Efficient and Scalable Protocol for the *Z*-Selective Synthesis of Unsaturated Esters by Horner–Wadsworth–Emmons Olefination

François P. Touchard,* Nicolas Capelle, Mathilde Mercier

Rhodia Recherches, Centre de Recherches de Lyon, 85 rue des frères Perret, BP 62, 69192 Saint Fons Cedex, France
Fax: (+33)-4-72-89-68-94, e-mail: francois.touchard@eu.rhodia.com

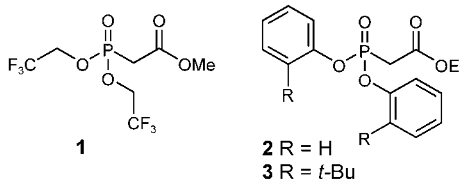
Received: November 2, 2004; Accepted: February 7, 2005

Abstract: The synthesis of a highly *Z*-selective Horner–Wadsworth–Emmons (HWE) reagent from cheap and readily available starting materials on a 200-g scale is described. The HWE reaction conditions have also been studied in order to design an efficient and scalable protocol leading to *Z*-selectivities close to 95% with aromatic and aliphatic aldehydes.

Keywords: alkenes; Horner–Wadsworth–Emmons reaction; olefination; preparative scale; stereoselectivity

Introduction

The Horner–Wadsworth–Emmons (HWE) reaction is a variant of the Wittig reaction that possesses a number of significant advantages. Not only is the work-up greatly facilitated since the phosphate salt formed is water-soluble but the reactivity of HWE reagents allows them to effect transformations that are either difficult or impossible using the analogous Wittig ylides. This reaction, which usually proceeds smoothly and under mild conditions with phosphonates bearing stabilising substituents, typically leads to the more stable *E*-disubstituted olefins.[1] As it is highly desirable to be able to prepare the *E* or *Z* isomer at will, Still,[2] in 1983, and Ando,[3,4] in 1995, developed two *Z*-selective reagents: methyl bis(trifluoroethyl)phosphonoacetate (**1**) and ethyl diphenylphosphonoacetate (**2**), respectively (Scheme 1).[5] However, the conditions required to obtain high *Z/E* ratios were fairly stringent and usually necessitated work at low temperatures.[6] With the aim of establishing an efficient and scalable protocol for the *Z*-selective olefination of aldehydes, we have decided to reinvestigate and modulate the Still/Ando procedures. Using Still's reagent, we have already shown that it is possible to work at 0 °C with K_2CO_3/10 mol % 18-crown-6 and to obtain selectivities up to 98%. However, these conditions are effective essentially with aromatic aldehydes.[7] More recently, we have also reported the phosphonate based upon 2-*t*-butylphenol (**3**; Scheme 1), to be highly selective at 0 °C with both aromatic and aliphatic aldehydes.[8] But in order to render the *Z*-selective synthesis of unsaturated esters even more practical, this article presents an improved and scalable synthesis of phosphonate **3** as well as optimisation of the HWE reaction conditions.



Scheme 1. *Z*-selective HWE reagents.

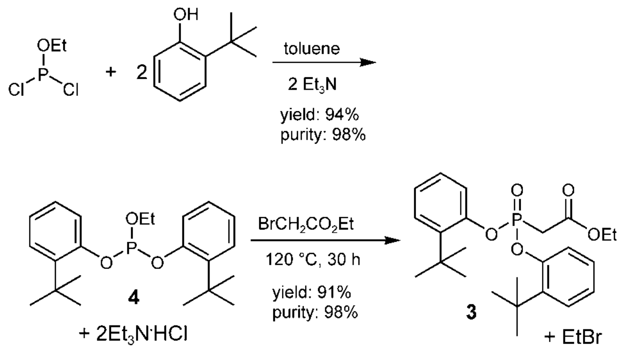
Results and Discussion

Phosphonate Synthesis Improvement

This is an important topic to address because as selective as the HWE reaction may be, the syntheses of diaryl phosphonoacetates published so far have not always been very practical, requiring moreover most of the time chromatographic purifications.

