

Reviews:

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

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

Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99.

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

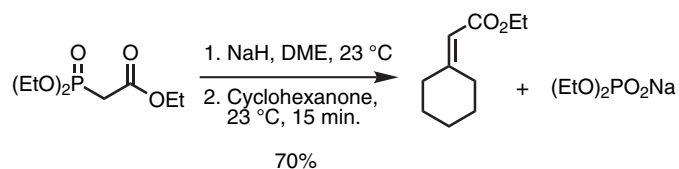
Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*, Cadogan, J. I. G., Ed.; Academic Press: New York, **1979**, pp. 155-205.

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

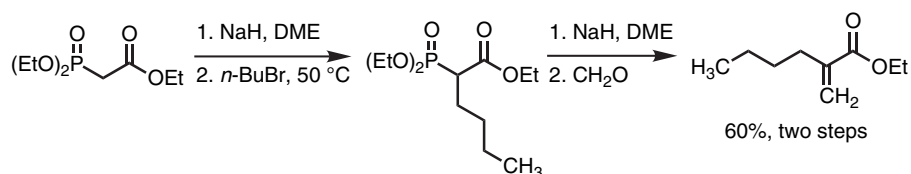
Asymmetric Wittig-Type Reactions: Rein, T.; Reiser, O. *Acta. Chem. Scand.* **1996**, *50*, 369-379.

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.



- 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:

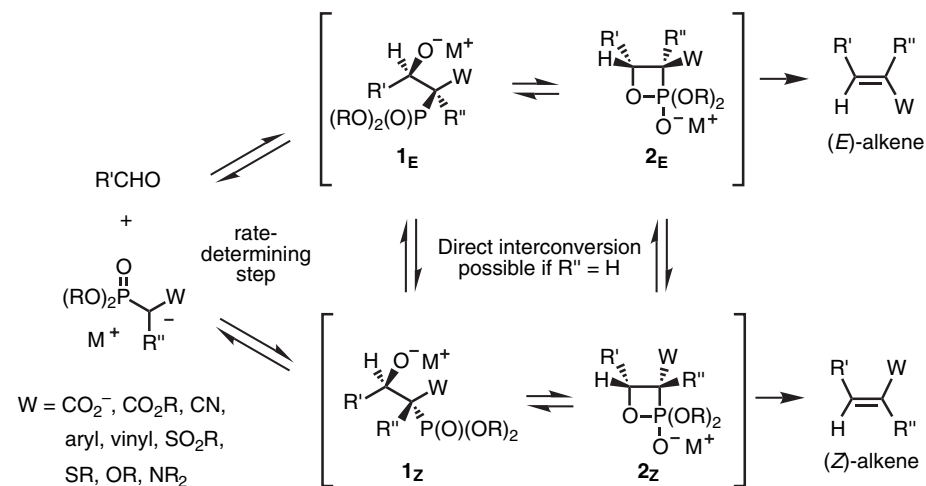


Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61-63.

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:



- Phosphonate anion addition to the carbonyl is rate determining (determined for olefination of aromatic aldehydes employing sodium ethoxide): Larsen, R. O.; Aksnes, G. *Phosphorus Sulfur* **1983**, *15*, 219-218.
- 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.
- Direct interconversion of intermediates **1_{E,Z}** or **2_{E,Z}** is possible when R'' = H: Lefèbvre, G.; Seyden-Penne, J. *J. Chem. Soc., Chem. Commun.* **1970**, 1308-1309.
- The ratio of olefin isomers is dependent upon the stereochemical outcome of the initial addition and upon the ability of the intermediates to equilibrate.

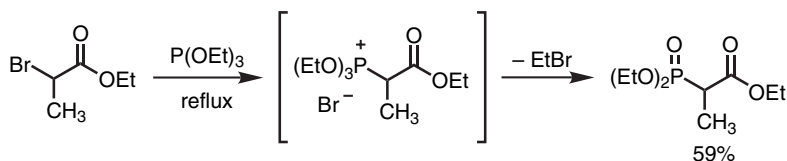
Acidity of Stabilized Phosphonates in DMSO:

$(\text{EtO})_2\text{P}(=\text{O})\text{CH}_2\text{W}$		
W	$\text{p}K_a$	
CN	16.4	• Phosphonium salts are considerably more acidic than the corresponding phosphonates: ($\text{Ph}_3\text{P}^+\text{CH}_2\text{CN}$) Cl^- : $\text{p}K_a = 6.9$
CO_2Et	18.6	
Cl	26.2	($\text{Ph}_3\text{P}^+\text{CH}_2\text{CO}_2\text{Et}$) Cl^- : $\text{p}K_a = 8.5$
Ph	27.6	
SiMe_3	28.8	Bordwell, F. G.; Zhang, X.-M. <i>J. Am. Chem. Soc.</i> 1994 , <i>116</i> , 968-972.

Preparation of phosphonates:

Michaelis-Arbusov Reaction:

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

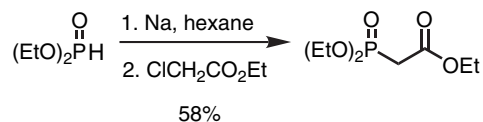


Arbusov, A. E.; Durin, A. A. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 295.

