Highly (*E*)-Selective Wadsworth−Emmons Reactions Promoted by Methylmagnesium Bromide
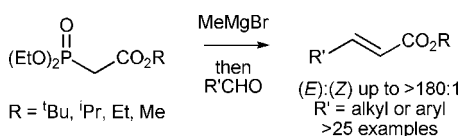
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ABSTRACT

An experimentally simple protocol for the very highly (*E*)-selective Wadsworth−Emmons reaction [(*E*):(*Z*) selectivities in excess of 180:1 in some cases] of a range of straight-chain and branched aliphatic, substituted aromatic, and base-sensitive aldehydes via reaction with an alkyl diethylphosphonoacetate and MeMgBr is reported.

(*E*)-α,β-Unsaturated esters are versatile intermediates in organic synthesis.[1] As part of our ongoing investigations concerned with the synthesis of libraries of β-amino acids utilizing the conjugate addition of homochiral lithium amides,[2] we required a simple and reliable protocol for the preparation of a structurally diverse range of (*E*)-α,β-unsaturated esters. A range of methodologies to facilitate this objective have been reported, including the Wittig,[3,4] Julia,[5] and Peterson[6] olefinations. A useful variant of the Wittig protocol is the Wadsworth−Emmons reaction.[7,8] In this reaction, alkali metal bases such as BuLi and NaH are commonly used to generate the reactive metalated phosphonate intermediate; however, the stereoselectivity can be heavily influenced by the nature of the metal counterion.[9] Within this arena, Masamune et al.[10] and Rathke et al.[11] have shown that either lithium or magnesium halides and a tertiary

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(4) For a review of the Wittig reaction and its variants, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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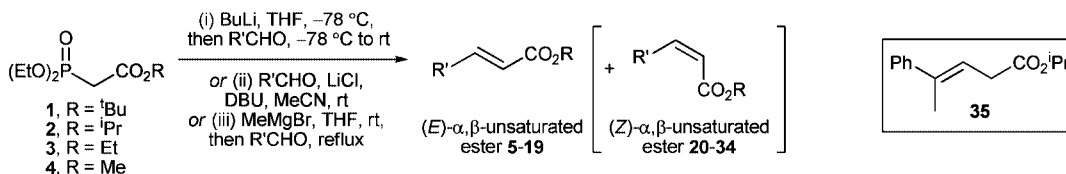
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(10) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

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(12) A related protocol to facilitate the preparation of α-fluoro-α,β-unsaturated esters from α-fluorophosphonate esters has been reported by Nagao et al., employing Sn(OSO$_2$CF$_3$)$_2$ and *N*-ethylpiperidine to achieve high levels of (*E*)-selectivity. Using MgBr$_2$/Et$_3$N or ^{i}PrMgBr to promote the reaction gave only modest levels of diastereoselectivity under a variety of conditions, although in an isolated case the stereoselective formation of the corresponding (*Z*)-olefin isomer [(*E*):(*Z*) ratio 5:95] was noted; see: Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777.

Scheme 1.

