A Dynamic Equilibrium of Oxaphosphetanes

Christian Geletneky, Frank-Holger Försterling, Willi Bock, and Stefan Berger*

Fachbereich Chemie der Universität Marburg,
Hans-Meerwein-Straße, D-35032 Marburg, FRG

The course of the Wittig reaction was investigated by rapid injection NMR spectroscopy. Rate constants for the formation of oxaphosphetanes were determined. A new dynamic equilibrium of oxaphosphetanes was observed for the first time. The solvent and substituent dependence of the new effect was investigated. By labeling various oxaphosphetanes with ^{13}C and [17]O the lithium salt dependence of the new equilibrium was shown. A lithium adduct of oxaphosphetanes under these conditions is proposed.

The Wittig reaction[1] is still one of the most significant methods for the generation of carbon-carbon double bonds, and many publications have delt with the mechanism and stereochemistry of this reaction[2]. In practice, the reaction was performed either under lithium salt-containing or lithium salt-free conditions, resulting in different stereochemical outcomes[3]. Furthermore, a distinction was made between stabilized, half-stabilized, and unstabilized ylides[2]. On the basis of early results of the Wittig reaction[4] betaines **3** were proposed as intermediates formed by the reaction of ylides **1** with aldehydes **2** (see Scheme 1). However, since the first NMR experiments to detect intermediates during the Wittig reaction by Vedejs[5] the existence of betaines **3** has not been proven; only the oxaphosphetanes **4** were shown to be true intermediates. Recent model calculations[6] have again raised the question whether the formation of oxaphosphe-

tanes occurs by a synchronous [2 + 2] addition or whether one of the four bonds of the four-membered oxaphosphetanes is closed first.

Results and Discussion

A. RI-NMR Spectroscopy

In recent years it has become possible to observe rapid chemical reactions by NMR spectroscopy by the use of the rapid injection technique (RI) as introduced by McGarrity[7]. We have therefore initiated a program to reinvestigate the course of the Wittig reaction with the help of the RI technology and discuss in this paper some surprising and unprecedented results. Although there are considerable technical difficulties in performing RI experiments during the Wittig reaction due to the heterogeneity caused by precipitation of triphenylphosphane oxide, we were able to record ^{31}P-NMR spectra of several different ylides by treating the ylide with benzaldehyde at very low temperatures during the first few seconds of the reaction. Rate constants of the olefin-forming reaction starting from oxaphosphetanes are known by earlier work[8]. In this paper, we report for the first time on rate constants for the formation of oxaphosphetanes. These are several orders of magnitude larger than those of the olefin formation. Using the RI technique, we can determine these constants both from the disappearance of the ^{31}P-NMR signal of the ylide and from the oxaphosphetane signal. For example, the rate constant of the formation of oxaphosphetane **4e** was determined to be 5 ± 3 $1 \cdot mol^{-1} \cdot s^{-1}$ at 183 K, of **4j** $3 \pm 3 \, 1 \cdot mol^{-1} \cdot s^{-1}$ at 233 K, and of **4h** $6 \pm 2 \, 1 \cdot mol^{-1} \cdot s^{-1}$ at 193 K. For the calculation of these rate constants, a second-order reaction model was used assuming equal concentrations of ylide and aldehyde at the outset of the reaction. Furthermore, back reaction and olefin formation were neglected at these temperatures. A sequence of ^{31}P-NMR spectra recorded during the first four seconds of the formation of **4h** at 213 K is shown in Figure 1.

However, as can be seen from Figure 1, no other intermediate could be observed prior to the formation of oxa-

