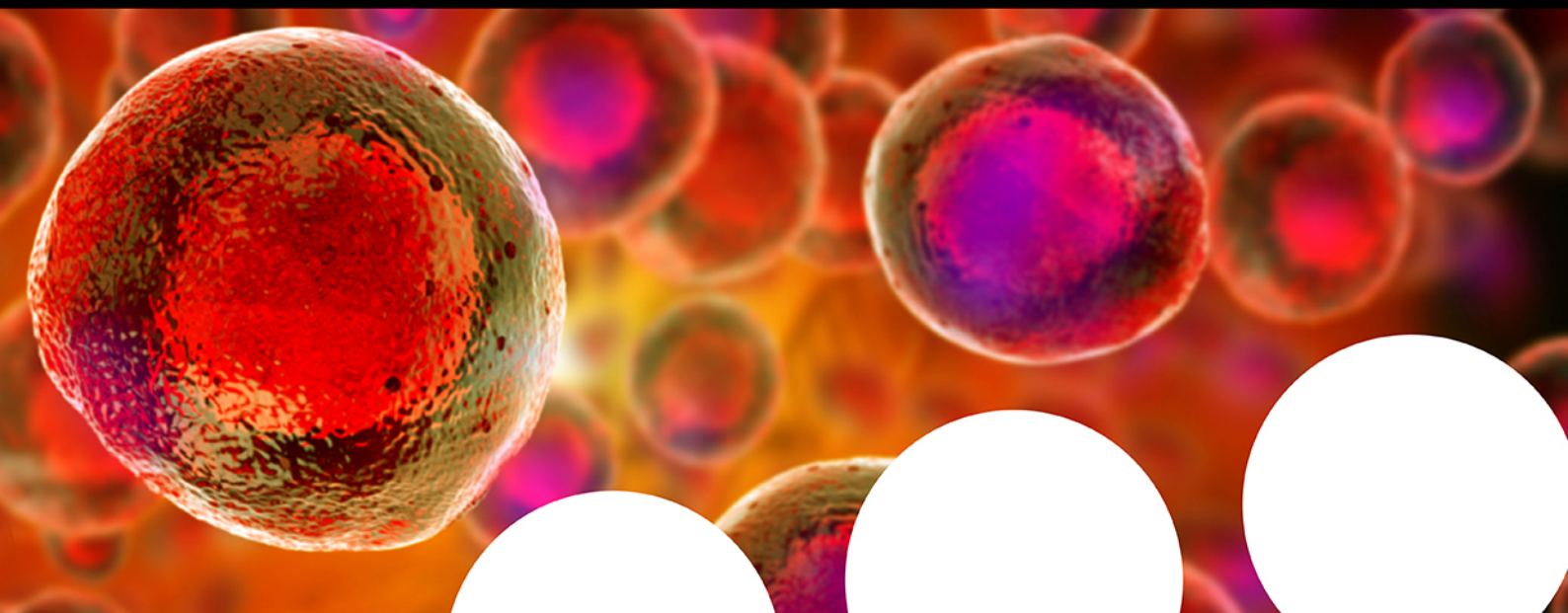


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Z-Selective Alkene Formation from Reductive Aldehyde Homo-Couplings

Juri Mai,^[a] Anna I. Arkhynchuk,^{*,[a]} Sebastian Wagner,^[a] Andreas Orthaber,^{*,[a]} and Sascha Ott^{*,[a]}

Current methodologies for the direct reductive coupling of two aldehydes to alkenes afford almost exclusively the thermodynamically favoured *E*-isomer. Recent efforts to find phosphorus-based reagents as replacements for the low-valent Ti species in McMurry couplings present opportunities to change this shortcoming, and to design new reagents that allow for the formation of high proportions of *Z*-alkenes under kinetic control. Here, we report the first example of such a reagent, a phosphanyl phosphonate Mes^FP(H)P(O)(OEt)₂, **6**, with an electron-deficient Mes^F=2,4,6-(CF₃)₃Ph substituent that promotes the reductive homo-coupling of (hetero)aromatic aldehydes to

alkenes with high *Z*-selectivity. Computational results indicate that the selectivity stems from the electron deficient Mes^F, which results in lowered activation barriers for the collapse of a cis-oxaphosphetane intermediate. In the absence of Mes^F, the *E*-isomer is exclusively observed experimentally. Directing the isomeric outcome of alkene formation by introducing electron withdrawing P-substituents bears resemblance to the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction where perfluorinated ethoxy substituents in the former also lead to high proportions of the *Z*-isomer.