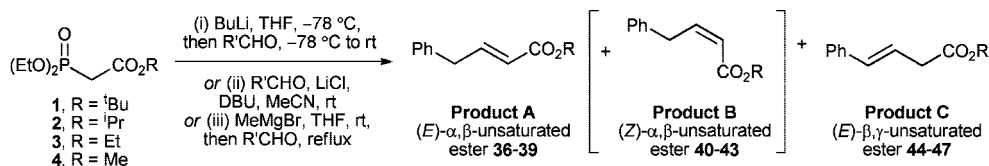|		products	(i) BuLi			(ii) LiCl/DBU			(iii) MeMgBr		
R	R'	(E):(Z)	conversion %[a]	(E):(Z) ratio[a]	yield %[b]	conversion %[a]	(E):(Z) ratio[a]	yield %[b]	conversion %[a]	(E):(Z) ratio[a]	yield %[b]
tBu	Cy	(E)-5:(Z)-20	100	43:57	(70)	96	99:1	79	100	>180:1	98
tBu	PhCH(Me)	(E)-6:(Z)-21	100	44:56	(99)	84	96:4	63	100	>180:1	quant
tBu	PhCH2CH2	(E)-7:(Z)-22	100	84:16	58	93	97:3	57	100	99:1	91
tBu	Pr	(E)-8:(Z)-23	100	73:27	24	85	98:2	16	100	98:2	88
tBu	iPr	(E)-9:(Z)-24	100	52:48	(28)	76	98:2	13	100	>150:1	89
tBu	iBu	(E)-10:(Z)-25	100	81:19	(56)	79	98:2	49	100	99:1	96
iPr	Cy	(E)-11:(Z)-26	100	64:36	(62)	100	99:1	72	100	99:1	64
iPr	PhCH(Me)	(E)-12:(Z)-27	100	68:32	(78)	100	--[c]	(60)[d]	100	98:2	61
iPr	PhCH2CH2	(E)-13:(Z)-28	100	84:16	46	100	99:1	49	100	99:1	46
Et	Cy	(E)-14:(Z)-29	88	64:36	29	88	99:1	65	100	99:1	84
Et	PhCH(Me)	(E)-15:(Z)-30	100	66:34	54	100	98:2	56	100	98:2	77
Et	PhCH2CH2	(E)-16:(Z)-31	100	82:18	(44)	84	99:1	49	100	99:1	44
Me	Cy	(E)-17:(Z)-32	91	69:31	30	83	99:1	48	100	99:1	62
Me	PhCH(Me)	(E)-18:(Z)-33	100	63:37	53	100	98:2	74	100	98:2	45
Me	PhCH2CH2	(E)-19:(Z)-34	100	87:13	31	100	98:2	49	100	98:2	36

[a] Determined by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yield of pure (E)-olefin (≥98:2 dr); yields in parentheses refer to the combined yield of both olefin diastereoisomers. [c] Reaction gave a 41:3:56 mixture of (E)- and (Z)-α,β-unsaturated esters 12 and 27, and the isomerized (E)-β,γ-unsaturated ester 35. [d] Isolated yield of a 43:57 mixture of 12:35.

amine base can be used to afford α,β-unsaturated esters with improved and generally high levels of (E)-selectivity.[12,13] Although these protocols are often effective for olefinations of base-sensitive aldehydes, they typically require rigorous application of anhydrous conditions and long reaction times (≥24 h), limiting the utility of this methodology. In this paper, we report an experimentally simple and general protocol for highly (E)-selective Wadsworth−Emmons reactions using MeMgBr as a base.

Under optimized conditions,[14] deprotonation of *tert*-butyl diethylphosphonoacetate 1 with MeMgBr at rt followed by addition of a range of straight-chain and branched aliphatic aldehydes and heating at reflux for 2.5 h gave complete conversion to the corresponding (E)-α,β-unsaturated ester in each case, with (E):(Z) selectivities in excess of 180:1 in some cases, and in high isolated yields (≥88%).[15] The

extremely high levels of diastereoselectivity were readily quantified using the protocol involving integration of the [13]C−[1]H satellite peaks, introduced in the preceding manuscript.[16] For example, in the reaction with iPrCHO, integration of the [12]C−[1]H peaks due to C(3)H for (Z)-24 and the corresponding [13]C−[1]H satellite peaks of (E)-9 gave a ratio of 54:46, hence the ratio of [12]C−[1]H of (Z)-24 to [13]C−[1]H satellite of (E)-9 to [12]C−[1]H of (E)-9 is 54:46:8211, and the (E):(Z) ratio is 152:1, or >150:1. Using BuLi as the base in these reactions gave mixtures of the corresponding (E)- and (Z)-α,β-unsaturated esters. Under Masamune−Roush conditions (LiCl/DBU),[10] high levels of selectivity were noted although at the expense of reaction conversion. In each case examined, the diastereoselectivity and yield obtained from the MeMgBr promoted reaction was equal or superior to that

Scheme 2.

	products	(i) BuLi			(ii) LiCl/DBU			(iii) MeMgBr		
R	A:B:C	conversion %[a]	ratio A:B:C[a]	yield %[b]	conversion %[a]	ratio A:B:C[a]	yield %[b]	conversion %[a]	ratio A:B:C[a]	yield %[b]
tBu	36:40:44	100	53:0:47		96	61:0:39	(63)	100	99:1:0	60
iPr	37:41:45	100	75:0:25	(45)	79	19:0:81	(26)	100	86:0:14	39
Et	38:42:46	100	62:0:38	(55)	97	57:0:43	(33)	100	84:0:16	39
Me	39:43:47	100	85:0:15	(70)	100	28:0:72	(33)	100	74:0:26	23