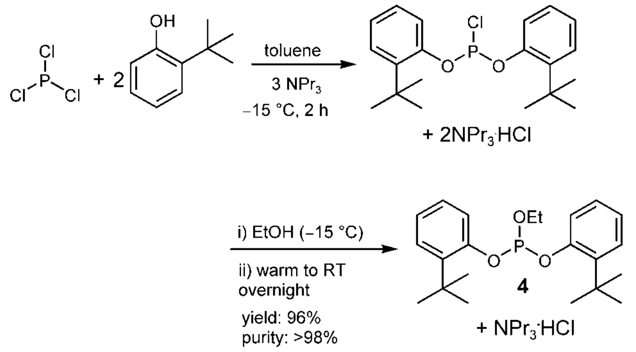
Compound **3** had been primarily prepared by Arbusov chemistry according to Scheme 2 and obtained as a white crystalline solid with 98% purity.[8]

Even if the Arbusov reaction proved to proceed quite well, the phosphite synthesis relying on $PCl_2(OEt)$ as a



Scheme 2. Former synthesis of phosphite **4** and phosphonate **3**.

DOI: 10.1002/adsc.200404338



Scheme 3. Improved synthesis of phosphite **4**.

starting material is not suitable for a high-scale implementation. This reagent is indeed not readily available. So, we have decided to look at the preparation of **4** by first reacting 2-*t*-butylphenol with PCl_3 and then treating the chlorophosphite thus formed with ethanol in a one-pot, two-step procedure (Scheme 3).

This strategy proved to be especially effective thanks to the steric crowding of the 2-*t*-butyl group; the reaction has been carried out twice on a 3-L scale and the mixed phosphite was twice obtained with an unoptimised yield of 95% and a purity higher than 98% (^{31}P NMR). We thus prepared close to 500 g of **4** without noticeable contamination by other phosphites (see the Experimental Section).[9]

Then, since the first time we carried out the Arbusov reaction (Scheme 2),[8] 30 h were required for it to go to completion, we decided to perform a kinetic study to better control the phosphonate formation. ^{1}H/^{31}P NMR experiments were thus carried out at several temperatures and various initial compositions (Figure 1).

The data collected proved to be consistent with the reaction being first order concerning both reagents : $v = k[\mathbf{4}][BrCH_2CO_2Et]$, with $k = A \exp(-Ea/RT)$; $A \approx 5.7 \times 10^9$, $Ea \approx 81$ kJ/mol.

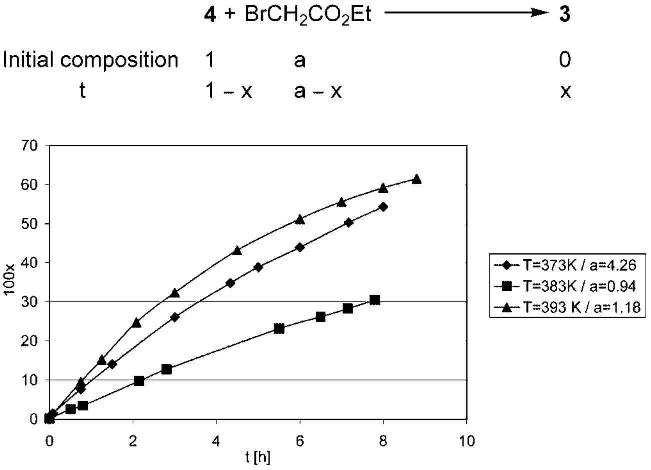


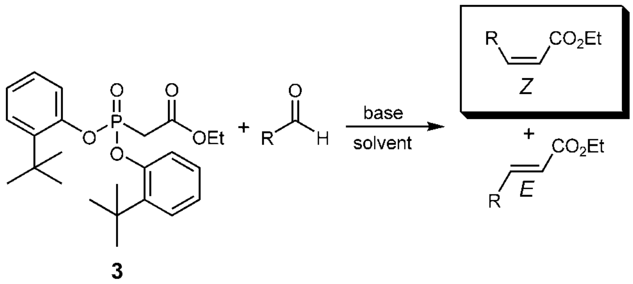
Figure 1. Phosphonate formation during the Arbusov reaction.

This kinetic law also proved to be quite in agreement with experimental observations on a larger scale. We indeed observed conversions of over 95% in 8 h when working at 130 °C with 2 molar equivalents of ethyl bromoacetate. After the removal of excess $BrCH_2CO_2Et$, the crude phosphonate was further purified to over 99 mol % by recrystallisation in heptane.[10] This has been done twice on a 200-g scale leading to 440 g of **3** (see the Experimental Section).