Introduction

The carbon-carbon double bond is one of the most important structural motifs in molecular chemistry, and a valuable functionality for further chemical transformations.^[1] Amongst various methods for their formation, a large variety of carbonyl olefination methods has been developed over the years.^[1c] A crucial aspect in all these reports is the stereochemical control that the reaction may offer, and the selective formation of either *E*- or *Z*-alkenes in high isomeric purity is of obvious importance.^[2] In general, most methods give rise predominantly to thermodynamically more stable *E*-alkenes, while methods towards *Z*-isomers are more scarce. Figure 1 summarizes commonly encountered methodologies to *E*- or *Z*-alkenes via direct aldehyde-aldehyde couplings or carbonyl olefination reactions. The McMurry coupling is the standard reaction for the direct conversion of two aldehydes, using low-valent titanium species as reductant and oxygen acceptor.^[3] Recently, several alternative approaches have been reported, e.g. Li *et al.* presented a Ru(II)-catalysed coupling of carbonyls,^[4] König *et al.* developed boron mediated photoredox coupling of aldehydes^[5]

and Voutchkova-Kostal *et al.* reported on a palladium-catalyzed method for the decarbonylative olefination of aldehydes.^[6] In parallel, we presented an approach via a phosphalkene intermediate.^[7] In one of these reports, substrate combinations were identified that resulted in the preferential formation of *Z*-alkenes.^[8] These reactions proceed under substrate control, and despite of these recent developments, there is currently no methodology to couple two aldehydes directly to the kinetic *Z*-alkene product under reagent control. Carbonyl olefinations with phosphorus stabilized carbanions like the Wittig and related reactions have served for several decades as powerful tools to construct carbon-carbon double bonds.^[1c,e,9] The “classic” Wittig,^[10] Horner-Wittig (HW),^[11] and Horner-Wadsworth-Emmons (HWE)^[12] reaction make use of phosphonium-, phosphane oxide-, and phosphate-stabilized carbanions as nucleophiles, respectively (Figure 1, right part). From a stereochemical point of view, the type of ylide or phosphonate, the type of carbonyl compound, the solvent, base, and even counter ion can be used to tune the isomeric outcome of these reactions.^[1d,9,13] Nevertheless, most of the above-mentioned name reactions give preferentially *E*-alkenes. In this regard, extensive efforts have been devoted to modifications to achieve a stereo-selective construction of *Z*-olefins.^[14] Amongst them, the Still-Gennari (SG)^[14d,15] variant which uses trifluoroethyl phosphonates is probably the most established and widely recognized method.^[13a] It is these electron withdrawing trifluoroethyl groups that render the phosphonate-*P* a stronger electrophile compared to that in classical HWE reagents, thereby accelerating the formation of key intermediates on the way to *Z*-alkenes which are produced under kinetic control.^[1d,13a] Tuning of additional reaction parameters such as low temperatures, salt-free conditions, particular bases and other additives can push the reaction further under kinetic control.^[1e,13a,14d,16]

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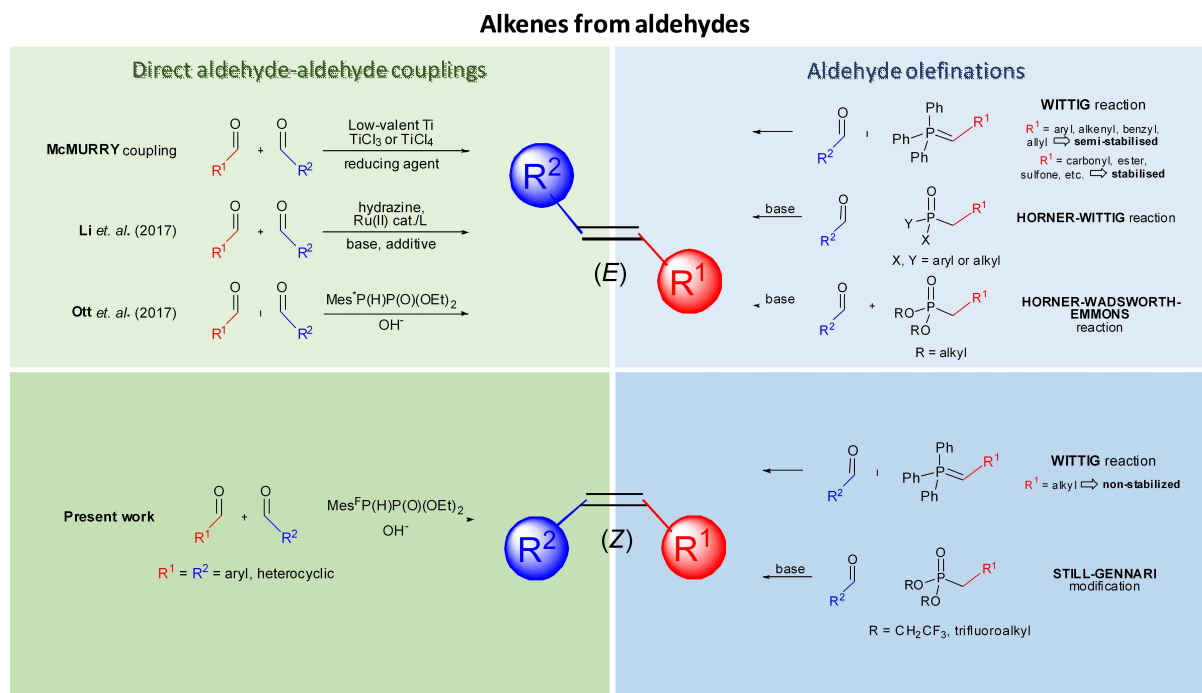