Scheme 1
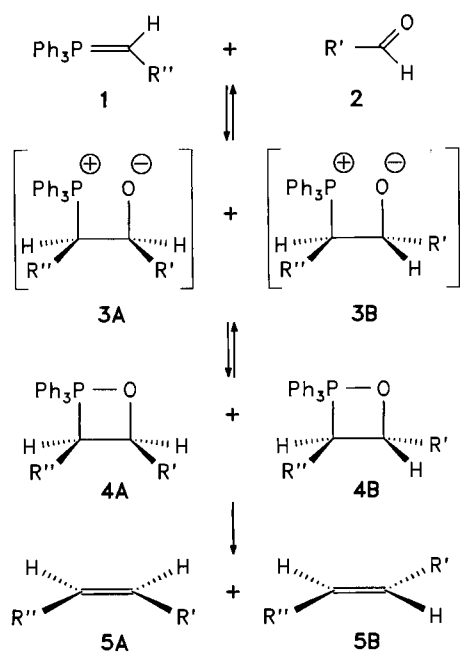
phosphetanes even by means of the RI-NMR technique. We should conclude, therefore, that the formation of betaines in the reaction of unstabilized ylides with aldehydes or ketones still cannot be proven.
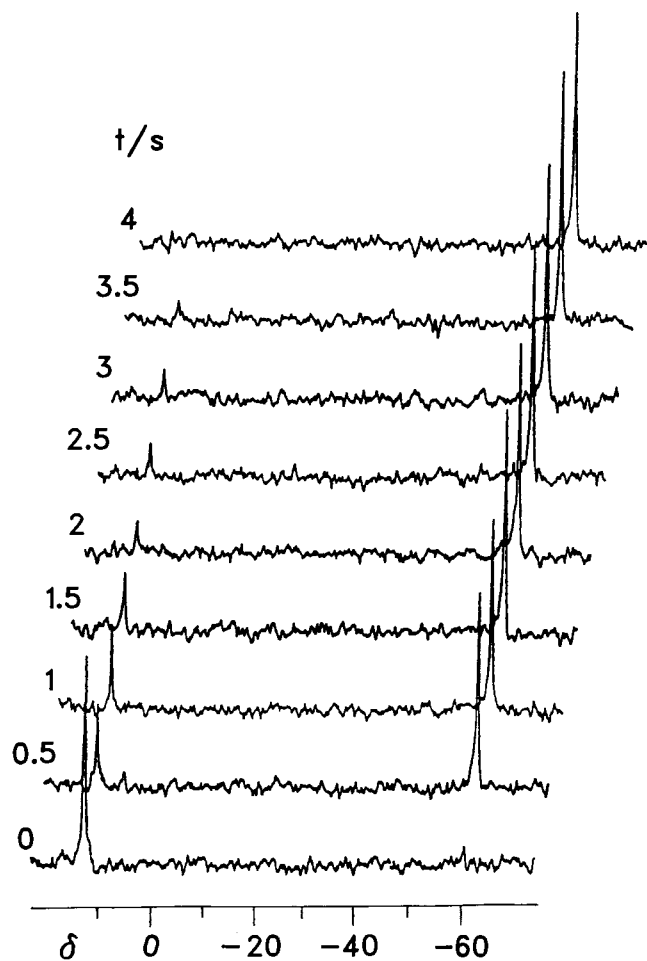

Figure 1. Sequence of ^{31}P-RI-NMR spectra during the formation of oxaphosphetane **4h** ($\delta = -62$), signals at $\delta = 13$ stem from ylide **1h**

B. Dynamic NMR Spectroscopy

During the course of these investigations it became apparent, that the ^{31}P-NMR signal of the oxaphosphetanes sometimes broadened at temperatures below 250 K. Such a broadening has been mentioned in the literature[2]; however, to the best of our knowledge, it was not investigated systematically. We have therefore set out to study this effect very closely. As can be seen in Figure 2, the ^{31}P-NMR signal of the oxaphosphetane **4e** at 243 K consists of two closely resonating lines at $\delta = -62$, which can be ascribed to the two components of the cis/trans mixture of **4e**. At lower temperatures, the signals broaden, and the two isomers can no longer be distinguished. At 203 K a new broad signal emerges at $\delta = -37$, the signal becomes stronger at lower temperatures and finally splits into two relatively sharp resonances, the intensity ratio of which resembles approximately the stereoisomeric ratio of the starting oxaphosphetane. Similarly, the oxaphosphetane signal becomes sharper,

and in some cases, the two stereoisomeric forms can be observed again at 173 K. This dynamic NMR process proved to be very similar for many different oxaphosphetanes and was fully reversible in all cases. Probably, the observation of this phenomenon was earlier not likely due to the use of rather low-field instruments for ^{31}P-NMR measurements.
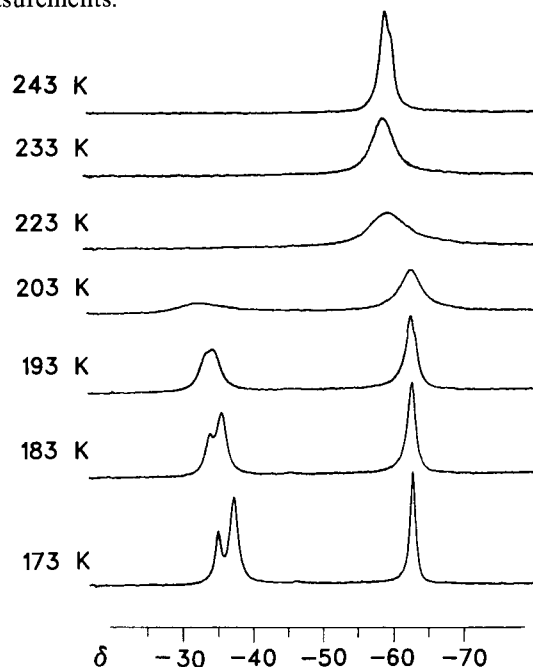