[a] Determined by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yield of product A, i.e. pure (E)-olefin (>99:1 dr); yields in parentheses refer to the combined yield of products A and C.
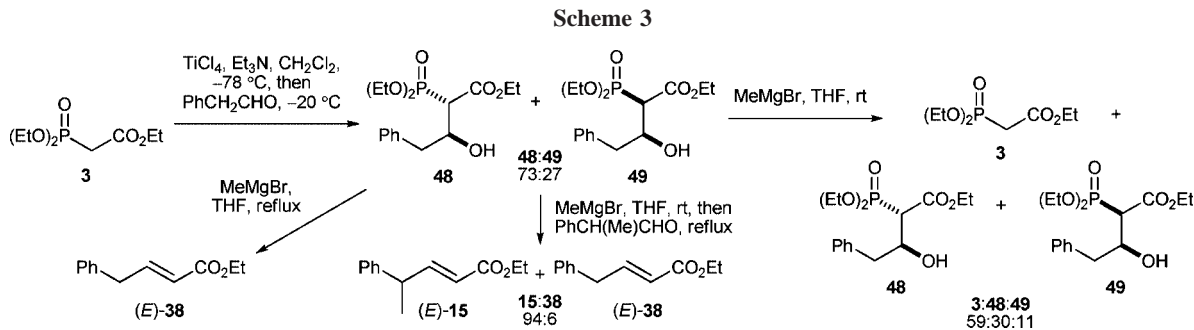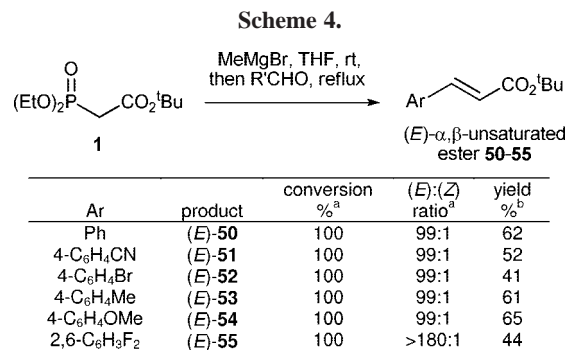
Scheme 3

obtained from both the BuLi and LiCl/DBU promoted reactions (Scheme 1).

Olefination of CyCHO, PhCH(Me)CHO, and PhCH₂CH₂CHO upon treatment with phosphonate esters **2−4** and BuLi, LiCl/DBU or MeMgBr gave the corresponding α,β-unsaturated isopropyl, ethyl and methyl esters (*E*)-**11**-**19** and (*Z*)-**26**-**34**. In each case olefination promoted by MeMgBr gave quantitative conversion to the corresponding (*E*)-α,β-unsaturated ester in ≥98:2 diastereoselectivity (Scheme 1).

In the case of olefination of PhCH₂CHO, the yields of the desired α,β-unsaturated esters were somewhat compromised by competing isomerization to the corresponding (*E*)-β,γ-unsaturated esters.[17] When compared to the reactions employing BuLi or LiCl/DBU, in all cases olefination with MeMgBr suppressed the isomerization (0−26%) and gave the highest isolated yield of pure (*E*)-α,β-unsaturated ester (Scheme 2).

The mechanism of this olefination protocol was next investigated. Tanabe et al. have shown that treatment of a phosphonate ester with TiCl₄ and Et₃N followed by an aldehyde gives *anti*-β-hydroxyphosphonate esters with high selectivity.[18] Under these conditions, treatment of phosphonate **3** with TiCl₄ and Et₃N followed by PhCH₂CHO gave a 73:27 mixture of two products, which were assigned as β-hydroxyphosphonate diastereoisomers *anti*-**48** and *syn*-**49**, respectively, by analogy to the observations of Tanabe.[18] Treatment of the 73:27 mixture of **48**:**49** with MeMgBr at 20 °C followed by quenching with satd aq NH₄Cl gave a 59:30:11 mixture of **3**:**48**:**49**, suggesting that the addition of phosphonate **3** to PhCH₂CHO is reversible under the reaction conditions. Treatment of the 73:27 mixture of **48**:**49** with MeMgBr followed by heating at reflux for 2.5 h resulted in complete conversion to (*E*)-**38** as the only product. This implies that stereospecific *syn*-elimination of **49**, leading to the (*E*)-olefin, and equilibration of **48** and **49** via retro-addition/addition, are both fast under the reaction conditions. Treatment of the 73:27 mixture of **48**:**49** with MeMgBr followed by heating at reflux in the presence of PhCH(Me)CHO gave a 94:6 mixture of (*E*)-α,β-unsaturated esters **15** and **38**, corroborating the hypothesis that condensation of the anion of phosphonate **3** with an aldehyde is reversible (Scheme 3). These results are consistent with this reaction proceeding via the accepted mechanism for the Wadsworth−Emmons reaction.[8]

