**Reviews:**

Vedejs, E.; Peterson, M. J. In *Topics in Stereochemistry*; Eliel, E. L. and Wilen, S. H. Ed.; John Wiley & Sons: New York, **1994**, Vol. 21, pp. 1–158.

Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.

Wittig Olefination, Background:

• Olefin synthesis employing phosphonium ylides was introduced in 1953 by Wittig and Geissler:
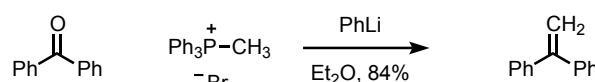

Wittig, G.; Geissler G. *Liebigs Ann.* **1953**, *580*, 44-57.

• Terminology introduced by Professor E. J. Corey in Chem 115 to help students conduct retrosynthetic analysis of trisubstituted olefins:
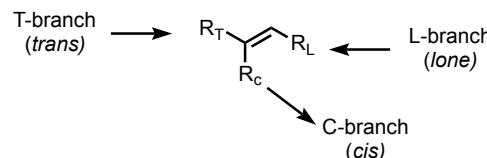

Mechanism:
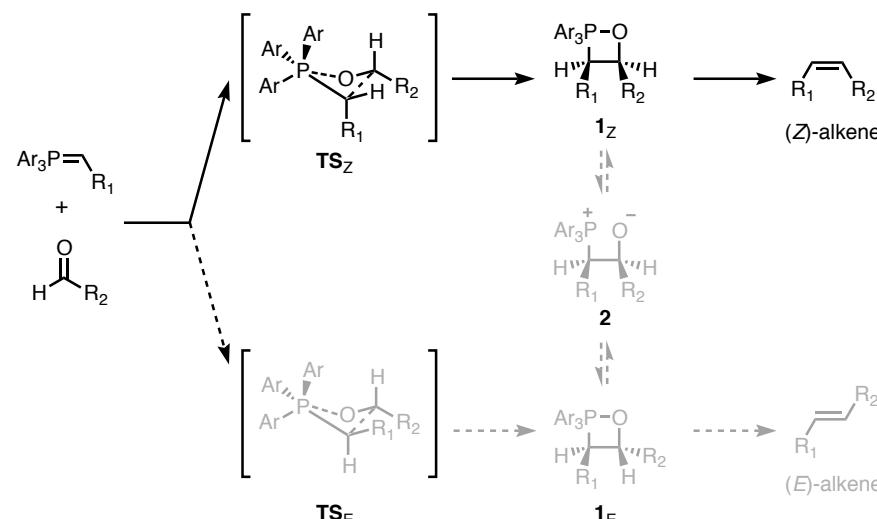
• Phosphonium ylides react with aldehydes to produce oxaphosphetane 1_Z or 1_E, which decomposes by a syn-cycloreversion process to the alkene.

• In the formation of *Z*-alkenes, an early, four-centered transition state is proposed. TS_Z is believed to be kinetically favored over TS_E because it minimizes 1,2 interactions between R_1 and R_2 in the forming C–C bond.

• The reaction of non-stabilized phosphonium ylides with aldehydes favors (*Z*)-alkene products.

**Non-stabilized Ylides:** $Ar_3P{=}\!\!\diagup R$ R = simple alkyl
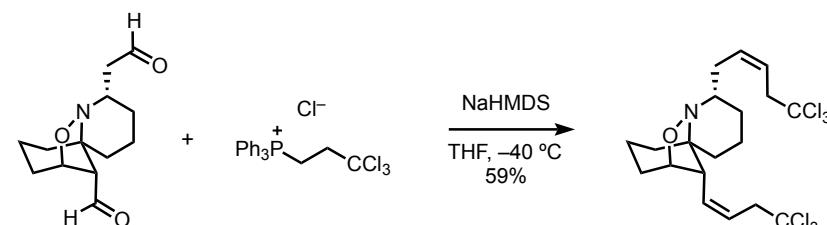
Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656–12657.

Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1–157.
Vedejs, E.; Peterson, M. J. *Advances in Carbanion Chemistry* **1996**, *2*, 1–85.

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- Stabilized ylides are proposed to have a later and more product-like transition state with 1_E thermodynamically favored over 1_Z.

- The reaction of stabilized phosphonium ylides with aldehydes favors (*E*)-alkene products. These reactions generally proceed at higher temperatures than reactions of non-stabilized ylides.

Stabilized Ylides: Ar_3P= with R = aryl, alkenyl, -CO_2R, or any anion-stabilizing groups.
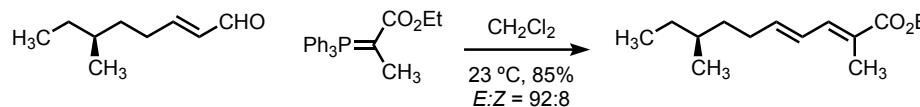
Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082–1100.

- Lithium ions catalyze the reversible formation of betaine **2** (depicted previous page), which contributes to erosion in stereoselectivity.
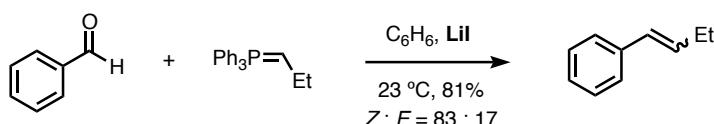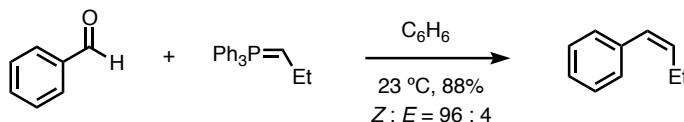
Schlosser, M. ; Christmann, K. F. *Liebigs Ann. Chem.,* **1976**, *708*, 1–35.

Synthesis of Phosphonium Ylides

$$Ph_3\overset{+}{P}CH_2R$$

R	pK_a (DMSO)
H	22.5
Ph	17.4
CN	6.9
O=CPh	6.1

- Phosphonium ylides are generally prepared by deprotonation of phosphonium salts, which come from the reaction of trialkyl or triarylphosphines with alkyl halides.

- Alkyl/aryl phosphonium halides are only weakly acidic. A strong base is required for deprotonation. Precursors to stabilized ylides are more acidic than alkyl phosphonium salts and can be generated using weaker bases.

Bordwell, F. G.; Zhang, X.-M. *J. Am. Chem. Soc.* **1994**, *116*, 968–972.
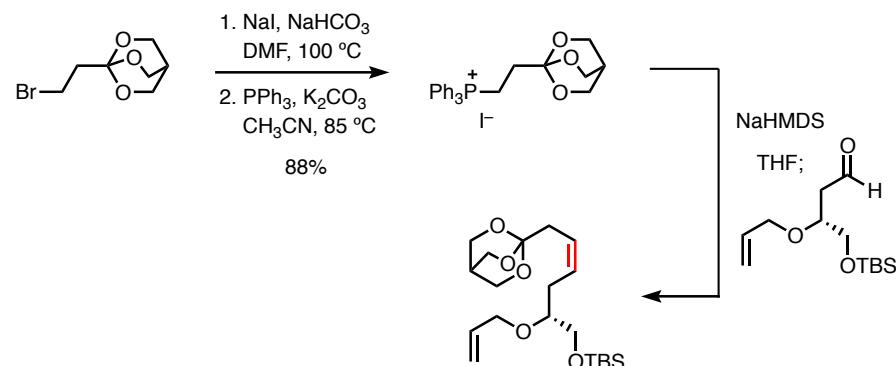
Keinan, E.; Sinha, S. C.; Singh, S. P. *Tetrahedron* **1991**, *47*, 4631–4638.
Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499–7504.

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2

Examples

- Industrial synthesis of vitamin A (>1000 tons of vitamin A are produced per year using this chemistry):


vitamin A
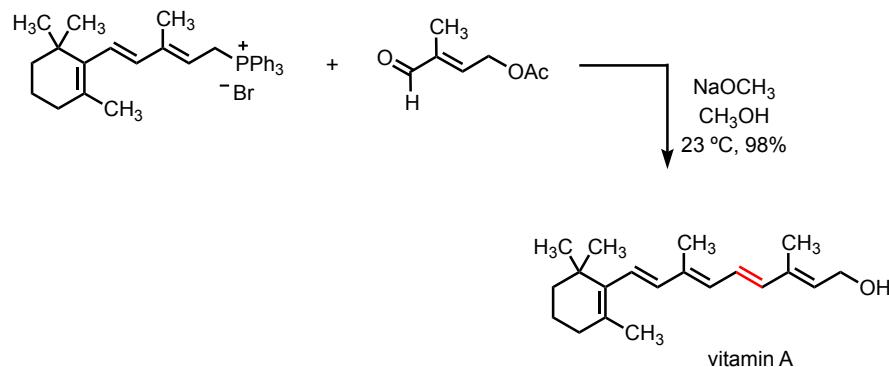
Pommer, H. *Angew. Chem.* **1960**, *72*, 811–819.
Pommer, H.; Nürrenbach, A. *Pure Appl. Chem.* **1975**, *43*, 527–551.
Paust, J. *Pure Appl. Chem.* **1991**, *63*, 45–58.

71%
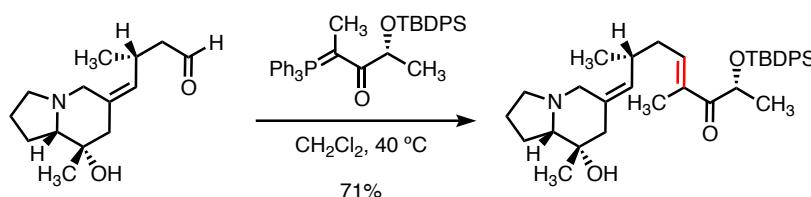
Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192–4201.

(2.00 kg)

1. SO₃•pyr, DMSO
   i-Pr₂NEt, CH₂Cl₂, 23 °C

2. Et₃P=CO₂Et

−5 → 23 °C, 86%

(2.17 kg)
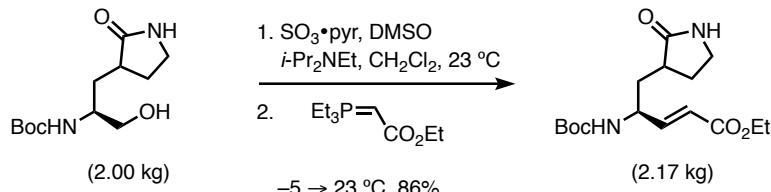
Chen, L.; Lee, S.; Renner, M.; Tian, Q.; Nayyar, N. *Org. Process Res. Dev.* **2006**, *10*, 163–164.

- α,β-unsaturated carbonyl compounds can undergo phosphoniosilylation and Wittig olefination to give substituted enones.

TBSOTf, PPh₃

THF, 23 °C

1. n-BuLi, THF, −78 °C

2.

TBAF

THF/Hexane

80%

86%, *E:Z* = 13:1
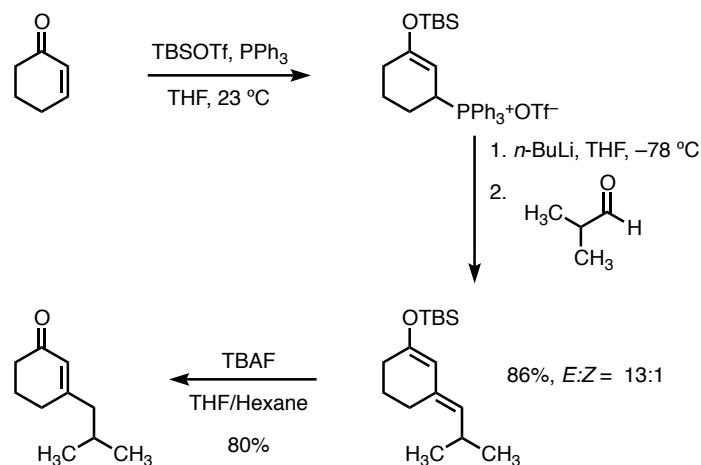
Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400–3402.

- Methoxymethylene ylides lead to vinyl ethers, which can be hydrolyzed to aldehydes. An example of this in synthesis:

1. Ph₃P=OCH₃
   THF, −30 °C

2. TfOH, i-PrOH
   CH₂Cl₂

77%
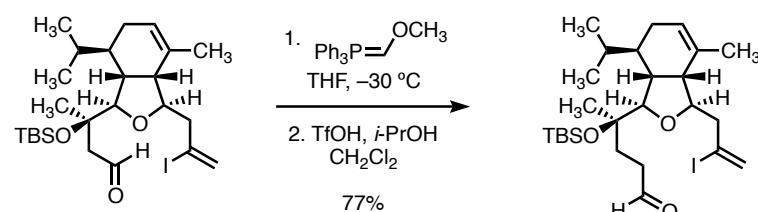
MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392.

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Schlosser's Modification:

- Reaction of non-stabilized phosphonium ylides with aldehydes can be made to favor formation of (*E*)-alkenes using a modified procedure.


71%
E:Z = 96:4.
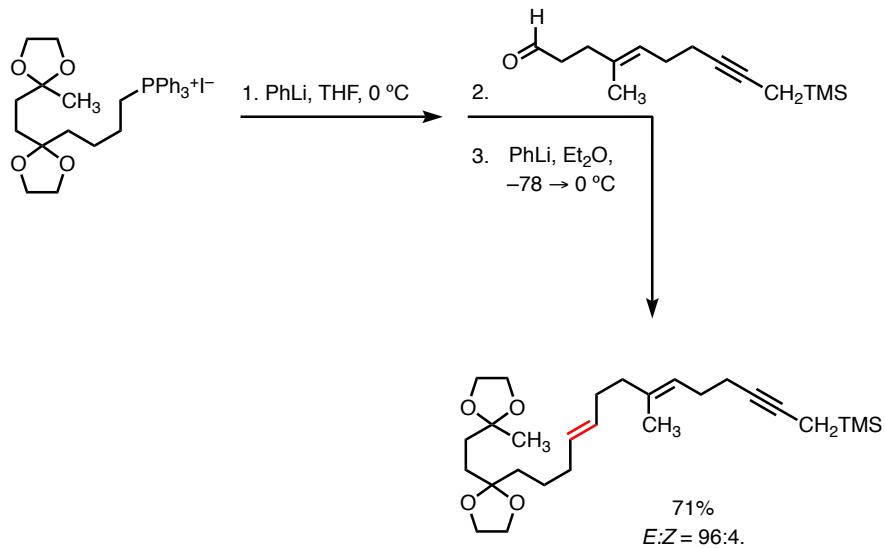
Schmidt, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980,** *102,* 5122–5123.

- The presence of soluble lithium salts promotes the reversible formation of betaine **2**. Addition of the second equivalent of PhLi deprotonates the α-position. The resulting β-oxido ylide is hypothesized to possess a cyclic geometry where steric interactions are minimized between the triphenylphosphonium group and R_2.