HWE Reaction

As mentioned in the Introduction, we have already described that **3** was a phosphonate of choice leading to selectivities close to 95% at 0 °C with benzaldehyde, cyclohexanecarboxaldehyde and octanal (Scheme 4).[8]

With the objective of working under more industrially realistic conditions, simplification of the basic system was studied. Beginning with KOH as the base, the reaction with benzaldehyde at 0 °C has first been carried out in THF and other ether solvents (Figure 2).



Scheme 4. HWE reaction of **3** with aldehydes.

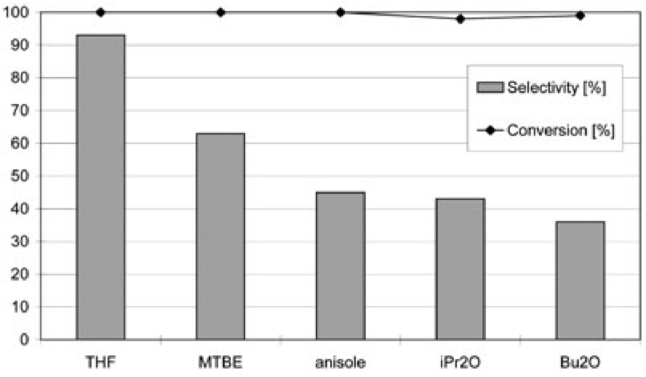


Figure 2. Reaction of **3** with benzaldehyde and KOH at 0 °C in THF and other ether solvents. Conditions: **3** (0.5 mmol, 1.1 equivs), benzaldehyde (0.44 mmol, 1 equiv.), KOH (0.70 mmol, 1.6 equivs.), solvent (10 mL), 0 °C. Selectivity, $S = Z/(Z+E)$, and benzaldehyde conversion were determined by GC.

Table 1. Reaction of **3** with NaOH or KOH at 0 °C in THF.[a]

Entry	Aldehyde	Base	Selectivity [%][b]	Conversion [%][c]
1	PhCHO	KOH	93	100
2	PhCHO	NaOH	86	100
3	CyCHO	KOH	95	100
4	CyCHO	NaOH	95	100
5	*n*-Octanal	KOH	93	100
6	*n*-Octanal	NaOH	93	100

[a] **3** (0.5 mmol, 1.1 equivs.), aldehyde (0.44 mmol, 1 equiv.), base (0.70 mmol, 1.6 equiv.), THF (10 mL), 0 °C, 1 h.

[b] Selectivity $S = Z/(Z+E)$ calculated by GC.

[c] Aldehyde conversion calculated by GC.

Although completion was observed within 2 h in each case, only THF led to an acceptable *Z*/*E* ratio. The selectivities and conversions then obtained in THF at 0 °C with benzaldehyde, cyclohexanecarboxaldehyde and octanal using either KOH or NaOH as bases are given in Table 1.

Completion was here observed in each case within 1 h, with selectivities very similar to those already reported with NaHMDS or KHMDS and NaI/TMG.[8] These results confirm that the cation plays a predominant role and that the *Z*/*E* ratio is not sensitive to the base strength. Unfortunately, the selectivity dropped dramatically when we increased the concentration. Working at 1 M with benzaldehyde and KOH, only 75% *Z*-selectivity was observed at 0 °C and 85% at −10 °C.

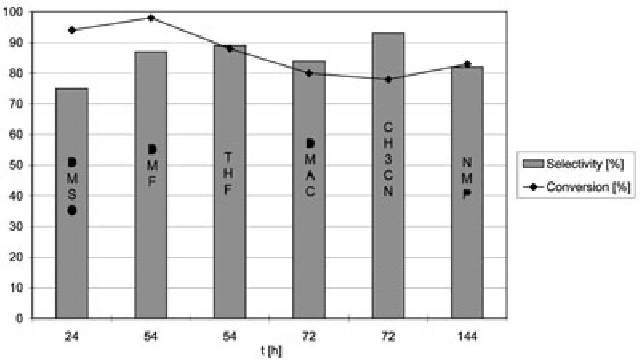


Figure 3. Reaction of **3** with benzaldehyde and K_2CO_3 at 20 °C. Conditions: **3** (0.5 mmol, 1.13 equivs.), benzaldehyde (0.44 mmol, 1 equiv.), K_2CO_3(0.88 mmol, 2 equiv.), solvent (10 mL), H_2O (0.88 mmol, 2 equivs.), 20 °C. Selectivity, $S = Z/(Z+E)$, and benzaldehyde conversion were determined by GC.