The generality of this olefination protocol was next established. Application to a range of substituted aromatic aldehydes gave complete conversion to the corresponding (*E*)-olefins **50−55** in uniformly high diastereoisomeric ratios [(*E*):(*Z*) ≥99:1],[16] although longer reaction times were required (Scheme 4).

Scheme 4.

Ar	product	conversion %[a]	(*E*):(*Z*) ratio[a]	yield %[b]
Ph	(*E*)-**50**	100	99:1	62
4-C₆H₄CN	(*E*)-**51**	100	99:1	52
4-C₆H₄Br	(*E*)-**52**	100	99:1	41
4-C₆H₄Me	(*E*)-**53**	100	99:1	61
4-C₆H₄OMe	(*E*)-**54**	100	99:1	65
2,6-C₆H₃F₂	(*E*)-**55**	100	>180:1	44

[a] Determined by peak integration of the ¹H NMR spectrum of the crude reaction mixture. [b] Isolated yield of pure (*E*)-olefin (>99:1 dr).

Olefination of the functionalized, homochiral aldehydes **56** and **59** was also investigated.[19] Olefination of **56** promoted by MeMgBr proceeded with an (*E*)-selectivity of >180:1, while using BuLi or LiCl/ⁱPr₂NEt gave (*E*):(*Z*) ratios of 86:14 and 96:4, respectively. Olefination of *cis*-dioxolane-containing aldehyde **59** promoted by BuLi or under Masamune−Roush

(13) For examples of the use of other bases to promote Wadsworth−Emmons reactions, see: Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774. Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, 7, 4281.

(14) The anion derived from deprotonation of phosphonate **1** with MeMgBr was noted to be much less reactive toward olefination of an aldehyde than the corresponding anion derived from deprotonation of phosphonate **1** with BuLi.

(15) Representative experimental procedure: preparation of (*E*)-**5**: MeMgBr (1.6 M in Et₂O, 0.49 mL, 0.79 mmol) was added dropwise to a stirred solution of *tert*-butyl diethylphosphonoacetate **1** (0.19 mL, 0.79 mmol) in anhydrous THF (10 mL) at rt under a nitrogen atmosphere. After the mixture was stirred for 15 min, cyclohexanal (0.11 mL, 0.87 mmol) was added dropwise via syringe and the reaction mixture was heated at reflux for 2.5 h. The reaction mixture was then allowed to cool to rt, satd aq NH₄Cl (4 mL) was added, and the mixture was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over magnesium sulfate, and concentrated in vacuo to give (*E*)-α,β-unsaturated ester **5** as a colorless oil (163 mg, 98%, (*E*):(*Z*) >180:1).

conditions gave (E)- and (Z)-olefin products **60** and **61**, and was accompanied by partial epimerization of the α-stereocenter within **59**, followed by olefination to furnish **62**.[20] However, sequential treatment of phosphonate **1** with MeMgBr and then aldehyde **59** gave (E)-**60** as the only product with an (E):(Z) ratio of >180:1[16] (Scheme 5).

