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Olefination reactions through phosphazenes

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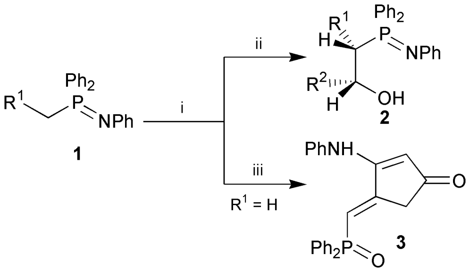
The first synthesis of di-, tri- and tetrasubstituted alkenes through reaction of lithium *P*-diphenyl(alkyl)(*N*-carboxymethyl)phosphazenes with aldehydes and ketones is reported.

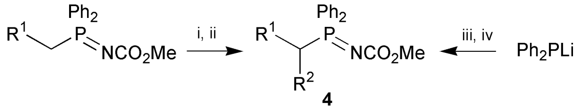
Phosphorus-stabilized carbanions are very important reactive intermediates in the stereoselective synthesis of olefins. Since the breakthrough of the Wittig reaction between phosphorus ylides and carbonyl compounds[1] in carbon–carbon double bond forming reactions, the usefulness of other phosphorus derivatives in this type of process has been demonstrated. The most relevant members of this class of compounds are phosphonates,[2] phosphonamides[3] and phosphine oxides.[4]

Phosphazenes are isoelectronic with phosphorus ylides and phosphine oxides. They are well known for the large number of synthetic applications of the P–N bond,[5] particularly in the preparation of heterocycles[6] based on the aza-Wittig reaction. However, the chemistry of their α-carbanions has received much less attention.[7] We have shown that lithiated *P*-diphenyl(alkyl)(*N*-phenyl)phosphazenes **1** add to aldehydes with a high diastereoselectivity yielding the corresponding β-hydroxy derivatives (Scheme 1).[8] These compounds are easily isolated and no trace of olefins were observed in the reaction even when forcing conditions were used.

Recently, in a synthesis of cyclopentenones **3** obtained by reaction of lithium *P*-diphenyl(alkyl)(*N*-phenyl)phosphazenes with dimethylacetylene dicarboxylate (DMAD) (Scheme 1) we proposed a reaction mechanism in which one intermediate phosphazene participated in an olefination step similar to the Horner carbon–carbon double bond synthesis using phosphine oxides.[9] No experimental evidence could be obtained regarding the structure of any reactive intermediate involved in the synthesis.



Scheme 1 *Reagents and conditions*: i, *n*-BuLi, −30 °C, THF; ii, R^2CHO, −70 °C; iii, DMAD, −70 °C.

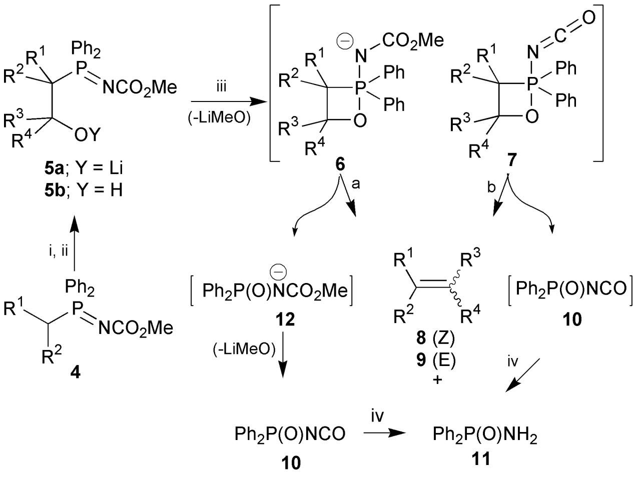


Scheme 2 *Reagents and conditions*: i, *n*-BuLi, −35 °C, THF; ii, R^2Br, −70 °C; iii, R^1R^2CHBr, −35 °C, THF; iv, N_3CO_2Me.

Here we report the first application of phosphazenes to the synthesis of di-, tri- and tetrasubstituted alkenes. The phosphazenes **4** used in this study are readily obtained, either by alkylation of the anion Ph_2P^- (generated by reaction of Ph_3P with lithium) followed by *in situ* addition of N_3CO_2Me, or through alkylation of simpler lithiated phosphazenes (Scheme 2). *P*-diphenyl(alkyl)(*N*-carboxymethyl)phosphazenes **4** were metallated with *n*-BuLi in THF at −35 °C over a 30 min period. The appropriate aldehyde or ketone was then added and the mixture was stirred for 4–20 h at rt. Aqueous work-up followed by distillation or filtration through a short path silica-gel chromatography column afforded the olefins **8**(*Z*)/**9**(*E*) (Scheme 3).† The diphenylphosphinamide **11** by-product was completely eliminated in the aqueous layer.

