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Saturation transfer and chemical exchange measurements of the stereochemical drift occurring during the Wittig reaction

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The Wittig reaction of butylidenetriphenylphosphorane with benzaldehyde using LiHMDS as base in THF was studied. The stereochemical drift (different ratio obtained in alkenes versus oxaphosphetane intermediates) was followed by low-temperature 1D NMR techniques. A retro-Wittig reaction is demonstrated using ^{13}C and ^{31}P saturation transfer experiments and homonuclear DPFGSE-ROE techniques.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{31}P NMR; Wittig reaction; saturation transfer experiment; DPFGSE-ROE

INTRODUCTION

The Wittig reaction[1] is one of the most important transformations in organic chemistry for the preparation of carbon–carbon double bonds, being used in natural product synthesis[2] and in industrial processes.[3] The double bond is introduced in place of the carbonyl functionality, therefore this reaction is regioselective and the stereochemistry can be controlled. The reaction of unstabilized ylides and aldehydes yields mainly (*Z*)-alkenes.[1]

Several mechanisms for the Wittig reaction have been proposed and have attracted the interest of different research groups. In our previous studies on the mechanism of the Wittig reaction, it has been shown that using rapid injection NMR (RI-NMR) techniques, at very low temperatures,[4] a new dynamic equilibrium between oxaphosphetanes and their lithium salt adducts could be detected. After the observation of the failure of the Wittig reaction in the case of dipyridyl ketone in the presence of Li ions,[5] we could show the existence of stable betaine–lithium salt adducts[6] using solid-state NMR. This was also the case when instead of dipyridyl ketone normal benzaldehyde was used as the carbonyl compound, but one, two or three phenyl rings in ethylidenetriphenylphosphorane were replaced with pyridyl rings.[7] Replacing the phenyl rings with 2-furyl substituents using BuLi as base, we were able to isolate a stable oxaphosphetane when all three phenyl rings of ethylidenetriphenylphosphorane were replaced.[8] In general, the replacement of phenyl rings by heterocyclic ring systems affects the stereoselectivity of the Wittig reaction considerably.[9]

Since we have been applying recent NMR methods for the investigation of the reaction mechanism of the Wittig reaction, we became interested in studying the stereochemical drift[10] occurring in the Wittig reaction of butylidenetriphenylphosphorane (**1**) with benzaldehyde as depicted in Scheme 1. The term stereochemical drift was coined by Maryanoff and co-workers, who observed different $E:Z$ ratios in the oxaphosphetane intermediates **2** and **3** versus the finally isolated alkenes **4** and **5**. The difference was dependent on concentration, lithium base, solvent, temperature and substitution. Chemical crossover experiments, carried out by Maryanoff's group, showed that addition of a second and different aldehyde after the complete formation of the oxaphosphetanes leads also to alkenes containing the organic residue of the second aldehyde, and this was interpreted as a consequence of a retro Wittig reaction.

We could confirm these stereochemical findings and observed in our hands a $Z:E$ ratio of 71:29 for the oxaphosphetanes **2** and **3**, whereas for the alkenes **4** and **5** a $Z:E$ ratio of 52:48 was found. This is a 19% larger production of (*E*)-alkene compared with (*E*)-oxaphosphetane. In addition to a retro-Wittig reaction, also an opening, rotating and reclosing of the oxaphosphetane ring system either between the former ylide carbon and phosphorus, between the former aldehyde carbon and oxygen or between the former ylide carbon and the former aldehyde carbon (with the rotation of one bond) could explain the results (see Scheme 2).