Figure 2. Dynamic ^{31}P-NMR spectra of oxaphosphetane **4e** recorded between 243 and 173 K

Numerous attempts have been made to assign a structure to the compound giving rise to the new ^{31}P-NMR signal. The first important observation was that the dynamic NMR effect was only observable in THF. In solvents like diethyl ether, dimethyl ether, or 2-methyltetrahydrofuran a significant broadening of the ^{31}P-NMR signal of the oxaphosphetanes was not observable. This led to the assumption that the effect depends on the lithium salt used, since only THF can dissolve a fair amount of the lithium salt formed during the Wittig reaction. Indeed, the preparation of the ylides in THF under salt-free conditions with sodium amide or potassium hexamethyldisilazide instead of n-butyllithium or tert-butyllithium did not give rise to a significant broadening. The addition of lithium bromide to such a solution, however, caused a broadening, whereas the addition of TMEDA or a crown ether such as 12-crown-4 to a solution of the oxaphosphetane prepared conventionally with n-butyllithium in THF caused a disappearance of the dynamic NMR effect. The relative intensity of the exchange signal increased with increasing concentration. Thus, all experiments described above ascertain that the appearance of the new ^{31}P-NMR signal and the dynamic broadening of the oxaphosphetane signal are only observed in the presence of lithium salts in solution.

The ^{31}P-chemical shift of the exchange species was observed about 10−25 ppm downfield with respect to the res-

onance position of the oxaphosphetane signal. This is still the chemical shift area of pentacoordinated phosphorus[9] and excludes betaines or betaine-like structures such as the lithium salt adducts of betaines. The chemical shifts of such species were found to be in the range of $\delta = +20$ to $+32$[10]. Thus, the ^{31}P-NMR spectra indicate that ring opening of the oxaphosphetanes involving the P,C or the P,O bond is highly unlikely. In contrast, the chemical shift difference seems to be too large to be explained by a different low-temperature conformation of the oxaphosphetanes as model studies of dynamic NMR spectra of pentacoordinated phosphorus compounds suggest[11].

It is important to note that the observed exchange phenomenon was independent of the precursor of the oxaphosphetanes. Thus, after the preparation of oxaphosphetanes by the reaction of β-hydroxyphosphonium salts with n-butyllithium the same exchange process was observed.
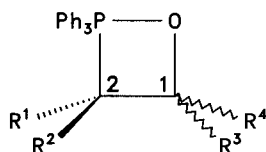
$$Ph_3P \overset{\text{2}\quad\text{1}}{\underset{R^2}{\overset{R^1}{\rule{0pt}{0pt}}}}\!\!\!\!\!\!\!O$$

Table 1. Substituent dependence of the dynamic exchange observed for oxaphosphetanes

4	R^1	R^2	R^3	R^4	exchange[a]	Δδ ^{31}P[b]
a	H	H	H	Ph	-	-
b	H	Me	H	Et	s	9
c	H	Me	H	n-Pr	s	10
d	H	Me	H	i-Pr	w	15
e	H	Me	H	Ph	s	25
f	H	Me	Me	Me	w	14
g	H	Me	Me	Ph	-	-
h	H	n-Pr	H	Ph	s	25
i	Me	Me	H	Et	-	-
j	Me	Me	H	Ph	-	-
k	Me	Et	H	Ph	-	-
l	H	Ph	H	Ph	-	-

[a] s = effect strongly observable at temperatures between 213 and 183 K, w = effect just observable at temperatures around 173 K, — = effect not observable, compare text. — [b] Difference between the ^{31}P-NMR signal of the exchange species and the oxaphosphetane signal.

