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Stereoselective Alkenylation of Aldehydes with Phosphorus Carbanions: Preparation of *E*- and *Z*-2-Alkoxy- and 2-Aryloxy-2-Alkenoates.

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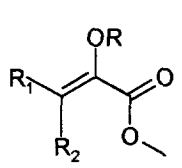
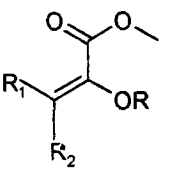
Abstract: Eighteen phosphorus-based alkenylation reagents **1a-6c** were synthesized and condensed with n-butyraldehyde **7a** and benzaldehyde **7f**. They were condensed with the aldehydes **7b-e,g-n** to produce 2-methoxy-2-alkenoates **8a-n** and 2-phenoxy-2-alkenoates **9a-n**. A discussion on different selectivities for the alkenylation reagents under different experimental conditions (base, solvent, temperature), the influence of the aldehydes on the geometrical outcome (electron rich or poor substituents, steric hindrance) and the selection of the most *E*- and *Z*- selective reaction conditions for each class of aldehydes are reported. Namely, triphenyl phosphonium salt **1a** at RT in THF with DBU was better for *Z*-selectivity while trifluoroethylphosphonates **5b**, **6b** and **6c** at -78° in THF with $KN(SiMe_3)_2$ were better for E-selectivity. © 1997 Elsevier Science Ltd.

The *Z*- and *E*- 2-alkoxy- or 2-aryloxy-2-alkenoate moieties (Figure 1) are structural features found in many natural and semisynthetic products, such as carbohydrates,[1] steroids,[2] alkaloids,[3] pigments,[4] and often their presence is related to, or even essential for specific biological activities as antibiotics,[5] antivirals,[6] immunostimulants[7] and hypolipidemics.[2]



***Z* isomer**

R_1=higher priority
R_2=lower priority



***E* isomer**

Figure 1

One of our research projects required a methodology for preparing pure *E*- and *Z*- isomers of 2-alkoxy- and 2-aryloxy-2-alkenoates with different R and R_1 groups (R_2=H). We chose the olefination of aldehydes **7** with phosphorus (*P* from now on) carbanions to prepare the desired compounds, *E*-,*Z*-**8** (R=Me, Scheme 1) and *E*-,*Z*-**9** (R=Ph, Scheme 1). The *P* anions were derived from phosphonium salts **1,2** (R=Me,Ph, Wittig reagents[8]), phosphine oxides **3,4** (R=Me,Ph, Horner reagents[9]) or phosphonates **5,6** (R=Me,Ph, Horner-Wadsworth-Emmons reagents[10]) where the methoxy and the phenoxy groups were selected as representatives of α-substitution on the *P* reagents.

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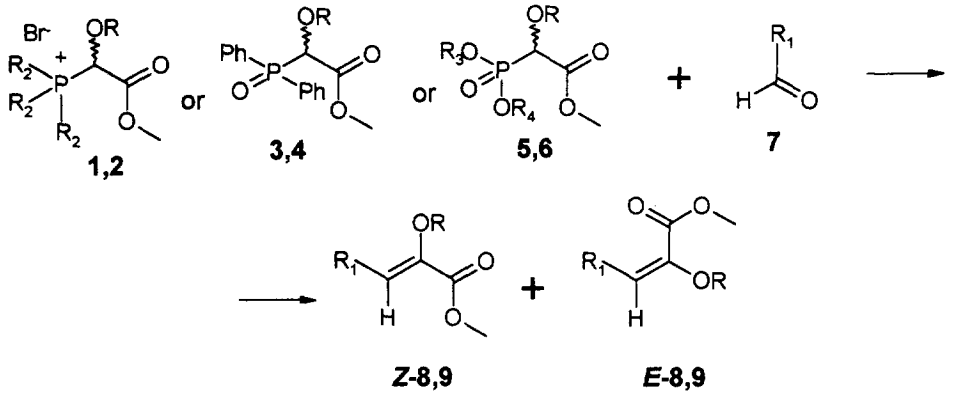
Many excellent recent reviews dealing with the olefination of carbonyl compounds by *P* based reagents were published[8b,8c,10a,10b] and from their evaluation some general considerations regarding the theoretical *E/Z* ratio for the reactions between compounds **1-6** and aldehydes **7** can be made.



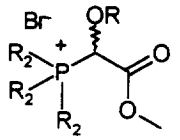
Scheme 1

The presence of an electron-withdrawing group α to the *P* atom such as the carboxylate (stabilized *P* carbanions) was shown to produce generally *E*-2-unsubstituted alkenoates.[8b,8c] The few examples of reactions with α-alkoxyphosphonoacetates, with α-aryloxyphosphonoacetates and with α-alkoxy-α-triphenylphosphonium acetate bromides reported in the literature[11] produced, with high selectivity, the corresponding *Z*-2-alkoxy or aryloxyalkenoates (priority of the OR group to the COOR, Figure 1). These *Z*-isomers could be also obtained from mixtures of *E*-and *Z*-compounds *via* base-catalyzed isomerization. Preparation of the *E*-2-substituted alkenoates would have required the adaptation of known techniques used for the preparation of *Z*-2-unsubstituted alkenoates from stabilized *P* carbanions.[12]

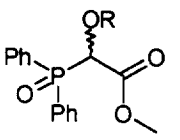
We chose to prepare a large set of *P* compounds **1-6** and react them with a model aliphatic and aromatic aldehyde. This allowed us to establish good methods for obtaining pure *E*- or *Z*- compound prior to submitting a large set of diverse aldehydes to these procedures. This second phase was aimed at establishing some general rules for the synthesis of geometrically pure 2-alkoxy- or 2-aryloxyalkenoates.

Results and Discussion

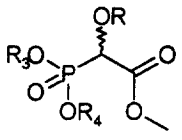
We prepared 18 alkenylation reagents (Figure 2), namely the methoxyphosphonium ylides **1a-h**, the phenoxyphosphonium ylides **2a-c**, the methoxy- and phenoxyphosphine oxides **3** and **4**, the methoxyphosphonates **5a,b** and the phenoxyphosphonates **6a-c**. Their syntheses were accomplished by α-bromination of either methyl methoxy- or phenoxyacetate, followed then by the reaction with trialkyl or triarylphosphines[13] for **1a-h** or **2a-c**, with ethyl diphenylphosphinite[14] for **3** and **4** or with triethyl phosphite[15] for **5a** and **6a** (Scheme 2).



1a,2a R=Me,Ph R_2=phenyl
1b,2b R=Me,Ph R_2=ethyl
1c,2c R=Me,Ph R_2=n-octyl
1d,e R=Me R_2=n-butyl, cyclohexyl
1f,g R=Me R_2=o-tolyl, 2-methoxymethoxyphenyl
1h Resin bound **1b**

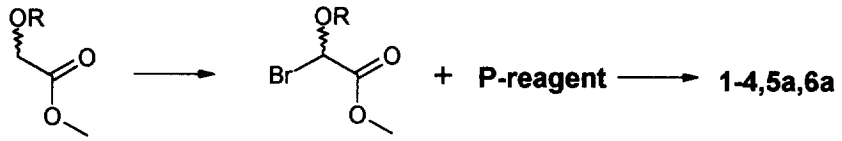


3 R=methyl
4 R=phenyl



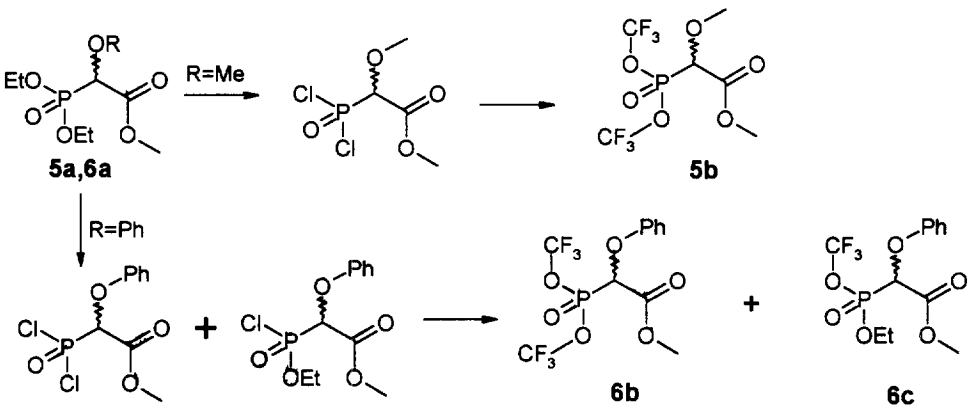
5a,6a R=Me,Ph R_3=R_4=ethyl
5b,6b R=Me,Ph R_3=R_4= =2,2,2-trifluoroethyl
6c R=Ph R_3=ethyl R_4=2,2,2-trifluoroethyl