Michaelis-Becker Reaction:

Worms, K. H.; Schmidt-Dunker, M. In *Organic Phosphorus Compounds*; Kosolapoff, G. M. and Maier, L. Ed.; Wiley: New York, **1976**, Vol. 7, pp. 27-28.

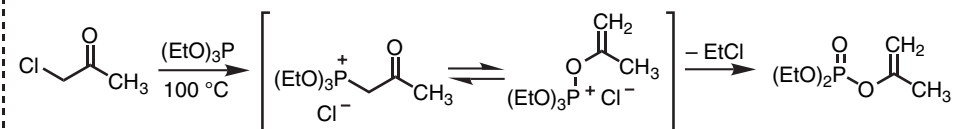
Muller, E. (ed.) *Methoden der Organischen Chemie* (Houben-Weyl); George Thieme Verlag: Stuttgart, **1964**, Vol 12/1, p. 446.



Kosolapoff, G. M. *J. Am. Chem. Soc.* **1946**, *68*, 1103-1105.

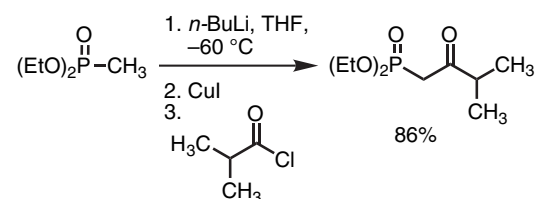
Acylation of Alkylphosphonate Anions:

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



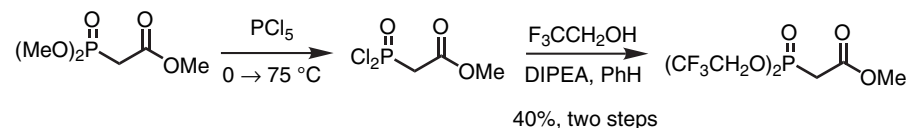
Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

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



Mathey, F.; Savignac, P. *Tetrahedron*, **1978**, *34*, 649-654.

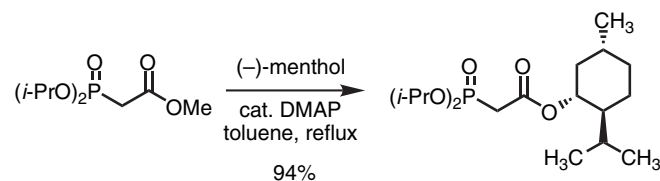
Phosphonate Ester Interchange:



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:



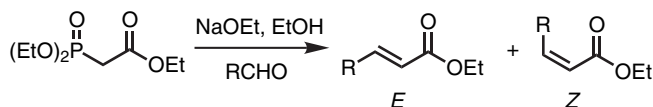
- The use of isopropyl phosphonates minimizes alkoxy exchange at phosphorus.

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

Stereoselectivity of HWE Olefination:

Disubstituted Olefins:

- Reaction of phosphonates with aldehydes favors formation of (*E*)-alkenes.



Aldehyde	Ratio of products (<i>E</i> : <i>Z</i>)
PhCHO	98 : 2
<i>n</i> -PrCHO	95 : 5
<i>i</i> -PrCHO	84 : 16

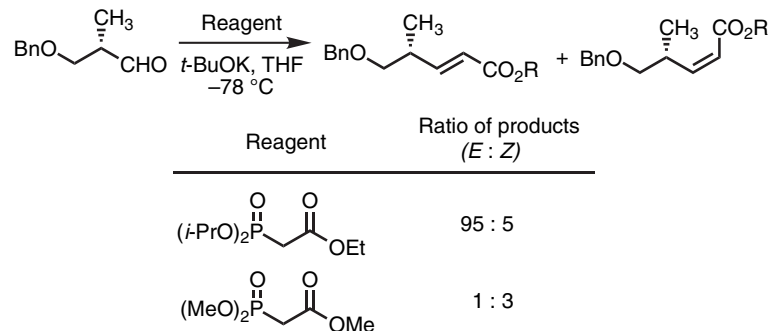
Larsen, R. O.; Aksnes, G. *Phosphorus Sulfur*, **1983**, *16*, 339-344.

- 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) $\text{M}^+ = \text{Li} > \text{Na} > \text{K}$,
 - (4) with increasing α -substitution of the aldehyde.

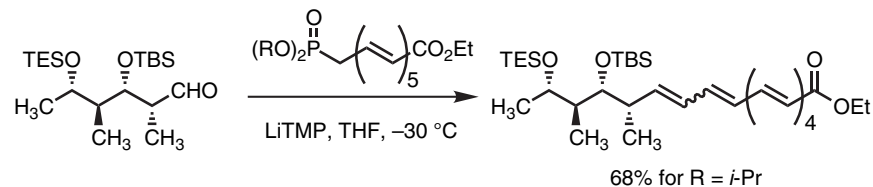
In general, conditions which increase the reversibility of the reaction (i.e., increase the rate of retroaddition relative to the rate of elimination) favor the formation of *E*-alkenes.

