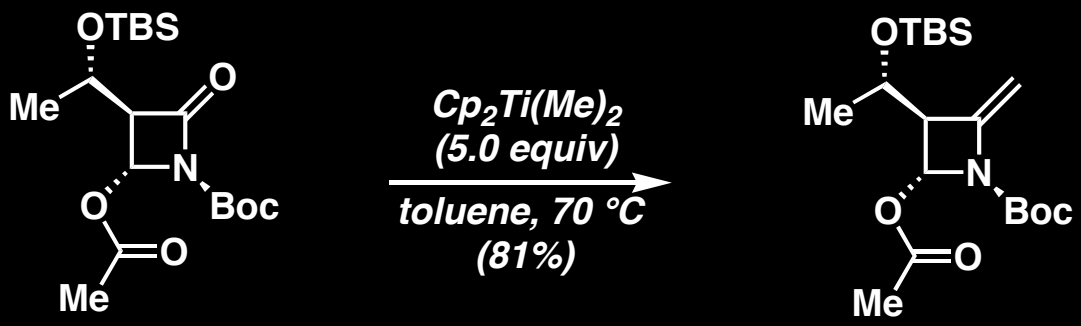
F. N. Tebbe, J. Am. Chem. Soc. 1978, 100, 3611.
N. A. Petasis, J. Am. Chem. Soc. 1990, 112, 6392.

Tebbe Olefination: Applications in Total Synthesis



I. Martinez, A. H. Howell, Tetrahedron Lett. 2000, 41, 5607.

Tebbe Olefination: Applications in Total Synthesis



General Trend of Functional Group Reactivity

Acids
Alcohols
Aldehydes
Ketones
Amides
Esters

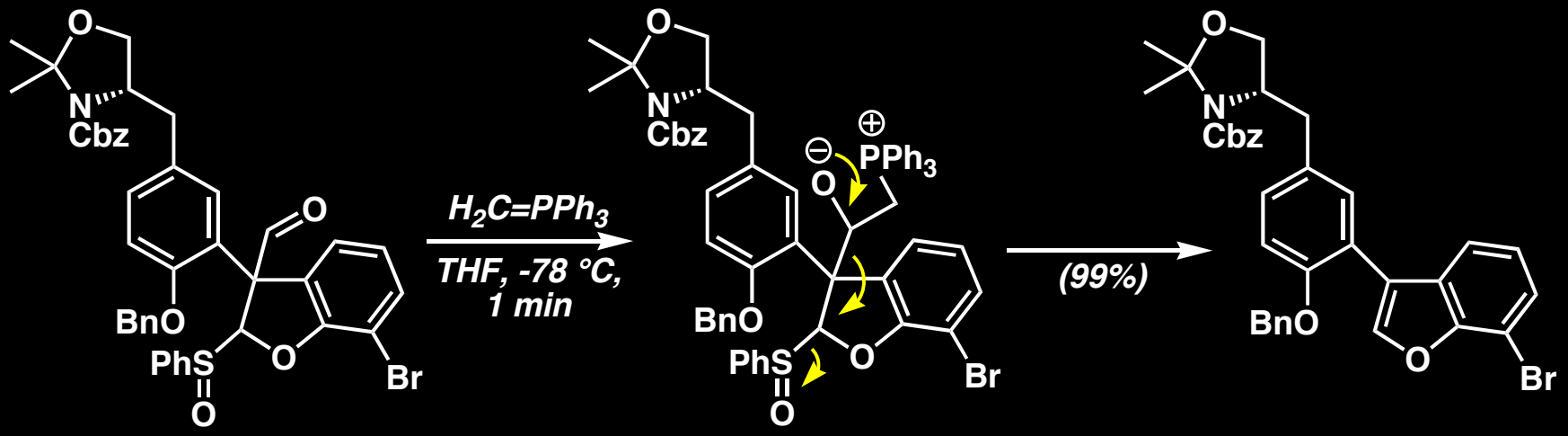
Functional group reactivity

Epoxides can sometimes survive; but tend not to be tolerated.

Note: Surprises are sometimes observed in highly functionalized cases.

I. Martinez, A. H. Howell, Tetrahedron Lett. 2000, 41, 5607.

Deoxygenation of Sulfoxides Using Tebbe Reagent: Discovery of a Novel Titanocene-Methylidene Mediated Process



K.C. Nicolaou, A.E. Koumbis, S.A. Snyder, K.B. Simonsen, Angew. Chem. Int. Ed. 2000, 39, 2529.

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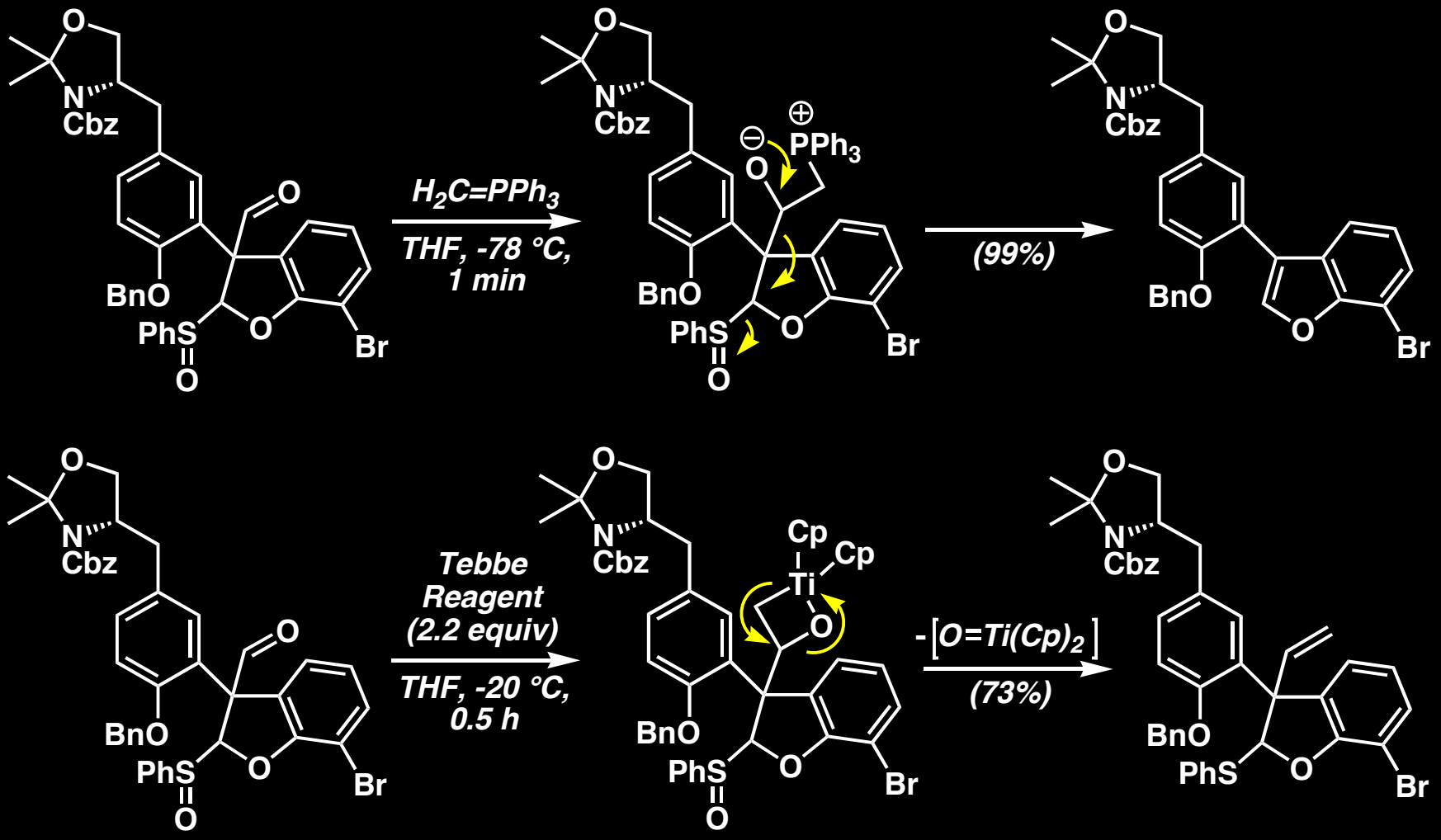
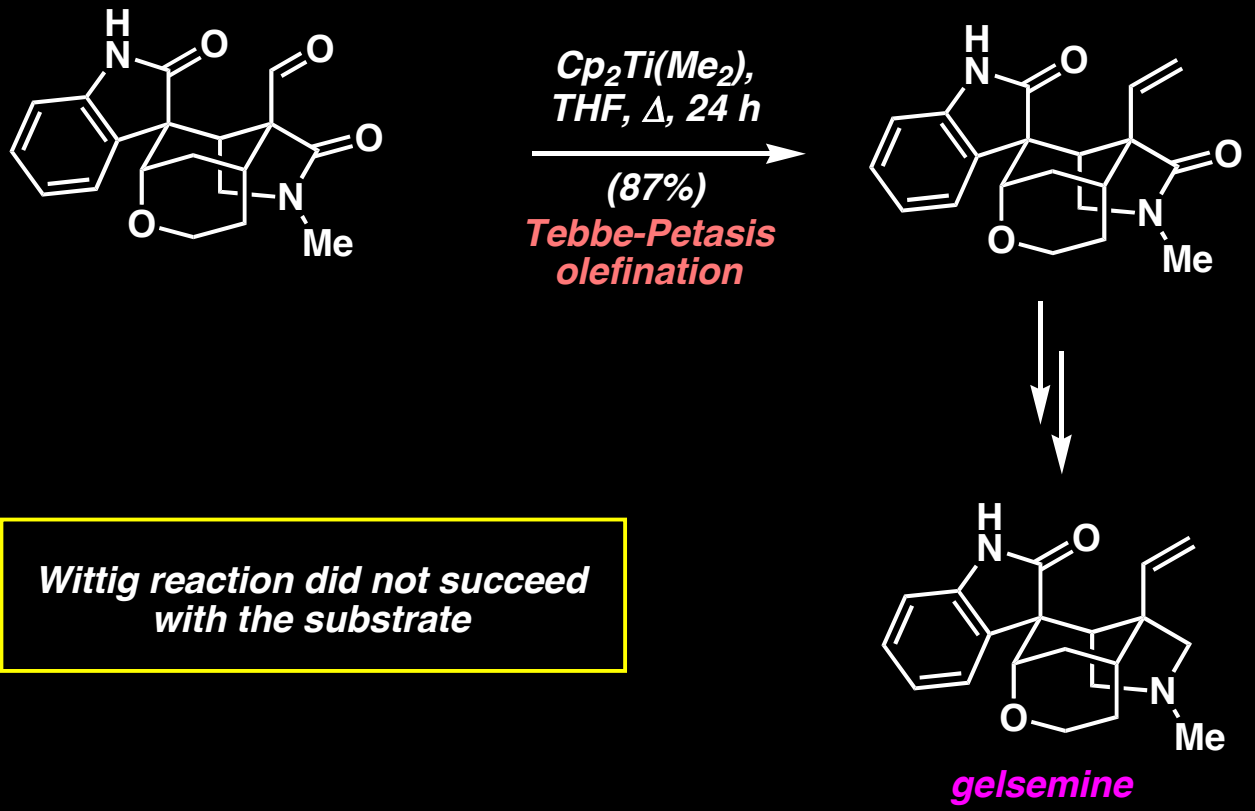


K.C. Nicolaou, A.E. Koumbis, S.A. Snyder, K.B. Simonsen, Angew. Chem. Int. Ed. 2000, 39, 2529.