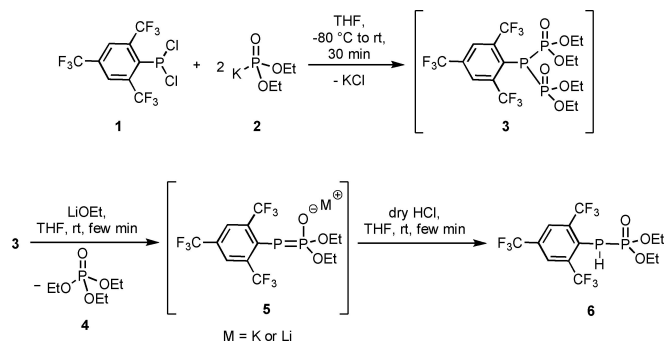
Figure 1. Overview about common aldehyde olefination methodologies. (Top left) Methods that use directly two aldehydes for the preparation of *E*-alkenes. The classical Ti-mediated McMurry coupling, the recently by Li *et al.* reported Ru(II)-catalysed method, and phosphorus mediated methodology from our group. (Top right) “Classic” Wittig- and HWE-type olefinations for *E*-alkenes. Here, an aldehyde reacts with an appropriate phosphonium ylide, phosphane oxide or phosphonate, respectively. (Bottom right) Corresponding variations of Wittig and HWE-type chemistry to give selectively *Z*-alkenes. (Bottom left) Novel phosphorus mediated method for the preparation of *Z*-alkenes via direct aldehyde-aldehyde coupling.

Inspired by the SG modification, we were intrigued by the possibility to modify the reagent that we developed for the reductive aldehyde coupling to an extent that it would promote the formation of *Z*-alkenes. More specifically, we hypothesized that replacement of the supermesityl (Mes^{*}) group at the reported phosphanyl phosphonate^[7a,b,17] by the more electron-deficient tris-trifluoromethyl phenyl group (Figure 1, bottom left) would increase the electrophilicity of the *P*-center in crucial reaction intermediates, thereby facilitating the formation of the kinetic *Z*-coupling product. If successful, this work would be the first of its kind that promotes the reductive aldehyde coupling to *Z*-alkenes under reagent control.

Results and Discussion

Synthesis and characterisation of phosphanyl phosphonate reagent 6

The synthesis of phosphanyl phosphonate **6** with an electron deficient 2,4,6-(CF₃)₃Ph (Mes^F) substituent at the ³¹P is outlined in Scheme 1. Phosphorylation of dichloro(2,4,6-tris(trifluoromethyl)phenyl)phosphane **1**^[18] with two equivalents of potassium diethylphosphite **2** affords *bis*(diethylphosphoryl)phosphane **3** in quantitative yields as long as the reaction is performed at −78 °C. The ³¹P NMR (C₆D₆) spectrum of compound **3** features a characteristic doublet at δ = 22.5 ppm and triplet of septet at δ = −58.0 ppm with coupling constants



Scheme 1. Synthetic route to phosphanyl phosphonate reagent **6** starting from dichloro(2,4,6-tris(trifluoromethyl)phenyl)phosphane **1** and potassium diethyl phosphite **2**. Preparation is performed as one-pot synthesis without isolation of the intermediate species **3** and **5**.

of ¹J_{P-P} = 187 Hz and ⁴J_{P-F} = 36.5 Hz. Treatment of crude **3** with one equivalent of LiOEt (anhydrous solution in THF) cleaves one phosphate group and releases phosphanyl phosphonate salt **5**. This step is accompanied by a diagnostic colour change of the solution from yellow to deep red. The correct choice of base for this step is crucial, and bases different from LiOEt often give rise to considerable amounts of side products.

In the last step, phosphanyl phosphonate **6** is generated by protonation of **5** with HCl (anhydrous solution) which is accompanied by a decolouration of the solution. All synthetic steps are performed in one-pot without the necessity of

isolation of bis(diethylphosphoryl)phosphane **3**. Both compounds **5** and **6** feature two characteristic doublets in their respective ^{31}P NMR spectrum. Compound **6** shows a doublet at $\delta = 29.0$ ppm and a doublet of septet at $\delta = -98.6$ ppm with a $^1J_{\text{P-P}} = 170$ Hz and $^4J_{\text{P-F}} = 28.9$ Hz. Interesting to note is that the P–P coupling constant is significantly smaller than that in the corresponding Mes* variant ($^1J_{\text{P-P}} = 222$ Hz).^[17] This indicates that the Mes^F group weakens the P–P bond. The same trend is observed in the deprotonated form where phosphanyl phosphonate **5** with the Mes^F group has a smaller coupling constant ($^1J_{\text{P-P}} = 530$ Hz) in comparison to the Mes* analogue ($^1J_{\text{P-P}} = 615$ Hz).^[17] Consequently, the $\Delta\delta$ between the resonances of the P(III) and P(V) centres in **5** are significantly larger. Furthermore, a coupling constant that is in the range of phosphoranylidene phosphines^[19] indicates a high double bond character between the two phosphorus atoms, and **5** is thus best described as the enolate form.