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:



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



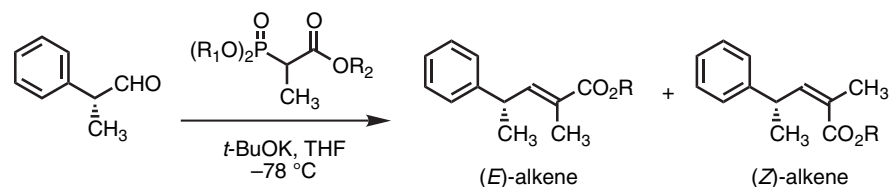
R	Ratio of products (<i>E</i> : <i>Z</i>)
Me	1 : 1.2
Et	1.75 : 1
<i>i</i> -Pr	<i>E</i> only
CH(Et) ₂	<i>E</i> only

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.



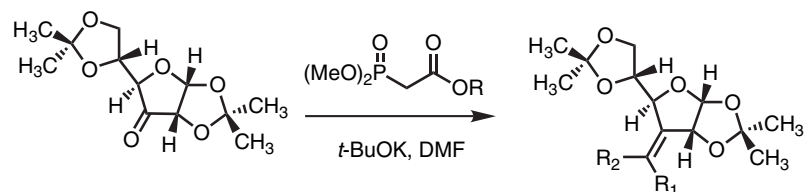
R ₁	R ₂	Ratio of products (<i>E</i> : <i>Z</i>)
Me	Me	5 : 95
Me	Et	10 : 90
Et	Et	40 : 60
<i>i</i> -Pr	Et	90 : 10
<i>i</i> -Pr	<i>i</i> -Pr	95 : 5

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

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

Olefination of Ketones:

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



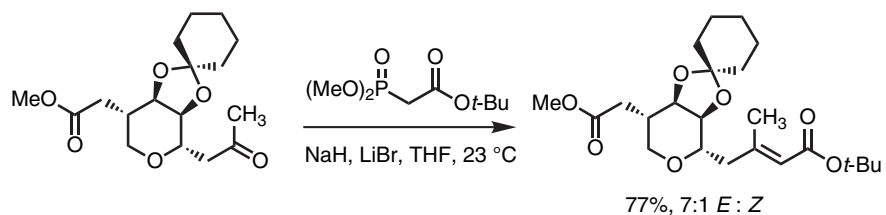
R	Ratio of products (A : B)
Me	2.7 : 1
t-Bu	9 : 1

A: R₁ = CO₂R, R₂ = H
 B: R₁ = H, R₂ = CO₂R

- The failure of this hindered ketone to react with Ph₃P=CHCO₂Et (benzene, reflux) provides an example of the increased reactivity of phosphonates in comparison to phosphonium ylides.

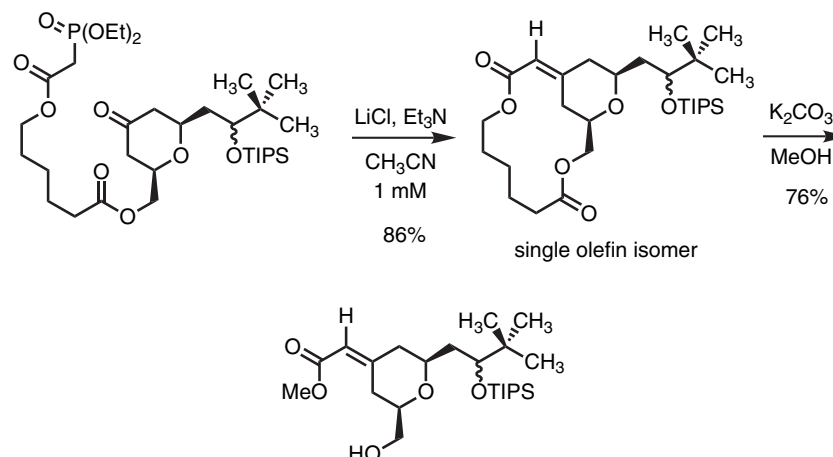
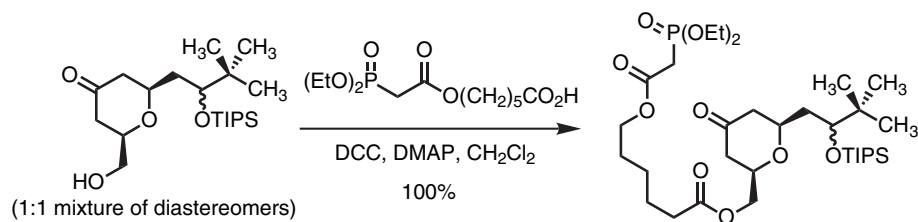
Mulzer, J.; Steffin, U.; Zorn, L.; Schneider, C.; Weinhold, E.; Münch, W.; Rudert, R.; Luger, P.; Hartl, H. *J. Am. Chem. Soc.* **1988**, *110*, 4640-4646.