We were therefore interested in whether, by more advanced NMR techniques, we could directly detect a retro-Wittig reaction or an equilibrium between the two stereoisomeric oxaphosphetanes without the use of chemical crossover experiments and thus shed some more light to the

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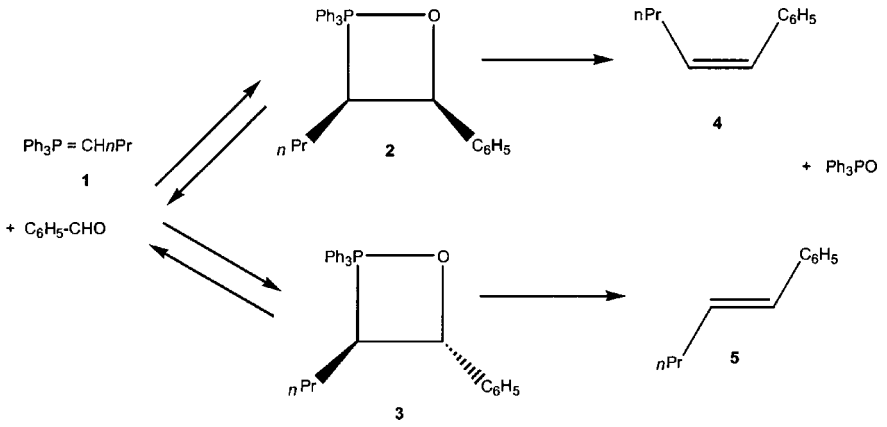
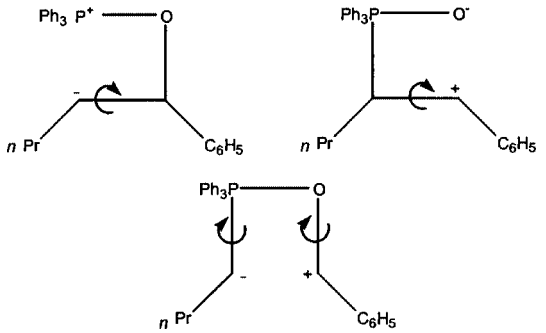


Scheme 1. Mechanism of the Wittig reaction.



Scheme 2. Possible intermediates of the Wittig reaction.

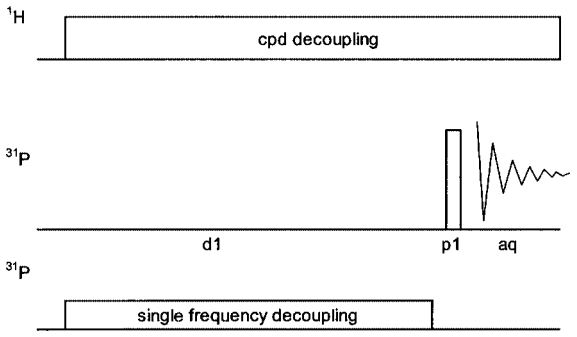


Figure 1. Pulse scheme for the saturation transfer experiment with three different r.f. channels, shown for the example of ^{31}P.