Single crystals suitable for X-ray analysis were obtained by recrystallization of purified phosphanyl phosphonate **6** in water-free *n*-hexane at -20°C . Compound **6** crystallizes in the

monoclinic space group C 2/c as colourless cubes. The solid state structure (Figure 2) shows a P1–P2 distance of 2.211(2) Å.

Application of **5** in reductive aldehyde homo-couplings

Since the reductive aldehyde coupling sequence is driven from the deprotonated form **5**, the preparation and isolation of **6** is actually not necessary. In fact, all reactions described hereafter were conducted using a stock solution of **5** that was prepared according to the procedure described in Scheme 1. Under an argon atmosphere, this stock solution shows good stability at room temperature, and can be stored for several days without significant changes. The reaction sequence for the one-pot reductive aldehyde-aldehyde coupling is depicted in Scheme 2. In a typical procedure, two equivalents of aldehyde are added to a solution of **5** at room temperature and the mixture is heated to 65°C for 10–15 minutes to form a phosphalkene **8** in a phospho HWE reaction.^[16] The elevated reaction temperature in this step is necessary because of the decreased

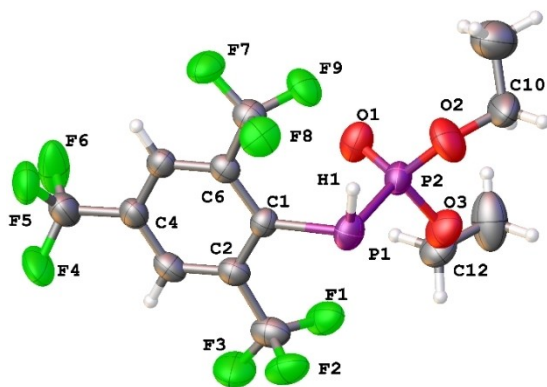
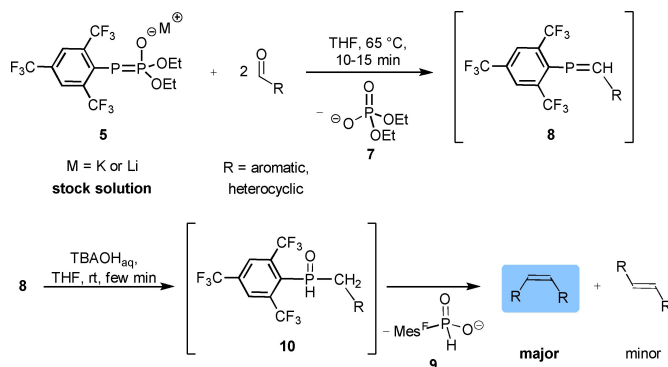


Figure 2. ORTEP representation of phosphanyl phosphonate **6** shown with 50% displacement ellipsoids. Only one of the disordered trifluoromethyl and ethyl groups is shown for clarity. Selected bond length [Å] and angles [°]: C1–P1 1.861(4), P1–P2 2.211(2), P2–O1 1.447(4), P2–O2 1.561(4), P2–O3 1.578(4), C1–P1–P2 98.78(14).



Scheme 2. Reaction sequence for the reductive aldehyde homo-coupling to *Z*- and *E*-alkenes via phosphalkene intermediate **8**. The reaction is performed as one-pot coupling with a phosphanyl phosphonate **5** stock solution and high *Z* selectivity for the olefin (*R* = aromatic, heterocyclic).

Table 1. Reductive aldehyde-aldehyde homo coupling with corresponding *E/Z* product ratios. Isolated yields are referred to one equivalent of the aldehyde.

Entry	Aldehyde	Product	Conversion ^[a] (isolated yield) [%]	<i>E/Z</i> product ratio [%]
a			67 , (40)	9 : 91
b			49 , (45)	10 : 90
c			61 , (46)	20 : 80
d			60 , (60)	23 : 77
e			59 , (59)	28 : 72
f			59 , (51)	30 : 70
g			47 , (41)	47 : 53
h			74 , (44)	58 : 42

[a] Conversions refer to the reacted amount of aldehyde (see ESI for details).

