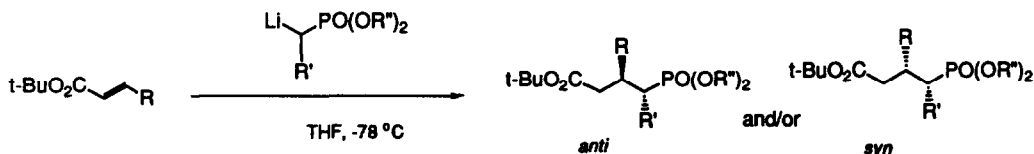


A STEREOSELECTIVE MICHAEL ADDITION OF α -LITHIATED PHOSPHONATES TO α,β -UNSATURATED ESTERS

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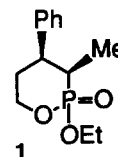
α -Lithiated phosphonates added to α,β -unsaturated t-butyl esters in 1,4-manner giving *anti*-3,4-disubstituted-4-phosphorylbutanoates in high yields.

Although the 1,2-addition reactions of α -lithiated phosphonates to esters are a well-documented process in organic synthesis,¹⁾ 1,4-addition reaction to α,β -unsaturated esters was not known. During our studies on the new synthetic methodologies based on the Michael-type reactions,²⁾ lithiated phosphonates were found to undergo stereoselective 1,4-addition (Scheme 1, Table 1).



Typical procedures are shown for the synthesis of t-butyl *anti*-4-diethylphosphoryl-3-methylpentanoate: Under a nitrogen atmosphere, a hexane solution (1.28 mL) of butyllithium (2 mmol) was added to a THF (2 mL) solution of diethyl ethylphosphonate (332 mg, 2 mmol) at -78°C , and the solution was stirred for 30 min. Then, t-butyl crotonate (142 mg, 1 mmol) in THF (2 mL) was added, and after 2 h the reaction was quenched with saturated aqueous ammonium chloride. A usual workup gave the product in 78 % yield (240 mg).

The use of methyl, ethyl, or *i*-propyl crotonate gave a mixture of 1,2- and 1,4-adducts. Interestingly, the 1,4-adducts were single isomers concerning two continuous asymmetric centers, and the stereochemistry was determined by converting an adduct to 1,2-oxaphosphorinane **1**. Compound **1** was obtained as a mixture of stereoisomers concerning the phosphorous center, and both isomers showed the coupling constant $J=4\text{Hz}$ between 3- and 4-hydrogens indicating the *cis*-relation.

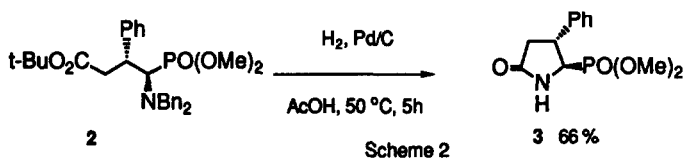


4-Amino-4-phosphonobutanoic acid derivatives³⁾ were synthesized by employing (*N,N*-dibenzylamino)methylphosphonates (Table 1).⁴⁾ Lithiated dimethyl phosphonate showed high *anti*-selectivities when ether instead of THF was used as the solvent. As shown in Scheme 2, the deprotection of 4-(*N,N*-dibenzylamino)butanoate **2** was carried out by a reductive treatment giving lactam **3**. Mp $117.5\text{--}118.0^{\circ}\text{C}$ (AcOEt-hexane).

Table 1. A Stereoselective Michael Addition of α -Lithiated Phosphonates to α,β -Unsaturated Esters

Phosphonate	R	Yield (%) ^{a)}	<i>anti</i> : <i>syn</i>
MePO(OEt) ₂	Me	70	—
	n-C ₄ H ₉	69	—
EtPO(OEt) ₂	Me	78	<i>anti</i> ^{c)}
	n-C ₄ H ₉	80 ^{b)}	<i>anti</i> ^{c)}
	Ph	78	<i>anti</i> ^{c)}
n-PrPO(OEt) ₂	Me	84	<i>anti</i> ^{c)}
	Et	80	<i>anti</i> ^{c)}
Bn ₂ NCH ₂ PO(OMe) ₂	Me	77	15 : 1 ^{d)}
		67	2 : 1 ^{e)}
	n-C ₄ H ₉	72	16 : 1 ^{d)}
Bn ₂ NCH ₂ PO(OEt) ₂	Ph	94	50 : 1 ^{d)}
	Me	70	7 : 1 ^{d)}

a) Isolated yields are shown. All the products gave satisfactory ¹H-NMR, ¹³C-NMR, IR, MS spectra, and/or elemental analysis by HRMS. b) Lithiation was carried out at 0 °C. c) The other isomer was not detected by ¹³C-NMR. d) The reaction was carried out in ether, and diastereomer ratio was determined by HPLC. e) The reaction was carried out in THF, and the ratio was determined by ¹³C-NMR.



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References

- 1) For an example; E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5654 (1966). 1,2-Addition to unsaturated ester was also reported: For an example; E. J. Corey, S. Ohuchida, and R. Hahl, *ibid.*, **106**, 3875 (1984).
- 2) M. Yamaguchi, M. Hamada, H. Nakashima, and T. Minami, *Tetrahedron Lett.*, **28**, 1785 (1987); and references cited therein.
- 3) 4-Amino-4-phosphonobutanoic acid is known to possess interesting biological activities. For an example; A. M. Lacoste, S. Mansour, A. Cassaigne, and E. Neuzil, *Experientia*, **41**, 643 (1985).
- 4) (Dibenzylaminomethyl)phosphonates were prepared from dialkyl phosphite, dibenzylamine, and formaldehyde: See; R. Tyka, *Tetrahedron Lett.*, **1970**, 677.