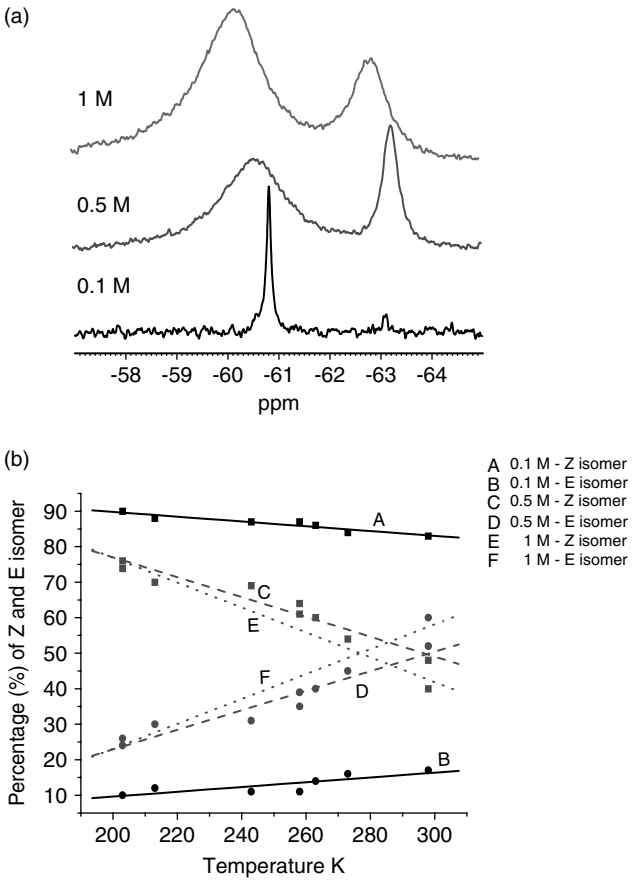


Figure 2. (a) ^{31}P NMR for the Wittig reaction at different reaction concentrations in THF at 203K; (b) stereochemical drift according to the NMR integration of the oxaphosphetanes.

mechanistic questions involved. As a central method within this study we used the saturation transfer method (Fig. 1), where dynamic equilibria are tested in the slow exchange limit by selective irradiation of one component.[11] Irradiation of one signal leads to an intensity decrease of those signals at all different chemical sites with which the irradiated signal is in chemical exchange.

RESULTS AND DISCUSSION

Figure 2(a) shows the low-temperature ^{31}P NMR spectra at 203 K in the oxaphosphetane region at different concentrations. In the spectra it can be seen that at 0.1 M, the oxaphosphetane signal appears as a sharp singlet; at 0.5 M the (Z)-oxaphosphetane signal becomes broader and at 1 M both oxaphosphetane signals are broad. From previous studies, we know that this broadening is caused by aggregation with the lithium ions. The resolution of the spectra decreases with increasing concentration of the reactants in THF, also owing to the large amounts of salt and phosphine oxide formed. As a compromise, we chose a 0.5 M reaction concentration for further investigation. At this point we still have a reasonable resolution and a large stereochemical drift.

From Fig. 2(b), it can be seen that the stereochemical drift occurs at different reaction concentrations, which is in accordance with the results of Maryanoff *et al.*[12] The graphic [Fig. 2(b)] shows the difference in the *E*-isomer production starting from the 203 K ratio of oxaphosphetanes, where the

first point results from ^{31}P NMR spectra recorded directly after adding the benzaldehyde, and the last one at 298 K from the ratio of alkenes (from ^{1}H NMR spectra) when the reaction was finished. All intermediate points represent the ratio of oxaphosphetanes determined by ^{31}P NMR at the given temperatures.

If one follows a Wittig reaction by means of NMR, one has the choice of observation by ^{31}P, ^{13}C or ^{1}H NMR. For ^{31}P the signals of the starting ylide, the oxaphosphetane signals and the signal of the final product triphenylphosphane oxide (TPPO) are of relevance. For ^{13}C and ^{1}H, the signals of the starting aldehyde, the oxaphosphetanes and the alkenes are of interest. If one labels the aldehyde carbonyl atom, an observation by ^{13}C NMR is especially easy. Since no considerable line broadening was observed for the ^{13}C NMR signals, we chose to apply the saturation transfer technique, which is known to extend the limits of dynamic NMR in the direction of slower exchange. For our ^{13}C saturation transfer experiment we used 98% labeled $C_6H_5{}^{13}CHO$. The ratio of starting materials, $C_6H_5{}^{13}CHO$: butylidenetriphenylphosphorane, was 1.2 : 1. We used excess of benzaldehyde to have the benzaldehyde signal always present for the saturation transfer measurements. Spectra were mainly recorded at 253 K where the reaction is very slow but the stereochemical drift is already occurring. We irradiated the ^{13}C signals in benzaldehyde, (*Z*)-oxaphosphetane and (*E*)-oxaphosphetane and we recorded in addition spectra with irradiation in a region where no signal was present as a negative control. The ^{31}P saturation transfer experiment was recorded using only 0.7 equiv. of benzaldehyde to ensure that excess of ylide was present in the reaction. In this respect, we irradiated the ^{31}P signals of the ylide, (*Z*)-oxaphosphetane and (*E*)-oxaphosphetane and we recorded a spectrum with irradiation of the TPPO formed in the reaction as a negative control, since it cannot be assumed that the TPPO contributes to the equilibrium.