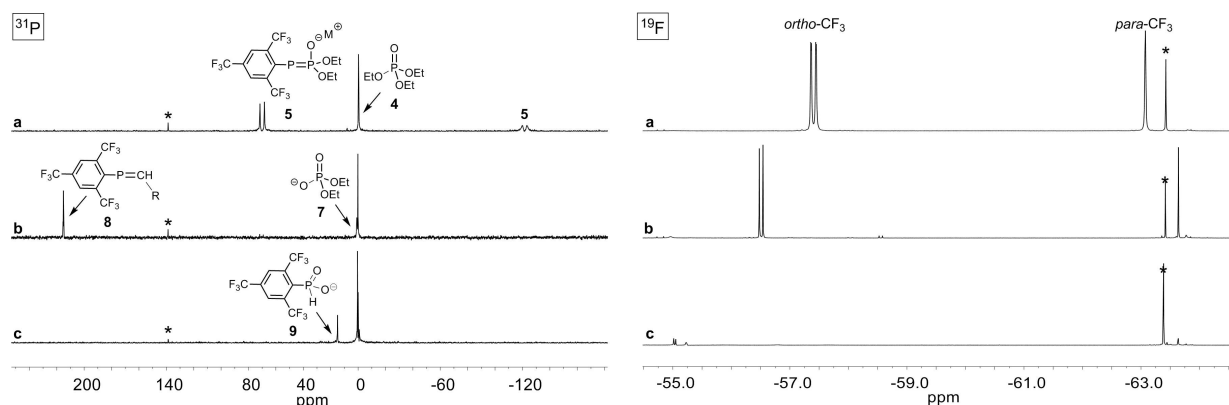
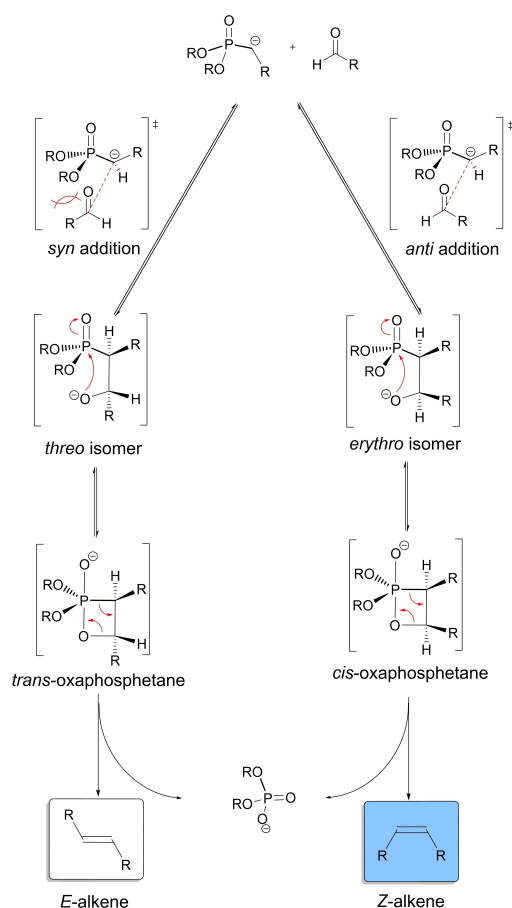


Figure 3. (Left) ^{31}P NMR spectroscopic monitoring of the reaction sequence. (a) Stock solution of phosphanyl phosphonate **5**, and its reaction with the first equivalent of aldehyde to yield a phosphalkene intermediate **8** (a→b). Activation of the phosphalkene by TBAOHaq and coupling with the second equivalent of aldehyde to give the alkene product and the $\text{Mes}^{\text{F}}\text{-P}(\text{OEt})_2$ by-product **9** (b→c). (Right) Corresponding ^{19}F NMR spectroscopic monitoring of the aldehyde olefination. R = benzofuran. (*) $\text{Mes}^{\text{F}}\text{P}(\text{OEt})_2$ as a side product that is formed during dephosphorylation of bis(diethylphosphoryl)phosphane **3**.



Scheme 3. General mechanism of the HWE reaction that typically gives rise to the *E*-alkene, and the Still-Gennari modification that favours *Z*-alkenes. The difference in reactivity is described to a high activation barrier of the irreversible phosphate elimination from the *cis*-oxaphosphetane intermediate in the HWE reaction, pushing the equilibrium to the pathway towards the *E*-alkene.

nucleophilicity of the P(III) centre in **5** that results from the electron-withdrawing character of the *P*-substituent.

The formed phosphalkene **8** is subsequently quenched by an aqueous tetrabutylammonium hydroxide solution (TBAOH_{aq}) at room temperature to form a phosphane oxide **10** intermediate that is however not observed under the reaction conditions as it immediately reacts further with the second equivalent of aldehyde under alkene formation. These steps of the sequence proceed faster compared to the case of the reaction with Mes^{F} as a result of the higher electrophilicity of the phosphorus centre in **8**, and higher acidity of the proton at the carbon neighbouring the *P*-centre of the resulting phosphine oxide **10**. The swiftness of the reaction is encouraging as it may be an indication for the irreversible formation of the kinetic olefin product and, most gratifyingly, *Z*-alkenes were indeed formed as the major isomers.