Figure 2



Scheme 2

The synthesis of the 2,2,2,-trifluoroethylphosphonates **5b**, **6b** and **6c** was realized from **5a** and **6a** by chlorination with phosphorus pentachloride and substitution with 2,2,2-trifluoroethanol[12c] (Scheme 3).



Scheme 3

While the reaction starting from **5a** produced only the bis(trifluoroethyl) compound **5b**, from **6a** we obtained, *via* incomplete chlorination, also the monoethyl-monotrifluoroethylphosphonate **6c** that was not previously reported as a Horner-Wadsworth-Emmons reagent.

Some of these reagents were known as inducers of inverse geometry for alkenations producing *Z*-2-unsubstituted alkenoates[12a-c] : the phosphonium salts **1f,g**[12a,12b] and the trifluoroethylphosphonates **5b** and **6b**.[12c] In analogy to this, we considered these reagents as potential *E*-inducers for our 2-alkoxy- and 2-aryloxy-2-alkenoates.

We selected as model aldehydes butanal (**7a**) and benzaldehyde (**7f**). We searched the optimal conditions using phosphonium salts **1a,b** and **2a,b**, reacting them with **7a** and **7f** in different experimental conditions. The results are summarized in Table I, where entries producing an isomeric ratio of 80/20 or better are highlighted (last column on the right, underlined with a single line when the *Z*-isomer is preponderant, with a double line when the *E*-isomer is more abundant). All the reactions from here on were performed on a 2-mmol scale as unoptimized single experiments, and various amounts of starting aldehyde were recovered; for additional details, see the Experimental Section.

Table I . Wittig reaction between *P* reagents **1a,b-2a,b** and aldehydes **7a,f**[a]

entry	aldehyde (1.5eq.)	*P* reagent (1.0eq.)	solvent	base (1.1eq.)	yield (*E*+*Z*)	*E*/*Z* ratio[b]
1	n-PrCHO	**1a**	THF	DBU	63	**8a**: 8/92
2	n-PrCHO	**1a**	THF	TMG	59	**8a**: 8/92
3	n-PrCHO	**1a**	THF	DBU/LiBr	46	**8a**: 10/90
4	n-PrCHO	**1a**	CH_2Cl_2	DBU	60	**8a**: 12/88
5	n-PrCHO	**1a**	MeOH	KOMe	39	**8a**: 10/90
6	n-PrCHO	**1a**	THF,reflux,4h	DBU	76	**8a**: 15/85
7	n-PrCHO	**1b**	THF	DBU	51	**8a**: 50/50
8	n-PrCHO	**1b**	THF	DBU/LiBr	65	**8a**: 15/85
9	n-PrCHO	**2a**	any[c]	any[c]	ND[d]	-
10	n-PrCHO	**2b**	THF	DBU	60	**9a**: 36/64
11	n-PrCHO	**2b**	THF	DBU/LiBr	47	**9a**: 19/81
12	PhCHO	**1a**	THF	DBU	82	**8f**: 6/94
13	PhCHO	**1a**	THF	TMG	69	**8f**: 8/92
14	PhCHO	**1a**	THF	DBU/LiBr	76	**8f**: 5/95
15	PhCHO	**1a**	CH_2Cl_2	DBU	72	**8f**: 8/92
16	PhCHO	**1a**	MeOH	DBU	80	**8f**: 7/93
17	PhCHO	**1a**	THF,reflux,4h	DBU	91	**8f**: 16/84
18	PhCHO	**1b**	THF	DBU	74	**8f**: 64/36
19	PhCHO	**1b**	THF	DBU/LiBr	74	**8f**: 48/52
20	PhCHO	**2a**	any[c]	any[c]	ND	-
21	PhCHO	**2b**	THF	DBU	61	**9f**: 40/60
22	PhCHO	**2b**	THF	DBU/LiBr	43	**9f**: 50/50

[a] Reactions carried out at rt for 24h except for entries 6 and 17; for other details, see Experimental Section; [b] calculated by NMR (+/- 2%); [c] all the experimental conditions used with **1a** were tried unsuccessfully; [d] not detectable (<2%).

The reaction with methoxyarylphosphonium salt **1a** was strongly *Z*-selective, as expected,[11] and the selectivity was not significantly affected by changes of solvent or base. Reactions at lower temperature were too slow (data not shown), while higher temperatures reduced the *Z*-selectivity (compare entries 1 with 6, 12 with 17). The corresponding phenoxy salt **2a** did not react with **7a,f** under any of the conditions tried, including high temperatures and excess of reagents, probably due to the additional steric hindrance of the phenoxy group.

Reaction with the alkylphosphonium salts **1b** and **2b** was not very selective, and again various solvents or bases did not influence significantly the *E/Z* ratio (data not shown). The only exception was the use of LiBr and DBU with **7a** (compare entries 7 with 8 and 10 with 11) that increased *Z*-selectivity.

We selected DBU as a base and THF as a solvent at rt for 24 hours as a Wittig experimental procedure, applying it subsequently to the other phosphonium salts **1c-h** and **2c**. The results are summarized in Table II.

The reaction with salts **1c-e** and **2c** did not show a significant selectivity, as seen for **1b** and **2b**. The substituted aryl salts **1f,g**, that were potential *E*-inducers,[12a,12b] failed to react under any experimental conditions most likely due to steric hindrance problems as already seen for **2a**. The resin-bound salt **1h** gave yields and *Z*-selectivities comparable with its "free" analog **1a** (compare entries 28 and 34 respectively with entries 1 and 12, Table I), so that this resin bound Wittig reagent could be used for the synthesis of combinatorial libraries of functionalized *Z*-α-alkoxy- or α-aryloxy-α,β-unsaturated carboxylic acid derivatives.

Then we moved to the phosphine oxides **3** and **4**, whose behaviour in the Horner reaction with aldehydes **7a,f** is reported in Table III. The reaction produced directly the alkenes, while the intermediate erythro and threo β-hydroxyphosphine oxides, that should have been the reaction products at least with nBuLi,[16] were not observed.

Under the both chosen experimental conditions the phosphine oxides showed generally moderate *Z*-selectivity and lower yields than the Wittig phosphonium salts. Due to these results, we did not investigate further the use of phosphine oxide reagents.

Finally we moved to the phosphonates **5a,b** and **6a-c** The results of their Horner-Wadsworth-Emmons reaction with aldehydes **7a,f** are reported in Table IV.

While the ethyl phosphonates **5a** and **6a**, as expected, did not show *E*-selectivity when treated as in entries 43, 44, 53 and 54 (for **6a**, data not shown), the use of strong dissociating conditions improved the *E*-selectivity for reactions using aldehyde **7a** (entries 45 and 49). The best *E*-selectivities were obtained, as expected,[12c] with the mono- and di-trifluoroethylphosphonates **5b**, **6b** and **6c** using $KN(SiMe_3)_2$ as a base and 18-crown-6 as a chelating agent (entries 48, 50, 52 and 58), with the only exception of the reaction between **7f** and **6b,c** where no selectivity was found (entries 60 and 62). Other experimental conditions employing the same trifluoroethylphosphonates (entries 46 and 56, 47 and 57) were less *E*-selective.