The difficulty with the saturation transfer experiment as applied here is the circumstance that all signals decrease owing to the ongoing chemical reaction. Hence each irradiation experiment will invariably lead to a decrease in all other signals, simply owing to the time that the irradiation experiment needs. The experiments were therefore performed with multiple times and at different temperatures. Owing to the limitation in the exact reproducibility of organometallic sample preparation, the signal intensities of the individual experiments cannot be analyzed all together but, nevertheless, by careful comparison and statistical data analysis of the individual decay curves we were able to detect exchange between the irradiated species. To our knowledge, this is the first time that the saturation transfer technique has been applied during an ongoing reaction.

Results of ^{31}P saturation transfer

After using standard 1D processing and careful integration of the signals, the results in Fig. 3(a) and (b) were obtained.

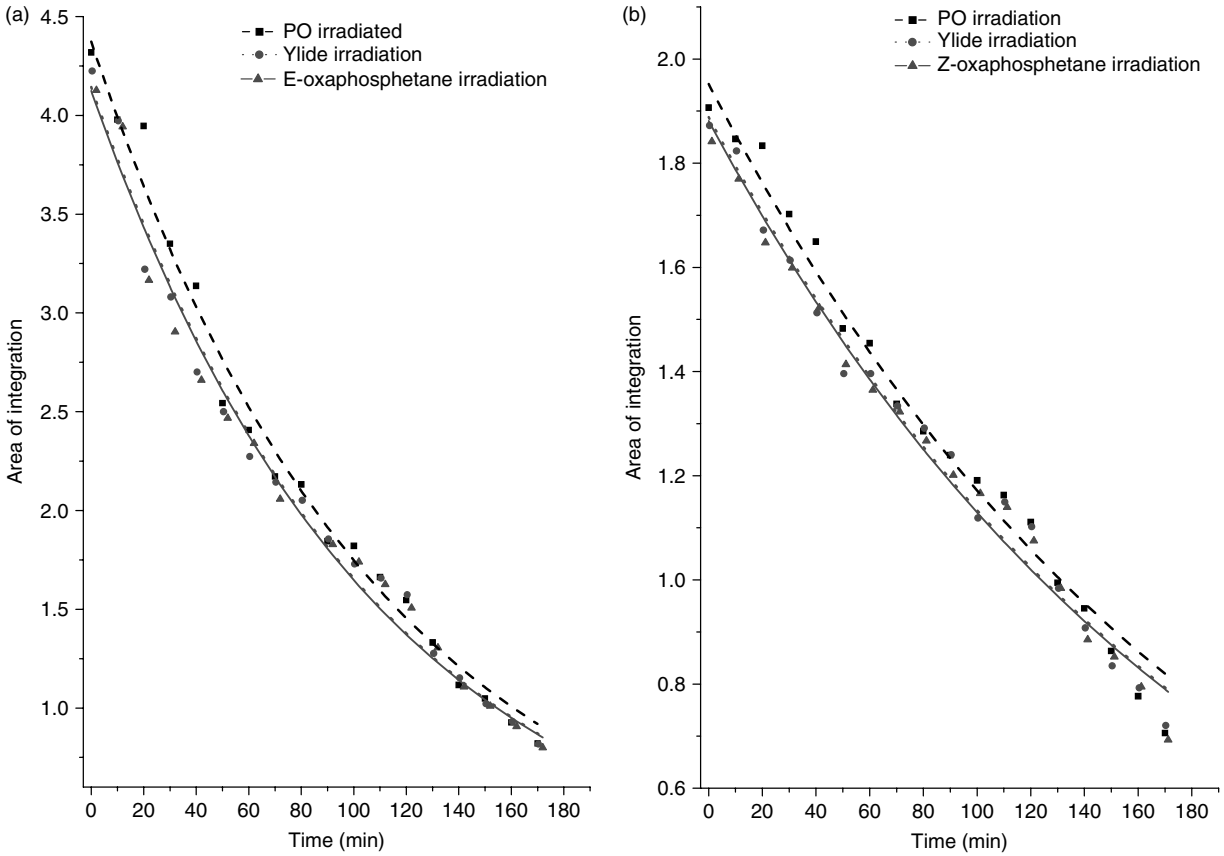


Figure 3. Time behaviour of the ^{31}P NMR signals of the (a) (*Z*)- and (b) (*E*)-oxaphosphetane signals during the Wittig reaction at 253 K. The curves show the situation when the phosphane oxide signal was irradiated as a control (■) and the situation when the ylide signal (●) or the other stereoisomer of the oxaphosphetane (▲) was irradiated.