With a reliable protocol for the preparation of coupling reagent **5** in hand, and a good understanding of the coupling sequence (Scheme 2), the reactivity towards different aldehydes and the substrate scope were investigated. As summarized in Table 1, the aldehyde-aldehyde homo-coupling generally proceeds well with conversions of 50–75% for all aromatic and heterocyclic aldehydes tested herein. The coupling tolerates substituents in *ortho*-, *meta*- and *para*-positions. As a general trend, it emerges that more electron deficient aldehydes give rise to higher proportions of *Z*-isomer. Along these lines, it is interesting to note that the percentage of the *Z*-isomer actually correlates well with the ^{31}P NMR chemical shifts of the corresponding phosphalkene intermediates **8** (see ESI for details).^[20] The tendency is that phosphalkenes with more downfield ^{31}P chemical shifts and thus more deshielded *P*-centres will give rise to higher *Z*-isomeric ratios. This analysis is in line with the increased electrophilicity of the *P*-centre in electron-deficient phosphalkenes, which result in faster reactions and higher amounts of the kinetic *Z*-product. The increased reactivity of phosphalkenes with strongly electron-withdrawing C-substituents can be observed in the most extreme cases in Table 1 (entry a and b). In these examples, the phosphalkenes are not stable under the basic reaction conditions and react further all the way to the respective

olefins. In these examples, the homo-coupling is driven solely by the addition of **5** to solutions of the aldehyde, and does not require any TBAOH_{aq} addition.

The only example where the correlation between the amount of observed *Z*-isomer and ³¹P chemical shift of the corresponding phosphalkene does not hold is in case of *ortho*-bromobenzaldehyde (entry c, Table 1). We ascribe this behaviour to the so-called *ortho*-effect. This phenomenon has previously been described by Gilheany *et al.* who could show that *ortho*-substituted aldehydes can give rise to unusually high *Z*-selectivity in Wittig-type olefinations^[21] an effect that we also observed in carbonyl coupling chemistry.^[8]

It is important to emphasise at this point that the coupling step from phosphalkene to alkene is performed at room temperature. This is a practical improvement to *Z*-selective modifications of the HWE reaction that often require low temperatures to favour the kinetic *Z*-isomer. Only some rare examples are known in the literature in which it is possible to obtain *Z*-olefins at 0 °C or higher temperatures.^[14h,22]

The phosphorus and fluorine centres in the coupling reagent are convenient spectroscopic handles to follow the reaction progress by ³¹P and ¹⁹F NMR spectroscopy. As shown representatively for the homo-coupling of benzofuran-2-carboxaldehyde in Figure 3, anionic phosphanyl phosphonate **5** reacts with the first equivalent of aldehyde to form the corresponding phosphalkene **8** (215 ppm in ³¹P NMR). This step is accompanied by the generation of the diethyl phosphate by-product **7** (at 1 ppm). Addition of a TBAOH_{aq} solution at this point leads to rapid consumption of the phosphalkene and the formation

of the olefinic product. Corresponding signals for **5** in its ¹⁹F NMR spectrum are a doublet of doublet and a broad singlet for the *ortho*-CF₃ and *para*-CF₃ moieties, respectively. The two *ortho*-CF₃ groups show typical couplings towards both phosphorus atoms (⁴J_{F-P} = 31.4 Hz and ⁵J_{F-P} = 4.5 Hz). In case of phosphalkene intermediates, these are a doublet signal with a coupling constant of ⁴J_{F-P} = 23.5 Hz (*ortho*-CF₃) and a singlet (*para*-CF₃) signal.

Mechanistic considerations for *Z*-selectivity

From the overall mechanism depicted in Scheme 2, it is clear that the stereochemical outcome of the entire coupling is determined in the last step of the sequence, *i.e.* the reaction between the deprotonated phosphane oxide **10** and a second equivalent of aldehyde in a Horner Wittig-type reaction. This reaction proceeds with 100% *E*-selectivity when the *P*-substituent is a supermesityl (Mes*) group,^[7a] but is highly *Z*-selective when the substituent is changed to the Mes^F group in **10**. Thus, this part of the sequence was scrutinized computationally, as well as by drawing parallels to the highly *Z*-selective SG variant of the HWE olefination.