Table II. Wittig reaction between *P* reagents **1c-h** and aldehydes **7a,f**[a]

entry	aldehyde (1.5)	*P* reagent (1.0)	yield (*E*+*Z*)	*E*/*Z* ratio[b]
23	n-PrCHO	**1c**	56	**8a**: 50/50
24	n-PrCHO	**2c**	48	**9a**: 41/59
25	n-PrCHO	**1d**	72	**8a**: 55/45
26	n-PrCHO	**1e**	21	**8a**: 35/65
27	n-PrCHO	**1f,1g**	ND[c]	-
28	n-PrCHO	**1h**	77	**8a** :19/81
29	PhCHO	**1c**	68	**8f**: 62/38
30	PhCHO	**2c**	59	**9f**: 50/50
31	PhCHO	**1d**	86	**8f**: 62/38
32	PhCHO	**1e**	16	**8f**: 35/65
33	PhCHO	**1f,1g**	ND[c]	-
34	PhCHO	**1h**	86	**8f**: 8/92

[a] Reactions carried out at rt for 24h with DBU (1.1eq) in THF; for other details, see Experimental Section; [b] calculated by NMR (+/- 2%); [c] all the experimental conditions used with **1a** (Table I) were tried unsuccessfully.

Table III. Horner reaction between phosphine oxides **3,4** and aldehydes **7a,f**.[a]

entry	aldehyde (1.5eq)	*P* reagent (1.0eq)	base (1.1eq)	T(°C), t(h)	yield (*E*+*Z*)	*E*/*Z* ratio[b]
35	n-PrCHO	**3**	nBuLi	-78° to rt, 16	32	**8a**: 60/40
36	n-PrCHO	**3**	DBU	rt, 24	47	**8a**: 60/40
37	n-PrCHO	**4**	nBuLi	-78° to rt, 16	52	**9a**: 30/70
38	n-PrCHO	**4**	DBU	rt, 24	44	**9a**: 19/81
39	PhCHO	**3**	nBuLi	-78° to rt, 16	64	**8f**: 18/82
40	PhCHO	**3**	DBU	rt, 24	55	**8f**: 18/82
41	PhCHO	**4**	nBuLi	-78° to rt, 16	64	**9f**: 25/75
42	PhCHO	**4**	DBU	rt, 24	49	**9f**: 30/70

[a] Reactions carried out in THF as solvent; for other details, see Experimental Section; [b] calculated by NMR (+/- 2%).

Table IV. Horner-Wadsworth-Emmons reaction of phosphonates **5a,b** and **6a-c** with aldehydes **7a,f**[a]

entry	aldehyde (1.5eq)	*P* reagent (1.0eq)	base (1.1eq[b])	T(°C),t(h), solvent	yield (*E*+*Z*)	*E*/*Z* ratio[c]
43	n-PrCHO	**5a**	NaH	-78°,2,THF	85	**8a**: 50/50
44	n-PrCHO	**5a**	DBU	rt,24,THF	62	**8a**: 40/60
45	n-PrCHO	**5a**	[d]	-78°,2,THF	75	**8a**: 90/10
46	n-PrCHO	**5b**	[e]	-78°,2,THF	77	**8a**: 68/32
47	n-PrCHO	**5b**	[f]	-20°,2,THF	67	**8a**: 65/35
48	n-PrCHO	**5b**	[d]	-78°,2,THF	72	**8a**: >95/5
49	n-PrCHO	**6a**	[d]	-78°,2,THF	68	**9a**: 87/13
50	n-PrCHO	**6b**	[d]	-78°,2,THF	63	**9a**: 85/15
51	n-PrCHO	**6b**	DBU/LiCl	rt,16,MeCN	66	**9a**: 57/43
52	n-PrCHO	**6c**	[d]	-78°,2,THF	72	**9a**: >95/5
53	PhCHO	**5a**	NaH	-78°,2,THF	76	**8f**: 36/64
54	PhCHO	**5a**	DBU	rt,24,THF	67	**8f**: 16/84
55	PhCHO	**5a**	[d]	-78°,2,THF	84	**8f**: 24/76
56	PhCHO	**5b**	[e]	-78°,2,THF	76	**8f**: 73/27
57	PhCHO	**5b**	[f]	-20°,2,THF	65	**8f**: 71/29
58	PhCHO	**5b**	[d]	-78°,2,THF	79	**8f**: 90/10
59	PhCHO	**6a**	[d]	-78°,2,THF	79	**9f**: 50/50
60	PhCHO	**6b**	[d]	-78°,2,THF	72	**9f**: 51/49
61	PhCHO	**6b**	DBU/LiCl	rt,16,MeCN	70	**9f**: 87/13
62	PhCHO	**6c**	[d]	-78°,2,THF	68	**9f**: 45/55

[a] For other details, see Experimental Section; [b] except for [d,e,f], see below; [c] calculated by NMR (+/-2%); [d] $KN(SiMe_3)_2$ (2.0eq), 18-crown-6 (5.0eq); [e] $LiN(SiMe_3)_2$ (2.0eq), 12-crown-4 (5.0eq); [f] KOtBu (2.0eq), 18-crown-6 (5.0eq).

Rather surprisingly, milder deprotonation conditions reported to produce *Z*-2-unsubstituted alkenes from base-sensitive aldehydes and trifluoroethylphosphonates[12e] were less effective than $KN(SiMe_3)_2$ on aldehyde **7a** (compare entries 50 and 51) but significantly better on aldehyde **7f** (compare entries 60 and 61). We planned to test the two experimental conditions on different aldehydes to check the occurrence of this phenomenon. The comparison among the phenoxymono- (**6c**) and ditrifluoroethylphosphonate (**6b**) showed that the former has at least the same *E*-selectivity as the latter (compare entries 50 with 52, 60 with 62). This reagent was considered worthy of further investigations.

A comparison with reported data[12e] for 2-unsubstituted and 2-methyl-2-alkenoates showed a reduced *E*-selectivity for the α-oxytrifluoroethylphosphonates when using benzaldehyde (compare *E*/Z values for entry 58 and especially 60 with the reported values of >50/1 for trifluoroethylphosphonoacetate and of 30/1 for 2-methyltrifluoroethylphosphonoacetate[12e]). This may result from additional steric hindrance (alkyl substituents larger than methyl were reported to slow down the phosphonate oxide elimination, increasing the equilibration/elimination ratio) and/or from electronic effects of the substituted oxygen atom.

The results obtained with aldehydes **7a** and **7f** allowed us to select some representative procedures to be tested on a wide selection of aldehydes. The reaction with phosphonium salt **1a** was chosen to prepare *Z*-isomers **8** with a

good selectivity, while the alkyl salts **1c** and **2b** were chosen to check the behaviour of alkoxy- and aryloxyalkylphosphonium salts. Trifluoroethylphosphonates **5b**, **6b** and **6c** were selected to prepare the *E*-isomers **8** and **9** using $KN(SiMe_3)_2$/18-crown-6 or DBU/LiCl.

The selected aldehydes are shown in Figure 3. We chose α-branched acyclic (**7b,c**) and cyclic (**7d**) aliphatic aldehydes, an α,β-unsaturated aldehyde (**7e**) and some aromatic aldehydes with additional steric hindrance due to various electron-donating substituents (**7g-i**), electron-withdrawing substituents (**7j-l**) and alkyl groups (**7m,n**). In order to determine the configuration of the pure geometric isomers obtained from the olefinations, we used the NMR mixed coupling constant between the 1-carbon and the 3-hydrogen of the resulting alkenoates (Table V). A small value (1-4 Hz) was characteristic for a *cis* *Z*-configuration, while a value between 8 and 11 Hz was due to a *trans* *E*-configuration; all the values obtained for the different isomers are reported in Table V.