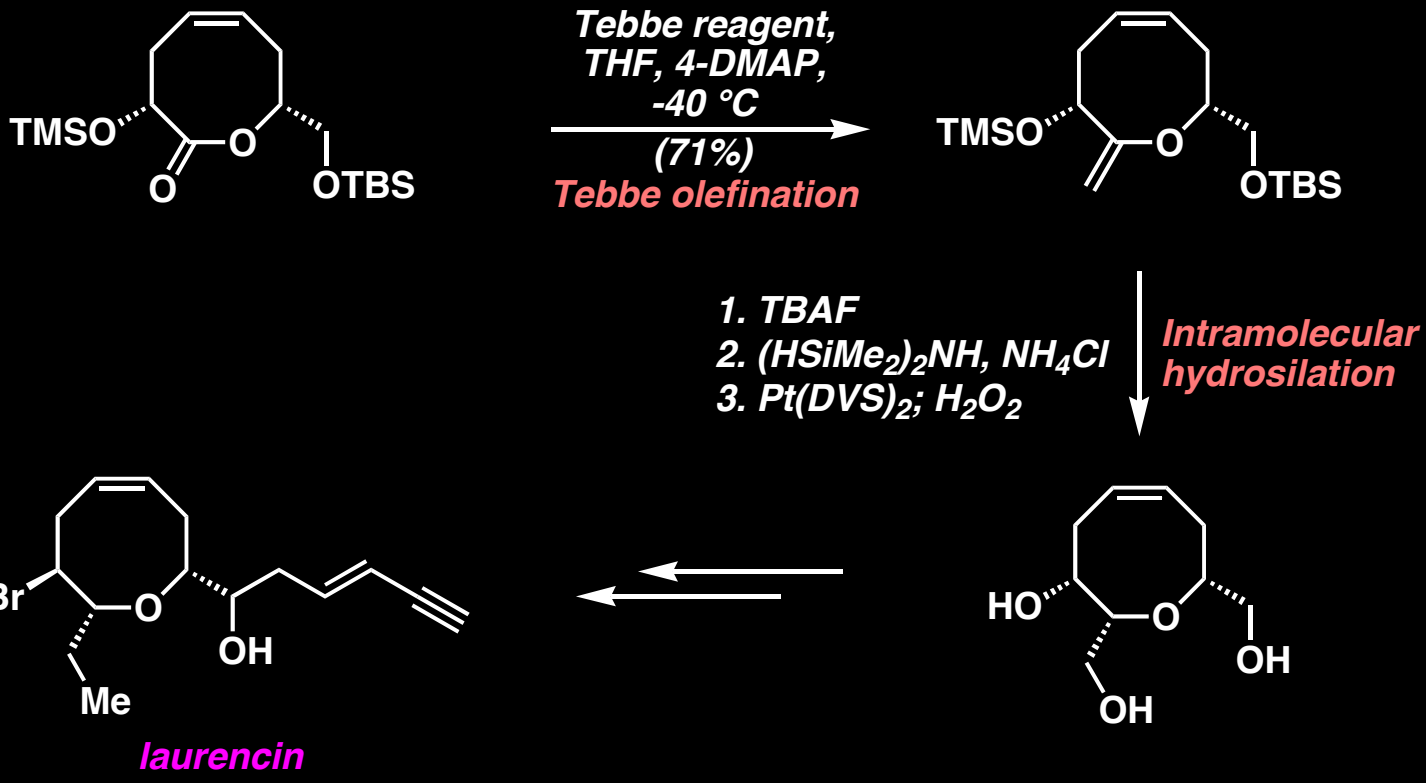
Tebbe Olefination: Applications in Total Synthesis



Wittig reaction did not succeed with the substrate

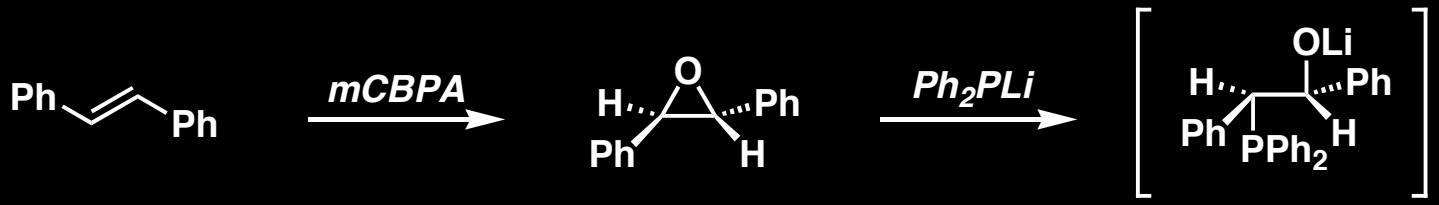
D. J. Hart and co-workers, J. Am. Chem. Soc. 1997, 119, 6226.

Tebbe Olefination: Applications in Total Synthesis



A. H. Holmes and co-workers, J. Am. Chem. Soc. 1993, 115, 10400.

Oops, I Made the Wrong Alkene: Olefin Inversion Reactions



E. Vedejs and co-workers, J. Am. Chem. Soc. 1971, 93, 4070.

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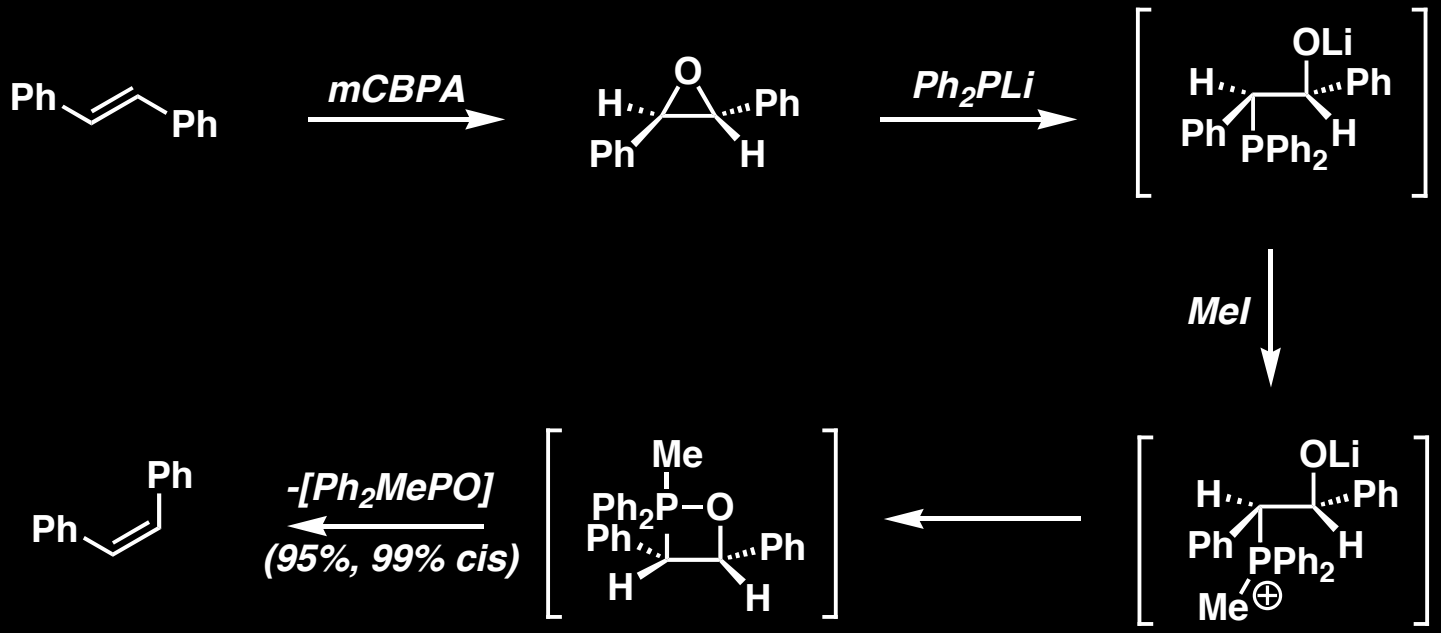