In general, the stereochemistry in any HWE-type olefination is determined by the relative orientation of the R-groups in two conceivable diastereomeric oxaphosphetane intermediates. The latter are formed by the preceding *syn* or *anti* addition of a phosphonate olefination reagent to the aldehyde (Scheme 3). While all reaction intermediates up to the oxaphosphetanes are

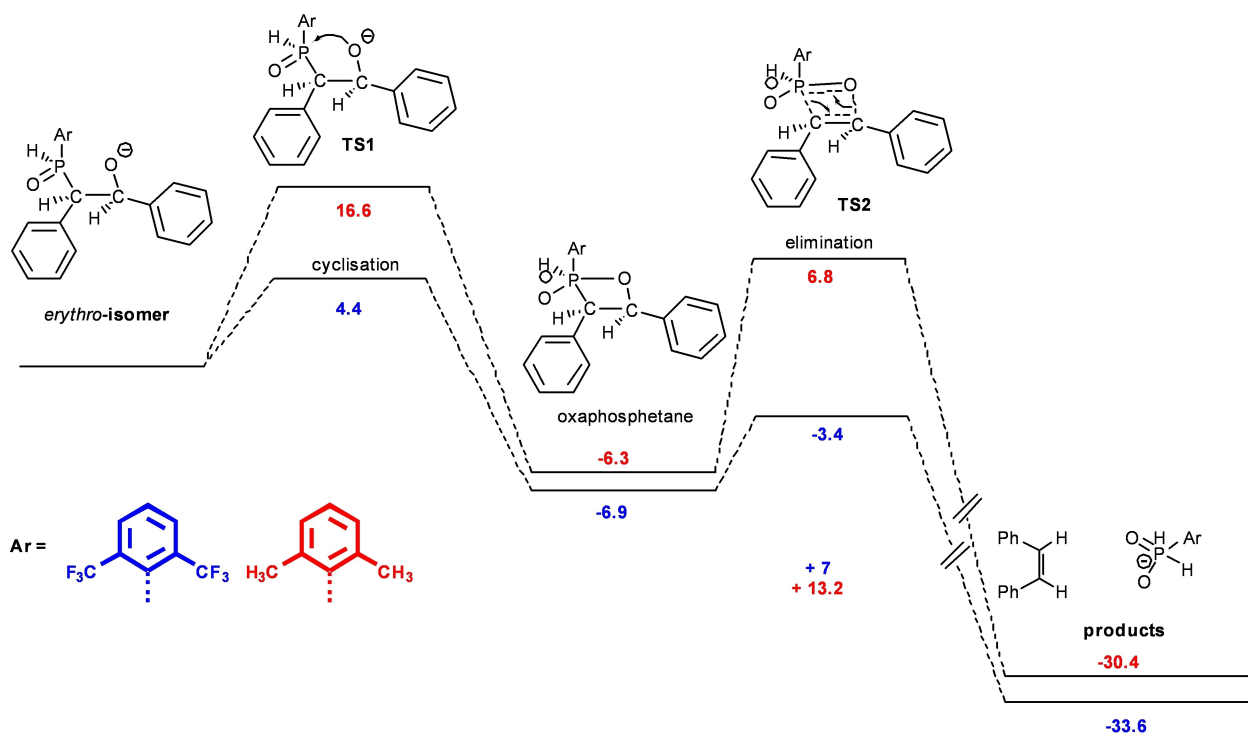


Figure 4. Comparison of the reaction profiles for fluorinated (*R* = CH₃) and non-fluorinated reagents (*R* = CF₃). Free energies are calculated in gas phase at the MO6-2X level of theory with a 6-311 + G(d,p) basis. Transition states and local minima are confirmed by the absence or presence of one and no imaginary frequency, respectively.

in equilibrium, subsequent phosphate elimination to form the alkene products is irreversible. The difference between classical HWE reactions and the SG modification is that in the former, the collapse of the *cis*-oxaphosphetane that would give rise to the *Z*-alkene is hampered by a high activation barrier. Owing to the electron deficient perfluoroethoxy-groups in the SG modification, this barrier is lowered, and the *Z*-isomer is formed.

Extrapolation of this literature knowledge, supported by DFT calculation of the key steps of the specific system at hand, allows us to postulate a mechanism that explains the observed *Z*-selectivity of the reductive aldehyde coupling driven by **5** (Figure 4). All calculations were performed at the MO6-2X level of theory with a 6-311++G(d,p) basis set. In the first step, the Li-salt of the electron deficient phosphane oxide **10** adds to the aldehyde. This initial nucleophilic attack is characterized by negligible barriers for both, the *E* (5.4 kJ mol⁻¹) and *Z* (6.2 kJ mol⁻¹) alkene pathway (see ESI for details). As either of the attacks are energetically viable, the pathway towards the *Z*-isomer was scrutinized in more detail. In order to illustrate the effect of the electron withdrawing Mes^F group in **10**, the reaction mechanism towards formation of the *Z*-isomer was calculated for two different *P*-substituents, a bis(trifluoro)methylphenyl group (Ph^F) as a mimic for Mes^F, and a dimethylphenyl (Me₂Ph) substituted reagent as a model for Mes^{*}. The two groups are close to identical in size, and will thus report exclusively on electronic differences. As shown in Figure 4, both groups give rise to highly exothermic overall processes (−33.6 and −30.4 kJ mol⁻¹). Furthermore, the free energy profile is generally more shallow for Ph^F with lower activation barriers as compared to that with Me₂Ph. In detail, both transition states, *i.e.* the cyclisation to the oxaphosphetane and the subsequent elimination of the alkene from the oxaphosphetane intermediate, respectively, display slightly higher barriers for the Me₂Ph-derivatives compared to their Ph^F-substituted counterparts (16.6 vs. 4.4 kJ mol⁻¹ and 13.1 versus 3.5 kJ mol⁻¹, respectively). Even though the absolute energies are not enormous, they parallel the situation in the SG modification of the HWE, in which the former also features lower activation energies for the collapse of the corresponding *cis*-oxaphosphetane than the latter.^[1d,13a] The design strategies that differentiate the reaction outcome between the classical HWE reaction and its SG modification is thus transferable from phosphonates to phosphane oxides, and electron deficient *P*-substituent as in **5** drive the reaction towards the *Z*-product.