The purification of single isomers was generally performed by preparative TLC. These samples were used to determine the *E*- or *Z*-configuration of compounds **8**,**9**. Some of the values in Table V are missing because the corresponding isomer was not obtained in a sufficient quantity for performing the necessary NMR experiments. An additional analytical characterization (^1H NMR, IR, MS, microanalysis) was performed on the purified reaction products (pure isomers or *E*/*Z* mixtures, see Experimental Section for more details).

n-PrCHO	i-PrCHO	t-BuCHO
7a	**7b**	**7c**

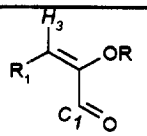
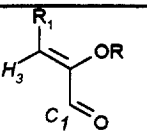
cyclohexylCHO	PhCH=CHCHO	PhCHO
7d	**7e**	**7f**

G-PhCHO

7g G=2-OMe; **7h** G=2,4,5-triOMe; **7i** G=3,4,5-triOMe; **7j** G=2-NO_2; **7k** G=2,6-diNO_2; **7l** G=3-NO_2,4-Cl; **7m** G=2-Me; **7n** G=2,4,6-triMe

Figure 3

Table V. *E*- and *Z*-attribution for **8,9a-n** (NMR).[a]

				
compounds	***E*-8** $C_1(\delta)$, $^3J_{CH}$(Hz)	***E*-9** $C_1(\delta)$, $^3J_{CH}$(Hz)	***Z*-8** $C_1(\delta)$, $^3J_{CH}$(Hz)	***Z*-9** $C_1(\delta)$, $^3J_{CH}$(Hz)
8,9a	163.8 10.6	163.1 9.6	NM[b]	163.0 <1.0
8,9b	163.8 9.9	163.7 9.6	164.4 2.8	163.7 3.5
8,9c	NM	NM	NM	NM
8,9d	163.6 9.2	NM	164.3 2.1	163.8 2.8
8,9e	NM	163.4	163.2 2.1	NM
8,9f	164.2 9.5	163.58 9.2	164.7 3.2	163.97 2.8
8,9g	NM	163.9 9.9	NM	164.1 2.8
8,9h	164.4 9.9	163.9 10.7	164.8 2.8	164.4 2.1
8,9i	164.5 9.2	NM	164.5 3.6	163.8 2.3
8,9j	163.0 10.7	162.7 9.2	163.8 3.3	NM
8,9k	162.1 8.9	162.1 9.2	NM	NM
8,9l	163.1 9.9	162.7 9.5	163.6 3.3	163.1 <1.0
8,9m	163.9 10.3	NM	165.0 2.8	NM
8,9n	163.0 10.5	NM	164.5 3.7	163.8 2.8

[a] spectra recorded in $CDCl_3$ at 300°K with a 200MHz instrument,; [b] not measured.

At first we submitted the aliphatic aldehydes **7b-d** and the unsaturated **7e** to the selected panel of olefination reactions. The results are shown in Table VI.

The presence of alkyl substituents at the α-carbon required prolonged reaction times (Wittig) or increased temperatures (Horner-Wadsworth-Emmons), and significant amounts of starting aldehydes were recovered. The behaviour of various *P* reagents was similar to that observed for **7a** but with somewhat reduced selectivities due to the α-branching, as already observed for 2-unsubstituted trifluoroethylphosphonates.[12c] Generally, good to excellent selectivities were obtained with aldehydes **7b,d**, while the more hindered **7c** either failed to react (entries 69, 72 and 73) or gave lower yields and sometimes also reduced selectivity (entry 74). The DBU/LiBr conditions on **6c** produced a slightly reduced selectivity compared to the classical $KN(SiMe_3)_2$/18-crown-6 conditions (entries 74 and 75).

Table VI. Alkenation reactions of aldehydes **7b-e**[a]

entry	aldehyde (1.5eq)	*P* reagent (1.0eq)	base (1.1eq[b])	T(°C),t(h), solvent	yield (*E*+*Z*)	*E*/*Z* ratio[c]
63	**7b**	**1a**	DBU	rt,48,THF	62	**8b**: 10/90
64	**7b**	**1c**	DBU	rt,48,THF	46	**8b**: 65/35
65	**7b**	**5b**	[d]	-78° to rt,24,THF	61	**8b**: 80/20
66	**7b**	**2b**	DBU	rt,48,THF	26	**9b**: 44/56
67	**7b**	**6b**	[d]	-78° to rt,24,THF	57	**9b**: 89/11
68	**7b**	**6c**	[d]	-78° to rt,24,THF	57	**9b**: 88/12
69	**7c**	**1a**	DBU	reflux,48,THF	TOP[e]	-
70	**7c**	**1c**	DBU	rt,48,THF	7	**8c**: 60/40
71	**7c**	**5b**	[d]	-78° to rt,24,THF	38	**8c**: 83/17
72	**7c**	**2b**	DBU	reflux,48,THF	TOP[e]	-
73	**7c**	**6b**	[d]	-78° to rt,24,THF	TOP[e]	-
74	**7c**	**6c**	[d]	-78° to rt,24,THF	18	**9c**: 66/34
75	**7c**	**6c**	DBU/LiCl	rt,16,MeCN	25	**9c**: 55/45
76	**7d**	**1a**	DBU	rt,48,THF	26	**8d**: 8/92
77	**7d**	**1c**	DBU	rt,48,THF	27	**8d**: 63/37
78	**7d**	**5b**	[d]	-78° to rt,24,THF	69	**8d**: 83/17
79	**7d**	**2b**	DBU	rt,48,THF	10	**9d**: 45/55
80	**7d**	**6b**	[d]	-78° to rt,24,THF	64	**9d**: 93/7
81	**7d**	**6c**	[d]	-78° to rt,24,THF	76	**9d**: ≥95/5
82	**7e**	**1a**	DBU	rt,24,THF	77	**8e**: 15/85
83	**7e**	**5b**	[d]	-78°,2,THF	70	**8e**: 90/10
84	**7e**	**2b**	DBU	rt,24,THF	59	**9e**: 50/50
85	**7e**	**6b**	[d]	-78°,2,THF	72	**9e**: 95/5
86	**7e**	**6c**	[d]	-78°,2,THF	74	**9e**: 91/9

[a] For other details, see Experimental Section; [b] except for [d], see below; [c] calculated by NMR (+/-2%); [d] $KN(SiMe_3)_2$ (2.0eq), 18-crown-6 (5.0eq); [e] traces of product (<5%).

The unsaturated trans-cynnamaldehyde **7e** afforded, with good yields and selectivities, the expected ***Z*-8** (entry 82) and ***E*-8**, ***E*-9** isomers (entries 83, 85 and 86).

Then wemoved to substituted aromatic aldehydes, starting from methoxysubstituted compounds **7g-i**. The reactivity of these aldehydes was reduced in comparison with benzaldehyde **7f**, and prolonged reaction times and/or increased temperatures, as seen for **7b-d**, had to be used (Table VII).