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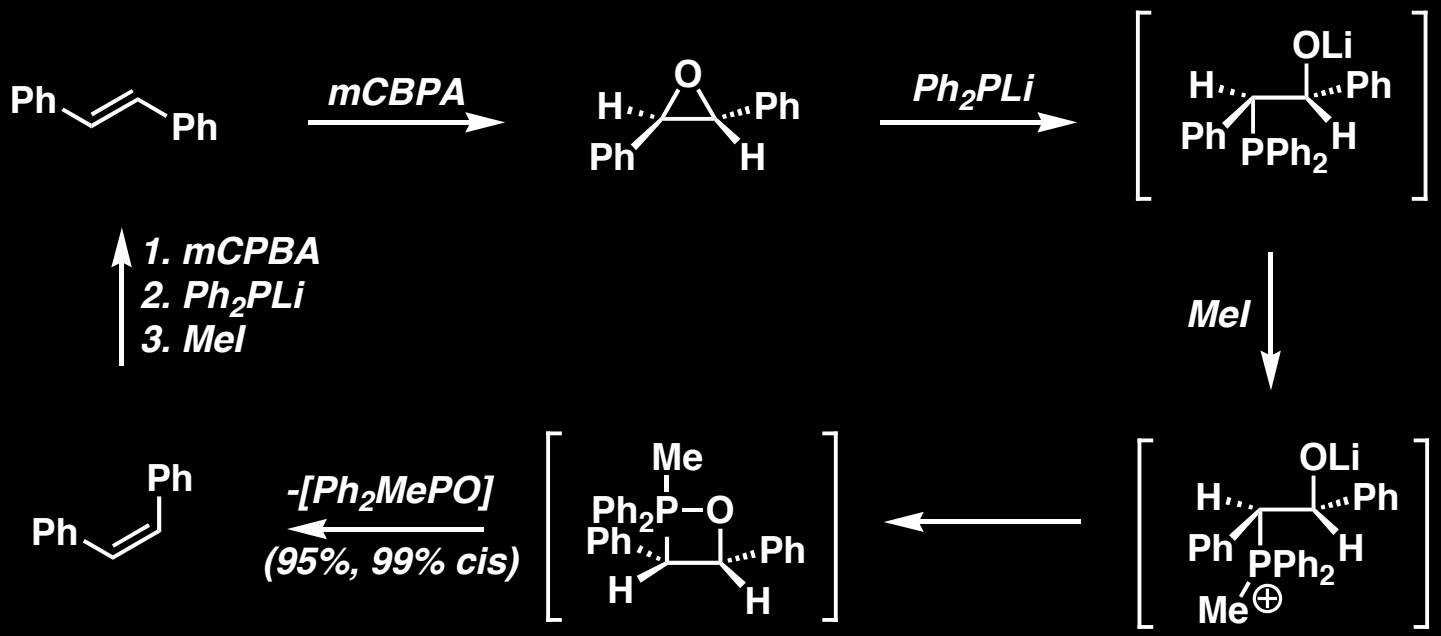

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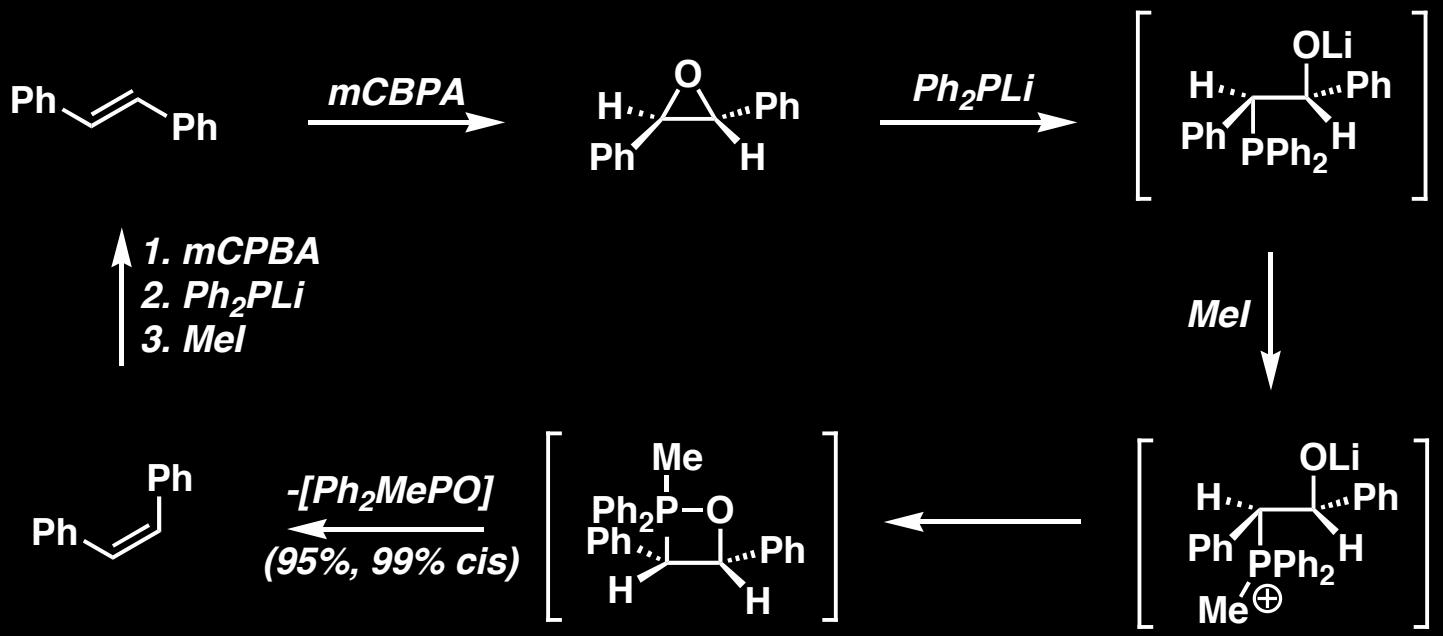