(*E*)-alkene
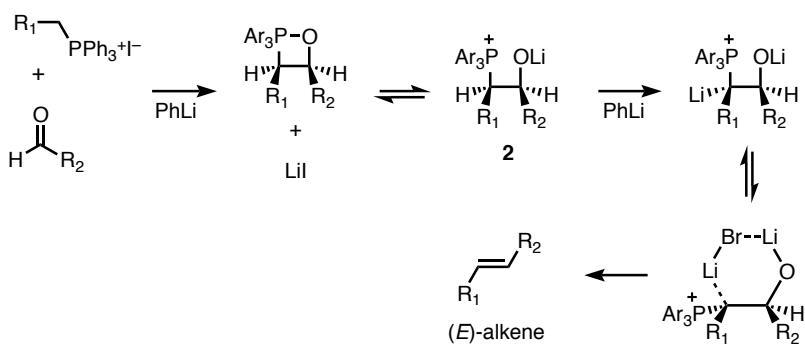
Corey, E. J.; Ulrich, P.; Venkateswarlu, A. *Tetrahedron Lett.* **1977**, *18*, 3231–3234.

- The ylide intermediate can be trapped with formaldehyde, providing a stereospecific synthesis of *Z*-trisubstituted alcohols (note the hydroxymethyl group is in the C-branch).

1. *n*-BuLi, THF, 0 ºC

3. *sec*-BuLi, –25 ºC
4. $(CH_2O)n$, 0 ºC

50%, *single isomer*
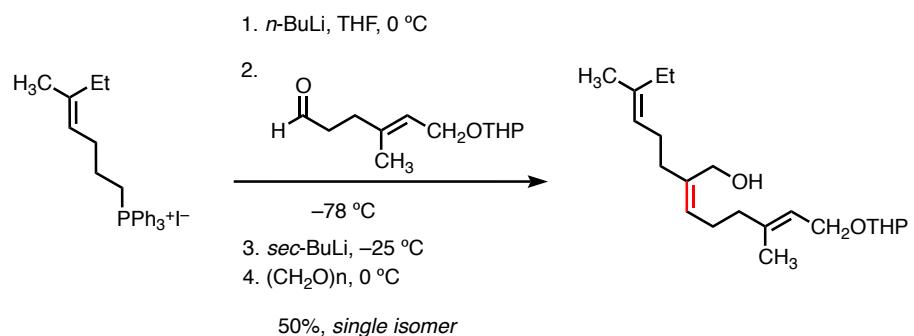
Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 6636–6637

- Haloalkenes can also be prepared:

47%, *E : Z* = 1 : 99
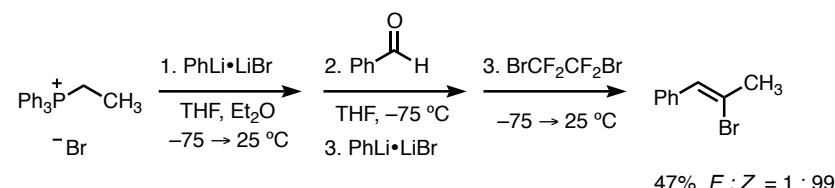
- Interestingly, bromination is very sensitive to the size of the alkylidene: increasing the size of the ylide led predominantly to *E*-alkenes:

82%, *E : Z* > 99 : 1
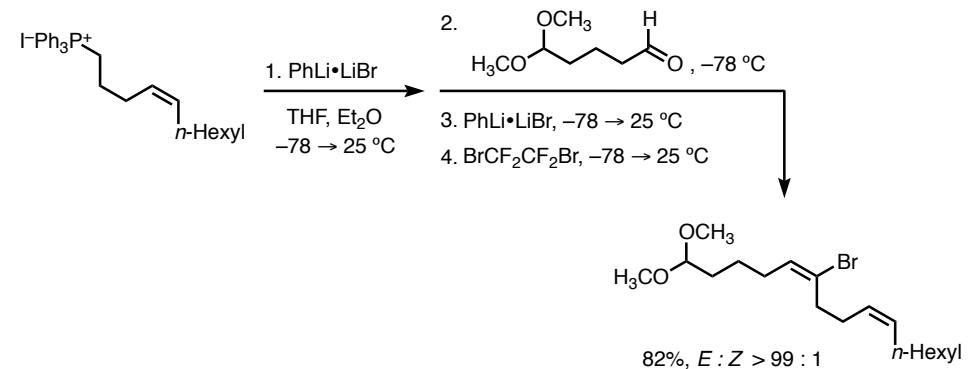
Wang, Q.; Deredas, D.; Huynh, C.; Schlosser, M. *Chem. Eur. J.* **2003**, *9*, 570–574.
Hodgson, D. M.; Arif, T. *J. Am. Chem. Soc.* **2008**, *130*, 16500–16501.

Fan Liu

Reviews:

Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253.

Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I. Ed.;
Pergamon: Oxford, **1991**, Vol. 1, pp. 729–817.

Applications in Natural Product Synthesis: Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A.
*Liebigs Ann./Recueil* **1997**, 1283–1301.

Asymmetric Wittig-Type Reactions: Rein, T.; Reiser, O. *Acta. Chem. Scand.* **1996**, *50*, 369–379.

Development and General Aspects:

• Olefin synthesis employing phosphonium ylides was introduced in 1953 by Wittig and Geissler.
Wittig, G.; Geissler G. *Liebigs Ann.* **1953**, *580*, 44-57.

• In 1958, Horner disclosed a modified Wittig reaction employing phosphonate-stabilized
carbanions; the scope of the reaction was further defined by Wadsworth and Emmons.

70%
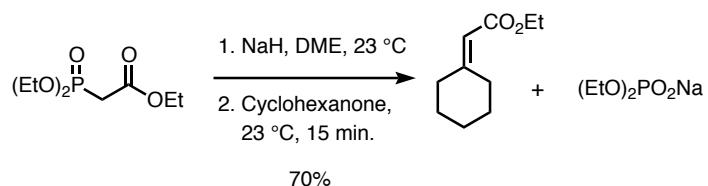
• Phosphonate-stabilized carbanions are more nucleophilic (and more basic) than the
corresponding phosphonium ylides.

• The by-product dialkylphosphate salt is readily removed by aqueous extraction.

• In contrast to phosphonium ylides, phosphonate-stabilized carbanions are readily alkylated:


60%, two steps
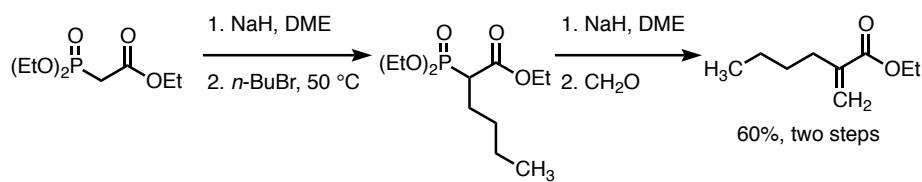
Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61–63.
Horner, L.; Hoffmann, H. M. R.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505.
Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1961**, *83*, 1733–1738.

Mechanism:
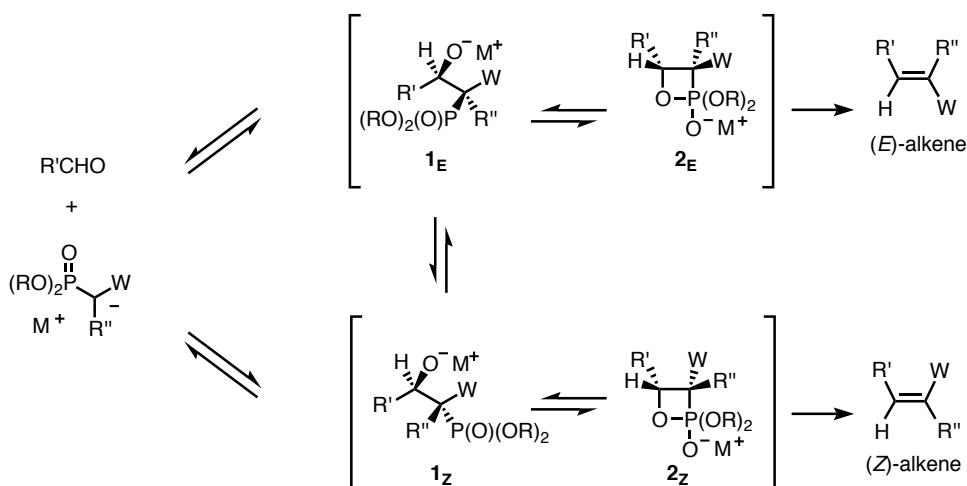
$W = CO_2^-, CO_2R, CN,$ aryl, vinyl, SO_2R, SR, OR, NR_2

• Phosphonate anion addition to the carbonyl or breakdown of the oxaphosphetane intermediate can
be rate-determining, depending on the identity of OR.

• Carbanion-stabilizing group (W) at the phosphonate-substituted carbon is necessary for elimination
to occur; nonstabilized phosphonates (W = R or H) afford stable β-hydroxyphosphonates.

Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654-5656.

• The ratio of olefin isomers is dependent upon the stereochemical outcome of the initial addition and
upon the ability of the intermediates to equilibrate.

Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

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Acidity of Stabilized Phosphonates in DMSO:

W	pK_a
CN	16.4
CO$_2$Et	18.6
Cl	26.2
Ph	27.6
SiMe$_3$	28.8

Bordwell, F. G. *Acc. Chem. Res*. **1988**, *21*, 456-463.;

Bordwell, F. G. Unpublished results.
(http://daeiris.harvard.edu/DavidEvans.html)

• Phosphonium salts are considerably more acidic than the corresponding phosphonates:

(Ph$_3$P$^+$CH$_2$CN)Cl$^-$: pK_a = 6.9

(Ph$_3$P$^+$CH$_2$CO$_2$Et)Cl$^-$: pK_a = 8.5

Bordwell, F. G.; Zhang, X.-M. *J. Am. Chem. Soc*. **1994**, *116*, 968–972.

**Preparation of phosphonates:**

Michaelis-Arbusov Reaction:

Review: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.

59%
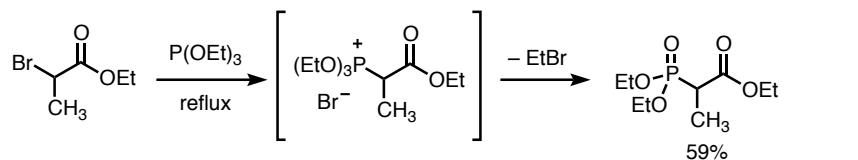
Arbusov, A. E.; Durin, A. A. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 295.

• The synthesis of β-ketophosphonates from α-haloketones by the Michaelis-Arbusov reaction can be impractical due to competing formation of dialkyl vinyl phosphates by the Perkow reaction:

major product
(yield not provided)
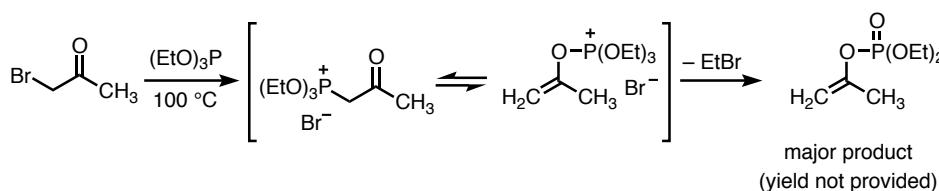
Machleidt, H.; Strehlke, G. U. *Angew. Chem. Int. Ed.* **1964,** *3*, 443–444.
Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.

Michaelis-Becker Reaction:

58%
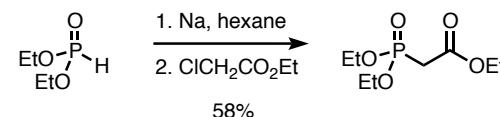
Kosolapoff, G. M. *J. Am. Chem. Soc.* **1946**, *68*, 1103–1105.

Acylation of Alkylphosphonate Anions:

• β-ketophosphonates are prepared by acylation of alkylphosphonate anions:

86%
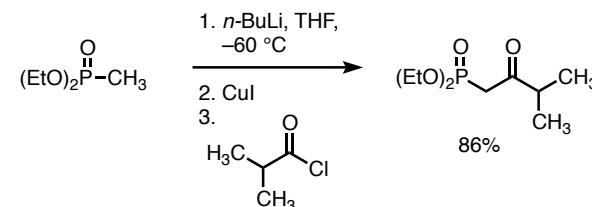
Mathey, F.; Savignac, P. *Tetrahedron*, **1978**, *34*, 649–654.

Phosphonate Ester Interchange:

40%, two steps
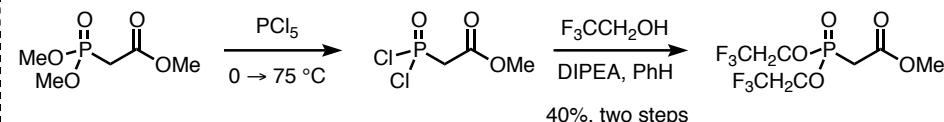
Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
Bodnarchuk, N. D.; Malovik, V. V.; Derkach, G. I. *Zh. Obshch. Khim.* **1970**, *40*, 1210.

Ester Interchange:

• The use of isopropyl phosphonates minimizes alkoxy exchange at phosphorus.


94%
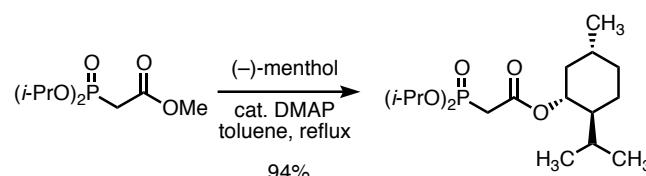
Hatakeyama, S.; Satoh, K.; Kuniya, S.; Seiichi, T. *Tetrahedron Lett.* **1987**, *28*, 2713–2716.

Kent Barbay

6

Stereoselectivity of HWE Olefination:

Disubstituted Olefins:

• Reaction of phosphonates with aldehydes favors formation of (*E*)-alkenes.
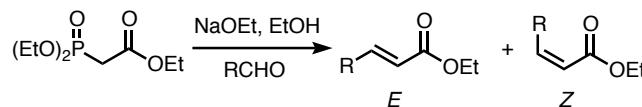
Aldehyde	Ratio of products (*E* : *Z*)
PhCHO	98 : 2
n-PrCHO	95 : 5
i-PrCHO	84 : 16

Larsen, R. O.; Aksnes, G. *Phosphorus Sulfur*, **1983**, *16*, 339–344.

• In a systematic study of the synthesis of disubstituted olefins by HWE, *E* : *Z* ratio increases:
  (1) in DME relative to THF,
  (2) at higher reaction temperatures,
  (3) M$^+$ = Li > Na > K,
  (4) with increasing α-substitution of the aldehyde.

> In general, conditions which increase the reversibility of the reaction (i.e., increase the rate of retroaddition relative to the rate of elimination) favor the formation of *E*-alkenes.

Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386–3388.

• Bulky phosphonate and ester substituents enhance (*E*)-selectivity in disubstituted olefin synthesis:

Reagent	Ratio of products (*E* : *Z*)
(*i*-PrO)$_2$P(O)CH$_2$CO$_2$Et	95 : 5
(MeO)$_2$P(O)CH$_2$CO$_2$Me	1 : 3

Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888.