Table VII. Alkenylation reactions of aldehydes **7g-i**[a]

entry	aldehyde (1.5eq)	*P* reagent (1.0eq)	base (1.1eq[b])	T(°C),t(h), solvent	yield (*E*+*Z*)	*E*/*Z* ratio[c]
87	**7g**	**1a**	DBU	rt,48,THF	61	**8g**: 5/95
88	**7g**	**5b**	[d]	-78° to rt,24,THF	57	**8g**: 50/50
89	**7g**	**5b**	DBU/LiCl	rt,16,MeCN	60	**8g**: 44/56
90	**7g**	**6b**	[d]	-78° to rt,24,THF	54	**9g**: 75/25
91	**7g**	**6b**	DBU/LiCl	rt,16,MeCN	61	**9g**:78/22
92	**7g**	**6c**	[d]	-78° to rt,24,THF	61	**9g**: 75/25
93	**7h**	**1a**	DBU	reflux,48,THF	ND[e]	-
94	**7h**	**1c**	DBU	rt,48,THF	24	**8h**: 41/59
95	**7h**	**5b**	[d]	-78° to rt,24,THF	59	**8h**: 82/18
96	**7h**	**2b**	DBU	reflux,48,THF	TOP[f]	-
97	**7h**	**6b**	[d]	-78° to rt,24,THF	43	**9h**: 61/39
98	**7h**	**6c**	[d]	-78° to rt,24,THF	48	**9h**: 82/18
99	**7i**	**1a**	DBU	rt,48,THF	52	**8i**: 7/93
100	**7i**	**1c**	DBU	rt,48,THF	38	**8i**: 67/33
101	**7i**	**5b**	[d]	-78° to rt,24,THF	52	**8i**: 60/40
102	**7i**	**2b**	DBU	rt,48,THF	20	**9i**: >5/95
103	**7i**	**6b**	[d]	-78° to rt,24,THF	48	**9i**: 67/33
104	**7i**	**6c**	[d]	-78° to rt,24,THF	46	**9i**: 80/20

[a] For other details, see Experimental Section; [b] except for [d], see below; [c] calculated by NMR (+/-2%); [d] $KN(SiMe_3)_2$ (2.0eq), 18-crown-6 (5.0eq); [e] not detectable (<2%); [f] traces of product (<5%).

The *Z*-selectivity for reagent **1a** was confirmed (entries 87 and 99) except for compound **7h**, which proved to be virtually unreactive with phosphonium salts (entries 93, 94 and 96). The trifluoroethylphosphonates **5b** and **6c** gave good *E*-selectivities with aldehydes **7h,i** (entries 95 and 101, 98 and 104), while worse results were obtained with trifluoroethylphosphonate **6b** (entries 97 and 103). Aldehyde **7g** gave moderate *E*-selectivity with the three trifluoroethylphosphonates (entries 88, 90 and 92). The use of DBU/LiCl as reaction conditions (entries 89 and 91) produced results comparable to the ones obtained with $KN(SiMe_3)_2$ and 18-crown-6.

An alkenylation of nitrosubstituted benzaldehydes **7j-l** was then attempted. Their reactivity was higher than that observed with benzaldehyde and reaction yields were generally improved, except for entry 114 (Table VIII).

The behaviour of **7l** with the phosphonium salts **1a**, **1c** and **2b** was normal (entries 118, 119 and 121), while good *Z*-selectivity was attained for aldehyde **7j** with **1c** (entry 106) and not with **1a** (entry 105) and good or excellent *E*-selectivity was obtained by reaction of **7k** with the Wittig salts **1a**, **1c** and **2b** (entries 111, 112 and 114).

The "inverse" behaviour of the di-orthonitrosubstituted **7k** was found also with *P* reagents **6b,c** (entries 115 and 116), that produced excellent ***Z***-selectivities, while only with reagent **5b** the expected isomer ***E*-8k** was obtained with good selectivity (entry 113). Both the hindrance of the two nitro substituents in ortho position and their strong electron-withdrawing properties could have played a significant role in the reactivity of aldehyde **7k**; nevertheless, the

partial reversion obtained by the use of DBU/LiCl with trifluoroethylphosphonate **6c** (compare entries 117 and 116) pointed also towards a strong influence of the reaction conditions.

The mono-orthonitrosubstituted **7j** showed no selectivity when reacted with **5b** (entry 107) and good *E*-selectivity with **6b,c** (entries 109 and 110). The compound **7l** showed a generally poor selectivity with phosphonates **5b**, **6b** and **6c** (entries 120, 122 and 123); the use of DBU/LiCl increased only marginally the *E*-selectivity with reagent **6c** (compare entries 123 and 124).

Table VIII. Alkenylation reactions of aldehydes **7j-l**[a]

entry	aldehyde (1.5eq)	*P* reagent (1.0eq)	base (1.1eq[b])	T(°C),t(h), solvent	yield (*E*+*Z*)	*E*/*Z* ratio[c]
105	**7j**	**1a**	DBU	rt,24,THF	89	**8j**: 34/66
106	**7j**	**1c**	DBU	rt,24,THF	90	**8j**: 88/12
107	**7j**	**5b**	[d]	-78°,2,THF	93	**8j**: 45/55
108	**7j**	**2b**	DBU	rt,24,THF	42	**9j**: 62/38
109	**7j**	**6b**	[d]	-78°,2,THF	65	**9j**: 90/10
110	**7j**	**6c**	[d]	-78°,2,THF	66	**9j**: 80/20
111	**7k**	**1a**	DBU	rt,24,THF	87	**8k**: 83/17
112	**7k**	**1c**	DBU	rt,24,THF	81	**8k**: 93/7
113	**7k**	**5b**	[d]	-78°,2,THF	89	**8k**: 92/8
114	**7k**	**2b**	DBU	rt,24,THF	18	**9k**: 81/19
115	**7k**	**6b**	[d]	-78°,2,THF	82	**9k**: 12/88
116	**7k**	**6c**	[d]	-78°,2,THF	84	**9k**: >5/95
117	**7k**	**6c**	DBU/LiCl	rt,16,MeCN	83	**9k**: 55/45
118	**7l**	**1a**	DBU	rt,24,THF	85	**8l**: 8/92
119	**7l**	**1c**	DBU	rt,24,THF	87	**8l**: 65/35
120	**7l**	**5b**	[d]	-78°,2,THF	88	**8l**:70/30
121	**7l**	**2b**	DBU	rt,24,THF	82	**9l**: 41/59
122	**7l**	**6b**	[d]	-78°,2,THF	86	**9l**: 37/63
123	**7l**	**6c**	[d]	-78°,2,THF	87	**9l**: 50/50
124	**7l**	**6c**	DBU/LiCl	rt,16,MeCN	84	**9l**: 58/42

[a] For other details, see Experimental Section; [b] except for [d], see below; [c] calculated by NMR (+/-2%); [d] $KN(SiMe_3)_2$ (2.0eq), 18-crown-6 (5.0eq).

Finally we examined the behaviour of methylsubstituted aromatic aldehydes **7m,n** (Table IX). Their reactivity was comparable to that of the methoxy-substituted aldehydes **7g-i**.

The monosubstituted aldehyde **7m** reacted with moderate to good yields with all the *P* reagents, and the expected *Z*- (entry 125) and *E*-selectivities (entries 127, 129 and 130) were found. The more hindered aldehyde **7n** gave poor yields (or failed to react as in entries 135 and 136), while the expected behaviour with the different *P* reagent in terms of selectivity was generally found.

Table IX. Alkenylation reactions of aldehydes **7m,n**[a]

entry	aldehyde (1.5eq)	*P* reagent (1.0eq)	base (1.1eq[b])	T(°C),t(h), solvent	yield (*E*+*Z*)	*E*/*Z* ratio[c]
125	**7m**	**1a**	DBU	rt,48,THF	61	**8m**: 15/85
126	**7m**	**1c**	DBU	rt,48,THF	69	**8m**: 78/22
127	**7m**	**5b**	[d]	-78° to rt,24,THF	78	**8m**: 90/10
128	**7m**	**2b**	DBU	rt,48,THF	32	**9m**: 60/40
129	**7m**	**6b**	[d]	-78° to rt,24,THF	61	**9m**: 82/18
130	**7m**	**6c**	[d]	-78° to rt,24,THF	59	**9m**: 80/20
131	**7n**	**1a**	DBU	rt,48,THF	9	**8n**: >5/95
132	**7n**	**1c**	DBU	rt,48,THF	27	**8n**: 59/41
133	**7n**	**5b**	[d]	-78° to rt,24,THF	48	**8n**: 50/50
134	**7n**	**2b**	DBU	rt,48,THF	8	**9n**: 13/87
135	**7n**	**6b**	[d]	-78° to rt,24,THF	TOP[e]	-
136	**7n**	**6c**	[d]	-78° to rt,24,THF	ND[f]	-

[a] For other details, see Experimental Section; [b] except for [d], see below; [c] calculated by NMR (+/-2%); [d] $KN(SiMe_3)_2$ (2.0eq), 18-crown-6 (5.0eq); [e] traces of product (<5%); [f] not detectable (<2%).

