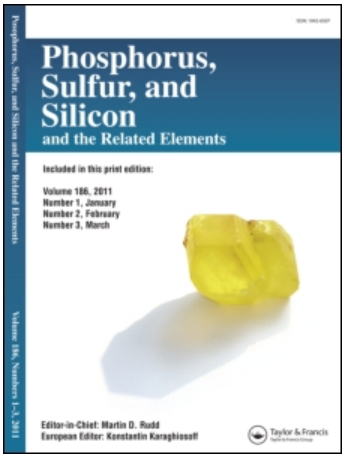

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1,3-Dimthyl-1,3,2-Diazaphospholidines-2-Ones : Unanticipated Precursors of (z) Acrilyc Acid Esters

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1,3-DIMETHYL-1,3,2-DIAZAPHOSPHOLIDINES-2-ONES : UNANTICIPATED PRECURSORS OF (Z) ACRILYC ACID ESTERS

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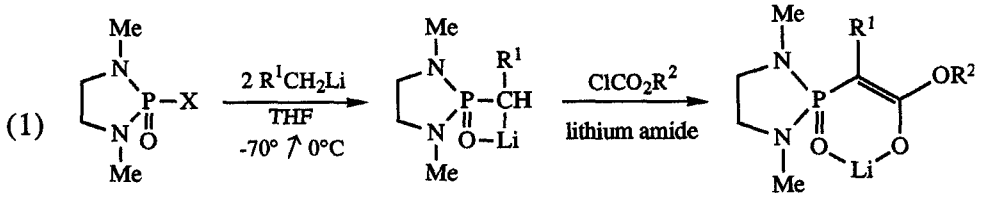
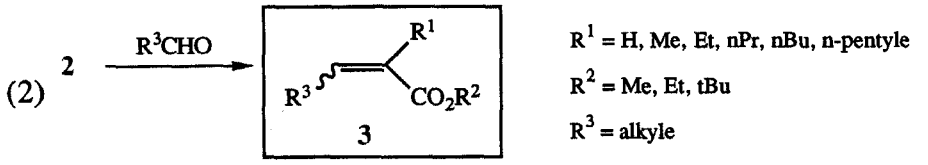
Abstract The title compounds allow the Wittig-Horner synthesis of acrylic acid esters with Z:E ratios superior to 90:10 (THF, Li^+). The selectivity is mainly controlled by the concentration and the temperature of the reaction medium.

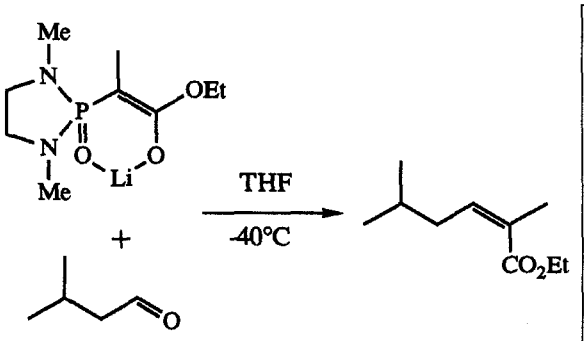
Looking for stereocontrol in the synthesis of acrylates via phosphonate reagents, one needs to perform many test reactions with a variety of reasonably accessible precursors to get a hint of the key reaction parameters. In this way, our straightforward alkylation-metallation-functionalisation sequence displays ideal conditions, because it allows the one-pot versatile preparation of many such precursors (Eq. 1), which can be evaluated under contrasting experimental conditions (temperature, solvent, concentration, additives...).