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



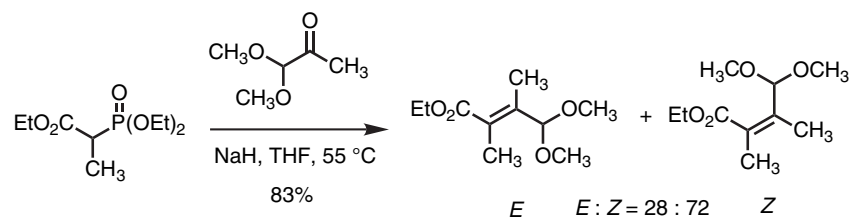
White, J. D.; Theramongkol, P.; Kuroda, C.; Engelbrecht, J. R. *J. Org. Chem.* **1988**, *53*, 5909-5921.

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



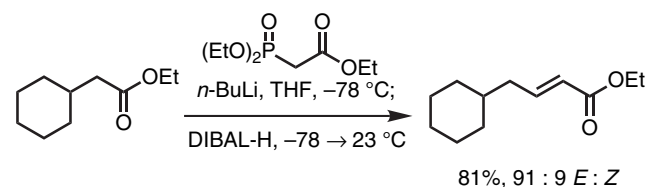
Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703-4706.

- Tetrasubstituted olefins can be prepared in some cases, but isomeric mixtures are obtained:



Bestmann, H. J.; Ermann, P.; Ruppel, H.; Sperling, W. *Liebigs. Ann. Chem.* **1986**, 479-498.

Single-step two-carbon homologation of esters:

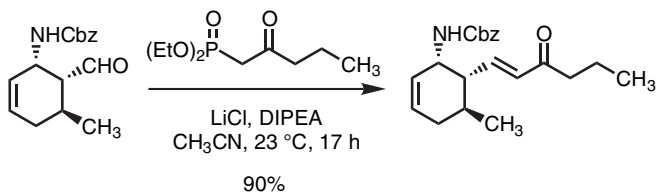


- Ester reduction in the presence of the phosphonate minimizes overreduction of the intermediate aldehyde.

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

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:



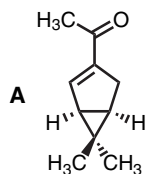
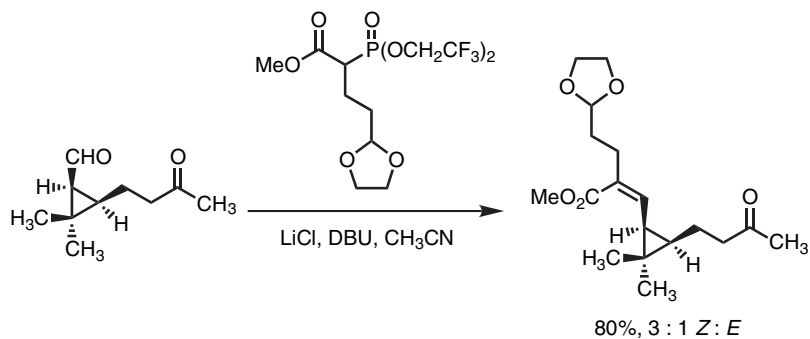
- This aldehyde substrate epimerizes under standard HWE conditions (NaH as base).
- Addition of LiCl enhances acidity of phosphonate, allows use of weak bases (DBU, *i*-Pr₂NEt) and ambient temperature.

	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.; Essensfeld, 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):

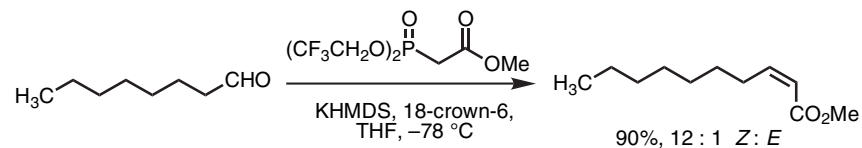


- Application of the normal conditions for (*Z*)-selective HWE (KHMDS, 18-crown-6) yielded only the internal aldol product **A**.

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

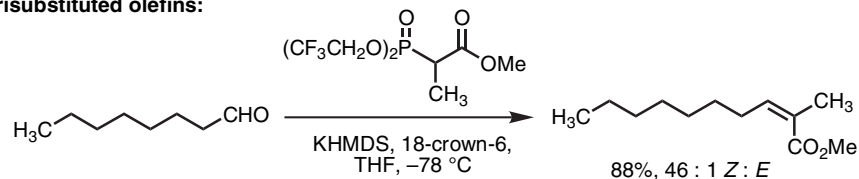
(*Z*)-Selective Olefination – Still Modification of HWE Olefination:

Disubstituted olefins:



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

Trisubstituted olefins:



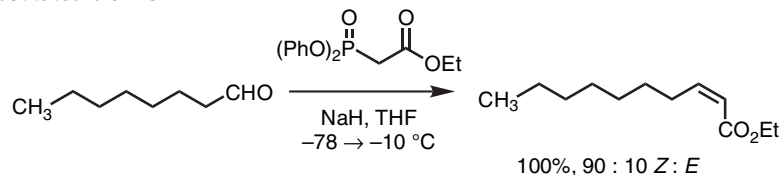
aldehyde	product	Z : E	yield, %
		>50 : 1	79
		>50 : 1	80
		30 : 1	>95

From: Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

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

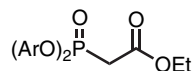
(Z)-Selective Olefination – (Diarylphosphono)acetates:

Disubstituted olefins:



aldehyde	product	base	Z : E	yield, %
		Me ₃ NBuOH	89 : 11	97
		NaH	91 : 9	98
		Me ₃ NBuOH	93 : 7	98
		NaH	94 : 6	100
		NaH	97 : 3	78

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



- 93 : 7 – 99 : 1 (Z)-selectivity, 92–100% yield.
- Aryl, α,β -unsaturated, alkyl, branched alkyl, and α -oxygenated aldehydes are suitable substrates.