68% for R = *i*-Pr

R	Ratio of products (*E* : *Z*)
Me	1 : 1.2
Et	1.75 : 1
i-Pr	E only
CH(Et)$_2$	E only
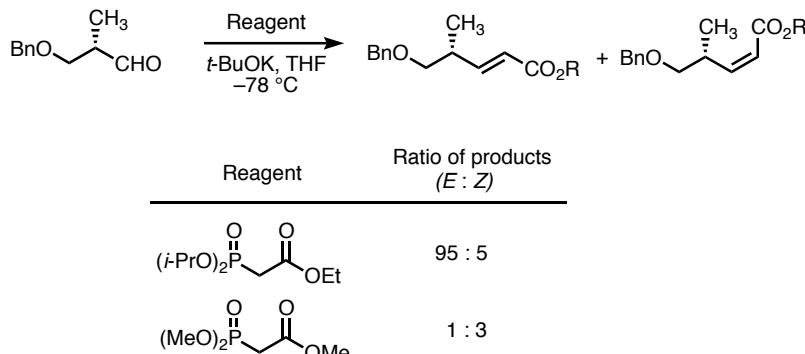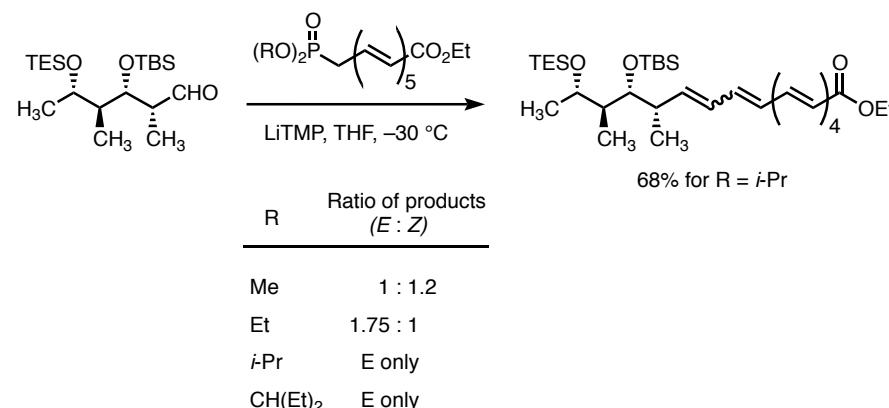
Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239–5242.

Trisubstituted Olefins:

Reaction of α-Branched Phosphonates with Aldehydes:

• The size of the phosphonate and ester substituents plays a critical role in determining the stereochemical outcome in the synthesis of trisubstituted olefins – large substituents favor (*E*)-alkenes.
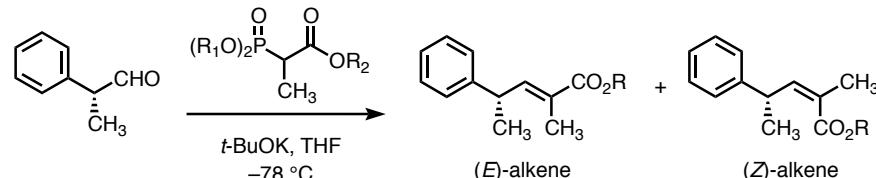
R$_1$	R$_2$	Ratio of products (*E* : *Z*)
Me	Me	5 : 95
Me	Et	10 : 90
Et	Et	40 : 60
i-Pr	Et	90 : 10
i-Pr	*i*-Pr	95 : 5

Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888.

• (*Z*)-selective olefination with the trimethyl phosphonate (R$_1$, R$_2$ = CH$_3$) is unsuccessful with aromatic aldehydes. The Still modification of the HWE olefination (see below) can be applied for (*Z*)-selective olefination of aromatic aldehydes.

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Olefination of Ketones:

• (*E*)-selectivities are typically modest in condensations with ketones. In some cases, use of a bulky ester increases the selectivity:
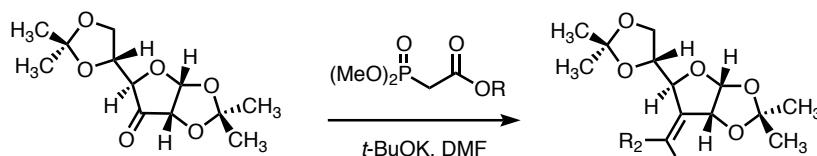

R	Ratio of products (**A** : **B**)
Me	2.7 : 1
t-Bu	9 : 1

A: R$_1$ = CO$_2$R, R$_2$ = H
B: R$_1$ = H, R$_2$ = CO$_2$R

• The failure of this hindered ketone to react with Ph$_3$P=CHCO$_2$Et (benzene, reflux) provides an example of the increased reactivity of phosphonates in comparison to phosphonium ylides.

Mulzer, J.; Steffin, U.; Zorn, L.; Schneider, C.; Weinhold, E.; Münch, W.; Rudert, R.; Luger, P.; Hartl, H. *J. Am. Chem. Soc.* **1988**, *110*, 4640–4646.

Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1201–1210.

77%, 7:1 *E* : *Z*
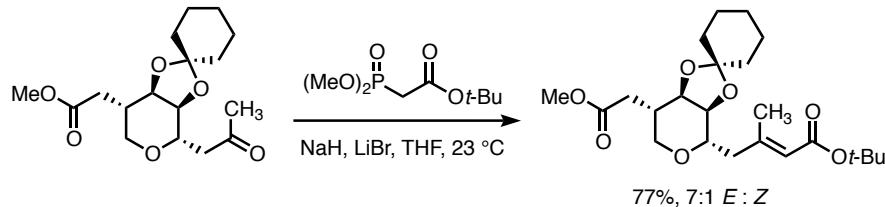
White, J. D.; Theramongkol, P.; Kuroda, C.; Engelbrecht, J. R. *J. Org. Chem.* **1988**, *53*, 5909–5921.

• Control of double-bond geometry in tri-substituted olefin synthesis has been accomplished by the use of a tethered HWE reagent:

(1:1 mixture of diastereomers)

100%
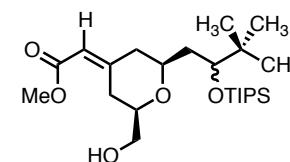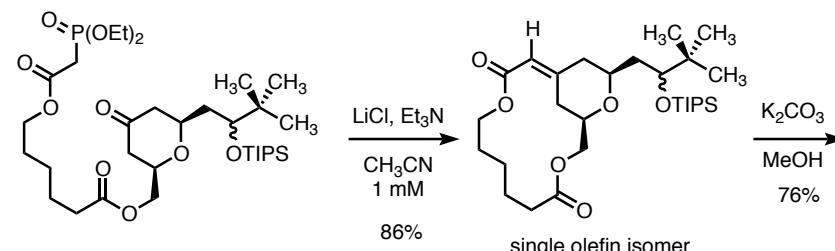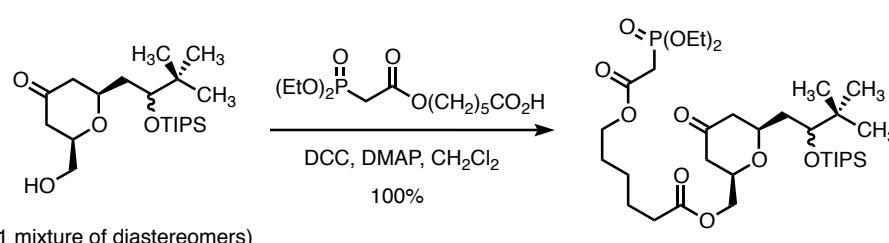
Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703–4706.

• Tetrasubstitued olefins can be prepared in some cases, but isomeric mixtures are obtained:

83%

E : *Z* = 28 : 72
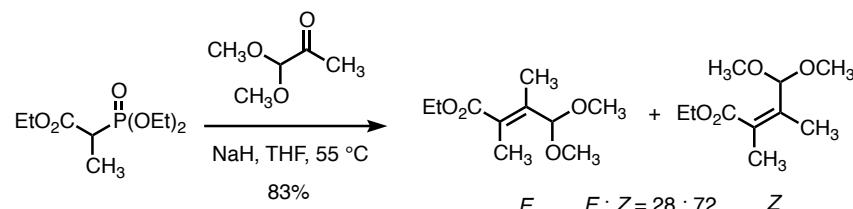
Bestmann, H. J.; Ermann, P.; Rüppel, H.; Sperling, W. *Liebigs. Ann. Chem.* **1986**, 479–498.

**Single-step two-carbon homologation of esters:**

81%, 91 : 9 *E* : *Z*
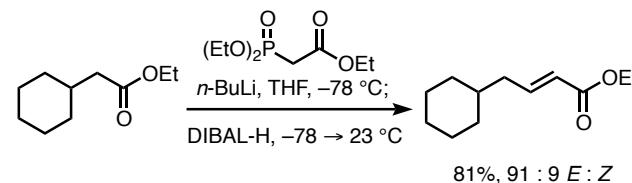
• Ester reduction in the presence of the phosphonate minimizes overreduction of the intermediate aldehyde.

Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257–1260.

Kent Barbay

8

Olefination of Base-Sensitive Substrates (Masamune-Roush Conditions):

• Masamune and Roush reported mild conditions (LiCl, amine base, ambient temperature) for olefinations employing base-sensitive substrates or phosphonates:
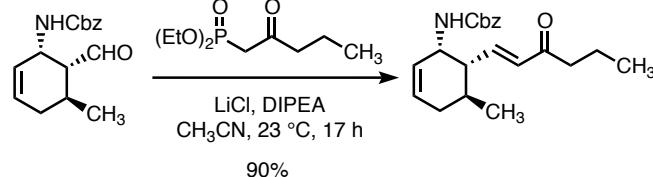

• This aldehyde substrate epimerizes under standard HWE conditions (NaH as base).

• Addition of LiCl enhances acidity of phosphonate, allows use of weak bases (DBU, *i*-Pr$_2$NEt) and ambient temperature.

M	solvent	pKa
K	DMSO	19.2
Li	diglyme	12.2

• Application of the Masamune-Roush conditions does not alter the inherent (*E*)-selectivity of the HWE reaction.

Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

• Application of mild HWE conditions to (*Z*)-selective olefin synthesis (see adjacent column):
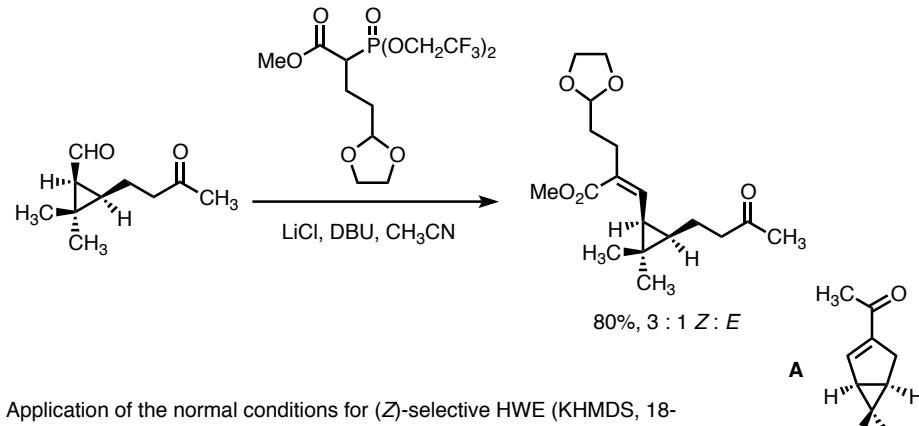
• Application of the normal conditions for (*Z*)-selective HWE (KHMDS, 18-crown-6) yielded only the internal aldol product **A**.

Hammond, G.S.; Cox Blagg, M.; Weimer, D. F. *J. Org. Chem.* **1990**, *55*, 128.

(*Z*)-Selective Olefination – Still Modification of HWE Olefination:

Disubstituted olefins:

aldehyde	product	*Z* : *E*	yield, %
		>50 : 1	87
		4 : 1	74
		>50 : 1	>95
		22 : 1	81

Trisubstituted olefins:

aldehyde	product	*Z* : *E*	yield, %
		>50 : 1	79
		>50 : 1	80
		30 : 1	>95
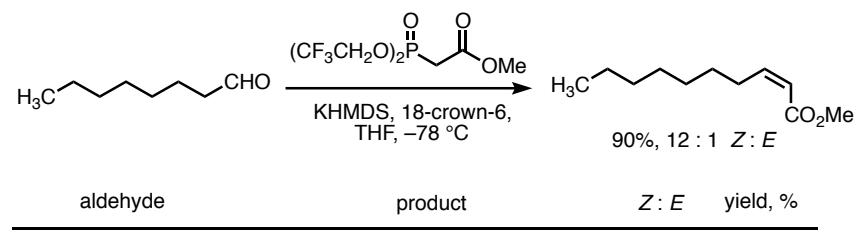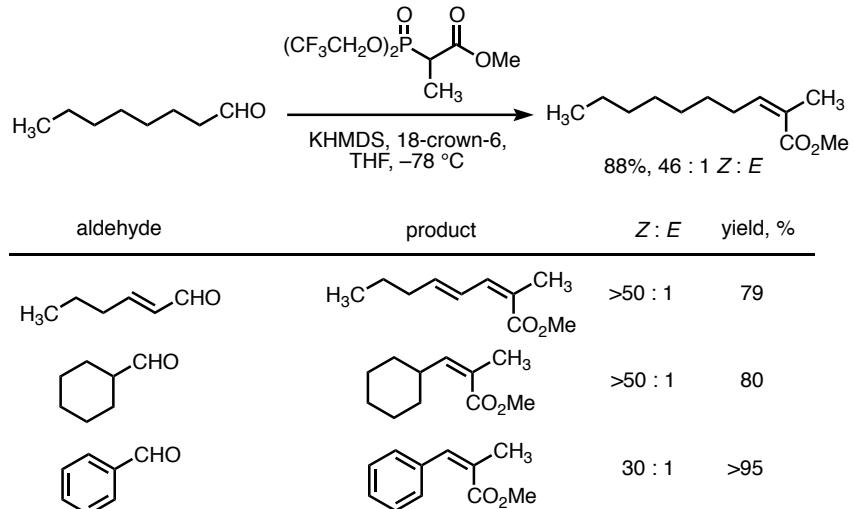
From: Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

• The electrophilic phosphonate and the use of strongly dissociating conditions favor rapid breakdown of the oxaphosphetane, resulting in excellent (*Z*)-selectivity.