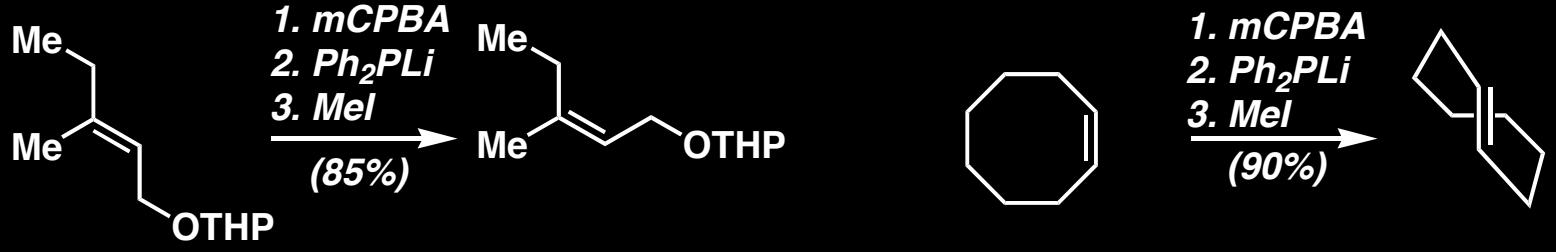

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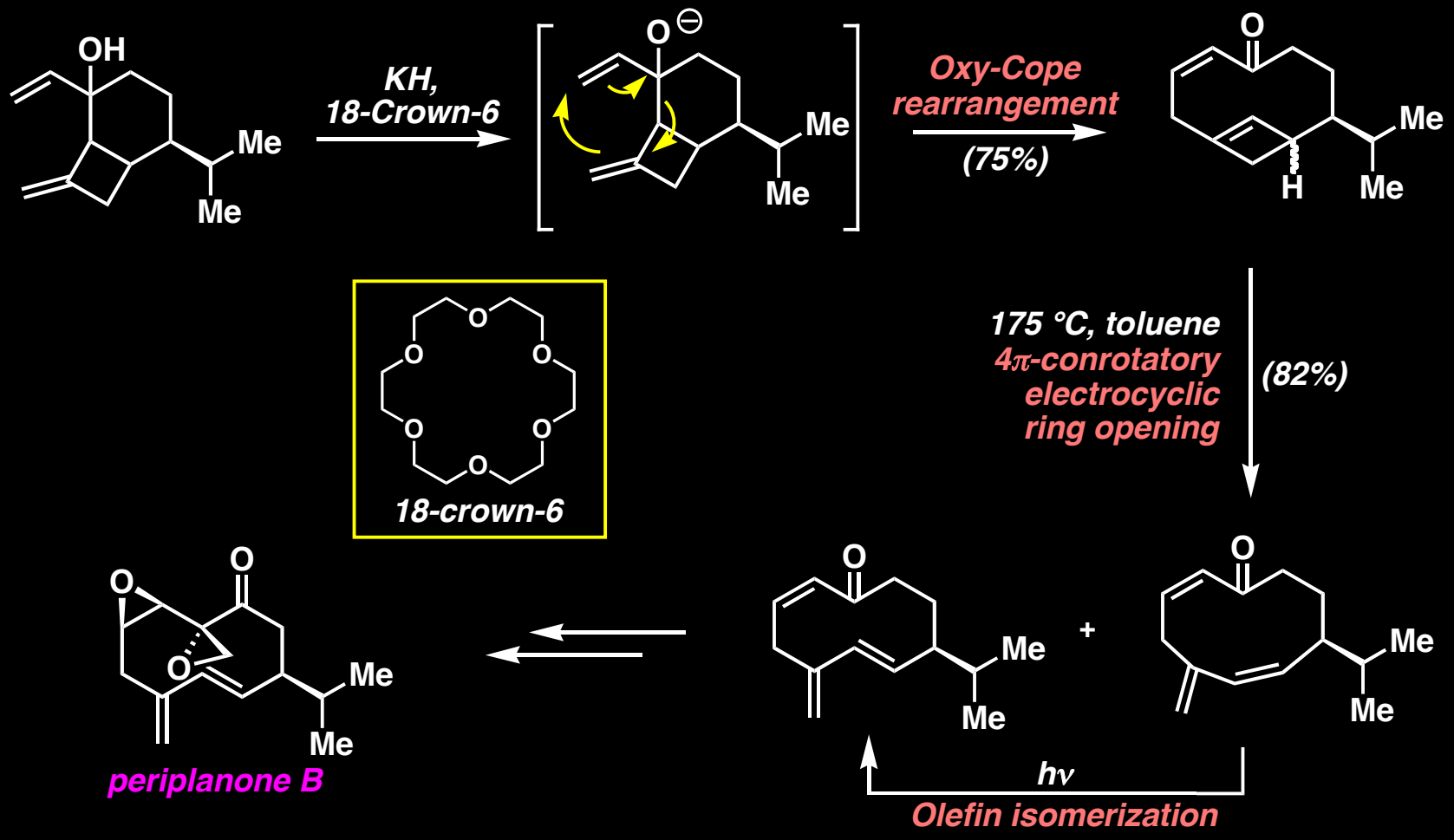
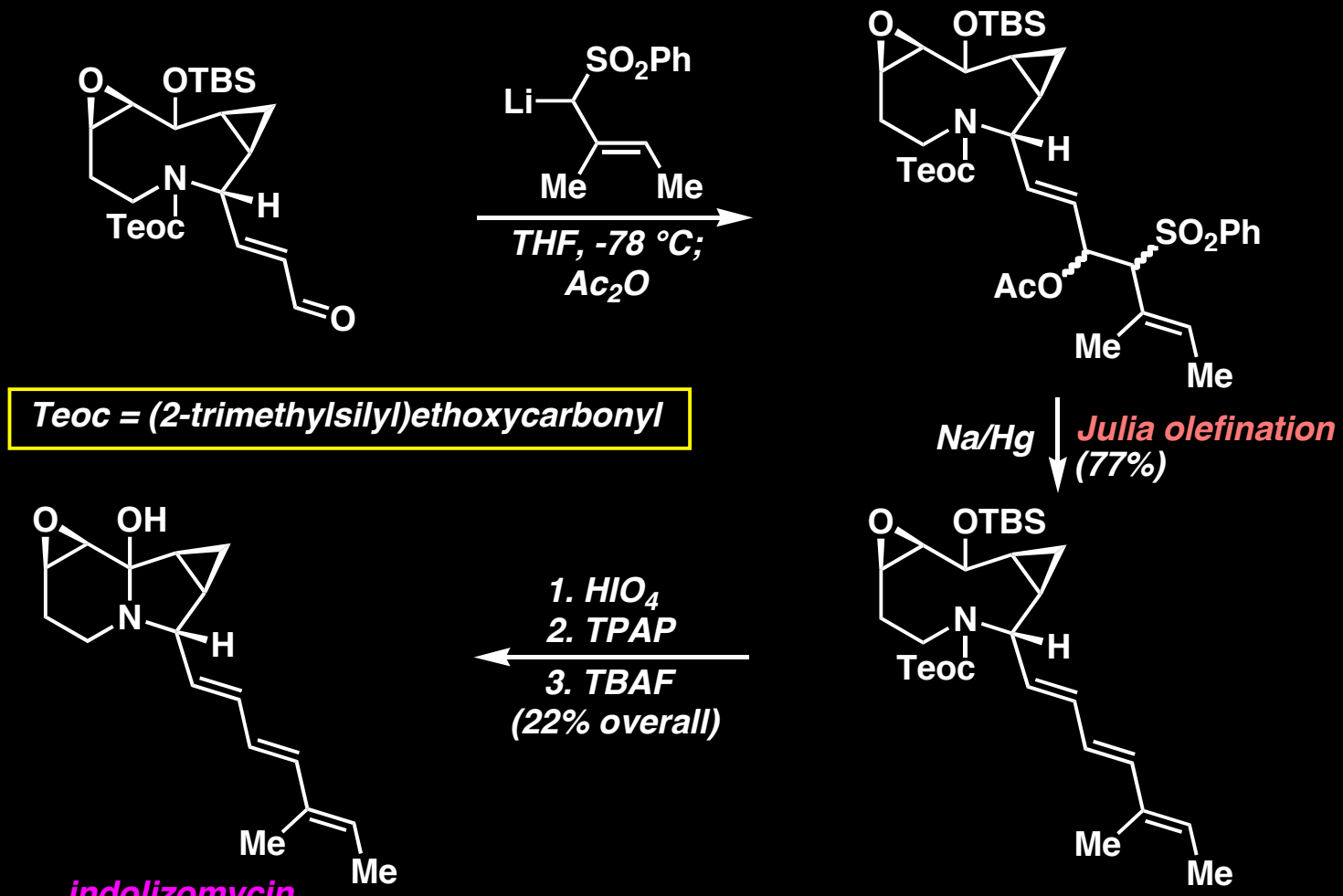


S. L. Schreiber, C. Santini, J. Am. Chem. Soc. 1984, 106, 4038.
For a review, see: Classics in Total Synthesis I, Chapter 21

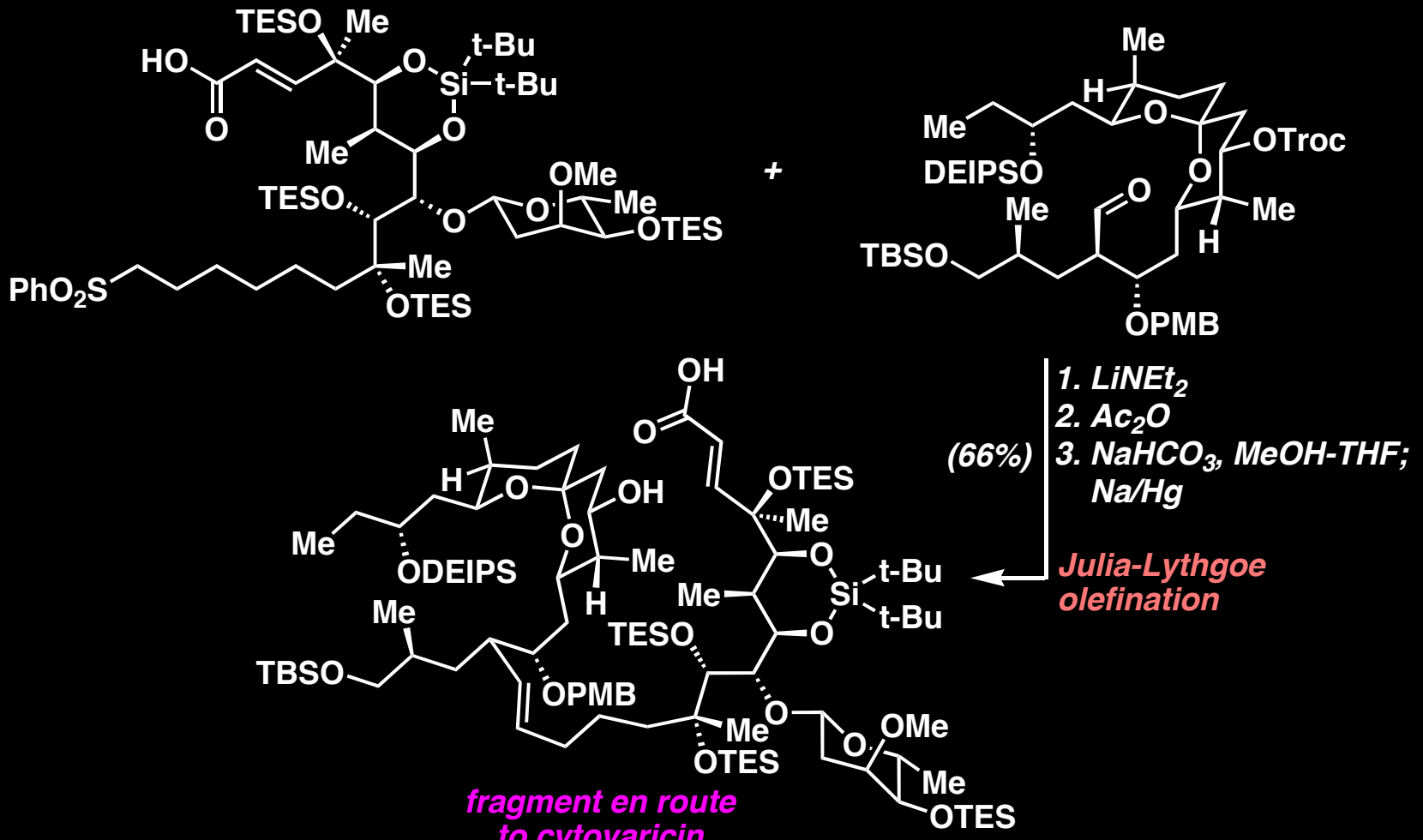
Julia-Lythgoe Olefination: Applications in Total Synthesis



Teoc = (2-trimethylsilyl)ethoxycarbonyl

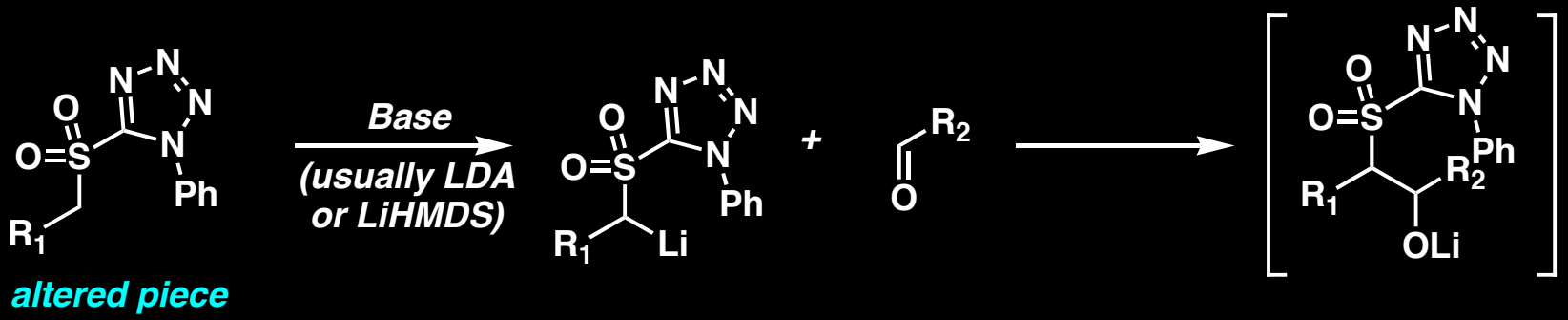
S. D. Danishefsky and co-workers, J. Am. Chem. Soc. 1993, 115, 30.