A list of the compounds obtained, as well as the isolated yields and the diastereomeric ratios observed are given in Table 1.[10] The stereochemistry of the tri-substituted alkenes was easily assigned through 2D NOESY spectra measured from the mixture of isomers. For the di-substituted derivatives the geometry of the double bond was deduced from the magnitude of the vicinal coupling constants or chemical shifts of the olefinic protons.

Reaction yields were higher than 90% in all cases except for the phosphazene having R^1 = Me and R^2 = ^{n}Bu. In this case only a 16% yield of the *E*/*Z* alkenes was obtained under the standard conditions. However, this yield increased to 70% without changes in the isomeric ratio when a large excess of aldehyde (10 equiv.) was used. Worthy of note is the high yield obtained when benzophenone is used as electrophile giving rise to the tetrasubstituted alkene **8j**. The olefin *E* predominates in all cases except for phosphazenes bearing a benzyl group where the *Z* alkene is favoured (Table 1, entries 7, and 8). Good to excellent stereoselectivies are obtained for phosphazenes with R^1 = Ph, CO_2Me and R^2 = H (Table 1, entries 1–5). Using the synthesis of alkenes **8/9d** as reference, under the same reaction conditions the appropriate phosphazene, phosphine oxide, phosphonate, and phosphonium salt afforded essentially the *E* isomer (*Z*:*E* 1:99) in similar yields. Curiously, the stereoselectivity of the Wittig reaction showed a slight decrease (*Z*:*E* 4:96) when the olefination was carried out with the isolated phosphorus ylide. However, the reported reactions of $Ph_3P{=}CHPh$ with benzaldehyde using BuLi or PhLi as a base



Scheme 3 *Reagents and conditions*: i, *n*-BuLi, −35 °C, THF; ii, R^3R^4CO, rt; iii, 4–20 h; iv, H_2O.

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Table 1 Alkenes **8**, **9** obtained, including isomeric ratio of the mixture and isolated yield

	Alkene	R^1	R^2	R^3	R^4	Z:E (%)[a]	Yield (%)
1	**8**, **9a**	Ph	H	H	Ph	17:83	92
2	**8**, **9b**	Ph	H	H	$(CH_3)_3C$	4:96	95
3	**8**, **9c**	CO_2Me	H	H	Ph	1:99	85
4	**8**, **9d**	CO_2Me	H	H	p-Cl-C_6H_4	1:99	88
5	**8**, **9e**	CO_2Me	H	H	C_6H_{11}	4:96	90
6	**8**, **9f**	Me	$CH_3(CH_2)_2CH_2$	H	Ph	34:66	16 (70)[b]
7	**8**, **9g**	$PhCH_2$	$CH_3(CH_2)_2CH_2$	H	p-Cl-C_6H_4	72:28	86
8	**8**, **9h**	Me	$PhCH_2$	H	$(CH_3)_3C$	74:26	85
9	**8**, **9i**	Me	CH_2=$CHCH_2$	H	p-MeO-C_6H_4	32:68	90
10	**8j**	Me	CH_2=$CHCH_2$	Ph	Ph		85

[a] Determined from the integrals of the olefinic protons and/or the methyl signals in the ^1H NMR spectrum of the mixture. [b] When a large excess of aldehyde is used.

are clearly less stereoselective (Z:E 34:66 and 30:70, respectively)[1b,11] than the analogous synthesis of stilbene through phosphazenes (Table 1, entry 1). The olefination reported here is sensitive to the degree of substitution in the carbanion and modest *Z/E* ratios are obtained when α,α-disubstituted phosphazenes are used (*cf.* entries 6–9 in Table 1). This is a known characteristic of Horner olefination.[5]