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(Z)-Selective Olefination – (Diarylphosphono)acetates:

Disubstituted olefins:

CH$_3$(CH$_2$)... CHO → CH$_3$... CO$_2$Et, with (PhO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, −78 → −10 °C

100%, *Z* : *E* = 90 : 10
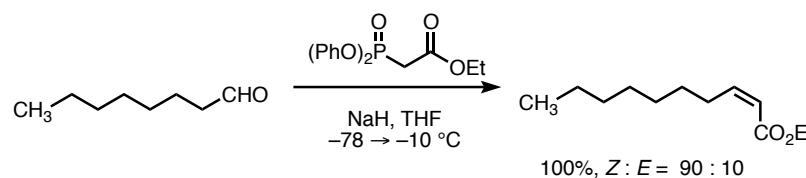
aldehyde	product	base	*Z* : *E*	yield, %
CH$_3$...CHO	CH$_3$...CO$_2$Et	Me$_3$NBuOH	89 : 11	97
cyclohexyl-CHO	cyclohexyl...CO$_2$Et	NaH	91 : 9	98
Ph-CHO	Ph...CO$_2$Et	Me$_3$NBuOH	93 : 7	98
CH$_3$...CHO (with CH$_3$ branch)	CH$_3$...CO$_2$Et (with CH$_3$ branch)	NaH	94 : 6	100
CH$_3$...CHO, TBSO	CH$_3$...CO$_2$Et, TBSO	NaH	97 : 3	78

• (*Z*)-Selectivity was further enhanced using *ortho*-alkyl substituted (diarylphosphono)acetates:

(ArO)$_2$P(O)CH$_2$CO$_2$Et

Ar = *o*-MePh, *o*-EtPh, *o*-i*-*PrPh
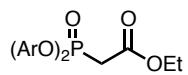
• 93 : 7 – 99 : 1 (*Z*)-selectivity, 92–100% yield.
• Aryl, α,β-unsaturated, alkyl, branched alkyl, and α-oxygenated aldehydes are suitable substrates.

• In analogy to Still's (*Z*)-selective HWE reaction employing [bis(trifluoroethyl)phosphono]acetates, (*Z*)-selectivity is attributed to the electron-withdrawing nature of the aryloxy substituent, which accelerates elimination relative to equilibration of oxaphosphatane intermediates.

Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.

• For (diphenylphosphono)acetate esters, (*Z*)-selectivity increases with increasing steric bulk of the ester moiety.

Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408.

Trisubstituted olefins:

RCHO → R...R'...CO$_2$Et, with (ArO)$_2$P(O)CH(R')CO$_2$Et, base, THF
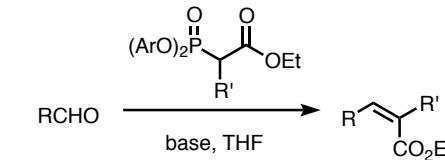
aldehyde	Ar	R'	product	base	*Z* : *E*	yield, %
n-Pr...CHO	*o*-MePh	Me	*n*-Pr...CH$_3$...CO$_2$Et	Me$_3$NBuOH	89 : 11	97
Ph-CHO	*o*-i*-*PrPh	Me	Ph...CH$_3$...CO$_2$Et	*t*-BuOK	97 : 3	100
cyclohexyl-CHO	Ph	*n*-Bu	cyclohexyl...*n*-Bu...CO$_2$Et	NaH	96 : 4	91
n-Bu...CHO, CH$_3$	Ph	*n*-Bu	*n*-Bu...*n*-Bu...CO$_2$Et, CH$_3$	NaH	95 : 5	85
n-C$_7$H$_{15}$CHO	Ph	*i*-Pr	*n*-C$_7$H$_{15}$...CH$_3$/CH$_3$...CO$_2$Et	NaH–LiBr	91 : 9	75
CH$_3$...CHO, OCH$_2$Ph	Ph	*i*-Pr	CH$_3$...CH$_3$/CH$_3$...CO$_2$Et, PhCH$_2$O	NaH	98 : 2	65

Ando, K. *J. Org. Chem.* **1998**, *63*, 8411–8416.

• Masamune and Roush's mild conditions have been adapted for (*Z*)-selective olefin synthesis using (diarylphosphono)acetates:

(PhO)$_2$P(O)CH$_2$CO$_2$Et

1. NaI, DBU, THF, 0 °C
2. CH$_3$/CH$_3$...CHO, NHSO$_2$Ar, −78 → 0 °C

→ CH$_3$/CH$_3$...ArSO$_2$N(H)...CO$_2$Et

89%, 87 : 13 *Z* : *E*
• no racemization

Ar = 2,4,6-trimethylphenyl
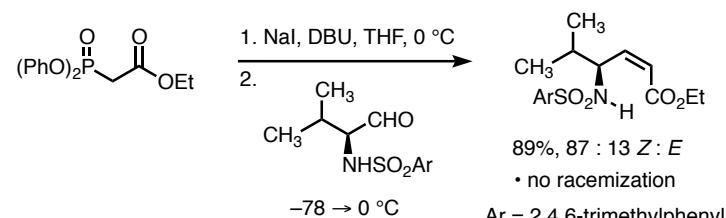
Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

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**HWE Reaction in Macrolide Synthesis:**

(–)-Vermiculine:
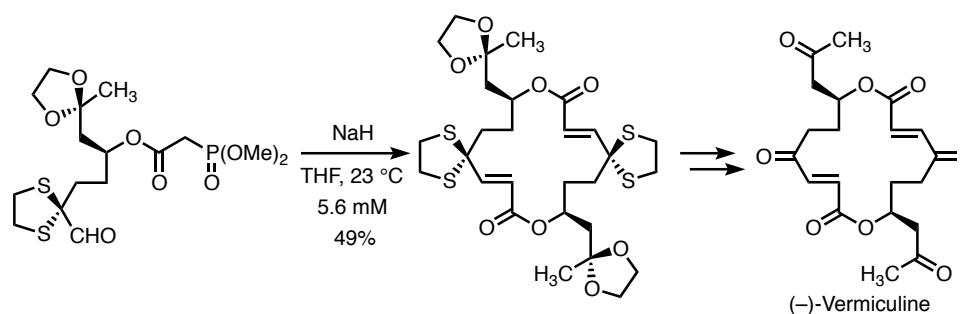
· High-dilution or syringe-pump additions are frequently required to achieve high-yielding
 macrocyclizations.

Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069–7071.

(–)-Asperdiol:

(*E*) only
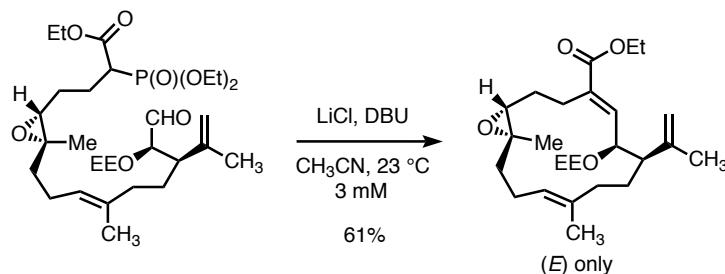
Tius, M.A.; Fauq, A. *J. Am. Chem. Soc.* **1986**, *108*, 6389–6391.

· Intramolecular HWE olefinations are usually selective for (*E*)-alkenes, but the selectivity can vary
  based on ring size and substitution. For example, compare to above:

2 : 1 *E* : *Z*
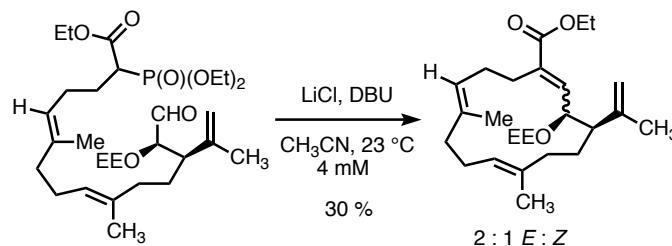
Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035–1039.

Amphotericin B:

Amphotericin B
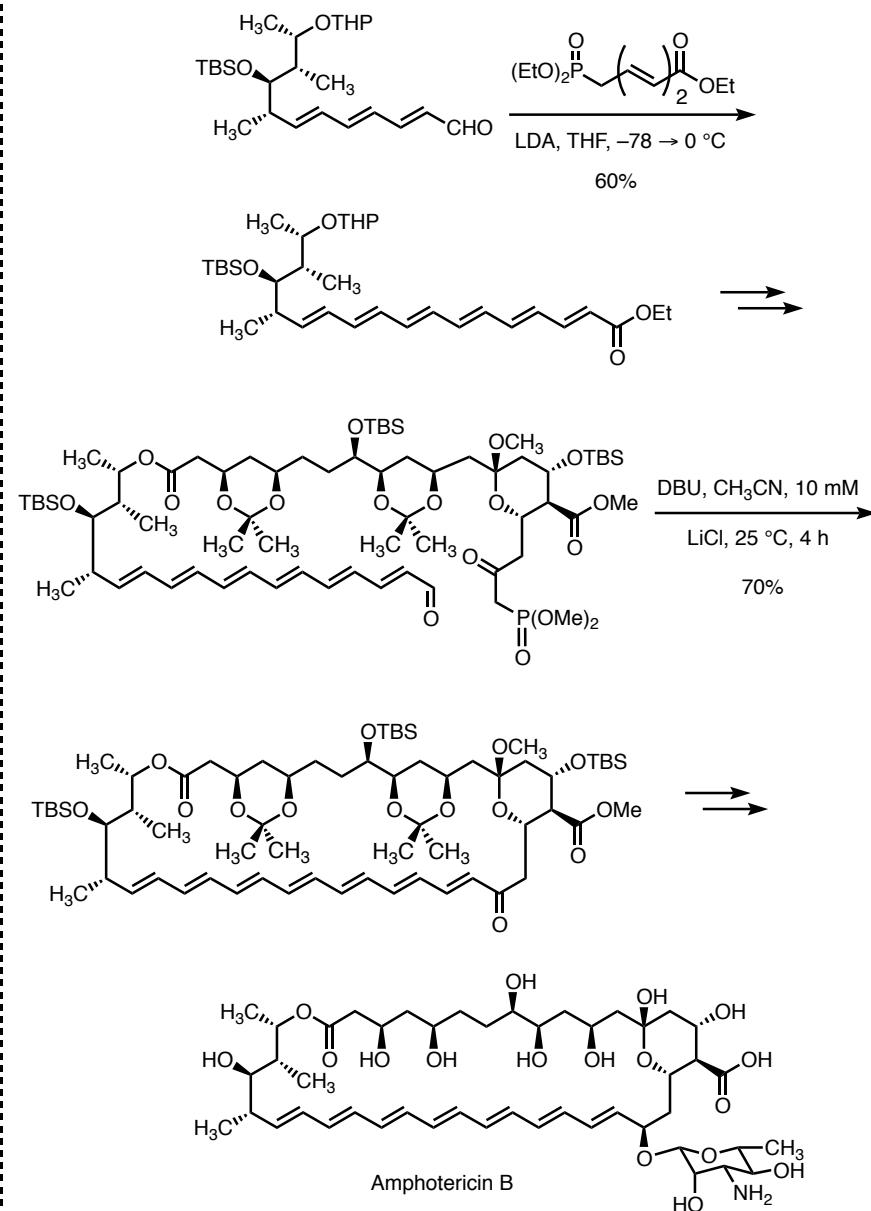
Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696.

Nicolaou, K.C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705.

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Asymmetric HWE:

Chiral Phosphonamidates:

94-98%, 88-100% de

R	yield, %	ee, %
t-Bu	65	>99
Me	72	86
Ph	71	>99
CO$_2$*t*-Bu	75	95
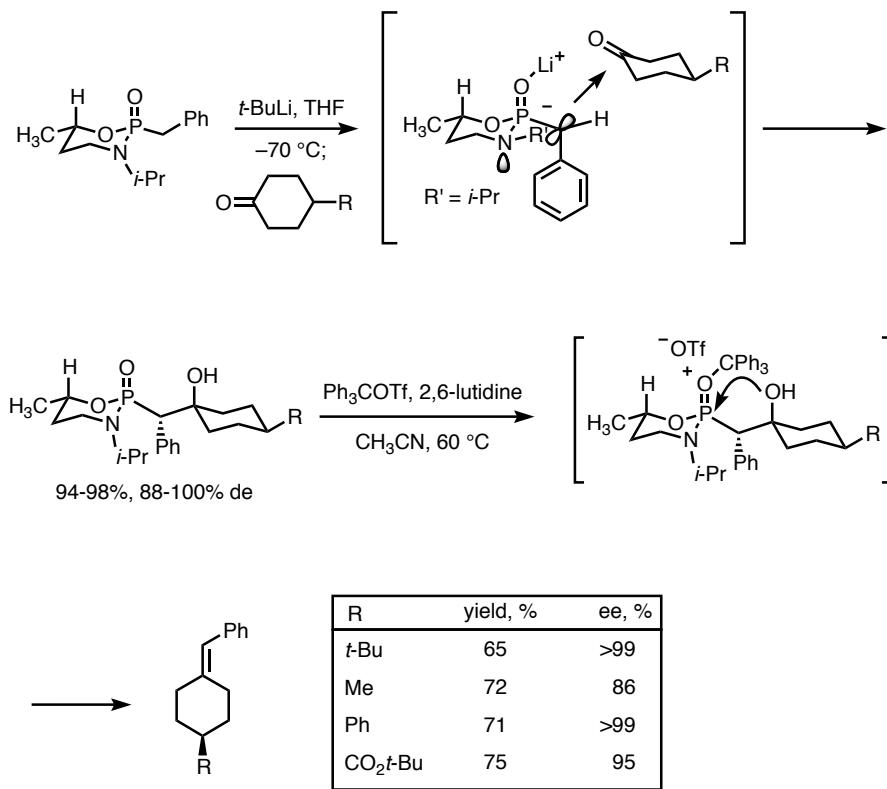
• Electrophilic attack occurs from the less hindered α-face of the phosphonamidate-stabilized carbanion. Bulky nucleophiles display high selectivity for equatorial attack on cyclohexanones.

• Stable β-hydroxy phosphonamidates are isolated and transformed to alkenes by electrophilic activation with trityl salts. This procedure results in stereospecific syn-cycloelimination.

(Attempted base-catalyzed olefin formation led to retroaddition.)

Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674–10676.
Denmark, S. E.; Chen, C.-T. *J. Org. Chem.* **1994**, *59*, 2922–2924.

Asymmetric Olefin Synthesis – Chiral Ester:

Attack by β-face of phosphonate on convex face of ketone

93%, 90% de
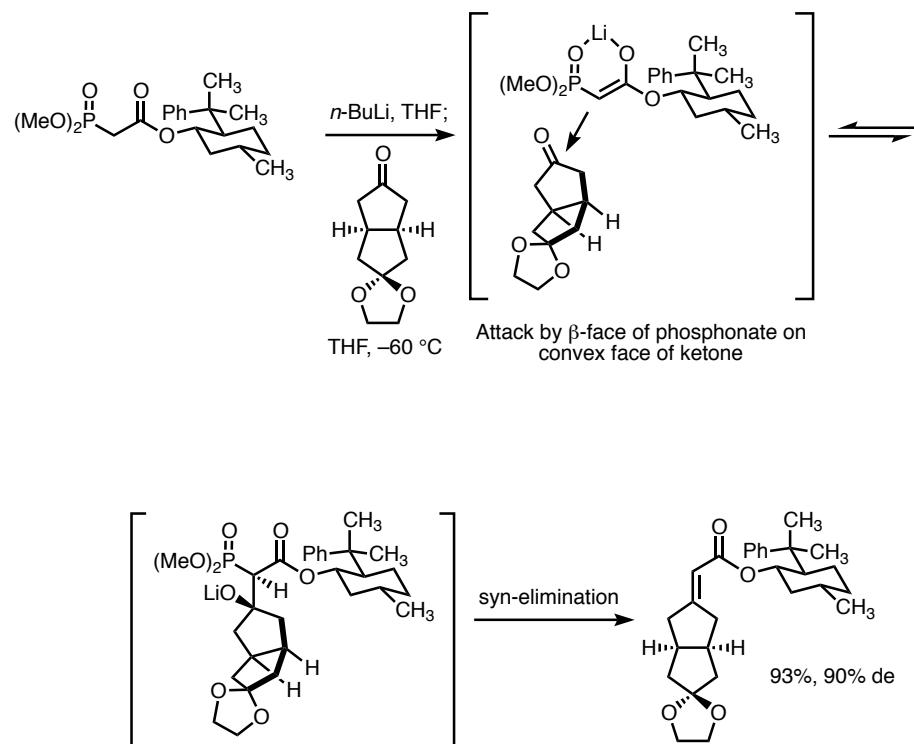
Gais, H.-J.; Schmeidl, G.; Ball, W. A.; Bund, J.; Hellmann, G.; Erdelmeier, I. *Tetrahedron Lett.* **1988**, *29*, 1773–1774.