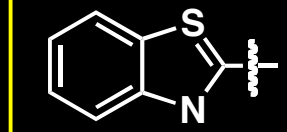
Julia-Lythgoe Olefination: Applications in Total Synthesis



D. A. Evans and co-workers, J. Am. Chem. Soc. 1990, 112, 7001.

Kocienski-Modified Julia-Lythgoe Olefination: A One Step Procedure



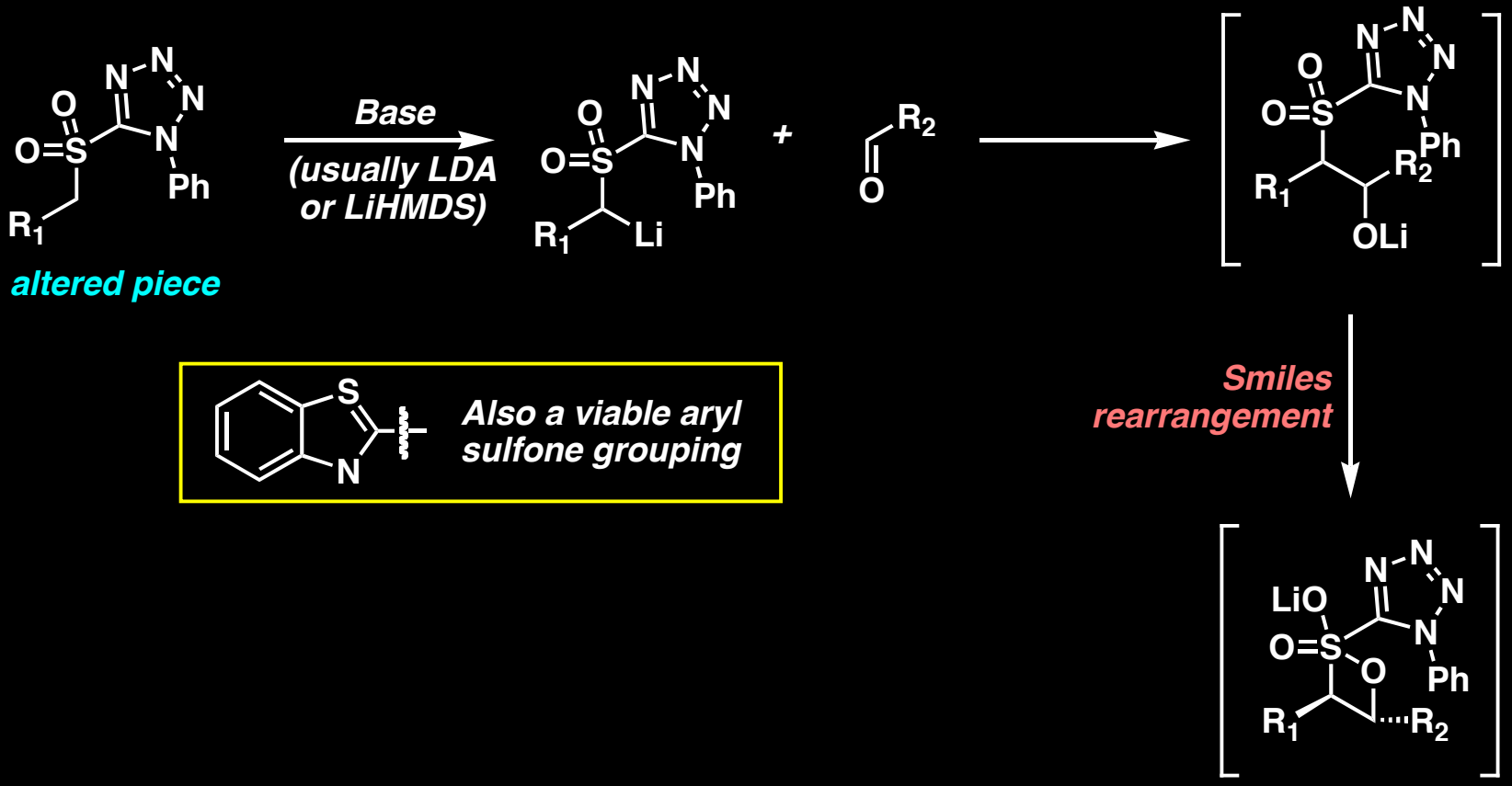


Also a viable aryl sulfone grouping

Affords E-alkene products only in one-pot;
kinetically controlled, irreversible addition gives anti-β-alkoxysulfones

P. Kochienski and co-workers, Synlett. 2000, 365.

Kocienski-Modified Julia-Lythgoe Olefination: A One Step Procedure



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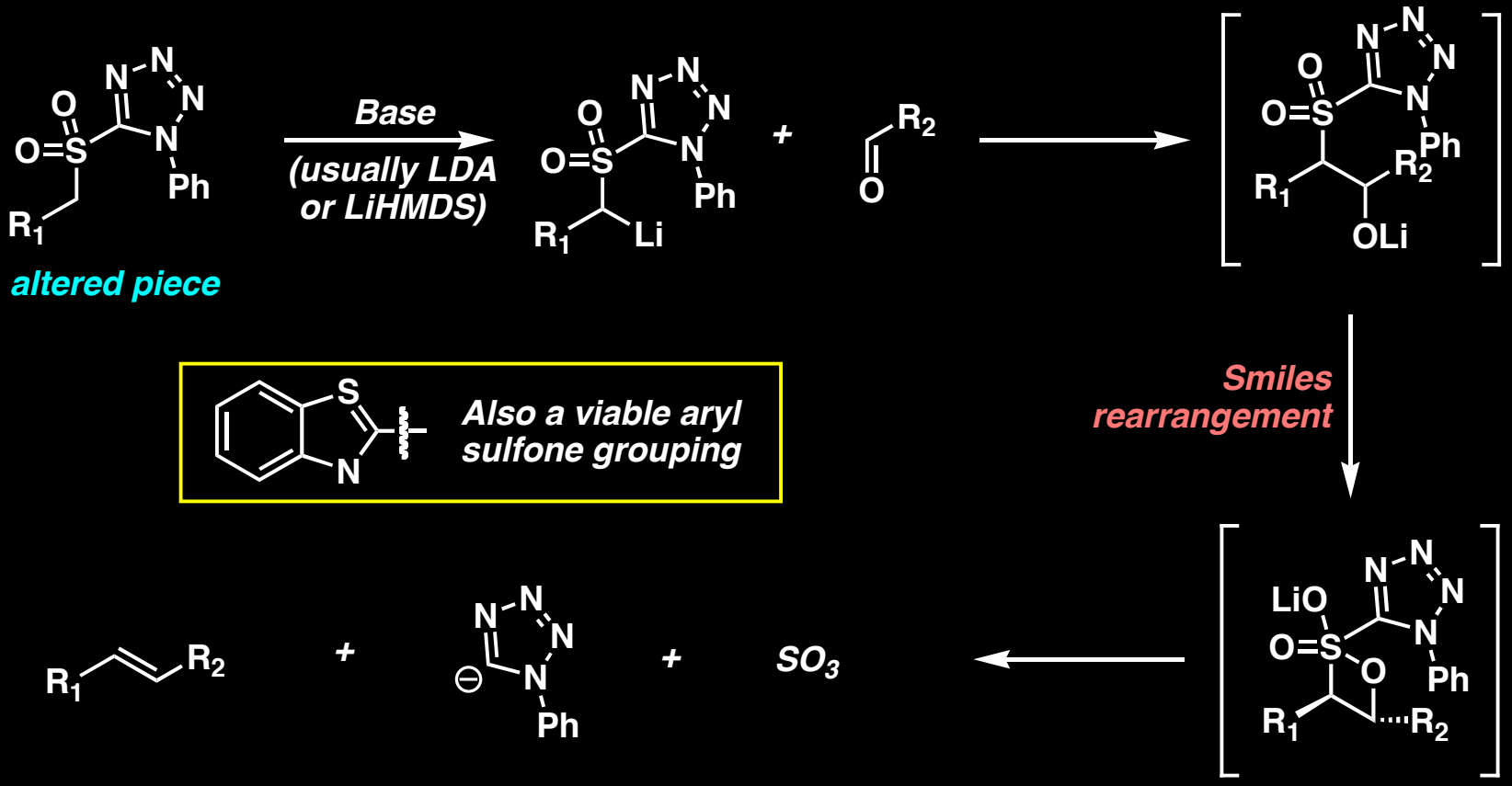
Kocienski-Modified Julia-Lythgoe Olefination: A One Step Procedure