To evaluate the obtained results in terms of the geometrical outcome, we planned to divide the aldehydes **7** into 7 different "classes": aliphatic (**7a**), α-branched aliphatic (**7b-d**), α,β-unsaturated (**7e**), aromatic (**7f**), electron-rich aromatic (**7g-i**), electron-poor aromatic (**7j-l**) and alkyl substituted aromatic (**7m-n**). We considered, among the *P*

Table X. Geometrical outcome for the alkenylation of aldehydes **7a-m**[a]

	1a	**1c**	**5b**	**2b**	**6b,c**
7a	+++*Z*	-	+++*E*	++*Z*	+++*E*
7b-d	++*Z*	+*E*	++*E*	-	++*E*
7e	++*Z*	-	+++*E*	-	+++*E*
7f	+++*Z*	-	+++*E*	-	++*E*
7g	+++*Z*	ND[b]	-	ND	+*E*
7h	NR[c]	-	++*E*	NR	++*E*
7i	+++*Z*	+*E*	+*E*	+++*Z*	++*E*
7j	+*Z*	++*E*	-	+*E*	+++*E*
7k	++*E*	+++*E*	+++*E*	++*E*	+++*Z*
7l	+++*Z*	+*E*	+*E*	-	-
7m	++*Z*	+*E*	+++*E*	+*Z*	++*E*
7n	+++*Z*	-	-	++*Z*	NR

[a] the most selective results were considered when a reaction was repeated in different experimental conditions;
[b] reaction not performed; [c] no reaction products.

reagents, as 2-methoxy the aryl phosphonium salts (**1a**), the alkylphosphonium salts (**1c**) and the trifluoroalkylphosphonates (**5b**); as 2-phenoxy, the alkylphosphonium salts (**2b**) and the trifluoroalkylphosphonates (**6b,c**). The results for each class are reported in Table X and roughly classified with a "-" (*E/Z* from 60/40 to 40/60), with a "+" (ratio from 80/20 to 60/40), with a "++" (ratio from 90/10 to 80/20) and with a "+++" (ratio from >95/5 to 90/10).

In general, the availability of *Z*- (**1a**) or *E*- (**5b**) 2-methoxyalkenoates and of *E*-(**6b,c**) 2-phenoxyalkenoates was proved with selectivities from good to excellent and with yields from moderate to excellent starting from different aldehydes. The lack of reactivity of the 2-phenoxy aryl phosphonium salt **2a** prevented the preparation of pure *Z*-2-phenoxyalkenoates that were sometimes available using the salt **2b** (Table X). The chemical yields were generally good to excellent, with the exception of some attempts with hindered aliphatic (**7c**) or aromatic (**7h**) aldehydes. Among the aromatic aldehydes the lack of steric hindrance and expecially the presence of one or more electron withdrawing substituents were shown to increase the reactivity of the aldehydes and the chemical yields of the reactions.

Among the aldehydes **7a-e**, the behaviour was very similar with somewhat reduced selectivities for branched aldehydes when compared to linear saturated (**7a**) or unsaturated (**7e**) ones, as expected.[12c] While the simple **7f** behaved similarly to the aliphatic aldehydes, the substituted aromatic aldehydes presented different behaviours among members of the same class, expecially in presence of strong electron-withdrawing substituents. It was then necessary to examine the individual behaviour of each of aldehydes **7g-n** (Table X).

While some compounds showed a partial or complete loss of selectivity when compared with benzaldehyde, either in *Z*- (**7j** with **1a**) or in *E*-producing conditions (**7g**, **7j** and **7n** with **5b**, **7g** and **7l** with **6b,c**), the *E*- or *Z*-selectivity was always in the same direction but for 2,6-dinitrobenzaldehyde **7k**. This aldehyde showed a pronounced selectivity with all the reagents, but with a complete inversion with the most selective *P* reagents, giving good *E* selectivity when reacted with **1a** and excellent *Z*-selectivity with **6b** and **6c** (see comments to Table VIII for a more detailed discussion).

Further attempts, aimed to clarify the uncommon behaviour of aldehyde **7k** by using other di-orthosubstituted electron poor aldehydes and to expand the range of the alkoxy or aryloxy substituents in position 2, are currently in progress.

EXPERIMENTAL SECTION

General.

Solvents and reagents were purified and dried by standard techniques.[18] Solvents were removed using a Buchi EL 131 rotary evaporator at bath temperatures varying from rt to 50°C. The reactions and the final compounds were analyzed by direct phase TLC using Merck Kieselgel 60 F_{254} thin-layer plates with eluent mixtures including CH_2Cl_2, MeOH, AcOEt and n-heptane. IR spectra ($CDCl_3$ solution) were recorded on a Perkin-Elmer 850 spectrometer and the values are reported in cm^{-1} (υ). ^1H NMR spectra were recorded at 200 MHz with a Bruker AC 200 at 303°K in $CDCl_3$. The chemical shifts (δ) are reported in ppm downfield from the internal reference, tetramethylsilane (TMS, δ 0.00). The coupling constants (J) are reported in Hz. Mass spectra were recorded on a Varian MAT 311 instrument under chemical ionization (CI) conditions (70eV, ion source temperature 140°). Mass spectra of pure isomer couples were recorded and found to be undistinguishable, so the

spectra were recorded as routine without isolation of pure single isomers. A Model 1106 Carlo Erba instrument was used for elemental analysis utilizing standard techniques.

Methyl 2-bromo-2-methoxyacetate: A suspension of methyl 2-methoxyacetate (88.2 g, 874 mmoles), NBS (151 g, 847 mmoles) and benzoyl peroxide (400 mg, catalytic) was refluxed for 4 hours. The resulting suspension was cooled to rt, filtered and concentrated at reduced pressure. The residual oil was distilled producing a fraction of pure title compound, b.p. 80-82°/0.1mm Hg (134 g, 73.2 mmoles, yield 86.5%). δ_H 6.01 (1H, s, CH), 3.85 (3H, s, OMe), 3.58 (3H, s, COOMe). Methyl 2-bromo-2-phenoxyacetate (eb. 150-153°/10mm Hg) was prepared in 82.0% yield by the same procedure.

Methyl 2-methoxy-2-(triphenylphosphonium)acetate bromide (1a): A suspension of methyl 2-bromo-2-methoxyacetate (13.0 g, 71.0 mmoles) and triphenylphosphine (18.7 g, 71.0 mmoles) in toluene (100 mL) was stirred vigorously at rt overnight. The reaction mixture was filtered, the precipitate was washed thoroughly with Et_2O and dried for 24 hours at 50° under vacuum. This produced pure **1a** (28.1 g, 63.2 mmoles, yield 89.1%) as a white solid, m.p. 138-140° dec. δ_H 8.15 (1H, d, J=13.0Hz, CH), 7.50-8.05 (15H, m, Ar), 3.85 (3H, s, OMe), 3.55 (3H, s, COOMe). Compounds **1b-h**, **2a-c**, **3**, **4**, **5a** and **6a** were prepared by the same procedure using phosphines,[13] phosphinites[14] or phosphites[15].