Ar = *o*-MePh, *o*-EtPh, *o*-*i*-PrPh

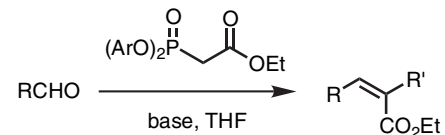
- In analogy to Still's (Z)-selective HWE reaction employing [bis(trifluoroethyl)phosphono]acetates, (Z)-selectivity is attributed to the electron-withdrawing nature of the aryloxy substituent, which accelerates elimination relative to equilibration of oxaphosphatane intermediates.

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.

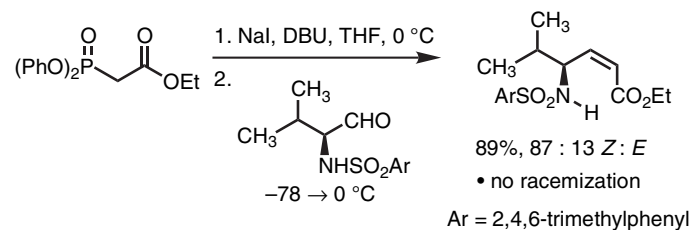
Trisubstituted olefins:



aldehyde	Ar	R'	product	base	Z : E	yield, %
	<i>o</i> -MePh	Me		Me ₃ NBuOH	89 : 11	97
	<i>o</i> - <i>i</i> -PrPh	Me		<i>t</i> -BuOK	97 : 3	100
	Ph	<i>n</i> -Bu		NaH	96 : 4	91
	Ph	<i>n</i> -Bu		NaH	95 : 5	85
	Ph	<i>i</i> -Pr		NaH–LiBr	91 : 9	75
	Ph	<i>i</i> -Pr		NaH	98 : 2	65

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

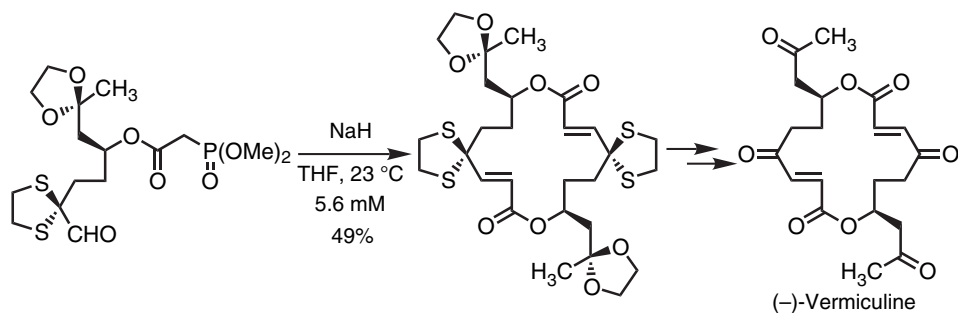
- Masamune and Roush's mild conditions have been adapted for (Z)-selective olefin synthesis using (diarylphosphono)acetates:



Ando, K.; Oishi, T.; Hiram, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

HWE Reaction in Macrolide Synthesis:

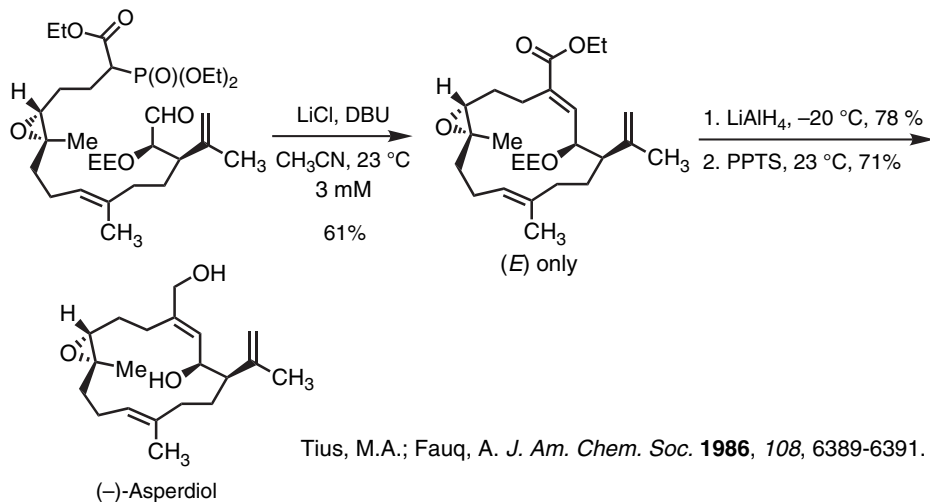
(-)-Vermiculine:



- High-dilution or syringe-pump additions are frequently required to achieve high-yielding macrocyclizations.