The curves fitted through the squares serve as controls obtained by irradiation of the TPPO signal, which cannot contribute to the equilibrium, hence these curves depict only the decrease due to the chemical reaction. It is obvious that the curves fitted through the circles and triangles, which were obtained by irradiation of the ylide signal and by irradiation of the other stereoisomer, are always lower than the control curves, indicating a saturation transfer between both the ylide and the oxaphosphetane and between the oxaphosphetanes themselves. This decrease proved to be statistically significant using the 3σ criterion.

Results of ^{13}C saturation transfer

Figure 4 shows the behaviour of (*Z*)-oxaphosphetane. The curves fitted through the squares serve as control by irradiation in a region far away from all ^{13}C NMR signals. Circles and triangles were obtained by irradiation of the benzaldehyde signal and by irradiation of the other stereoisomer. In the case of the benzaldehyde, the curve obtained is always lower than the control curve, indicating again saturation transfer between the benzaldehyde and the (*Z*)-oxaphosphetane. The (*E*)-oxaphosphetane curve (data not shown) is hardly distinguishable from the control curve.

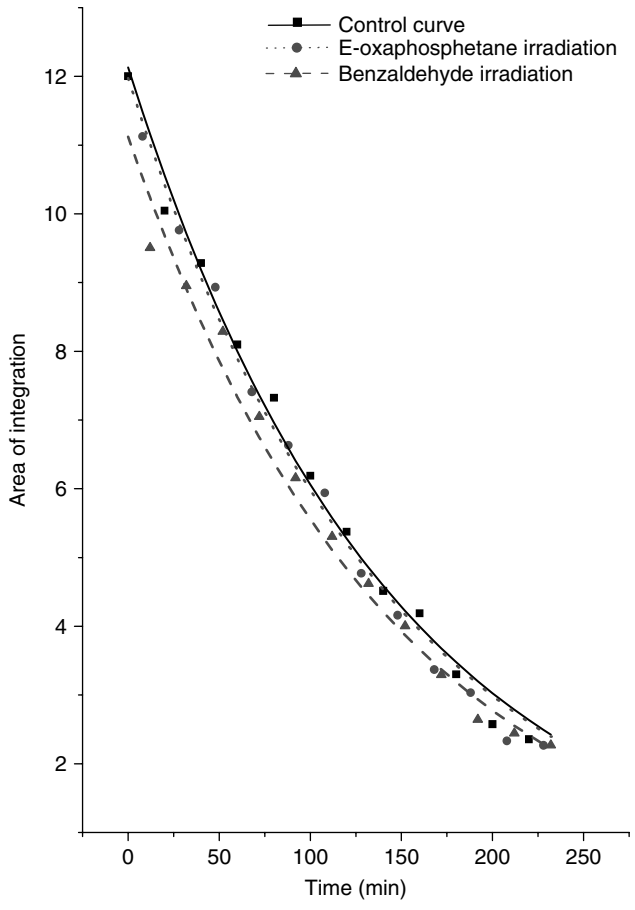


Figure 4. Time behaviour of the ^{13}C NMR signals of the (*Z*)-oxaphosphetane signals during the Wittig reaction at 253 K. The curves show the situation when the spectra was irradiated as a control (at a position where no signal was present) (■) and the situation when the benzaldehyde signal (▲) or the (*E*)-oxaphosphetane (●) was irradiated.