8-phenylmenthol: Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.

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12

Kinetic Resolution:

81%, 98% de   14%, 92% de

Crude *Z* : *E* = 85 : 15
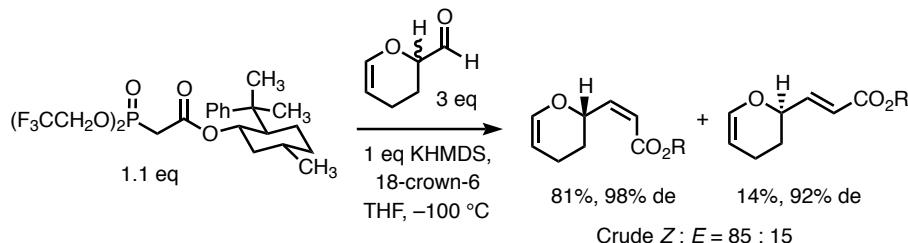
• *E* and *Z* products are formed from different enantiomers of the starting aldehyde.

• Mechanistic hypothesis:

major product

K⁺ • 18-crown-6

Felkin-Anh addition

(R$_L$ = OR)

Attack from β-face of (*Z*)-enolate

fast-reacting enantiomer

slow-reacting enantiomer

(Slow step may be addition or elimination)

syn-elimination

minor product
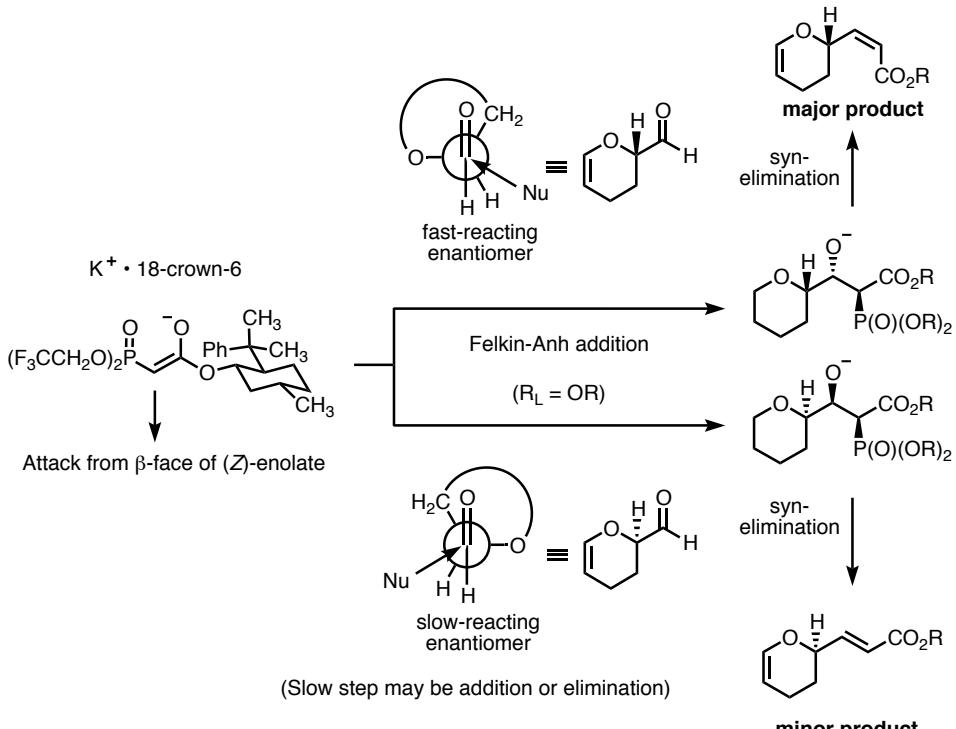
• For consideration of the stereochemical outcome of addition to α-alkyloxy aldehydes, see:

  Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353–3361.

Rein, T.; Kann, N.; Kreuder, R.; Benoit, G.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 556–558.

Rein, T.; Reiser, O. *Acta. Chem. Scand.* **1996**, *50*, 369–379.

Discrimination of enantiotopic or diastereotopic carbonyls:

83%, 96% de

53%, 90% de
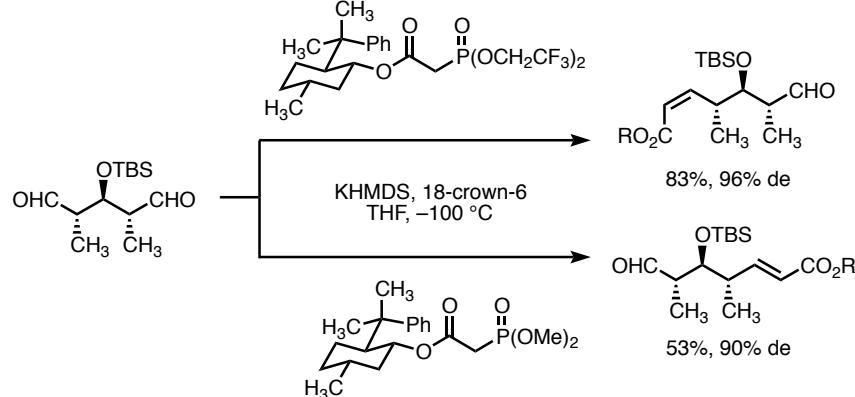
• Diastereoselectivity is dependent on conversion, because the minor diastereomeric products are preferentially bis-olefinated.

See: Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, 109, 1525-1529.

Exercise: Based on the previous example, rationalize the stereochemical outcome of these olefinations. (Note that the phosphonate used in this example is enantiomeric to that used in the previous example).

Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284-8294.

• Incapable of syn-elimination, therefore reverts

80%, 98% de
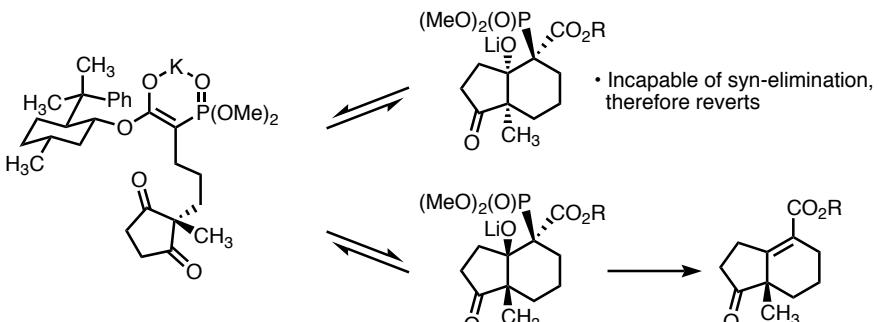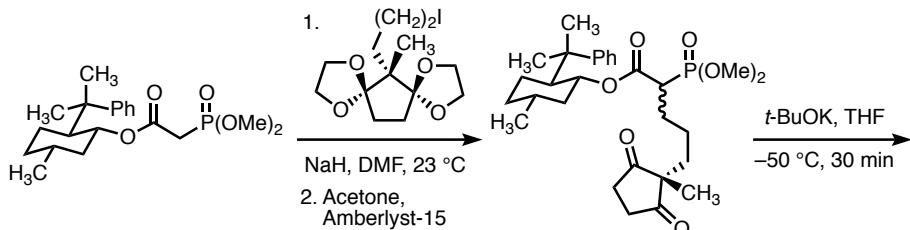
• Auxiliary shields α-face of (*Z*)-enolate

• Attack occurs at either diastereomeric carbonyl from the face opposite the methyl group.

Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847–5849.   Kent Barbay

13

Reviews

Kelly, S. E. Alkene Synthesis in *Comprehensive Organic Synthesis;* Trost, S. M.; Fleming, I., Ed.; Pergamon, Oxford, **1991**, *1*, 729–818.

Weber, W. P. Peterson Reaction in *Silicon Reagents for Organic Synthesis.* Springer-Verlag, Berlin, **1983**, *14*, 58–78.

Magnus, P. *Aldrichimica Acta* **1980**, *13*, 43.

Overview

- The Peterson olefination reaction was first reported in 1968. It is considered to be the silicon variant of the Wittig reaction.
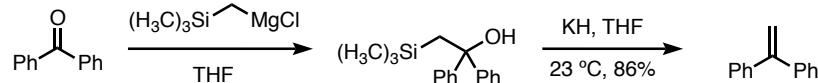
Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784.

- Magnesium and lithium alkoxides are not prone to elimination while sodium and potassium alkoxides readily form the product alkene.

Mechanism
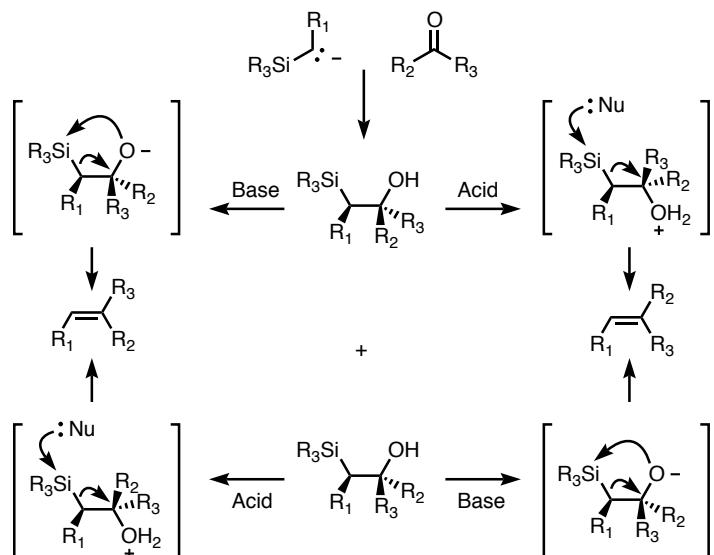
- The silicon-substituted carbanion adds irreversibly to the carbonyl substrate, producing a mixture of diastereomeric β-silylcarbinols. Each diastereomer undergoes stereospecific decomposition to give either *E* or *Z* alkenes depending on the elimination conditions, as shown above.

- when R$_1$ = EWG, the intermediate β-silyl alkoxide undergoes spontaneous fragmentation as it is formed to give the olefinic products.

Advantages over the Wittig Reaction

- The Peterson reagents are more basic and nucleophilic and less sterically hindered. As a result, they are more reactive than phosphorus ylides.

- The byproduct siloxanes tend to be easier to remove than phosphorus byproducts.

Synthesis of Peterson Reagents, Applications

• **via halogen-metal exchange**
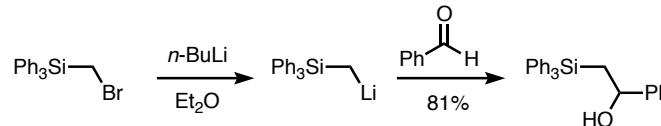
Brook, A. G.; Duff, J. M.; Anderson, D. G. *Can. J. Chem.* **1970**, *48*, 561–569.

• **via Deprotonation**

Substituted silanes can be metalated if an anion-stabilizing group is present.
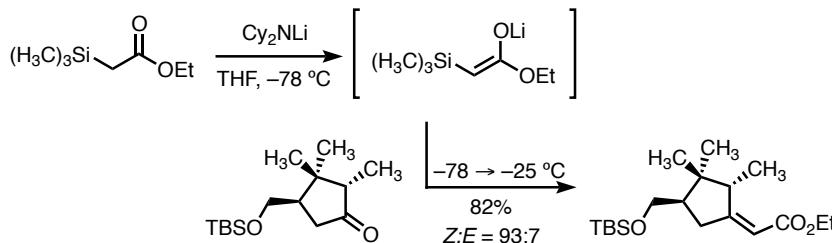
Galano, J.-M.; Audran, G.; Monti, H. *Tetrahedron Lett.* **2001**, *42*, 6125–6128.
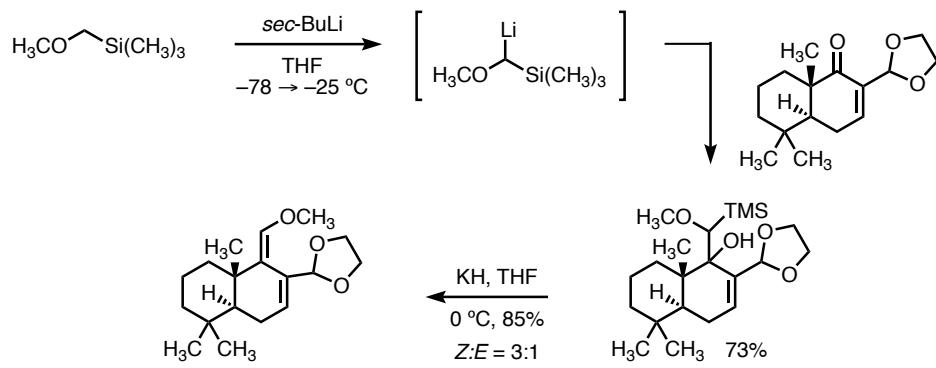
inseparable mixture of diastereomers

Analogous reactions with the corresponding phosphonium and phosphonate reagents were not as successful.

Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822–823.

Kende, A. S. Blacklock, T. J. *Tetrahedron Lett.* **1980**, *21*, 3119–3122.

Fan Liu

• **via addition of organometallics to vinylsilanes**
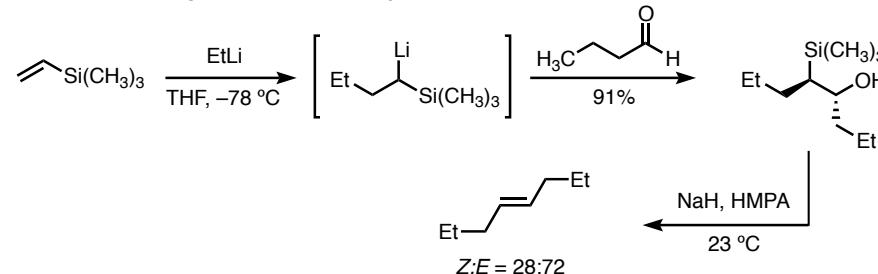
Hudrlik, P. F. Peterson, D. *Tetrahedron Lett.* **1974**, *15*, 1133–1136.