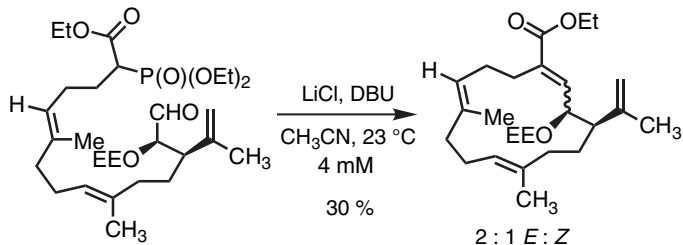
Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. J. *Am. Chem. Soc.* **1978**, *100*, 7069-7071.

(-)-Asperdiol:



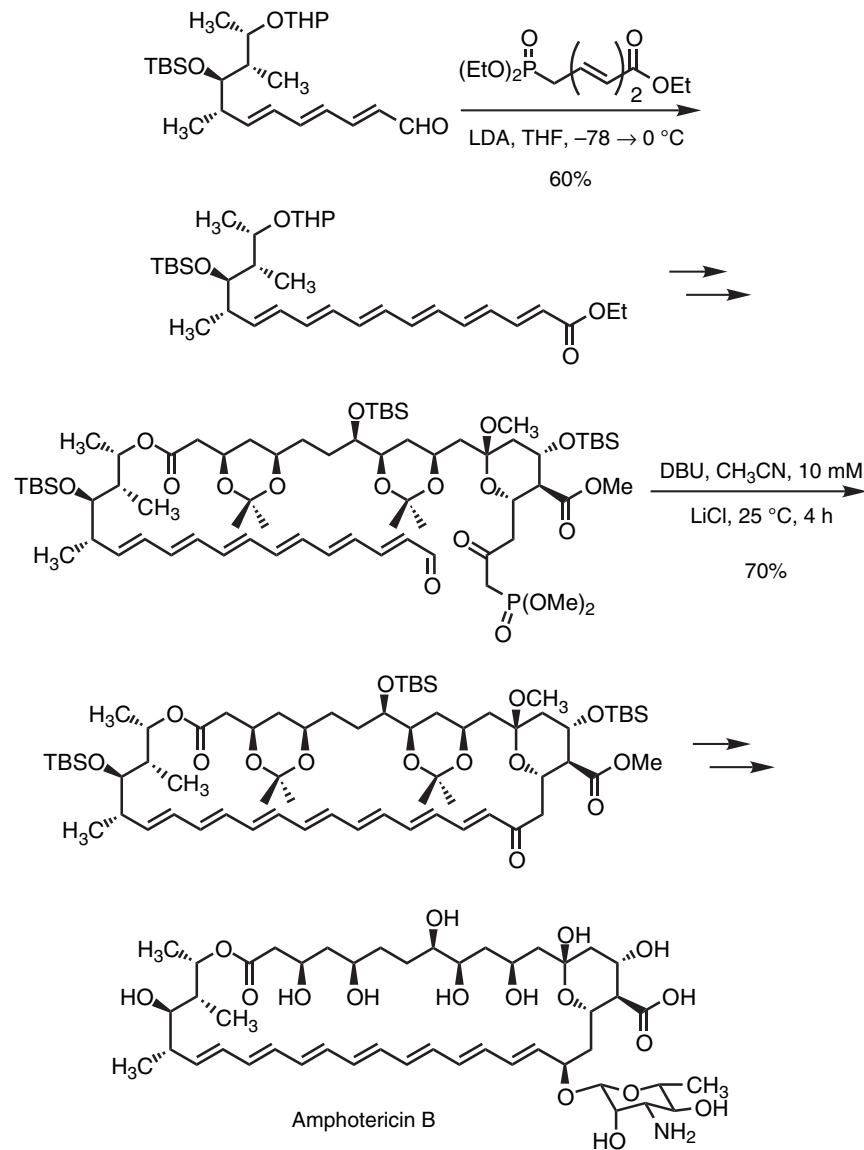
Tius, M.A.; Fauq, A. *J. Am. Chem. Soc.* **1986**, *108*, 6389-6391.

- 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:



Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035-1039.