We then carried on the evaluation of bases with K_2CO_3, the reaction with benzaldehyde being first performed in various aprotic solvents. Slow reaction rates were observed but addition of two equivalents of water proved to speed up the transformation, especially in THF, without any selectivity decrease. Both the selectivity and the conversion obtained in these conditions are shown in Figure 3.

DMSO thus led to the fastest reaction but with rather low selectivity (75%). DMF, DMAC and NMP then improved the *Z*/*E* ratio close to 85/15. THF enabled us to approach 90% and CH_3CN to reach 93% *Z*-selectivity. But reaction times higher than 48 h were required in these conditions for conversions to exceed 80%.

Trying to increase the reaction rate, we then turned our attention to Cs_2CO_3 and K_3PO_4. The former base enabled us to reduce noticeably the time to completion but did not improve the selectivities: 91% *Z*-selectivity was, for example, obtained with 99% conversion after 1 h in CH_3CN. K_3PO_4 led to the same observations but was further evaluated due to its low price and availability. The selectivities and conversions obtained with benzaldehyde, cyclohexanecarboxaldehyde and octanal in DMF, CH_3CN and THF are thus summarised in Table 2.

DMF always gave the highest reaction rates with conversions close to 90% in 1 h and mean selectivities of 85%. CH_3CN then led to the best selectivities with the three aldehydes being, respectively, 93%, 92% and 91% with benzaldehyde, cyclohexanecarboxaldehyde

Table 2. Reaction of **3** with K_3PO_4 at room temperature.[a]

Entry	Aldehyde	Solvent	Time [h]	Selectivity [%][b]	Conversion [%][c]
1	PhCHO	DMF	1	86	100
2	PhCHO	CH_3CN	2	93	95
3	PhCHO	THF	19	88	88
4	CyCHO	DMF	1	84	87
5	CyCHO	CH_3CN	2	92	81
6	CyCHO	THF	19	92	77
7	*n*-Octanal	DMF	1	85	97
8	*n*-Octanal	CH_3CN	2	91	91
9	*n*-Octanal	THF	19	90	94

[a] **3** (0.5 mmol, 1.13 equivs.), aldehyde (0.44 mmol, 1 equiv.), K_3PO_4 (0.88 mmol, 2 equivs.), solvent (10 mL), 20 °C.

[b] Selectivity $S = Z/(Z+E)$ calculated by GC.

[c] Aldehyde conversion calculated by GC.

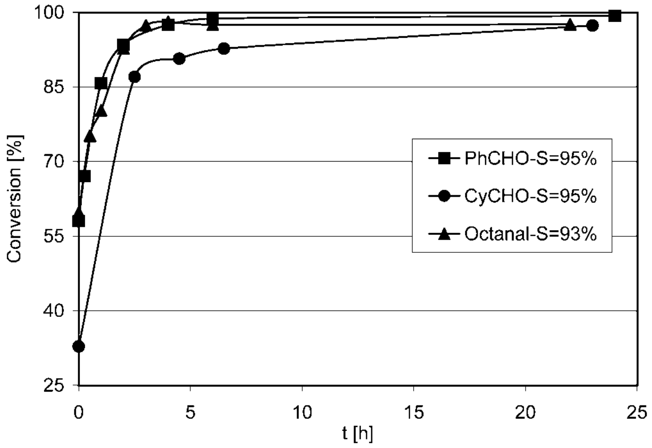


Figure 4. Reaction of **3** with benzaldehyde, cyclohexanecarboxaldehyde and octanal in CH_3CN at 0 °C. Conditions: **3** (35 mmol, 1.1 equivs.), aldehyde (31.8 mmol, 1 equiv.), K_3PO_4 (64 mmol, 2 equivs.), CH_3CN (35 mL), 0 °C. Selectivity, $S = Z/(Z+E)$, and aldehyde conversion were determined by GC.

and octanal at room temperature. THF finally also gave close to 90% *Z*-selectivity but with extended reaction times.

However, in contrast with what had been observed with KOH, we were delighted to observe that the selectivity was maintained upon increasing the concentration under the CH_3CN/K_3PO_4 conditions. This was checked with the three aldehydes by running the reaction at 0 °C, 1 M and on a 32-mmol scale. *Z*/*E* ratios close to 95/5 have been obtained with conversions of over 90% within 6 h (Figure 4).