Scheme 5
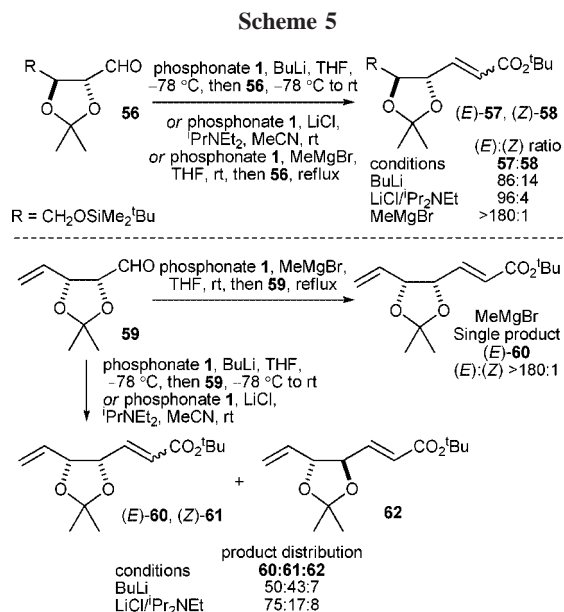
We have previously demonstrated that an N-acyl Super-Quat (5,5-dimethyloxazolidin-2-one) auxiliary is able to act

as a latent aldehyde equivalent through DIBAL-H reduction to the corresponding hemiaminal.[21] The compatibility of the Grignard-mediated olefination protocol to a tandem reduction/olefination reaction within this system was probed. Treatment of N-acyloxazolidinone **63** with DIBAL-H followed by the anion of phosphonate **1** (generated by deprotonation with MeMgBr) afforded the corresponding (E)-α,β-unsaturated ester **65** with an (E):(Z) ratio of >180:1,[16] and in excellent 98% yield after chromatography. The analogous reaction employing BuLi proceeded with significantly lower levels of selectivity, delivering (E)-**65** and (Z)-**66** in an 89:11 ratio, and in only 50% combined yield after chromatography (Scheme 6).

Scheme 6.
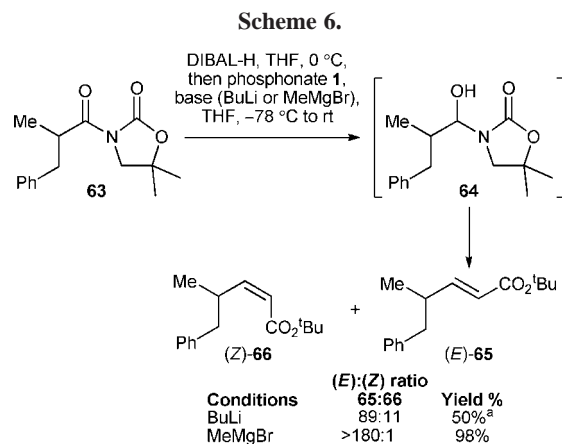
[a] Combined yield of both olefin diastereoisomers.

In conclusion, MeMgBr promotes highly (E)-selective Wadsworth−Emmons reactions between a range of alkyl diethylphosphonoacetates and a range of straight-chain and branched aliphatic, substituted aromatic, and base-sensitive aldehydes. Very high (E):(Z) selectivities were observed in all cases tested (>25 examples), with (E):(Z) selectivities of >180:1 being noted in several cases.

Supporting Information Available: Experimental procedures, characterization data, and copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Claridge, T. D. W.; Davies, S. G.; Polywka.; M, E. C.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D. *Org. Lett.* **2008**, *10*, 5433 (ol802211p)

(17) Deprotonation of ethyl 4-phenylbut-2-enoate and subsequent reprotonation has been shown to lead preferentially to the corresponding (E)-β,γ-unsaturated ester; see: Guha, S. K.; Shibayama, A.; Abe, D.; Sakaguchi, M.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2147.

(18) Katayama, M.; Nagase, R.; Mitarai, T.; Misaki, T.; Tanabe, Y. *Synlett* **2006**, 129.

(19) Aldehydes **56** and **59** were prepared and used immediately in the olefination reaction without purification. For the preparation of aldehyde **56**, see: Paquette, A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849. For the preparation of aldehyde **59**, see: Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

(20) In accordance with this hypothesis olefination of the corresponding trans-dioxolane containing aldehyde mediated by BuLi or under Masamune−Roush conditions gave (E)-α,β-unsaturated ester **62** as a single diastereoisomer.

(21) Bach, J.; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Tetrahedron Lett.* **1999**, *40*, 6677. Bach, J.; Blachère, C.; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Price, P. D.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2001. For selected examples of the application of this methodology in synthesis, see: Davies, S. G.; Hunter, I. A.; Nicholson, R. L.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron* **2004**, *60*, 7553. Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348.