Amphotericin B:

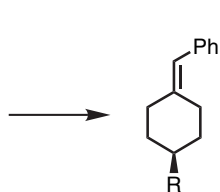
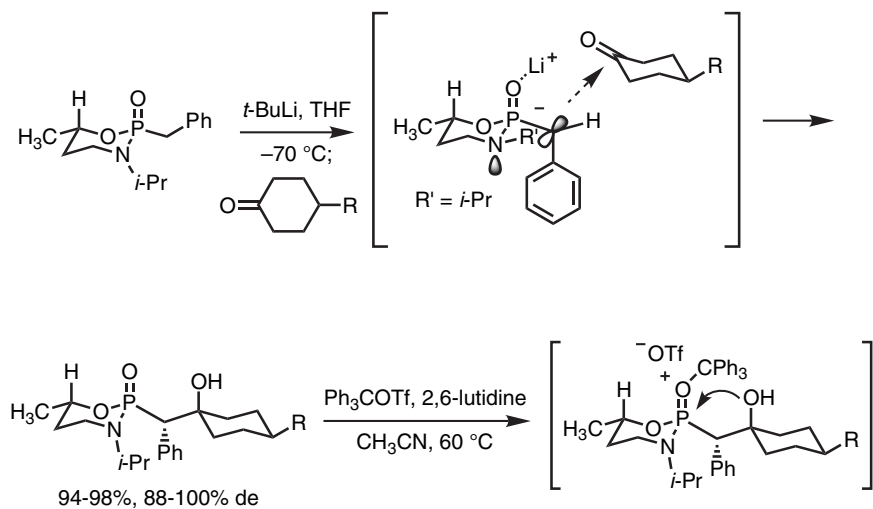


Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685-4696.

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

Asymmetric HWE:

Chiral Phosphonamidates:



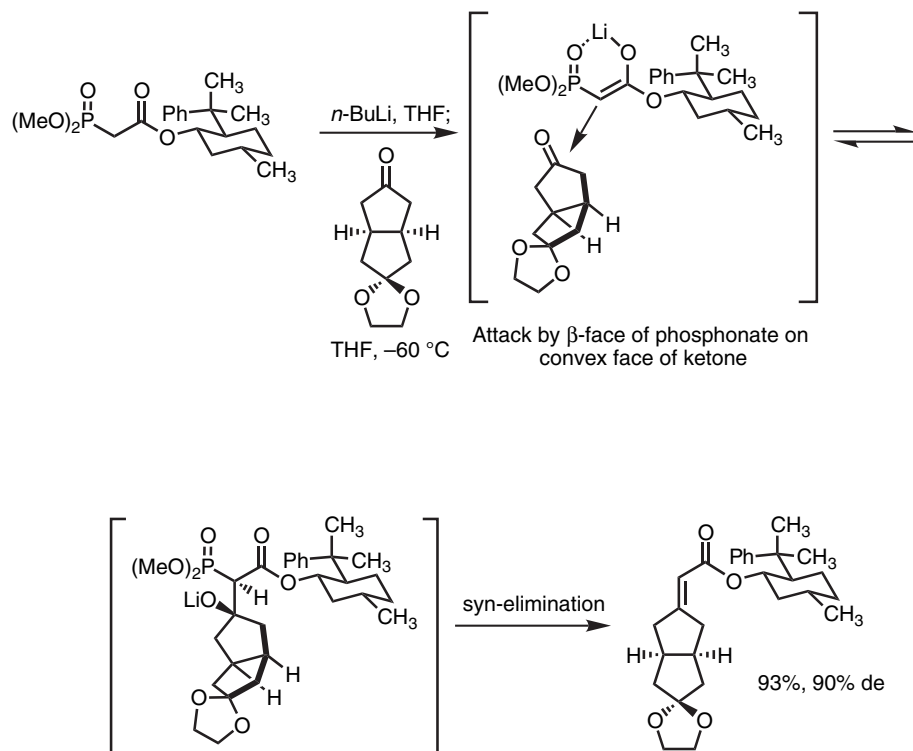
R	yield, %	ee, %
<i>t</i> -Bu	65	>99
Me	72	86
Ph	71	>99
$\text{CO}_2t\text{-Bu}$	75	95

- 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.

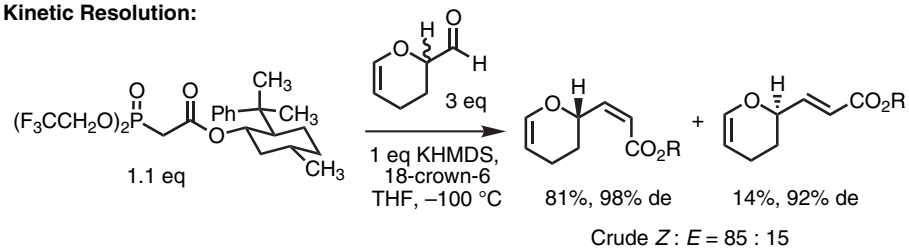
Asymmetric Olefin Synthesis – Chiral Ester:



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

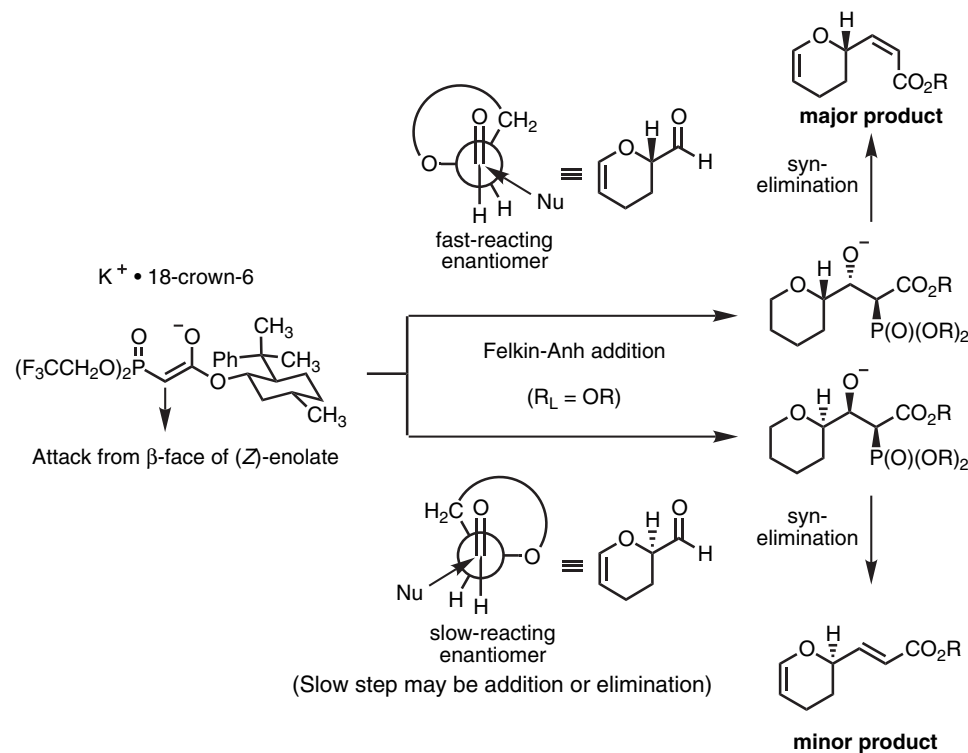
8-phenylmenthol: Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.

Kinetic Resolution:



• E and Z products are formed from different enantiomers of the starting aldehyde.

• Mechanistic hypothesis:

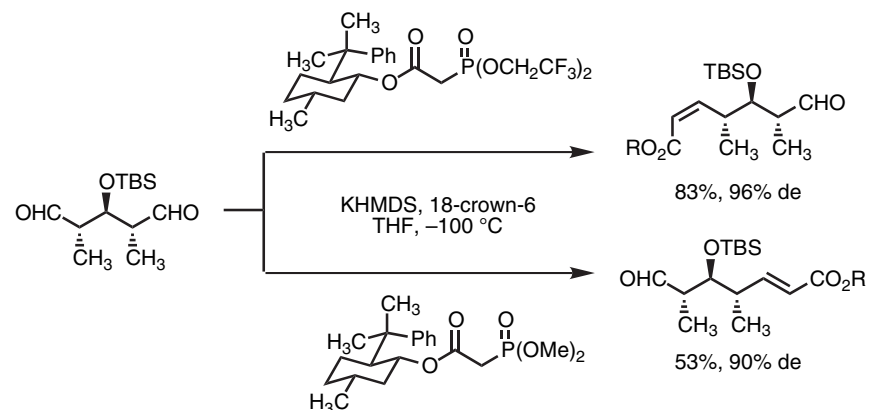


• For consideration of the stereochemical outcome of addition to α -alkoxy aldehydes, see: Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353-3361.

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:

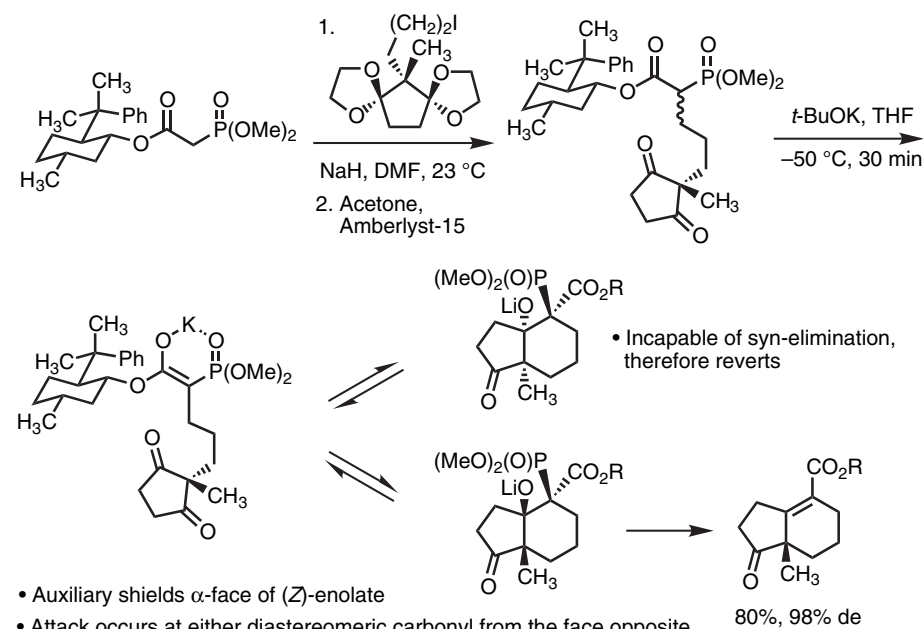


• Diastereoselectivity is dependent on conversion, because the minor diastereomeric products are preferentially bis-olefinated.

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.



• 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.