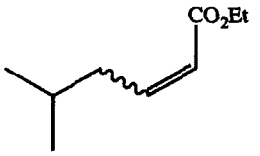
In our preliminary studies[1] to tailor a Z-selective phosphonate reagent, we first selected 5-membered cyclic bisamides **2** (title compound), which induced a 76:24 Z:E ratio at 20°C for the preparation of **3** (Eq. 2, $R^1 = R^3 = nPr$, $R^2 = Et$). Moreover, this moiety was fully compatible with the alkylation-metallation reaction depicted in Eq. 1. It appeared that **2** behaved very specifically, and that the stereoselectivity it induced, depended not only on traditional parameters (*temperature*, *solvent*, *cation*), but also of less traditional ones (*concentration*, *aggregation*, steric effect of the *secondary amine* used as base in Eq. 1). The selectivity was strikingly affected by the concentration of the reaction medium. It is

noteworthy that in absence of lithium salts, the lithiated carbanion **1** is soluble in THF at -78°C (several species in equilibrium as evidenced by ^{31}P NMR), but irreversibly precipitates at room temperature, probably due to the displacement of equilibria between aggregated forms of **1**. Addition of LiBr causes the total dissolution of the precipitate (single species in solution). These 5-membered ring lithiated species are very prone to oligomer or aggregate formation. Thus, it seems natural that the concentration of the reaction medium may have an important effect, either on the rate, or the selectivity, of the olefination. The magnitude of this effect can be seen in the table below. It was observed for all other R^1 substituents, but with decreasing importance as the size of R^1 increased.



Concentration	Z : E
150 mM	50 : 50
100 mM	71 : 29
65 mM	85 : 15
33 mM	91 : 09

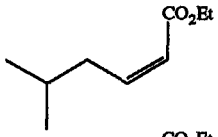
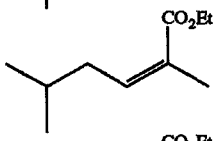
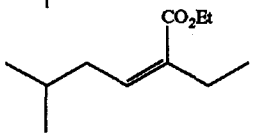
In the particular case of R^1 = H, in addition to a strong dilution effect, we observed that the conditions of preparation of **2** were very important. Z selectivity could only be achieved if *in situ* prepared **2** was intermediately warmed from -78°C to +20°C before reaction with an aldehyde at low temperature (-85°C). This difference of behaviour between *warm* and *cold* phosphonocarboxylates **2** can be explained by the same kind of irreversible displacement of equilibria as was found for the aggregation of **1**.



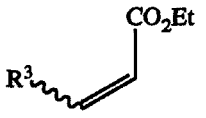
Temperature pathway			Z : E
-78°C ----------→ -80°C	"cold"		41 : 59
-78°C --→ -30°C --→ -75°C			40 : 60
-78°C --→ 0°C --→ -70°C			66 : 34
-78°C --→ +20°C --→ -68°C			76 : 24
-78°C --→ +20°C --→ -85°C	"warm"		86 : 14

The hindered lithium amide used to functionalise **1** had to be carefully chosen, because the regenerated free amine played a significant part upon the course of the olefination. The combination of either diisopropylamine or isopropylcyclohexylamine and lithium salts in the medium prevented the olefination at low temperature. By contrast, the reaction was problem-free in presence of lithium salts and tetramethylpiperidine (TMP) or dicyclo-

hexylamine. The observed inhibition is probably due to a complexation of enolate **2** by the free secondary amine[2] ; this complexation is sterically not possible in the case of very bulky amines. Therefore, the use of TMP allowed the olefination with reagents obtained according to Eq. 1, where the alkyllithium prepared at the laboratory contained LiBr.
The evaluation of the effect of the cation upon the selectivity of the olefination gave the following results. In the case of R^1 = H, changing from Li^+ to Na^+ or K^+ resulted in a loss of selectivity. The order is Li ≥ K/18-C-6 > Na > K. For the preparation of α-substituted olefins, Na^+ gave selectivities slightly superior to that obtained with Li^+, whilst the use of K^+ markedly induced lower selectivities. The order in the case of R^1 > H, is Na ≥ Li > K > K/18-C-6.