The *Z*/*E* ratios may still be further improved by modification of the conditions[11] but the system we have developed is a good starting basis for the practical synthesis of unsaturated esters with high *Z*-selectivities.

Moreover, the phosphate salt formed during the HWE reaction being only very slightly soluble in CH_3CN,[12] it can be easily removed by filtration from the reaction medium leaving the clean mixture of olefins in the filtrate for quantitative recovery (see the Experimental Section).[13]

Conclusion

In this study, we have first developed an efficient and scalable synthesis of **3**: 440 g of the phosphonate have thus been prepared in the laboratory from cheap and readily available starting materials with an overall unoptimised yield of 82%. Moreover, we have been able to delineate very simple, mild, productive and inexpensive conditions leading to selectivities close to 95% and quantitative yields with benzaldehyde, cyclohexanecarboxaldehyde and octanal at 0 °C.

In summary, we think we have developed a system to make the *Z*-selective synthesis of unsaturated esters by Horner–Wadsworth–Emmons olefination quite practical. Extension of these conditions to phosphonates bearing various stabilising groups would expand further the scope of the reaction.

Experimental Section

General Remarks

All the commercially available reagents were used as received without any further purification. The HWE reactions were performed in Schlenk-like flasks with magnetic stirring unless otherwise stated. All the compounds prepared (mixtures of olefins and phosphonate 3) were already known in the literature and their structures were confirmed by accordance with the published data (^1H, ^{13}C, ^{31}P NMR). The GC analyses were performed with a Varian 3400Cx apparatus equipped with a SGE BPX5(764) 25 m × 0.53 mm × 1 μm column and FID detector. Helium (5 mL/min) was used as vector gas and N_2 (25 mL/min) as make-up. Programme: 80 °C (4 min) → 170 °C with heating rate 7 °C/min → 300 °C (4 min) with heating rate 30 °C/min. In these conditions, the retention times of the analysed compounds are given hereafter.

Table 3.

Compound	Rt (min)
PhCHO	5.1
CyCHO	4.4
Octanal	5.7
Ph–CH=CH–CO_2Et (*Z* isomer)	14.1
Ph–CH=CH–CO_2Et (*E* isomer)	15.6
Cy–CH=CH–CO_2Et (*Z* isomer)	12.6
Cy–CH=CH–CO_2Et (*E* isomer)	14.4
n-C_7H_{15}–CH=CH–CO_2Et (*Z* isomer)	13.9
n-C_7H_{15}–CH=CH–CO_2Et (*E* isomer)	15.0
Phosphonate 3	22.5

Phosphonate 3[8]

In a 3-L vessel under nitrogen were introduced anhydrous toluene (1.6 L) and PCl_3 (100 g; 0.71 mol, 1 equiv.). The mixture was then cooled to −15 °C and 2-*t*-butylphenol (215 mL, 1.39 mol, 1.95 equivs.) was introduced within 10 minutes. After the addition of tripropylamine (418 mL, 2.16 mol, 3.02 equivs.) over 2 h, the mixture was further stirred at −15 °C for 2 h. Absolute ethanol (40 mL, 0.68 mol, 0.96 equivs.) was then poured into the vessel over 30 minutes and the medium was slowly warmed to room temperature overnight. The mixture was then washed with water (775 mL) and the resulting organic phase was passed over a pad of basic alumina. Solvent evaporation under reduced pressure then led to a pale yellow oil; yield: 246 g (96%); purity > 98 mol % (NMR).

The above phosphite (231 g, 0.62 mol, 1 equiv.) was then added to ethyl bromoacetate (140 mL, 1.2 mol, 1.99 equivs.) over 1 h at 130 °C and the mixture was further stirred for 8 h under argon. The excess of ethyl bromoacetate was then removed under reduced pressure and the crude phosphonate obtained was further purified to over 99 mol % by recrystallisation in heptane leading to a white solid; yield: 230 g (86%); purity > 99% (NMR).

HWE Reaction with K_2CO_3, Cs_2CO_3, K_3PO_4; General Procedure (Figure 2, Table 2)

Phosphonate **3**, the base, the solvent and the aldehyde were mixed and stirred at room temperature. The reaction was then monitored by gas chromatography after quenching aliquots with saturated ammonium chloride and extracting the mixture with MTBE.