This may be due to the smaller amount present in the reaction in comparison with the (*Z*)-oxaphosphetane.

Results of DPFGSE-ROE

To confirm these results further, we tried to use an independent NMR method. Since 2D methods such as 2D ^{31}P-EXSY proved not to be sensitive enough, we turned to the ^{1}H-DPFGSE-ROE technique,[13] which, at these temperatures, is not prone to sign change problems compared with NOE. A mixing time of 1.4 s was shown to give the best results.^{1}H-DPFGSE-ROE gives higher values for intramolecular interaction, but the intermolecular interaction with the benzaldehyde can also be detected. As a control, we also measured spectra in which the irradiation was performed in a region without signals. Some typical results are shown in Fig. 5, showing weak signals of both the aldehyde proton at 10.1 ppm and the *ortho* aromatic protons of benzaldehyde at 8.1 ppm on irradiation of the oxaphosphetane signals.

The results of two independent NMR techniques on three different nuclei all show that in the case of the chemical system studied there is an ongoing equilibrium between aldehyde and oxaphosphetanes as determined by ^{13}C NMR, between ylide and oxaphosphetanes as determined by ^{31}P NMR and ^{1}H NMR. Hence the data confirm the double arrows in Scheme 1. However, these results cannot, at present, exclude one of the possibilities depicted in Scheme 2.

EXPERIMENTAL

Saturation transfer experiment. Spectral details

All spectra were recorded with a triple-channel Bruker DRX 400MHz spectrometer using a TBI probe head with an additional ^{13}C coil or a BBO probe head tuned to phosphorus. All ^{31}P chemical shifts were referenced using the Ξ scale.[14] The saturation transfer experiments[15] were performed according to Fig. 1 with the triple-channel possibility of the instrument. Typical data for the ^{31}P measurements were a time domain of 32K data points, a spectral width of 130 ppm with an acquisition time of 0.78 s. The irradiation time d1 was chosen to be 5 s and the pulse p1 was 5 μs, corresponding to 30° excitation. Eight scans were accumulated after four dummy scans. The power of the 300 W amplifier for single-frequency decoupling was attenuated by 69 dB. The ^{31}P decoupling bandwidth under these conditions was checked to be of the order of 50 Hz, which was chosen since the oxaphosphetane signals are typically separated by 300 Hz at 253 K.

The ^{13}C saturation transfer experiments were performed with the same pulse sequence, but using a spectral width of 230 ppm and a time domain of 64K data points yielding an acquisition time of 1.4 s. For ^{13}C a saturation time of 10 s was used and 16 scans were accumulated after four dummy scans at 253 K.

For the integration of the individual spectra, one common integral range file was created to ensure the same integration areas over the whole time of the reaction. Automatic baseline correction was used before integration and the integration was performed with and without phasing of the individual integrals.