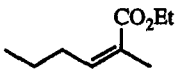
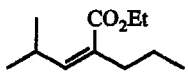
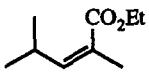
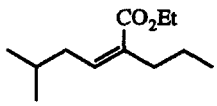
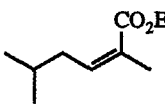
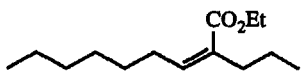
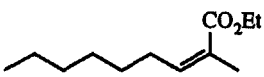
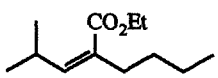
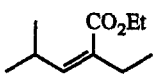
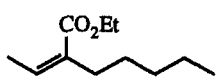
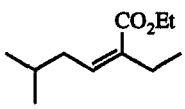
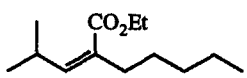
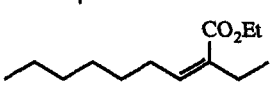
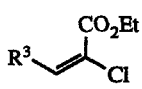
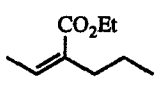
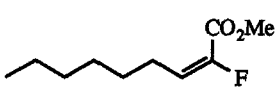
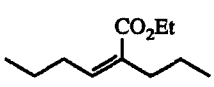
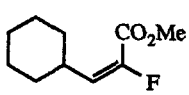
Olefin	Li^+	Li^+/12-C-4	Na^+	K^+	K^+/18-C-6
	86 : 14	64 : 36	55 : 45	70 : 30	82 : 18
	91 : 09	89 : 11	94 : 06	83 : 17	41 : 59
	92 : 08		94 : 06	63 : 27	

Under these experimental conditions, *dilution*, *low temperature* (e.g. R^1 = H : T°C < -78, R^1 = Me : T°C = -40, R^1 > Et : T°C = -20), *Li^+*, *TMP*, "*warm*" *enolate*, good to excellent Z selectivities were obtained.



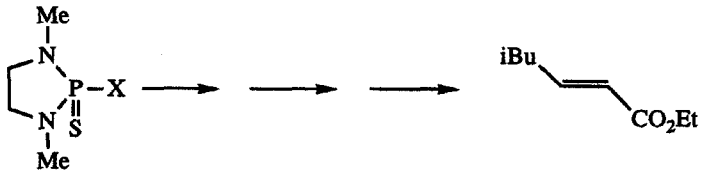
R^3	Z : E
nPr	82 : 18
iBu	86 : 14
nHex	82 : 18
iPr	43 : 57
cyHex	84 : 16
tBu	00 : 100

The remarkable Z selectivity induced by **2** is mainly due to a highly selective initial pro-Z aldolic condensation. This is supported by the excellent E:Z ratios obtained when a halogen (Cl or F) was introduced in R^1 position. In the case of R^1 = Cl, aliphatic aldehydes afforded > 97:03 E:Z ratios,[3] and when R^2 = F, selectivies were again very good, but clearly depended on the concentration, nature of the aldehyde, and R^2 group.

Olefin	Z : E	Olefin	Z : E
	90 : 10		97 : 03
	92 : 08		88 : 12
	91 : 09		90 : 10
	90 : 10		94 : 06
	96 : 04		89 : 11
	92 : 08		95 : 05
	91 : 09		> 97 : 03
	89 : 11		> 98 : 02
	90 : 10		98 : 02

The title compound was compared with bis-(trifluoroethyl)-phosphonoacetate 4 (Still and Gennari's reagent)[4] under strictly equivalent conditions : Li^+, THF, low temperature, one-pot generation of the phosphonate precursor, in presence and absence of 12-C-4 crown ether. With aliphatic aldehydes, 2 gave the better selectivities. For instance, the preparation of 3 (R^1 = H, R^2 = Et, R^3 = iBu) was achieved in 86:14 Z:E ratio with 2, whereas in 47:53 Z:E ratio with 4. In the case of 3 (R^1 = Me, R^2 = Et, R^3 = iBu), the ratios were 91:09 for 2, and 57:43 for 4. In all cases, the addition of 12-C-4 was ineffective.

To conclude, we wish to mention that the parent thionophosphonate led, for example in the case of R^1 = H, R^2 = Et, R^3 = iBu, to a 05:95 Z:E ratio at -78°C.



[1] Patois C., Savignac P., *Tetrahedron Lett.*, **1991**, *10*, 1317. [2] Seebach D., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1624. [3] Patois C., Savignac P., *Synlett*, **1991**, *7*, 517. [4] Still W., Gennari C., *Tetrahedron Lett.*, **1983**, *24*, 4405.