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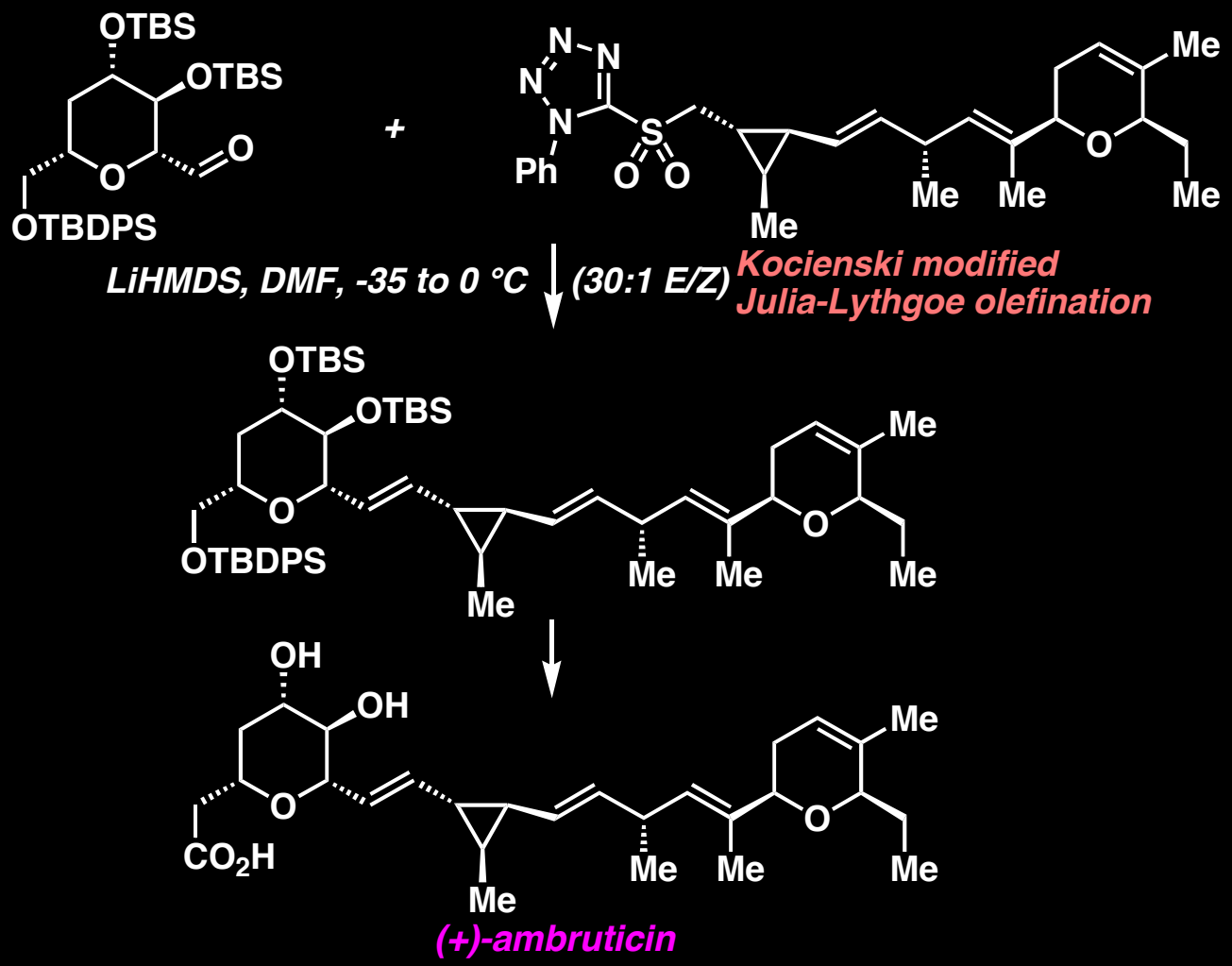
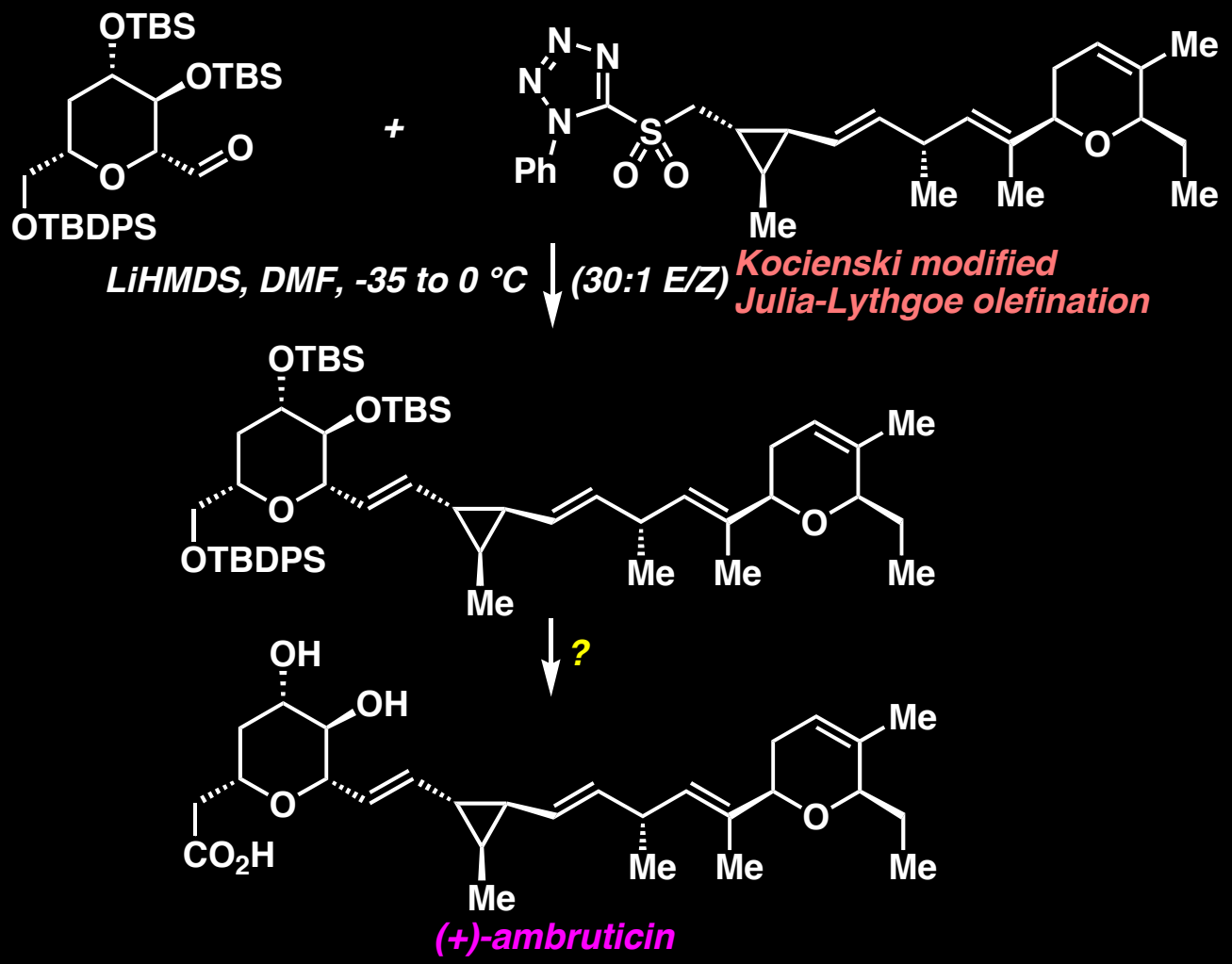
P. Kochienski and co-workers, Synlett. 2000, 365.

Julia-Lythgoe Olefination: Applications in Total Synthesis



E. N. Jacobsen and co-workers, J. Am. Chem. Soc. 2001, 123, 10772.

Julia-Lythgoe Olefination: Applications in Total Synthesis



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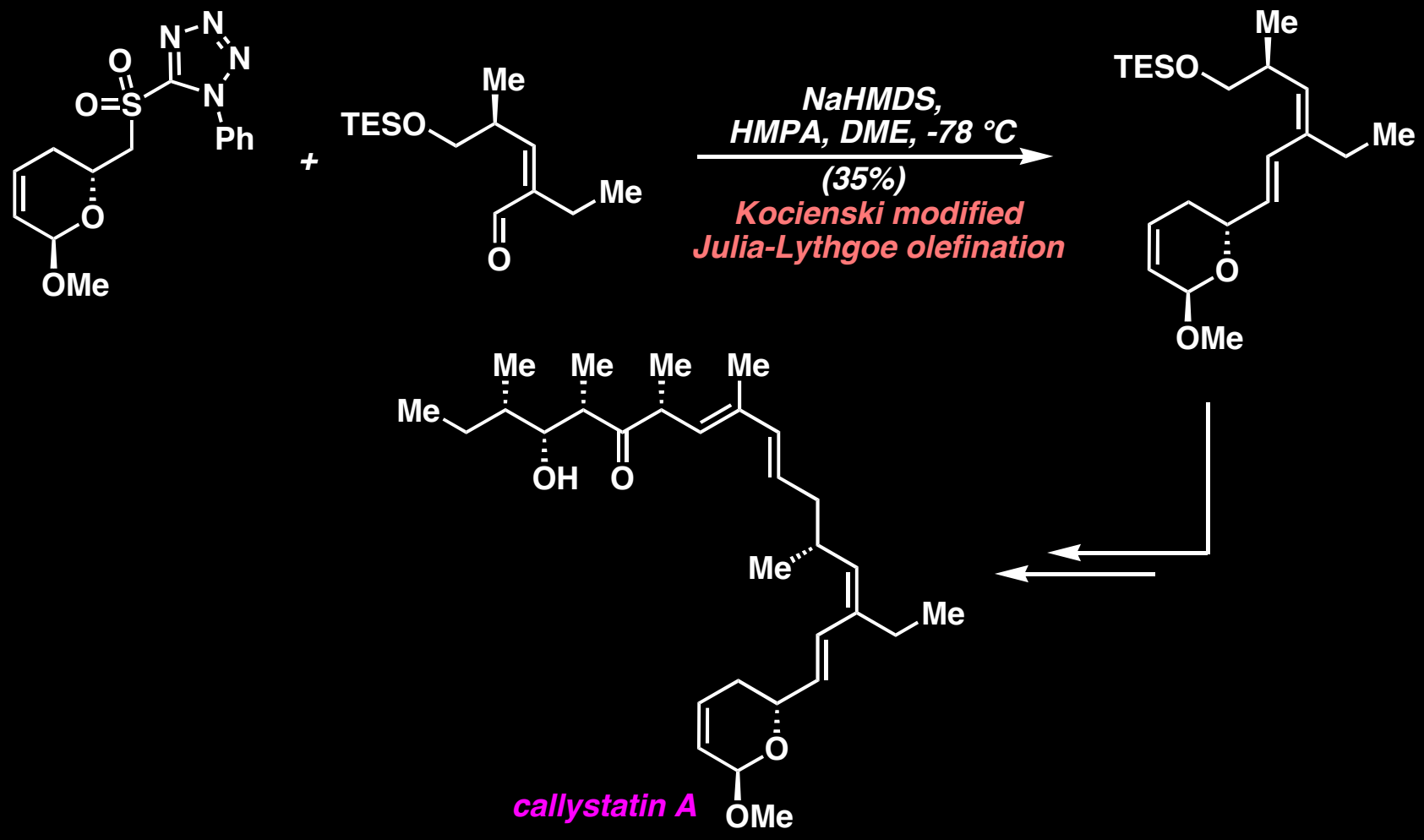
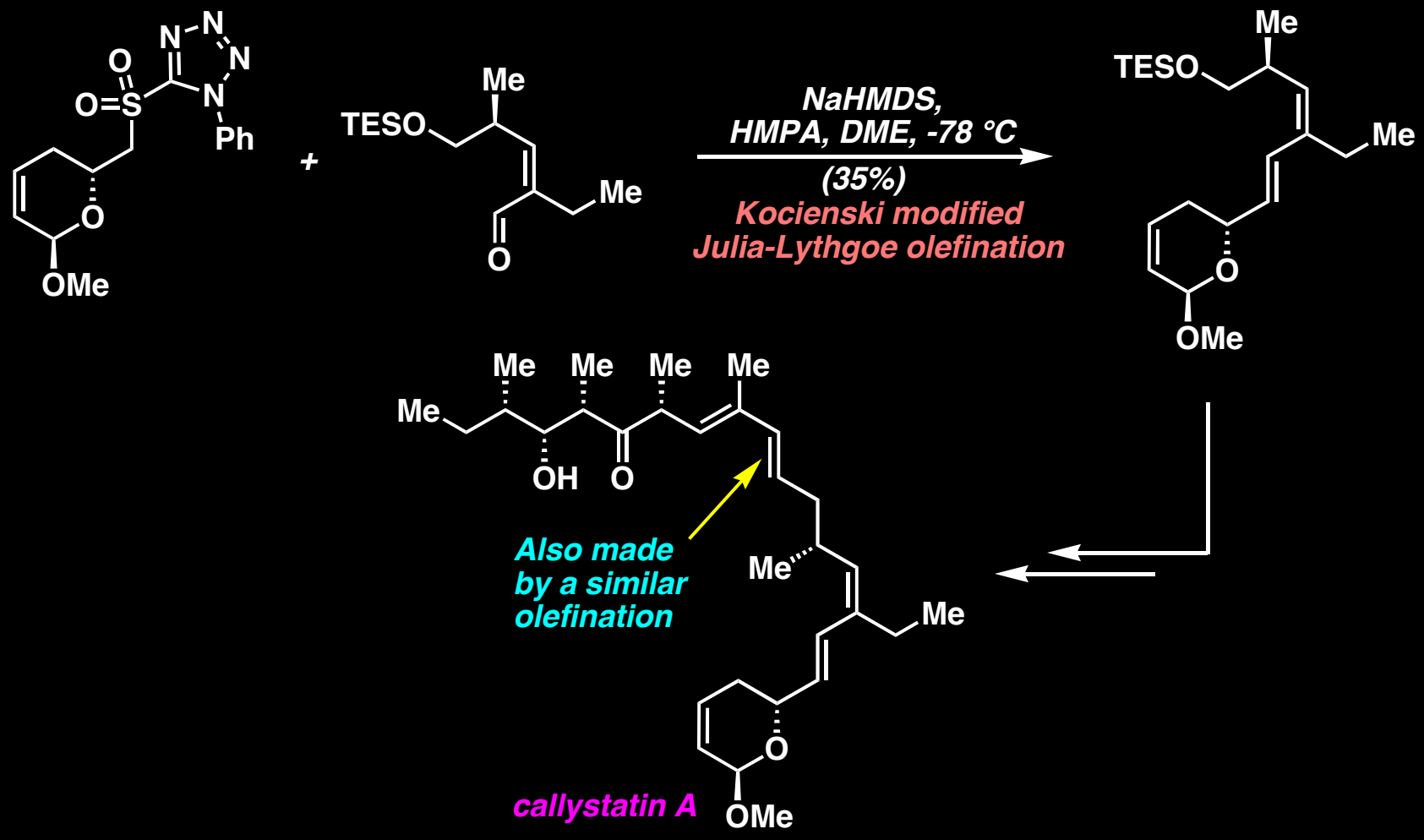