Methyl 2-(di(2',2',2'-trifluoroethoxy)phosphoryl)-2-phenoxyacetate (6b) and Methyl 2-(ethoxy(2',2',2'-trifluoroethoxy)phosphoryl)-2-phenoxyacetate (6c): PCl_5 (37.5 g, 180 mmoles) was added portionwise under vigorous stirring at 0° to phosphonate **6a** (24.17 g, 70 mmoles) and the reaction mixture was warmed to rt during 1 hour. After heating at 75° for 3 hours the crude mixture was cooled to rt and distilled first at 20mm Hg to eliminate $POCl_3$ (30°-40°), then at 0.04mm Hg where a first fraction of PCl_5 (28-35°) was followed by a yellow oil, b.p. 122-135°/0.04mm Hg (16.6 g, theoretically 60 mmoles). This crude dichloride was dissolved in benzene (80 mL) at 0° with stirring and a solution of 2,2,2-trifluoroethanol (10.1 mL, 130 mmoles) and DIEA (23 mL, 130 mmoles) was added dropwise at 0°C. The reaction mixture was gently warmed to rt, stirring was continued for 2 hours, then the solvent was concentrated and the residue chromatographed on silica gel (EtOAc/n-heptane 1/4 as eluant mixture). A first fraction of **6b** (9.56 g, 23.3 mmoles, yield 33.3%) and a second of **6c** (7.52 g, 21.1 mmoles, yield 30.1%) were obtained. **6b**: R_f 0.39 (4/1 n-heptane/AcOEt); δ_H 7.31 (2H, m, Ar), 7.08 (1H, t, Ar), 6.94 (2H, d, Ar), 5.19 (1H, d, J=19.6, CH), 4.54 (4H, m, CH_2), 3.86 (3H, s, OM*e*). **6c**: R_f 0.25 (4/1 n-heptane/AcOEt); δ_H 7.31 (2H, m, Ar), 7.05 (1H, t, Ar), 6.92 (1H, d, Ar), 5.11 (1H, 4, J=19.6, CH), 4.50 (2H, m, CH_2CF_3), 4.34 (2H, m, CH_2CH_3), 3.84 (3H, s, OM*e*), 1.39 (3H, dt, CH_3).

Wittig reaction with methyl 2-methoxy-2-(triphenylphosphonium)acetate bromide 1a. *Z*-Methyl-3-(4-chloro-3-nitrophenyl)-2-methoxy-2-propenoate (*Z*-8l): A suspension of **1a** (890 mg, 2.0 mmoles) and DBU (330μL, 2.2 mmoles) in THF (20 mL) was stirred for 10 minutes at rt. Aldehyde **7l** (560 mg, 3.0 mmoles) was added and stirring at rt continued for 24 hours. The solvent was then concentrated at reduced pressure, the residue was taken up with AcOEt (30 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (2x10 mL). The organic phase was dried ($MgSO_4$), evaporated at reduced pressure and finally chromatographed on silicagel (9/1 n-heptane/AcOEt as eluant mixture) to give **8l** (461mg, 1.70 mmoles, yield 85.0%) as an oily 8/92 *E/Z* mixture (NMR). ***Z*-8l**: R_f (9/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1728, 1709, 1602, 1540, 1355; *m/z* 273 (33), 271 (M, 100), 197 (27), 181 (21), 123 (26) and 59 (35); δ_H 8.35 (1H, d, 2-H Ar), 8.03 (1H, dd, 6-H Ar), 7.75 (1H, d, 5-H Ar), 6.83 (1H, s, CH=), 3.86 (3H, s, O*Me*), 3.84 (3H, s, COO*Me*); δ_C 163.58 (C_1), $^3J_{CH}$=3.34; microanalysis: found C, 48.53; H, 3.74; N, 5.12; Cl(org.), 12.97, calculated for $C_{11}H_{10}ClNO_5$ C, 48.64; H, 3.71; N, 5.16; Cl(org.) 13.05%.

Wittig reaction with methyl 2-methoxy-2-(tributylphosphonium)acetate bromide 1c. *E*- and *Z*-Methyl 2-methoxy-4-methyl-2-pentenoate (*E*- and *Z*-8b): A suspension of **1c** (770 mg, 2.0 mmoles) and DBU (330μL, 2.2 mmoles) in THF (20 mL) was stirred for 10 minutes at rt. Freshly distilled aldehyde **7b** (275 μL, 3.0 mmoles) was added and stirring at rt continued for 48 hours. The solvent was then evaporated at reduced pressure, the residue was taken up with AcOEt (30 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (2x10 mL). The organic phase was dried ($MgSO_4$), concentrated at reduced pressure and finally chromatographed on silica gel (19/1 n-heptane/AcOEt as eluant mixture) to give **8b** (145 mg, 0.92 mmoles, yield 45.8%) as an oily 65/35 *E/Z* mixture (NMR). This mixture was submitted to preparative TLC (39/1 n-heptane/AcOEt, 5 runs) to give a first fraction of ***Z*-8b** (31 mg) and a second of ***E*-8b** (47 mg). ***E*-8b**: R_f 0.13 (39/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1730, 1625, 1240; δ_H 4.98 (1H, d, J=9.6Hz, CH=), 3.78 (3H, s, O*Me*), 3.54 (3H, s, COO*Me*), 3.22 (1H, m, *CH*-$(CH_3)_2$), 1.01 (6H, d, CH-*(*CH_3*)*$_2$); δ_C 163.79 (C_1), $^3J_{CH}$=9.93. ***Z*-8b**: R_f 0.15 (9/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1732, 1620, 1258; δ_H 6.09 (1H, d, J=9.9Hz, CH=), 3.77 (3H, s, O*Me*), 3.65 (3H, s, COO*Me*), 2.87 (1H, m, *CH*-$(CH_3)_2$), 1.03 (6H, d, CH-*(*CH_3*)*$_2$); δ_C 164.43 (C_1), $^3J_{CH}$=2.84. ***E/Z*-8b**: *m/z* 158 (M, 13), 143 (38), 115 (20), 111 (34), 99 (43) and 83 (100); microanalysis: found C, 60.61; H, 8.99, calculated for $C_8H_{14}O_3$ C, 60.74; H, 8.92%.

Horner-Wadsworth-Emmons reaction with methyl 2-(di(2',2',2'-trifluoroethoxy)phosphoryl)-2-methoxyacetate 5b ($KN(SiMe_3)_2$/18-crown-6). 2*E*,4*E* Methyl 2-methoxy-5-phenyl-2,4-pentadienoate (*E*-8e): To a solution of **5b** (700 mg, 2.0 mmoles) and 18-crown-6 (2.65 g, 10.0 mmoles) in dry THF (20 mL) stirred under an Ar atmosphere at -78°C (dry ice/acetone bath) was added $KN(SiMe_3)_2$ (0.5 M solution in toluene, 8 mL, 4.0 mmoles) dropwise under stirring. After 10 minutes **7e** (380 μL, 3.0 mmoles) was added and stirring ar-78°C continued for 2 hours. The reaction was then quenched with saturated NH_4Cl solution (2 mL), warmed to rt, diluted with Et_2O (30 mL) and washed with brine (3x30 mL). The organic phase was dried ($MgSO_4$), evaporated at reduced pressure and finally chromatographed on silicagel (9/1 n-heptane/AcOEt as eluant mixture) to give **8e** (310 mg, 1.41 mmoles, yield 70.0%) as an oily 90/10 *E/Z* mixture (NMR). ***E*-8e**: R_f 0.43 (9/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1738, 1692, 1602, 1638, 1602, 1390; *m/z* 218 (M, 30), 159 (27), 116 (23), 115 (44), 105 (52), 83 (25) and 77 (100); δ_H 7.86 (1H, dd, J=11.3,15.3Hz, 4-CH), 7.20-7.55 (5H, m, Ar), 6.65 (1H, d, J=15.8Hz, 5-CH), 6.08 (1H, d, 3-CH), 3.87 (3H, s, O*Me*), 3.72 (3H, s, COO*Me*); δ_C 163.71 (C_1), $^3J_{CH}$=10.15; microanalysis: found C, 71.36; H, 6.52, calculated for $C_{13}H_{14}O_3$ C, 71.54; H, 6.47%.