• **via reductive lithiation**

anti

syn

slow elimination
AcOH, 60 °C

fast elimination
−78 °C

68%
E:Z = 77:1
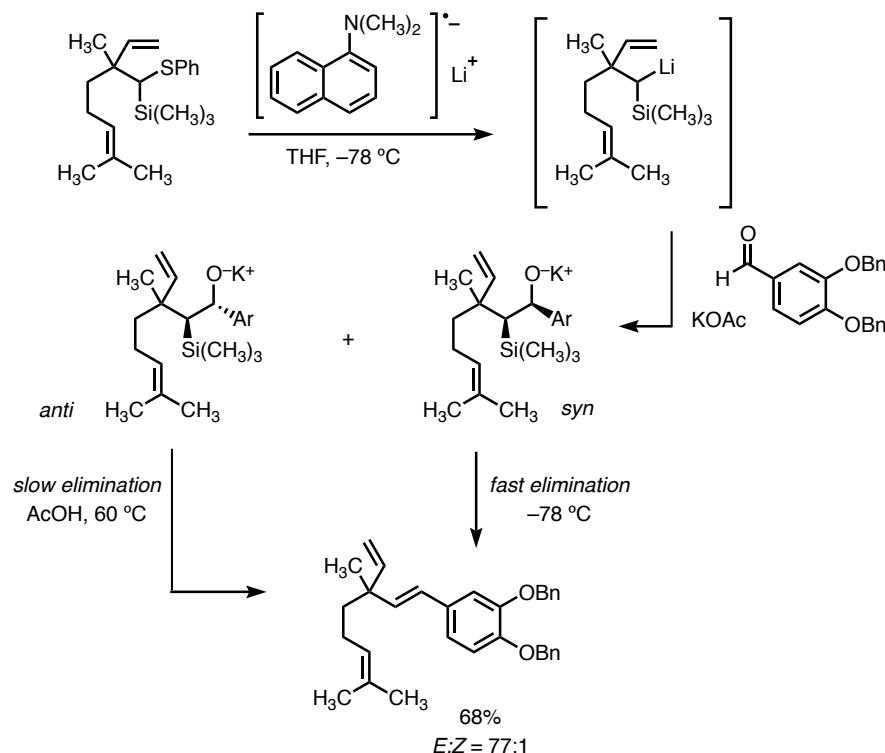
• The *syn*-hydroxysilane in the example above underwent facile (base-mediated) elimination at −78 °C while the *anti*-hydroxysilane did not react until acetic acid was added to give (after heating) the *E*-alkene.

Tamao, K.; Kawachi, A. *Organometallics* **1995**, *14*, 3108–3111.
Perales, J. B.; Makino, N. F.; Van Vranken, D. L. *J. Org. Chem.* **2002**, *67*, 6711–6717.

• **Methylenation using commercially available (trimethylsilyl)methyllithium or (trimethylsilyl)methylmagnesium chloride:**
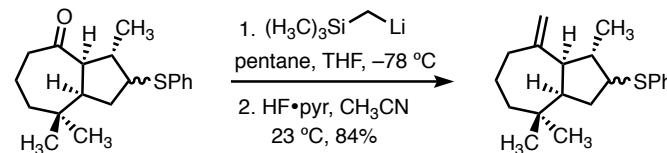
Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851–4852.
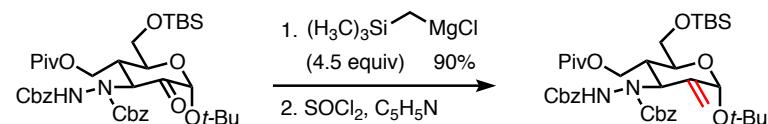
• Reaction with $Ph_3P=CH_2$ at room temperature was not successful and more forcing conditions resulted in decomposition.

Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2103–2112.

Stereoselective Synthesis of β-silylcarbinols

• Because α-silylcarbanion additions to carbonyl compounds are irreversible, the diastereomeric ratio in the addition step defines the *cis/trans*-alkene product ratio unless diastereomeric adducts can be separated and processed individually.

• Other approaches rely on the stereoselective generation of β-silylcarbinols.
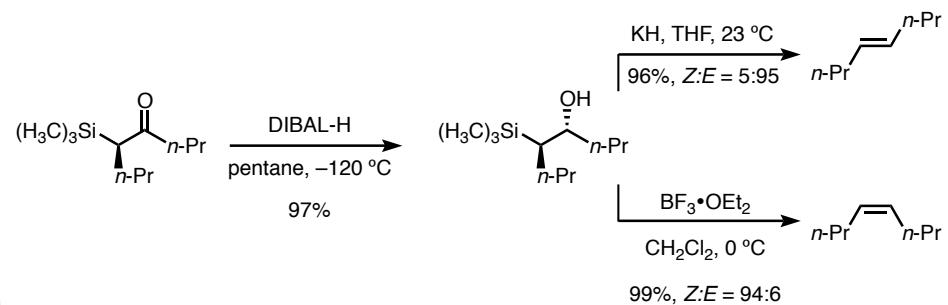
Hudrlik, P. F. Peterson, D. *Tetrahedron Lett.* **1974**, *15*, 1133–1136.
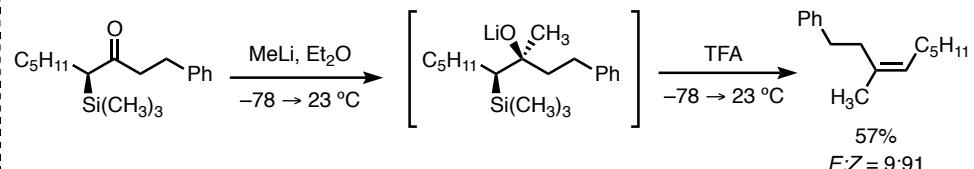
Barrett, A. G. M.; Flygare, J. A. *J. Org. Chem.* **1991**, *56*, 638–642.

Fan Liu

Reviews:

Oleg G. Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.

Petasis, N. A.;Hu, Y.-H. *Curr. Org. Chem.* **1997**, *1*, 249–286.

Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733–1744.

Generalized Reaction:

• The Tebbe and Petasis olefinations are useful methods for the methenylation of a wide variety of carbonyl compounds. The active complex is a titanocene methylidene complex, which can be generated from either the Tebbe reagent or the Petasis reagent.
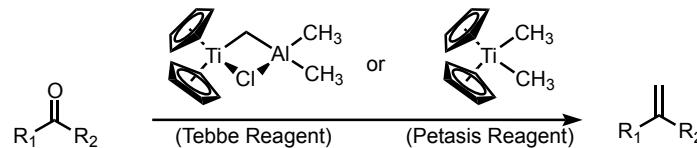
Tebbe reagent (1978):
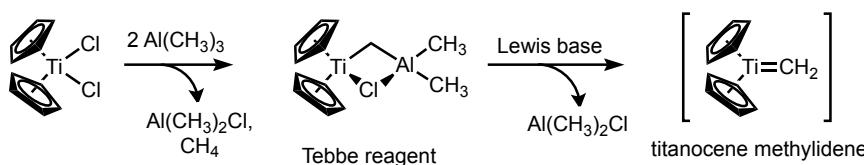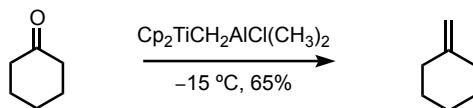
Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.

Mechanism:

• The Tebbe olefination reaction follows a mechanism similar to the Wittig olefination, but the titanocene methylidene is generally more nucleophilic and less basic than Wittig reagents.
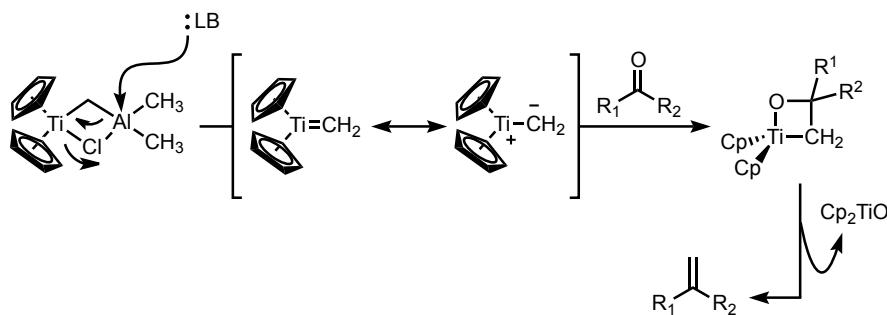
Petasis Modification (1990):
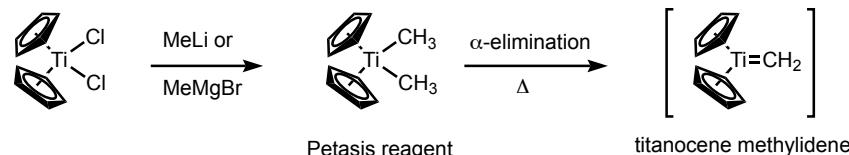
• This is a milder version of the Tebbe reagent, which avoids generation of the Lewis acidic aluminum intermediate.

• This reagent is also effective for olefination of silyl esters and acylsilanes.

Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.

Order of Reactivity:
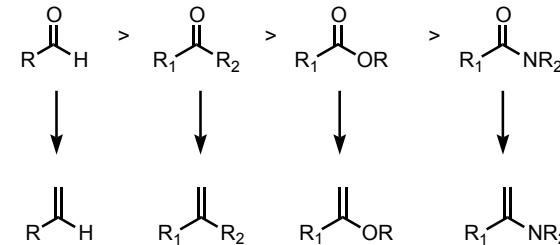
Acid halides and anhydrides:

• Acid halides provide ketones rather than olefins under Tebbe or Petasis conditions. Anhydrides give ketones under Tebbe conditions and olefins under Petasis conditions.
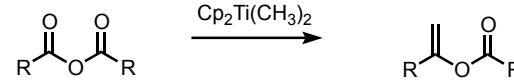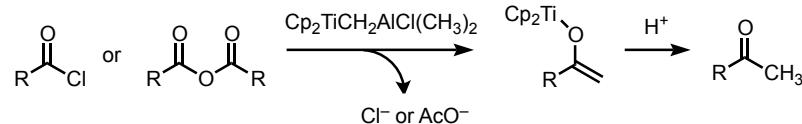
Chou, T.-S.; Huang, S.-B. *Tetrahedron Lett.* **1983**, *24*, 2169 - 2170.

Advantages:

• Reagents are relatively simple to prepare.

• Relatively bulky carbonyl groups can be olefinated.

• An alternative to the Wittig reaction, and works well on hindered carbonyls.

Disdvantages:

• A full equivalent of the reagent is required.

• Limited to methylenation: substituted olefinations are difficult.

Alpay Dermenci

| Substrate	Product	Temp. (°C)	Yield (%)
		60–65	43
		60–65	90
		60–65	60
		60–65	60
		60–65	41
		70	70
		65	67
		65	65
		70	54
		75	70

Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.
Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393 - 2396.

• Selective mono- or bis-methylenation of dicarbonyls can be achieved by varying the equivalents of reagent.

	10	:	1
1.0 equiv	10	:	1
2.0 equiv	2	:	1
4.0 equiv	0	:	1

1.5 equiv	1	:	0
4.0 equiv	1	:	20
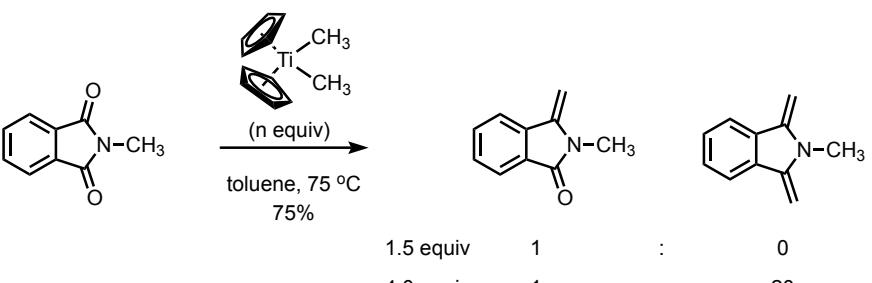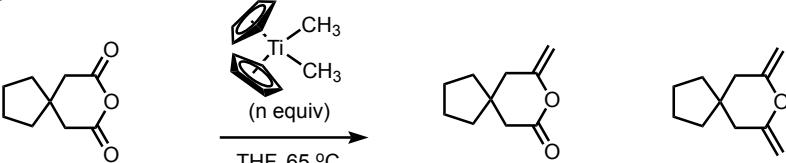
• **Hindered carbonyls:**
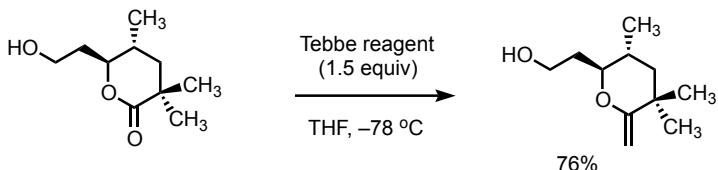
Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768 - 5779.

• **Site-Selective Olefination:**

Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918 - 5924.   Alpay Dermenci

• Acyl chlorides can be converted into the corresponding methyl ketones without epimerization.

(90.4% ee)   (1.2 equiv)   toluene, 0 °C   NH₄Cl 76%   (90.4% ee)
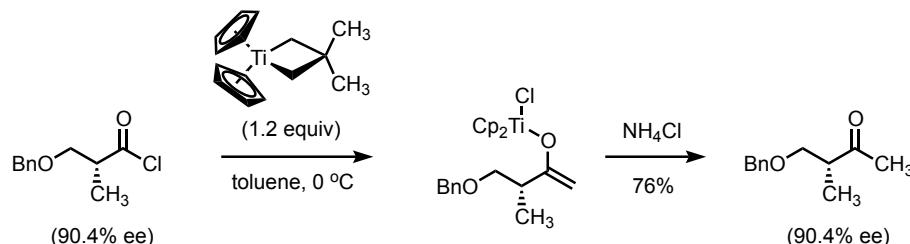
Tandem Olefination/Aldol:
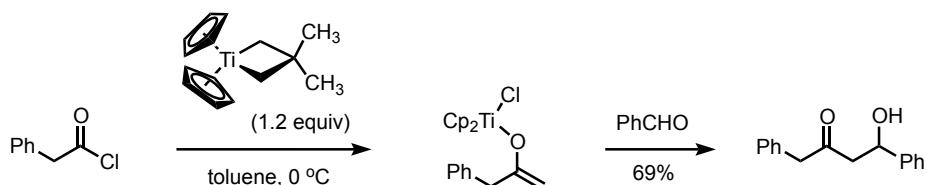
Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 1664–1665.