HWE Reaction with KOH, NaOH; General Procedure (Figure 3, Table 3)

Phosphonate **3**, the base and the solvent were mixed at 0 °C. The mixture was stirred until dissolution and the aldehyde was then added. When the transformation was performed at 1 M (KOH/THF) on a 32-mmol scale, the aldehyde was introduced over 1 h (exothermic addition). The reaction was then monitored by gas chromatography after quenching aliquots with saturated ammonium chloride and extracting the mixture with MTBE.

HWE Reaction with K_3PO_4/CH_3CN at 1 M; General Procedure

The experiments were carried out under argon in a standardised 100-mL reactor equipped with a pitched blade stirrer at 800 rpm. Acetonitrile (35 mL), K_3PO_4 (13.90 g, 64 mmol, 2.05 equivs.) and phosphonate **3** (15.15 g, 35 mmol, 1.1 equivs.) were first introduced at room temperature (20 °C). The mixture was then cooled to 0 °C with a cooling bath and the aldehyde (31.8 mmol, 1 equiv.) was slowly added over 30 minutes. The temperature was maintained at 0 °C and the reaction was then monitored by gas chromatography after quenching aliquots with saturated ammonium chloride and extracting the mixture with MTBE. After completion of the reaction, the salts were first removed by filtration and the reactor was rinsed with toluene (50 mL). The salts were then washed twice with toluene (2 × 50 mL) and the solvent was removed under reduced pressure.

The phosphate formed during the HWE reaction was not detected by NMR in the mixture, indicating the efficiency of the filtration step. The selectivities were then determined by GC and proved to be in accordance with ^{1}H NMR integration of the vinyl proton signals: 95% with both benzaldehyde and cyclohexanecarboxaldehyde and 93% with octanal.

The yields of the mixture of alkenes obtained in the reaction with benzaldehyde, cyclohexanecarboxaldehyde and octanal were determined to be 97%, 96% and 95%, respectively by ^{1}H NMR analysis (300 MHz) using dimethyl terephthalate as an internal standard.

Acknowledgements

François Metz and Laurent Saint-Jalmes are gratefully acknowledged for their advice.

References and Notes

[1] For a general review concerning the Wittig olefination reaction and modifications see: B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.

[2] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

[3] K. Ando, *Tetrahedron Lett.* **1995**, *36*, 4105–4108.

[4] Since the first publication of Ando,[3] many phosphonate modifications have been reported: a) K. Ando, *J. Org. Chem.* **1997**, *62*, 1934–1939; b) K. Ando, *J. Org. Chem.* **1998**, *63*, 8411–8416; c) K. Ando, *J. Org. Chem.* **1999**, *64*, 8406–8408; d) K. Ando, T. Oishi, M. Hirama, H. Ohno, T. Ibuka, *J. Org. Chem.* **2000**, *65*, 4745–4749; e) K. Kokin, J. Motoyoshiya, S. Hayashi, H. Aoyama, *Synth. Commun.* **1997**, *27*, 2387–2392; f) K. Kokin, K. Iitake, Y. Takaguchi, H. Aoyama, S. Hayashi, J. Motoyoshiya, *Phosphorus, Sulfur and Silicon* **1998**, *133*, 21–40.

[5] For recent reviews, see: a) K. Ando, *Yuki Gosei Kagaku Kyokaishi* **2000**, *58*, 869–876; b) J. Motoyoshiya, *Trends Org. Chem.* **1998**, *7*, 63–73.

[6] The phosphonate based on 2,4-difluorophenol described by Motoyoshiya et al.[4e, f] was until recently[8] the only one reported leading to selectivities over 92% at 0 °C with various aldehydes.

[7] F. P. Touchard, *Tetrahedron Lett.* **2004**, *45*, 5519–5523.

[8] F. P. Touchard, *Eur. J. Org. Chem.*, accepted.

[9] $P(OAr)_3$ and $P(OEt)_2(OAr)$, were only observed, if at all, as traces in the crude compound.

[10] The solubility of **3** in heptane was determined to be 1.3% (w/w) at 23 °C and 0.5% at 5 °C.

[11] For example, the selectivity was improved to 96% with benzaldehyde by running the reaction at –10 °C.

[12] The solubility was determined to be 0.05% (w/w) at room temperature.

[13] The yields of the mixture of alkenes obtained in the reaction with benzaldehyde, cyclohexanecarboxaldehyde and octanal were 97%, 96% and 95%, respectively.