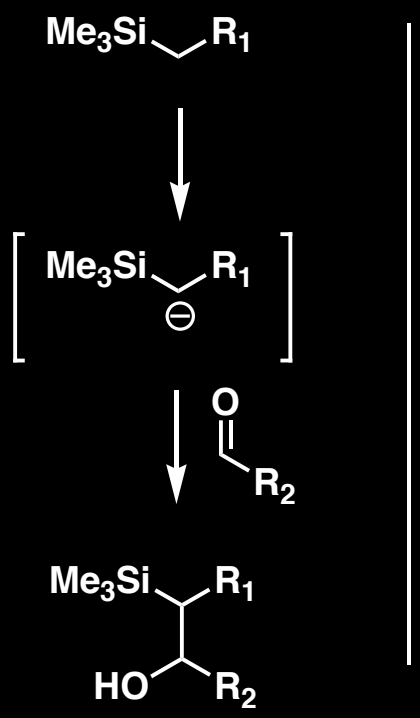
A. B. Smith and co-workers, Org. Lett. 2001, 3, 1685.

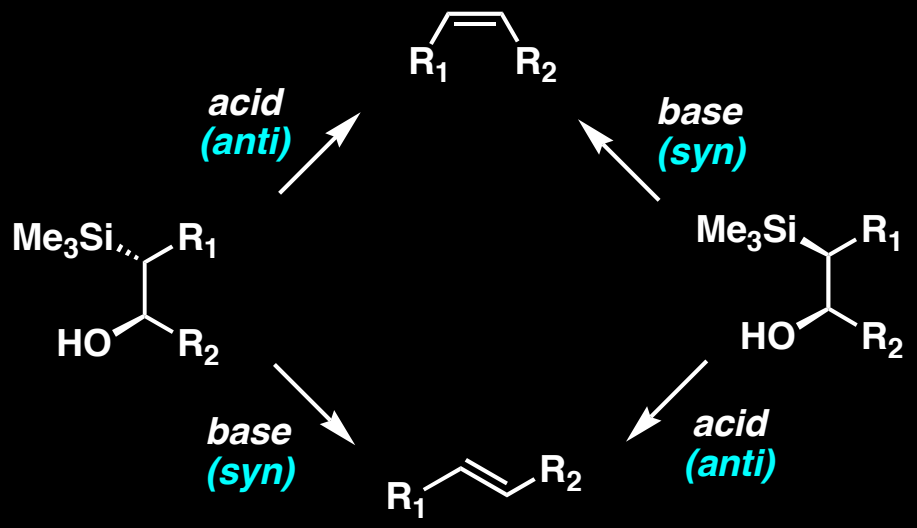
Julia-Lythgoe Olefination: Applications in Total Synthesis



A. B. Smith and co-workers, Org. Lett. 2001, 3, 1685.

Peterson Olefination: Background and Principles

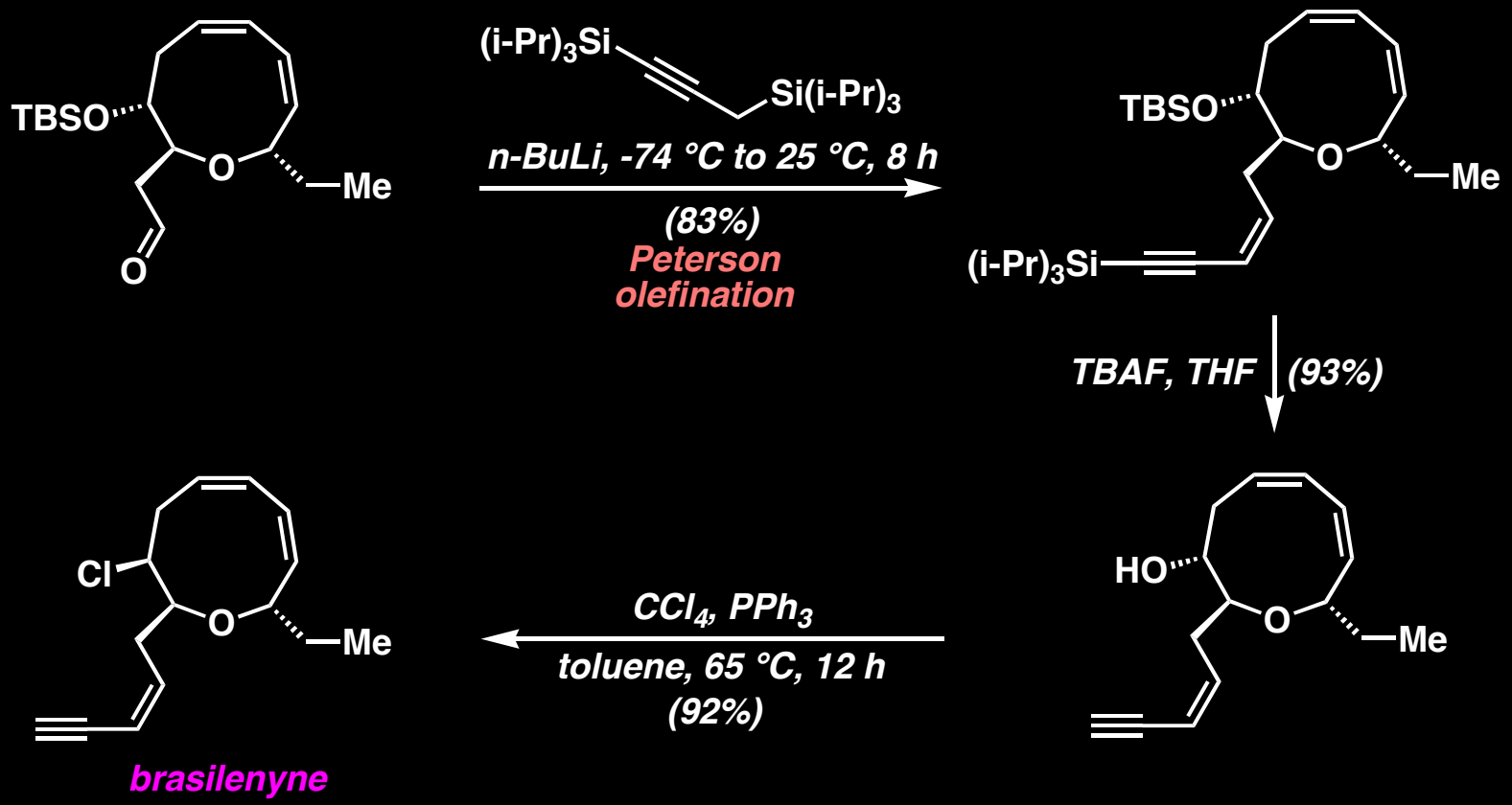




Nonstabilized Peterson reagents usually add with no diastereoselectivity, so hard to get E- and/or Z-selectivity; stabilized Peterson reagents are more controlled and typically give Z-olefins under basic reaction conditions