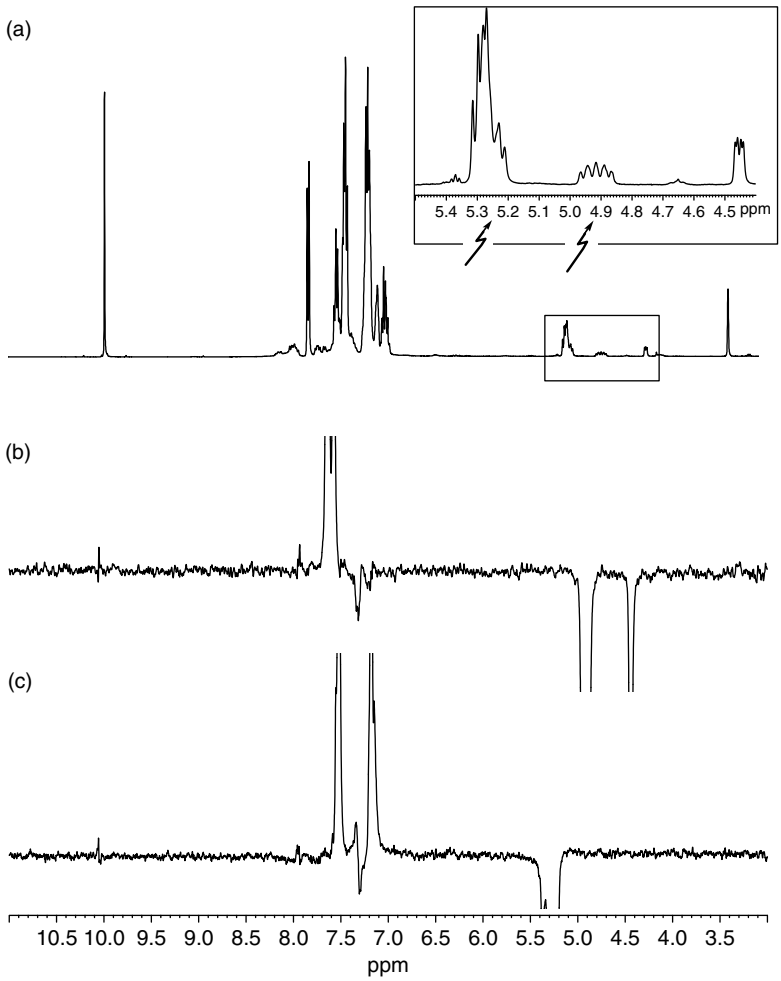


Figure 5. (a) ^{1}H NMR spectra, 0.5 M THF-d_8, 253 K; the oxaphosphetane protons were irradiated as shown; in (b) (*E*)-oxaphosphetane and (c) (*Z*)-oxaphosphetane. DPFGSE-ROE spectra were recorded at 253 K, 64 scans, mixing time 1.4 s, lb 2 Hz.

DPFGSE-NOE and DPFGSE-ROE. Spectral details

The 1D selective ROE spectra were obtained with the pulse sequence as described in Ref. 13; 32 scans were accumulated after four dummy scans with a time domain of 32K data points, using a spectral width of 14 ppm, yielding an acquisition time of 2.8 s and using a relaxation delay of 1 s. The selective 180° Gaussian-shaped pulse was 25 ms and the gradient pulses used were in the ratio 70 : 30. The hard 90° excitation pulse was 10.3 μs. The power level for the spin lock was set corresponding to a 21 μs 90° pulse. At this power level, 30° pulses (7 μs) were used, followed by a delay of 14 μs. The total duration of the spin-lock used was varied between 300 ms and 2 s.

General procedure for Wittig reaction

Phosphonium salt (0.5 mmol) together with solid LiHMDS (0.5 mmol) was suspended under nitrogen in 1 ml of THF-d_8. The mixture was stirred for 30 min at room temperature and a reddish orange solution was obtained. With careful exclusion of moisture and air the solution was transferred to an NMR tube. At −80 °C, 1.1 equiv. of benzaldehyde was added directly to the NMR tube through a septum. When measuring ylide behaviour, only 0.7 equiv. of benzaldehyde was added.

CONCLUSIONS

We have been able to prove, using NMR techniques, results which had previously been shown only by chemical crossover experiments. By saturation transfer experiments at low temperature, we could demonstrate exchange between reagents and reaction intermediates. Also, we confirmed these results with ^{1}H-DPFGSE-ROE. Further, we shall investigate direct exchange between oxaphosphetane intermediates.

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