Tandem Olefination/Metathesis:

• Cyclic enol ethers can be prepared through an olefination, ring-closing metathesis cascade sequence:

Tebbe reagent (4 equiv)

THF, 25 °C (20 min) then reflux (5 h), 71%

65%

Tebbe reagent (1.3 equiv) THF, 20 min 25 °C

77%

Tebbe reagent (2.0 equiv) THF, 3 h, reflux
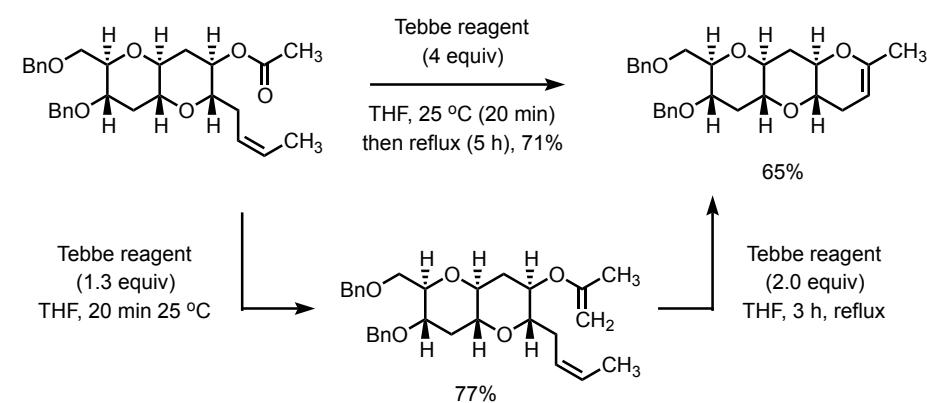
Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566.

• A strained enecarbamate was prepared using Petasis' olefination conditions:

Cp₂Ti(CH₃)₂

C₅H₅N, toluene 70 °C, 8 h, 77%

77%

14 steps

Gelsemoxonine
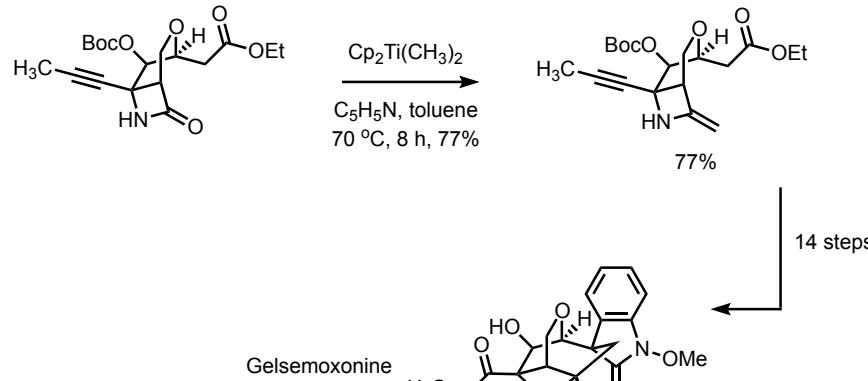
Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 8500–8503.

Industrial-Scale Petasis Reaction:

• Dimethyltitanocene was used to produce Aprepitant, a recently approved substance P antagonist used to prevent chemotherapy-induced nausea and vomiting:

(250 kg)   Cp₂Ti(CH₃)₂ (2.9 equiv) THF, 91%   (227 kg)   steps   Aprepitant (Emend®)
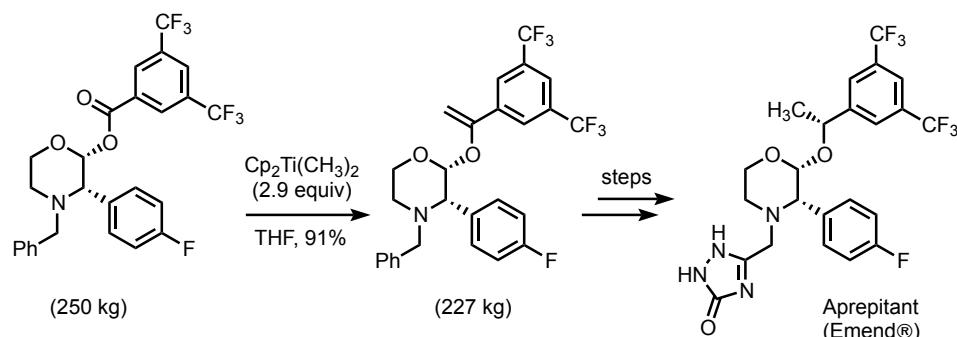
Relative reactivity:

R: alkyl, CH₂Ph
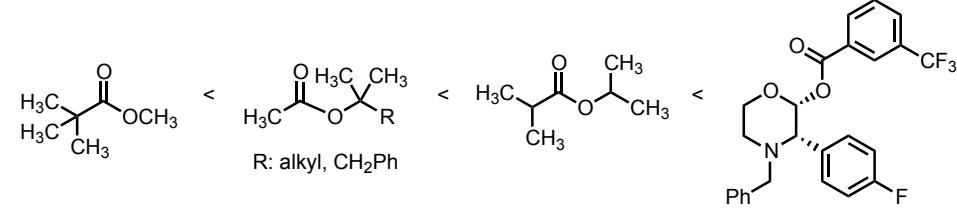
Payack, J. F.; Huffman, M. A.; Cai, D.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrell, I. F.; Tuma, L. D. *Org. Proc. Res. Dev.* **2004**, *8*, 256–259.

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Reviews:

Furstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.

Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36.

Reaction Overview:
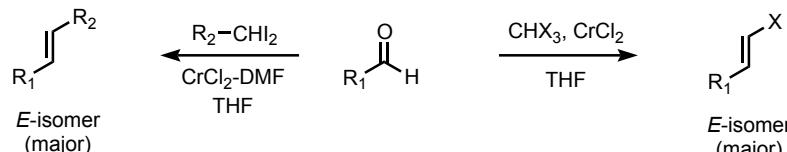
R$_2$=alkyl, aryl, B(OR)$_2$, SiR$_3$, SnR$_3$

Mechanism:
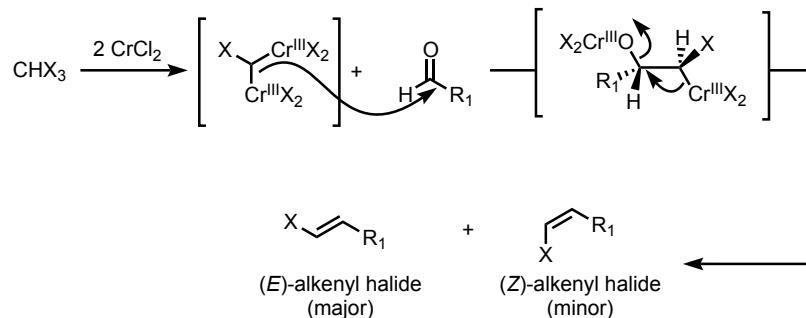
General Trends:
• Reactivity is dependent on the haloform: I > Br > Cl.
• *E/Z* ratios are greatest in the order Cl > Br > I.
• Aldehydes react faster than ketones.
• The *E*-isomer is the predominant product for both haloforms and 1,1-geminal dihalides.

Advantages
• Reagents are readily available.
• Reaction is selective for the *E*-isomer.
• High functional group tolerance.

Disadvantages
• Stoichiometric amounts of by-products are generated.
• Excess reagent is typically required.

Haloforms
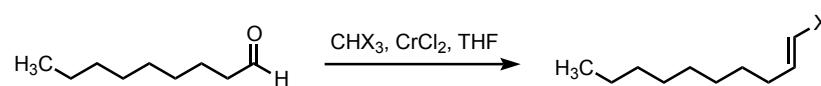
X[a]	Temp (ºC)	time (h)	yield (%)	*E/Z*
Cl	65	2	76	95/5
I	0	2	82	83/17
Br[b]	50	1	76	95/5

[a]Reaction conditions: aldehyde (1 equiv), CHX$_3$ (2 equiv), CrCl$_2$ (6 equiv), THF.
[b]CrBr$_3$ and LiAlH$_4$ (1:0.5) was employed in lieu of CrCl$_2$.

• Aldehydes are more reactive than ketones:
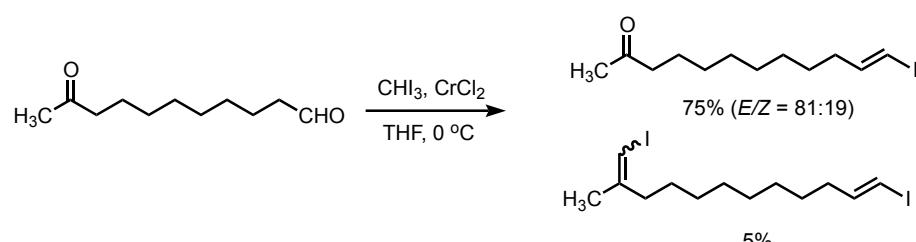
Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

1,1-Geminal Dihalides
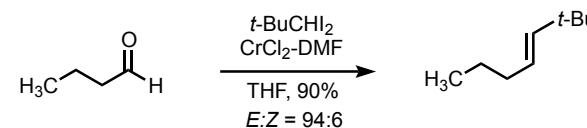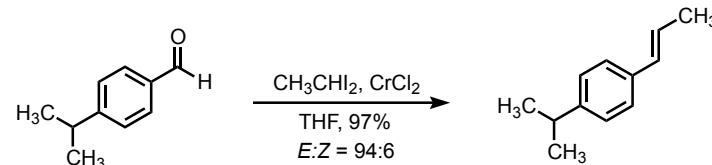
Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953.   Alpay Dermenci

• Olefination of ketones:
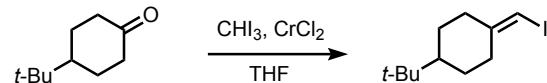
Lin, Y.-Y.; Wang, Y.-J.; Lin, C.-H.; Cheng, J.-H.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 6100–6106

**Takai Olefination in Natural Product Synthesis**

Sch-642305
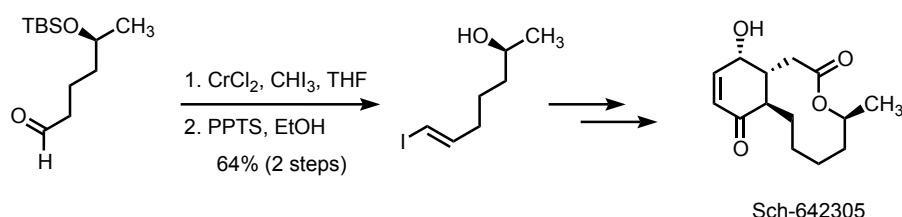
Dermenci, A; Selig, P. S.; Domaoal, R. A.; Spasov K. A.; Anderson, K. A.; Miller, S. J. *Chem. Sci.* **2011**, *2*, 1568–1572.

aplysiapyranoid C
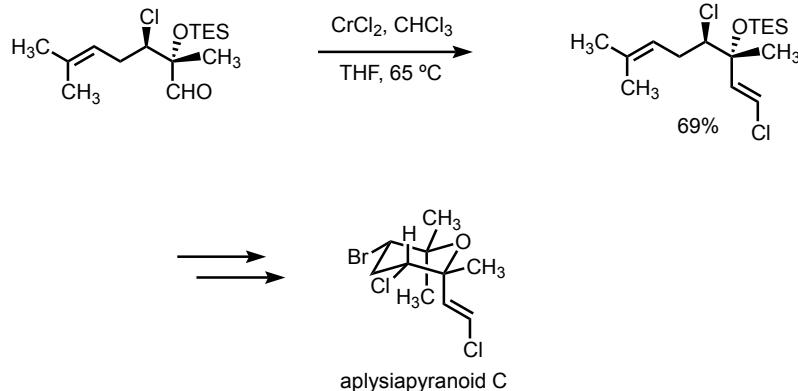
Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982–2987.

96%

Superstolide A
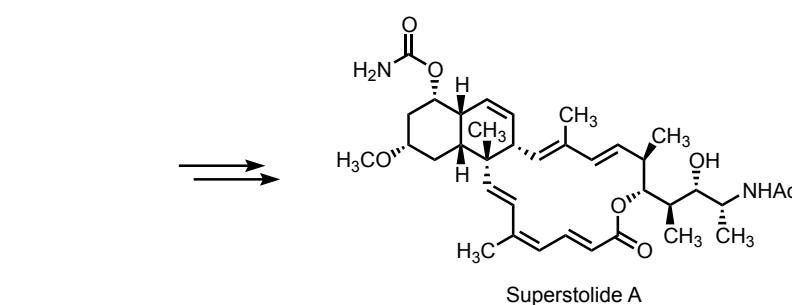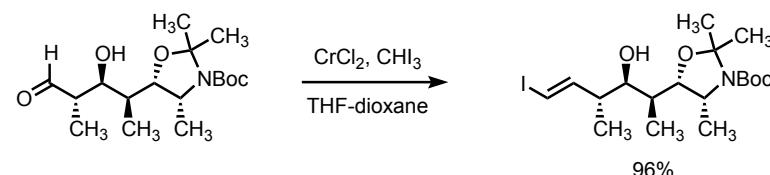
Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 9657 - 9667.

1. DMP
2. CrCl$_2$, CHI$_3$, THF
23 °C, 77%
E:Z = 19:1

Amphidinolide J
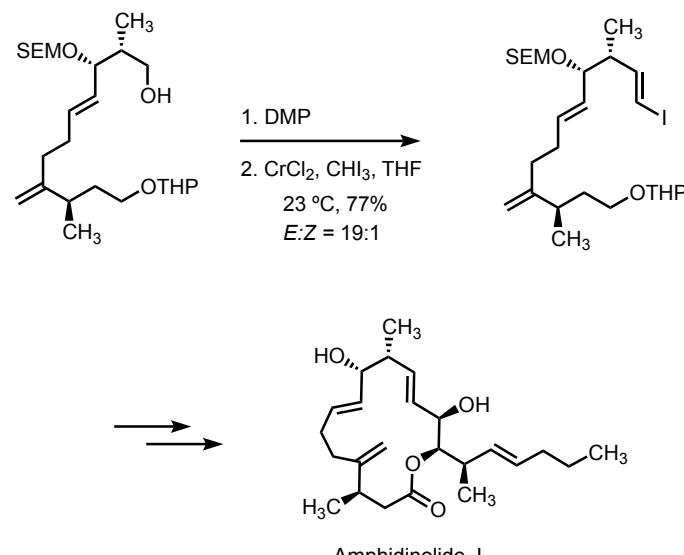
Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198–11199.

Alpay Dermenci

Reviews

Dumeunier, R.; Marko, I. E. *Modern Carbonyl Olefination* **2004**, 104–150.

Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763–768.

Reaction

- The Julia olefination and modified Julia olefination reactions involve the coupling of aryl sulfones with aldehydes or ketones to provide olefins.

- Initial Report:
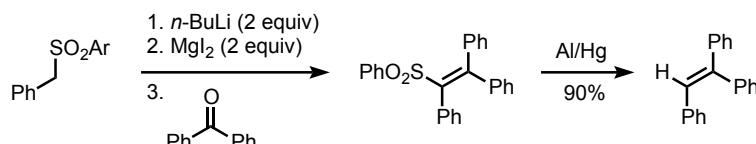
Pascali, V.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Comm.* **1973**, 351.

Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *49*, 4833–4836.

- The reaction predominantly forms *(E)*-olefins

- Typically, strong bases and stoichiometric quantities of reagents are required.