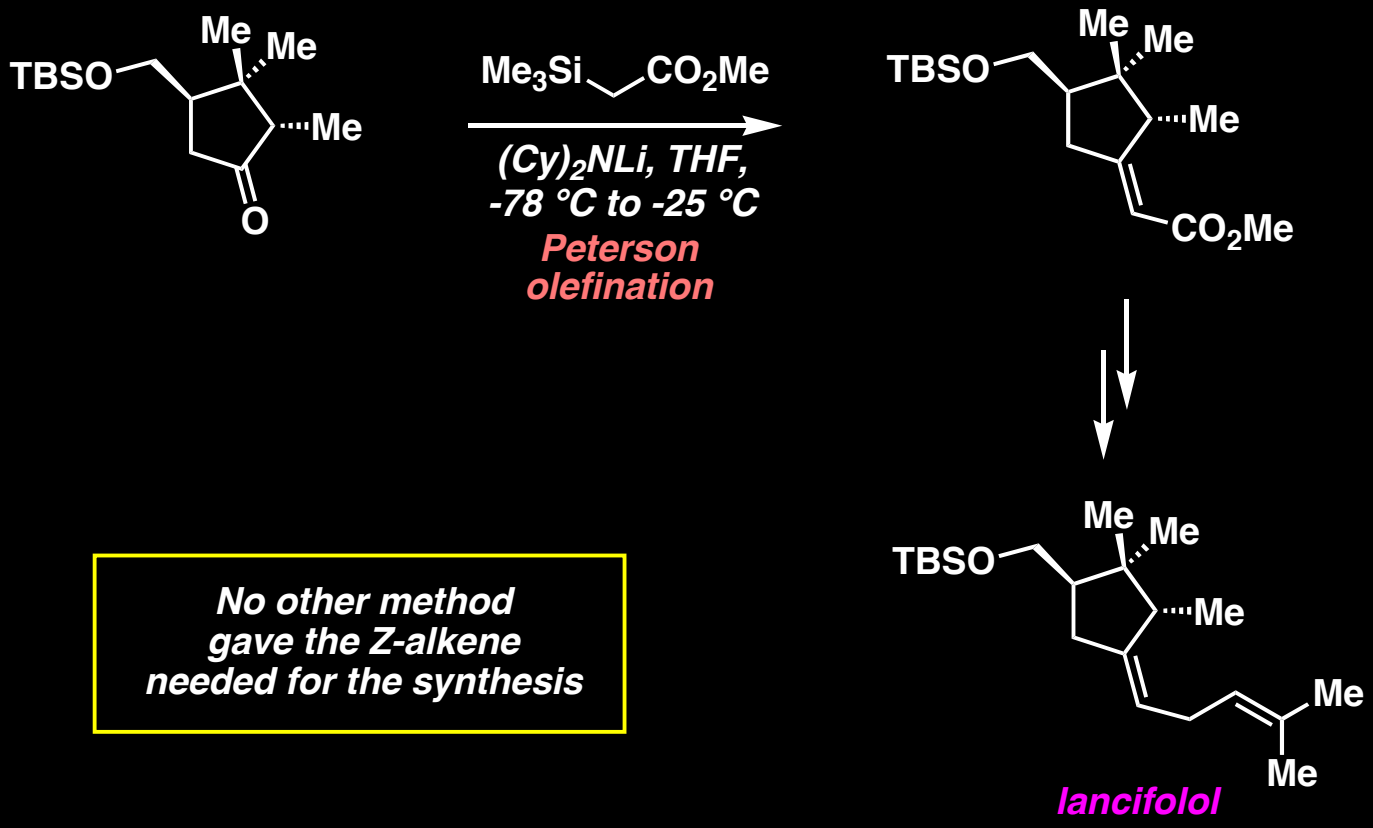
D. J. Peterson and co-workers, J. Org. Chem. 1968, 33, 780.
D. J. Peterson and co-workers, J. Am. Chem. Soc. 1975, 97, 1464.

Peterson Olefination: Applications in Total Synthesis



S. E. Denmark, S.-M. Yang, J. Am. Chem. Soc. 2002, 124, 15196.

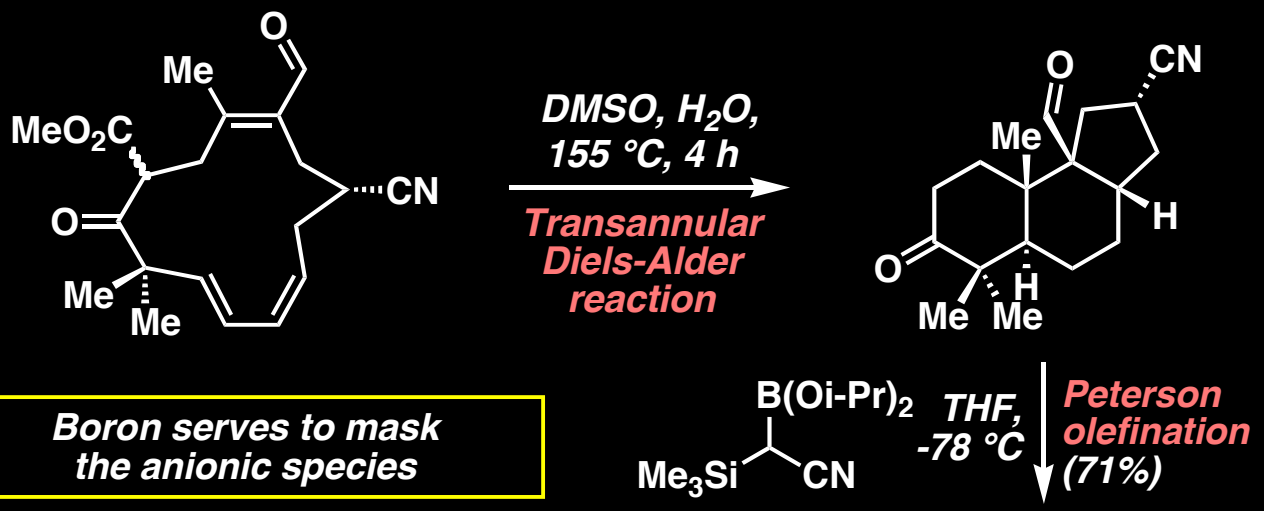
Peterson Olefination: Applications in Total Synthesis



No other method gave the Z-alkene needed for the synthesis

H. Monti and co-workers, Tetrahedron Lett. 2001, 42, 6125.

Peterson Olefination: Applications in Total Synthesis



A. Toro, P. Nowak, P. Deslongchamps, J. Am. Chem. Soc. 2000, 122, 4526.

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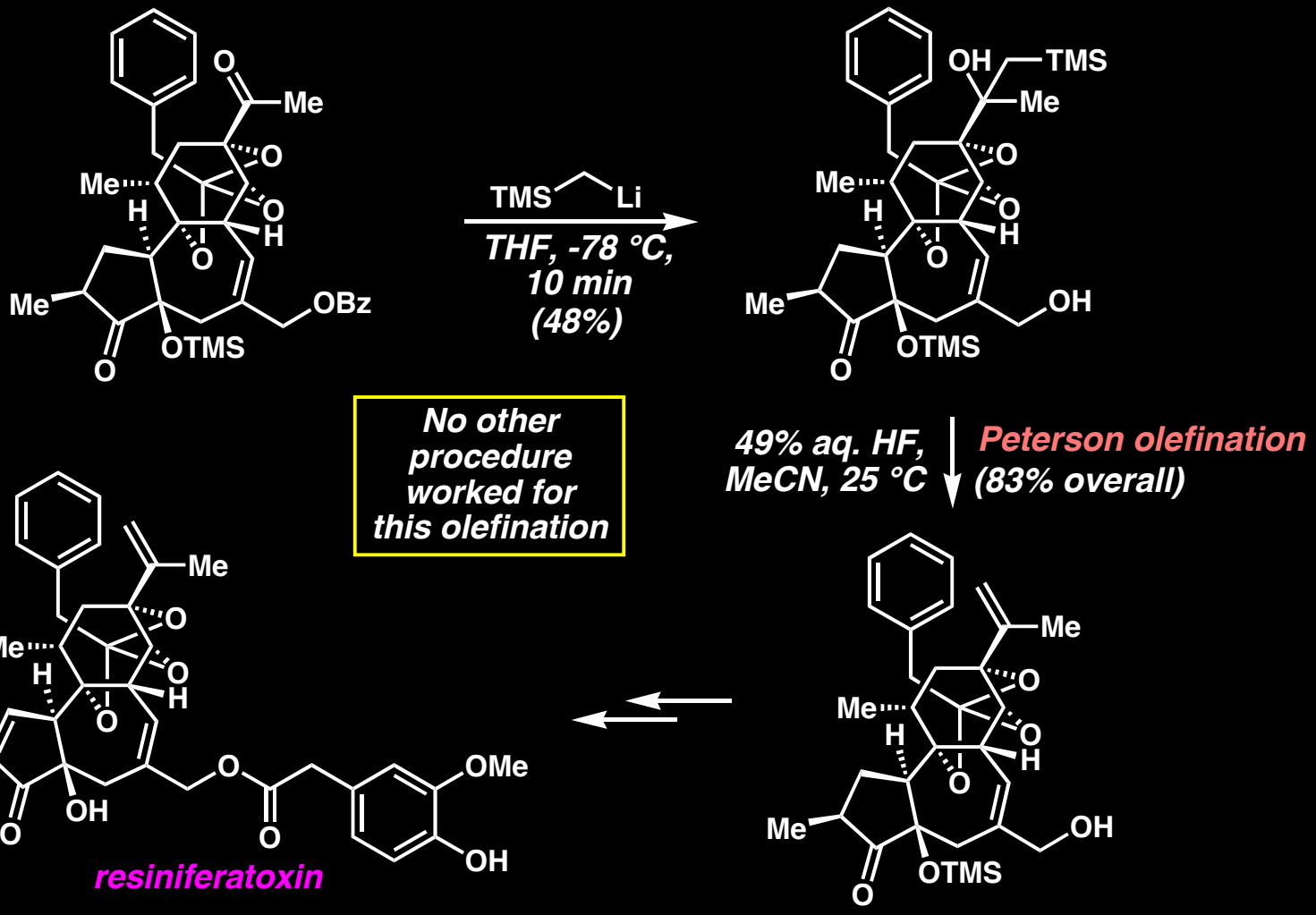

P. A. Wender and co-workers, J. Am. Chem. Soc. 1997, 119, 12976.