Wittig reaction with methyl-2-phenoxy-2-(triethylphosphonium)acetate bromide 2b. *E*- and *Z*-Methyl-3-(4-chloro-3-nitrophenyl)-2-phenoxy-2-propenoate (*E*- and *Z*-9l): A suspension of **2b** (730 mg, 2.0 mmoles) and DBU (330μL, 2.2 mmoles) in THF (20 mL) was stirred for 10 minutes at rt. Aldehyde **7l** (560 mg, 3.0 mmoles) was added and stirring at rt continued for 24 hours. The solvent was then concentrated at reduced pressure, the residue was taken up with AcOEt (30 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (2x10 mL). The organic phase was dried ($MgSO_4$), evaporated at reduced pressure and finally chromatographed on silica gel (4/1 n-heptane/AcOEt as eluant mixture) to give **9l** (547 mg, 1.64 mmoles, yield 81.5%) as an oily 59/41 *E/Z* mixture (NMR). Half of this mixture was chromatographed on preparative TLC (9/1 n-heptane/AcOEt, 5 runs) to produce a first fraction of ***E*-9l** (52 mg) and a second one of ***Z*-9l** (47 mg). ***E*-9l**: R_f 0.16 (9/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1760, 1724, 1640, 1380; δ_H 7.88 (1H, d, 2-H Ar), 7.00-7.55 (7H, m, Ar), 6.48 (1H, s, CH=), 3.71 (3H, s, COO*Me*); δ_C 162.67 (C_1), $^3J_{CH}$=9.47. ***Z*-9l**: R_f 0.14 (9/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1735, 1710, 1600, 1355; δ_H 8.36 (1H, d, 2-H Ar), 8.02 (1H, dd, 6-H Ar), 7.75 (1H, d, 5-H Ar),7.278 (1H, s, CH=), 6.90-7.40 (5H, m, Ar), 3.76 (3H, s, COO*Me*); δ_C 163.13 (C_1), $^3J_{CH}$<1.00. ***E/Z*-9l**: *m/z* 335 (30), 333 (M, 88), 274 (29), 202 (56), 166 (21), 165 (22), 110 (47), 107 (80), 94 (41) and 77 (100); microanalysis: found C, 57.53; H, 3.78; N, 4.15; Cl(org.), 10.54, calculated for $C_{16}H_{12}ClNO_5$ C, 57.58; H, 3.62; N, 4.20; Cl(org.) 10.62%.

Horner-Wadsworth-Emmons reaction with methyl 2-(di(2',2',2'-trifluoroethoxy)phosphoryl)-2-phenoxyacetate 6b ($KN(SiMe_3)_2$/18-crown-6). *E*-Methyl 2-phenoxy-2-hexenoate (*E*-9a): To a solution of **6b** (820 mg, 2.0 mmoles) and 18-crown-6 (2.65 g, 10.0 mmoles) in dry THF (20 mL) stirred under Ar atmosphere at -78°C (dry ice/acetone bath) was added $KN(SiMe_3)_2$ (0.5 M solution in toluene, 8 mL, 4.0 mmoles) dropwise under stirring. After 10 minutes **7a** (280 μL, 3.0 mmoles) was added and stirring at -78°C continued for 2 hours. The reaction was then quenched with saturated NH_4Cl solution (2 mL), warmed to RT, diluted with Et_2O (30 mL) and washed with brine (3x30 mL). The organic phase was dried ($MgSO_4$), evaporated at reduced pressure and finally chromatographed on silica gel (19/1 n-heptane/AcOEt as eluant mixture) to give **9a** (278 mg, 1.26 mmoles, yield 63.0%) as an oily 85/15 *E/Z* mixture (NMR). ***E*-9a**: R_f 0.41 (19/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1726, 1650, 1595, 1498, 1375; *m/z* 234 (M, 100), 159 (37), 131 (45), 119 (20), 105 (36), 94 (28) and 77 (74); δ_H 6.80-7.50 (5H, m, Ar), 5.94 (1H, t, J=7.8Hz, CH=), 3.72 (3H, s, COO*Me*), 2.59 (2H, dt, J=7.8Hz, =CH*CH*$_2$), 1.64 (2H, m, *CH*$_2$CH$_3$), 0.93 (3H, t, CH$_2$*CH*$_3$); δ_C 163.14 (C_1), $^3J_{CH}$=9.58; microanalysis: found C, 70.80; H, 7.36, calculated for $C_{13}H_{16}O_3$ C, 70.89; H, 7.32%.

Horner-Wadsworth-Emmons reaction with methyl 2-(ethoxy(2',2',2'-trifluoroethoxy)phosphoryl)-2-phenoxyacetate 6c ($KN(SiMe_3)_2$/18-crown-6). E-Methyl 2-phenoxy-3-(2,4,5-trimethoxyphenyl)-2-propenoate (E-9h): To a solution of **6c** (820 mg, 2.0 mmoles) and 18-crown-6 (2.65 g, 10.0 mmoles) in dry THF (20 mL) stirred under Ar atmosphere at -78°C (dry ice/acetone bath) was added $KN(SiMe_3)_2$ (0.5 M solution in toluene, 8 mL, 4.0 mmoles) dropwise under stirring. After 10 minutes **7h** (590 mg, 3.0 mmoles) was added at -78°C, then stirring was continued for 24 hours gently warming the reaction mixture to rt. The reaction was then quenched with saturated NH_4Cl solution (2 mL), diluted with Et_2O (30 mL) and washed with brine (3x30 mL). The organic phase was dried ($MgSO_4$), evaporated at reduced pressure and finally chromatographed on silica gel (4/1 n-heptane/AcOEt as eluant mixture) to give **9h** (265 mg, 0.94 mmoles, yield 47.5 %) as an oily 82/18 *E/Z* mixture (NMR). ***E*-9h**: R_f 0.18 (4/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1715, 1670, 1635, 1605, 1410; *m/z*; δ_H 6.95-7.35 (7H, m, Ar), 6.87 (1H, s, CH=), 3.96 (3H, s, OMe), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe), 3.72 (3H, s, COO*Me*); δ_C 163.90 (C_1), $^3J_{CH}$=10.65; microanalysis: found C, 59.49; H, 6.49, calculated for $C_{14}H_{18}O_6$ C, 59.57; H, 6.43%.

Horner-Wadsworth-Emmons reaction with methyl 2-(di(2',2',2'-trifluoroethoxy)phosphoryl)-2-phenoxyacetate 6b (DBU/LiCl). *E*-Methyl 2-phenoxy-3-phenyl-2-propenoate (*E*-9f): A suspension of **6b** (820mg, 2.0 mmoles), DBU (330μL, 2.2 mmoles) and anhydrous LiCl (95 mg, 2.2 mmoles) in dry THF (20 mL) was stirred under an Ar atmosphere for 10 minutes at rt. Redistilled aldehyde **7f** (310 μL, 3.0 mmoles) was added and stirring at rt continued for 16 hours. The solvent was then concentrated at reduced pressure, the residue was taken up with AcOET (30 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (2x10 mL). The organic phase was dried ($MgSO_4$), evaporated at reduced pressure and finally chromatographed on silica gel (19/1 n-heptane/AcOEt as eluant mixture) to give **9f** (354 mg, 1.39 mmoles, yield 69.5%) as an oily 87/13 *E/Z* mixture (NMR). ***E*-9f**: R_f 0.28 (9/1 n-heptane/AcOEt); υ_{max}/cm^{-1}: 1724, 1642, 1358; *m/z* 268 (M, 100), 195 (15), 167 (39), 165 (25), 119 (17), 118 (96), 94 (37) and 77 (43); δ_H 6.85-7.90 (10H, m, Ar), 6.73 (1H, s, CH=), 3.66 (3H, s, COO*Me*); δ_C 163.95 (C_1), $^3J_{CH}$=9.81; microanalysis: found C, 75.46; H, 5.60, calculated for $C_{16}H_{14}O_3$ C, 75.58; H, 5.55%.

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