A reaction mechanism explaining the formation of **8**, **9**, and **11** is shown in Scheme 3. First, one carbon–carbon bond is formed by addition of the C_α-metallated phosphazene to the carbonylic carbon of the electrophile affording the alkoxy intermediate **5a**. The nucleophilic oxygen of this adduct attacks the electrophilic phosphorus intramolecularly to yield an oxaphosphetane heterocycle **6** as proposed for the Wittig[1] and Horner[12] reactions. In this particular case, the oxaphosphetane **6** may break down to the alkenes **8**/**9** (route a) or may eliminate lithium methoxide affording the isocyanate derivative **7**. Ring opening of **7** would yield the alkenes **8**/**9** and diphenylphosphinoyl isocyanate **10** (route b), which by reaction with water would produce the diphenylphosphinamide **11**. Alternatively the isocyanate **10** may be formed by elimination of lithium methoxide from the lithium phosphinamide **12** (route a).

The intermediate adducts **5b** can be isolated as the corresponding (β-hydroxy)phosphazenes when the carbonyl compound is added at −70 °C and the reaction is stirred for 2 h at this temperature. Aqueous work-up yields a mixture of diastereomeric compounds **5b** in the same ratio as observed for the respective olefins. Therefore, the diastereoselectivity of the synthesis is determined by the addition step and no interconversion occurs between the two isomers. The (β-hydroxy)phosphazenes **5b** are converted quantitatively into the corresponding olefins by lithiation under the same reactions conditions used in the one-pot process.

Support for the participation of phosphinoyl isocyanates as intermediates in the formation of phosphinamides in the olefination reaction described above has been obtained from phosphinamide **13** synthesized by reaction of methoxycarbonyl azide with diphenylphosphine oxide. Compound **13** was treated with one equiv. of n-BuLi in THF at −30 °C (Scheme 4) and the reaction was stirred for 4 h at rt.[13] After aqueous work-up the phosphinamide **11** was isolated quantitatively.[14]

$$Ph_2P(O)H \xrightarrow{i} \underset{\mathbf{13}}{Ph_2P(O)NHCO_2Me} \xrightarrow{ii} \underset{\mathbf{10}}{[Ph_2P(O)NCO]} \xrightarrow{iii} \underset{\mathbf{11}}{Ph_2P(O)NH_2}$$

Scheme 4 *Reagents and conditions*: i, N_3CO_2Me, THF, rt; ii, n-BuLi, THF, −35 °C to rt; iii, H_2O.

In conclusion, the application of phosphazenes to the synthesis of alkenes through reaction with carbonyl compounds is described for the first time. The phosphazenes are readily available through conventional reactions, analogous to the preparation of phosphine oxides. High yields of di-, tri and tetrasubstituted olefins are obtained. The stereoselectivity depends on the substituents on the alkyl group bonded to phosphorus and for α-substituted phosphazenes the stereocontrol achieved is comparable to that obtained in the Wittig, Horner, and Wadsworth–Emmons reactions. A reaction mechanism is proposed which involves the sequential formation of an isolable (β-hydroxy)phosphazene and an oxaphosphetane intermediate.

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Notes and references

† Synthesis of methyl cinnamate **8**, **9c**: to a Schlenk with $MeO_2CCH_2(Ph)_2P$=NCO_2Me (0.2 g, 6 × 10^{-4} mol) dissolved in 25 mL of dry THF was added a solution of n-BuLi (0.45 mL of a 1.6 M solution in hexane, 7.2 × 10^{-4} mol) at −35 °C. After 30 min of metallation the temperature was lowered to −70 °C and benzaldehyde (61 μL, 6 × 10^{-4} mol) was added. The reaction mixture was stirred for 6 h and allowed to reach rt. Work-up (A): addition of diethyl ether (15 mL) to the reaction crude produced a white precipitate of $Ph_2P(O)NH_2$ (0.102 g, 78%), which was filtered off. The filtrate was evaporated to dryness and distilled under vacuum. Methyl cinnamate **8**, **9c** (Z:E 1:99) was isolated as a colourless liquid bp $122^{0.1}$ °C (lit. 120–$125^{0.1}$ °C)[15], (79 ×10^{-3} g, 81%). Work-up (B): Addition of water (25 mL) followed by extraction with CH_2Cl_2 (3 × 15 mL) and solvent evaporation under vacuum afforded one (almost pure) oil, which was further purified by distillation under vacuum bp $122^{0.1}$ °C (83 × 10^{-3} g, 85%). The same yields were obtained by filtration through a short path column of silica gel 60 (40–63 μm) using ethyl acetate:hexane (1:4) as eluent.

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