- Often Julia olefination requires trapping of the initially formed β-oxido sulfone, which is then reduced to give the *E*-alkene.
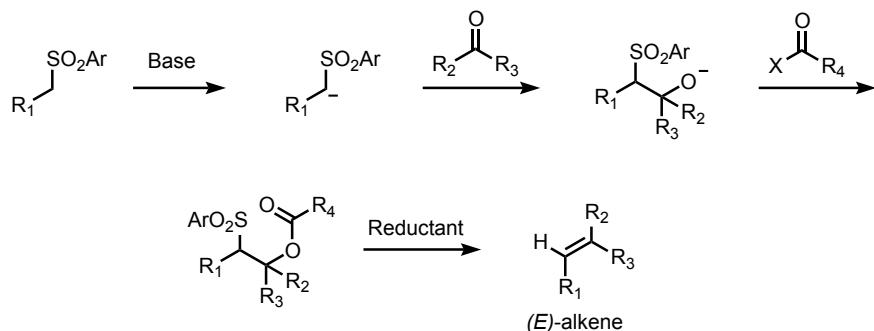

- A variety of different trapping and reducing agents can be used.

  Trapping agents: Ac_2O, BzCl, MsCl, TsCl

  Reducing agents: SmI_2 (most common), RMgX, Bu_3SnH, Li or Na in ammonia, $Na_2S_2O_4$, Raney/Ni, Al(Hg) amalgam, $LiAlH_4$, SmI_2/HMPA

- The reductive elimination step can follow two different pathways depending on the reducing agent, however each pathway shows a preference for forming the *E*-olefin isomer.

**Na(Hg)/MeOH Reduction:**
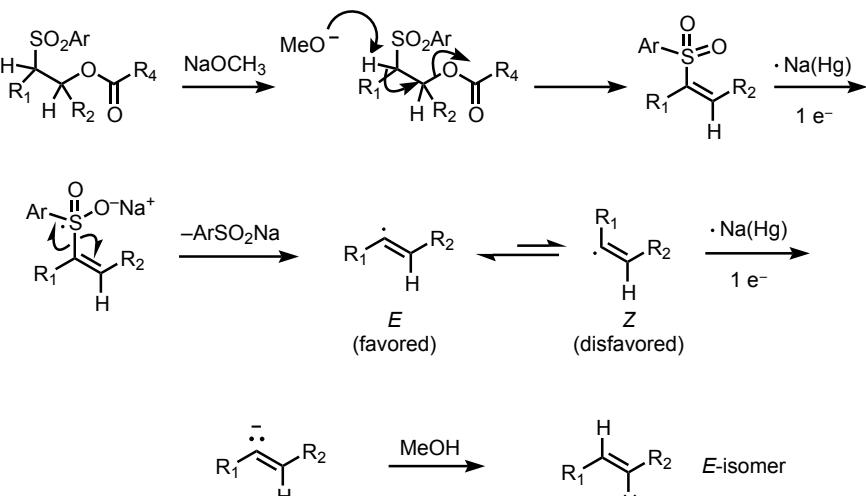
SmI_2 Reduction:
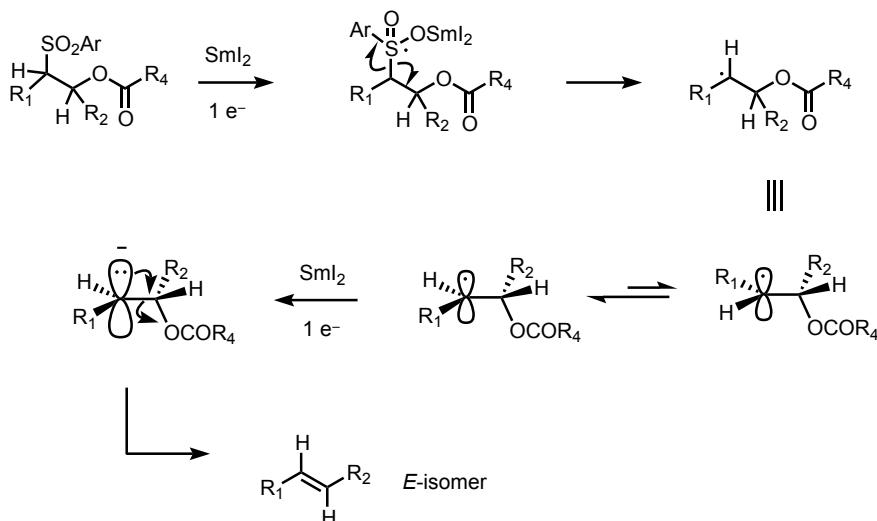
Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194–3204.

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• Second-generation Julia olefination reactions employ an one-pot procedure: use of specially designed heterocycles allows for *in situ* reductive elimination to occur, via a *Smiles rearrangement*-like mechanism.

Julia-Silvestre

Ar:
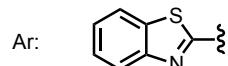
benzothiazole

"BT-sulfone"

Julia-Kocienski

Ar:

1-phenyl-1*H*-tetrazole

"PT-sulfone"

Mechanism:

Sulfone Preparation

commercially available

1. DIAD, PPh₃, THF
   0 → 23 °C, 89%

2. *m*-CPBA, NaHCO₃
   CH₂Cl₂, 23 °C, 68%
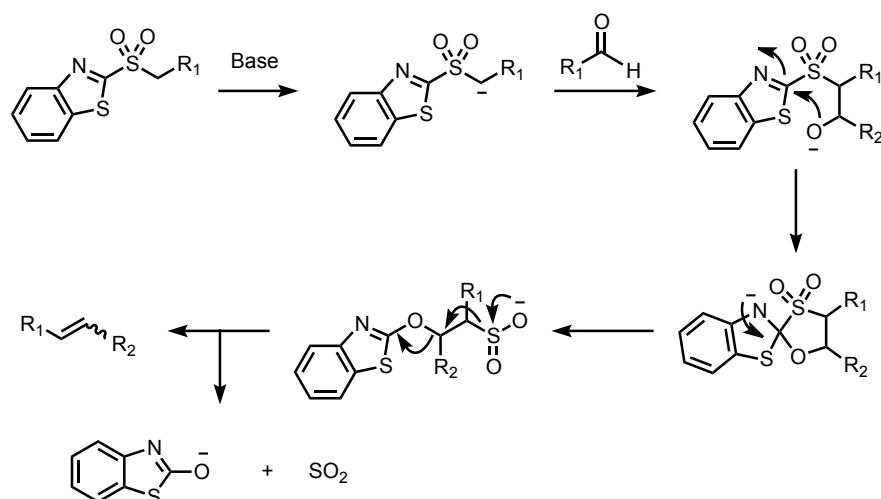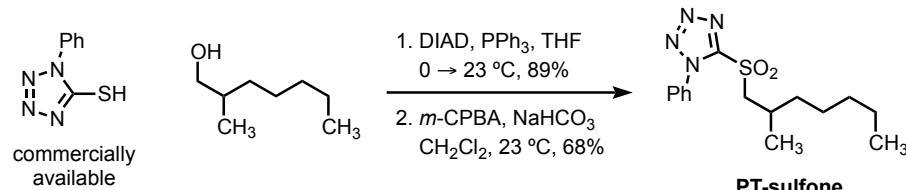
PT-sulfone

Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett.* **1998**, 26–28.

• In general, the *E/Z* ratio is dependent on reaction conditions, with PT-sulfones giving higher *E*-selectivities.
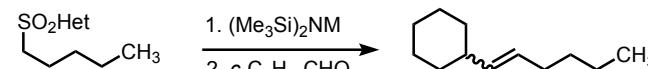

Solvent	M	BT-sulfone		PT-sulfone	
		Yield (%)	*E/Z*	Yield (%)	*E/Z*
DME	Li	2	70 : 30	94	72 : 28
	Na	32	75 : 25	95	89 : 11
	K	4	76 : 24	81	**99 : 1**

Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett.* **1998**, 26–28.

• Origin of Selectivity:

closed transition state   open transition state

Examples

| Conditions	E : Z
NaHMDS, THF, –78 ºC	1:8
LiHMDS DMF, DMPU, –35 ºC	>30:1
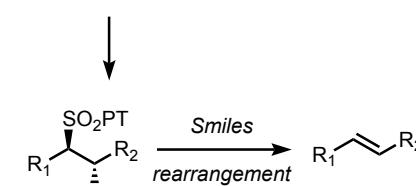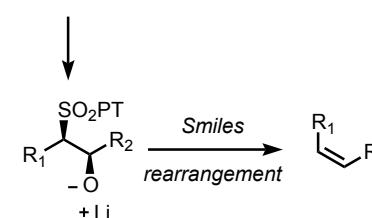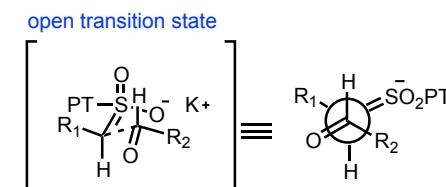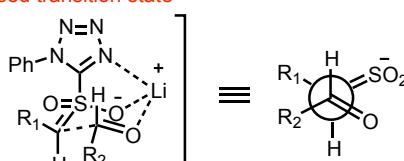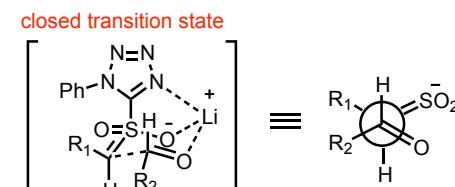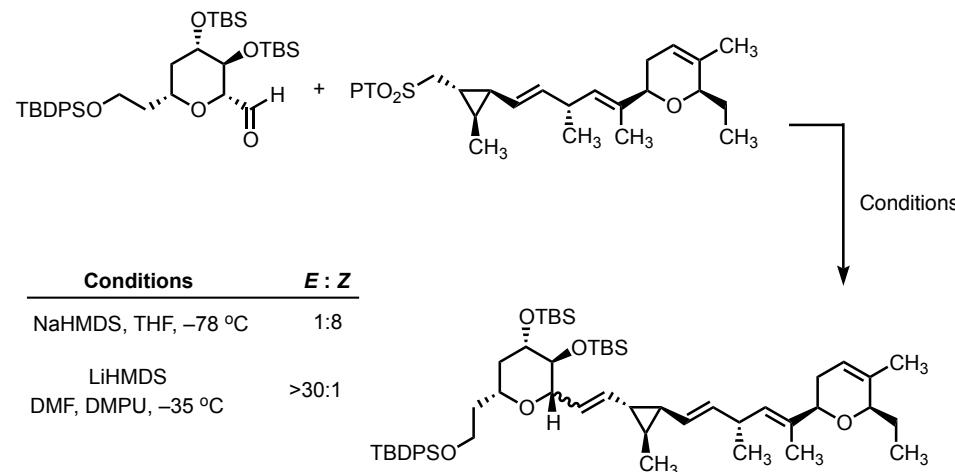
Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772 - 10773.

• The Julia olefination reaction was applied to the synthesis of LAF389, an anti-cancer agent. The addition of TMSCl was found to be crucial: the authors propose that TMSCl stabilizes the anionic intermediate and the sensitive aldehyde substrate by attenuating the basicity of the reaction.

(168.5 g)

(120.0 g)

1. *n*-BuLi, TMSCl
   THF, CH₃CN
2. MTBE
   (crystallization)

(65.9 g)

45%, single isomer
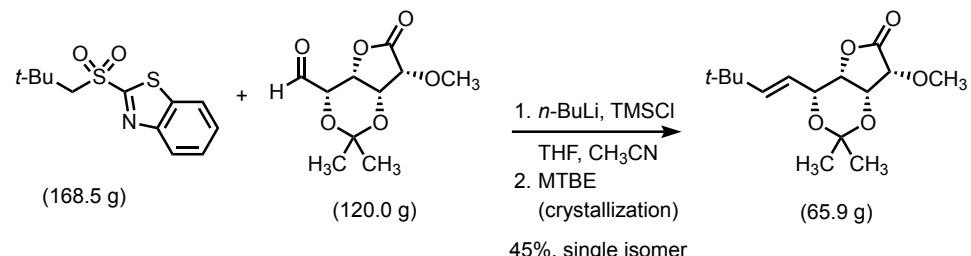
Xu, D. D.; Waykole, L.; Calienni, J. V.; Ciszewski, L.; Lee, G. T.; Liu, W.; Szewczyk, J.; Vargas, K.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 856–865.

• Application to the synthesis of BMS-644950, a next-generation statin candidate:

(27.5 kg)

(38.4 kg)

1. LHMDS, THF
2. EtOH, H₂O
   (crystallization)

(33.6 kg)

74%, *E : Z* = 91 : 1

1. HCl
2. NH₃

90%

BMS-644950

(27.6 kg)
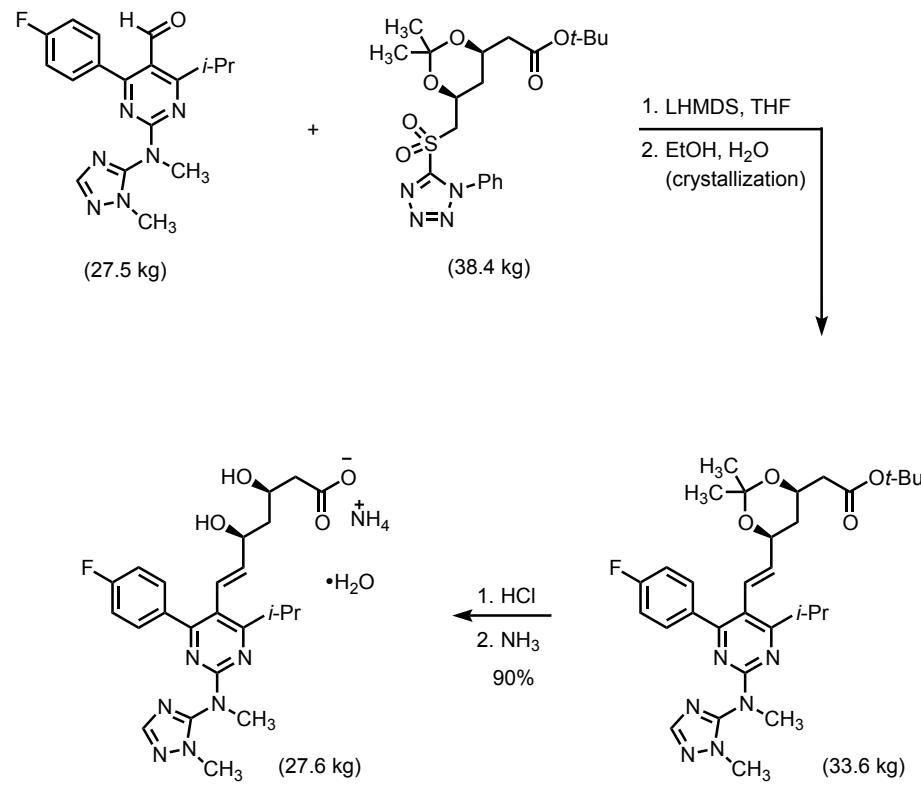
Hobson, L. A.; Akiti, O.; Deshmukh, S. S.; Harper, S.; Katipally, K.; Lai, C. J.; Livingston, R. C.; Lo, E.; Miller, M. M.; Ramakrishnan, S.; Shen, L.; Spink, J.; Tummala, S.; Wei, C.; Yamamoto, K.; Young, J.; Parsons, R. L. *Org. Process Res. Dev.* **2010**, *14*, 441–458.

Alpay Dermenci, Fan Liu