Conclusion

In summary, we have developed a reliable synthetic procedure for the preparation of a novel electron-deficient phosphanyl phosphonate reagent **5**, and explored its application in aldehyde-aldehyde homo-coupling reactions. The synthesis of the reagent is performed in a high yielding one-pot reaction to afford a phosphanyl phosphonate stock solution which is used as a reductive coupling reagent for aromatic and heterocyclic aldehydes. Two aldehydes are directly coupled to 1,2-disubstituted *Z*-alkenes that constitute the major isomers of the

reaction. This selectivity control is opposite to that provided by the McMurry reaction which affords the thermodynamic *E*-alkene product. Additional advantages compared to the McMurry coupling include relatively simple synthetic protocols, short reaction times, and the absence of any transition metals.

Computational results indicate that the observed *Z*-selectivity stems from the electron deficient Mes^F group in **5**, which results in lowered activation barriers for the collapse of a *cis*-oxaphosphetane intermediate to form the *Z*-alkene. In the absence of this electron-withdrawing group, the opposite *E*-isomer is exclusively observed experimentally.

From the viewpoint of synthetic ease, the presented methodology offers features that are advantageous compared to Wittig and HWE-type reactions, in that it omits a couple of synthetic steps that are required for the preparation of functionalised ylide/phosphonate precursors.

Experimental Section

General procedure for preparation of stock solution of reagent **5**

The preparation of the coupling reagent **5** is performed in a one-pot reaction without isolation of the intermediate species **3**. Potassium diethyl phosphite **2** (3.83 g, 21.74 mmol, 2 eq.) was dissolved in 50 ml anhydrous THF at room temperature. In a separate Schlenk-flask dichlorophosphane **1** (4.16 g, 10.87 mmol, 1 eq.) was dissolved in 50 ml anhydrous THF at room temperature. Both solutions were cooled down to −78 °C, and compound **1** was added dropwise *via* cannula to the phosphite solution. After complete addition, the deep red mixture was allowed to warm up to room temperature. The successful formation of bis(diethylphosphoryl)phosphane intermediate **3** was confirmed by ³¹P NMR spectroscopy. To the resulting pale-yellow solution, 1.1 eq. of lithium ethoxide (11.36 ml, 11.36 mmol) was added dropwise at room temperature. After complete addition, which was accompanied by a characteristic change of colour from pale yellow to dark red, the mixture was stirred for a few minutes at room temperature. After full conversion of intermediate **3** to phosphanyl phosphonate **5**, which was monitored by ³¹P NMR, the obtained stock solution was used as reagent in the reductive aldehyde homo-couplings.

General procedure for the reductive aldehyde homo-coupling

To 1.2 eq. of a stock solution of phosphanyl phosphonate reagent **5** (250 mg, 0.557 mmol), 2.0 eq. of aldehyde (0.928 mmol) were added at room temperature. The mixture was quickly put into a preheated oil bath at 65 °C and stirred for 10–15 min. The formation of the respective phosphalkene intermediates was monitored by ³¹P NMR spectroscopy using an external C₆D₆ standard. After complete transformation, which is typically accompanied with a colour change from deep red to dark yellow, the reaction mixture was quenched with 1.3 eq. of an aqueous tetrabutylammonium hydroxide solution (TBAOH_{aq}, 40 wt.% in H₂O) at room temperature and stirred for a few minutes. After completion of the coupling step, the crude mixture was diluted with ethyl acetate and washed with water. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried over MgSO₄. Evaporation of the solvents under reduced pressure afforded the crude olefin products, which were purified by silica gel column chromatography.

Crystal structure data

Crystallographic data of phosphanyl phosphonate **6** has been deposited.

Deposition Number 2155031 (for **6**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Ab initio calculations • Olefination • Phosphaalkene • Phosphorus reagent • Reaction mechanism

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