The dependence of the observed equilibrium on the substituents was thoroughly investigated. From an inspection of Table 1 several conclusions can be drawn. The oxaphosphetane with R^1, R^2, R$^3 = $ H 4a was not stable enough to provide a convincing proof of the NMR effect. This effect is most clearly observed if R^1, R$^3 = $ H and R^2, R$^4 = $ alkyl or aryl. In the case of R^2, R$^4 = $ alkyl, the ^{31}P-NMR chemical shift difference between the exchange species and the oxaphosphetane signal ranges from 9 to 15 ppm. In the case of

one aryl substituent, the chemical shift difference is larger, and the effect is therefore most easily observed. With only one hydrogen substituent the effect is just observable in the case of 4f, where the other substituents are methyl groups. Higher substitution apparently causes steric hindrance thus rendering the dynamic NMR effect unobservable. Preliminary results with α-hetero-substituted ylides which can additionally complex the lithium ion with the side arm[12], show the effect as expected very drastically.

C. ^{13}C-Labeled Oxaphosphetanes

Since the achievable concentration of oxaphosphetanes is too low to record dynamic ^{13}C-NMR spectra, we decided to label several oxaphosphetanes with ^{13}C to obtain further insights into the nature of the exchange species. Thus, either [α-^{13}C]-labeled benzaldehyde or [1-^{13}C]-labeled ethyltriphenylphosphonium iodide was used to obtain singly labeled oxaphosphetanes 4b, 4e, 4j, and 4k; in addition, 4e was obtained doubly labeled. Similarly labeled oxaphosphetanes have already been described in the literature; however, very low-temperature ^{13}C-NMR spectra have not been obtained[8,13]. As can be seen in Figure 3, there are two signals originating from C-1 in [1-^{13}C]-4e at $\delta = 68.6$ and 71.5 which are assigned to the cis and trans isomers, respectively. Both signals show additional splitting due to a ^2J(P,C) of
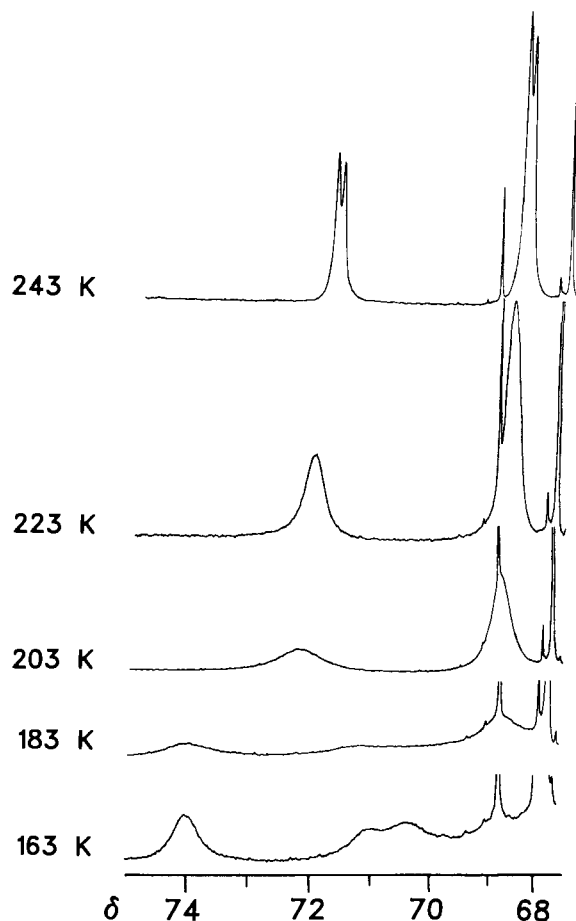

Figure 3. Dynamic ^{13}C-NMR spectra of oxaphosphetane [1-^{13}C]-4e recorded between 243 and 163 K

15 Hz. At lower temperatures, the signals of both isomers broaden, this broadening appearing however somewhat earlier for the *trans* isomer. At 163 K, a splitting is observed for both isomers. Also, the high-field part of the *cis* signal is hidden under the solvent signal of [D₈]THF. Similar observations have been made for [2-¹³C]-**4e** and [1,2-¹³C]-**4e**. It is important to note that these measurements show that the ¹³C signals of C-1 and C-2 of the exchange species appear in the chemical shift region of $\delta = 70$. As already discussed for the ³¹P chemical shifts, it is therefore again highly unlikely, that the oxaphosphetane ring opens during this process or experiences any other drastic rearrangement.

Both the dynamic ¹³C- and ³¹P-NMR spectra as well as the ¹H-NMR spectra were simulated by a complete line-shape analysis[14]. Although the dynamic behavior of the ³¹P spectra at first sight looks different from the ¹³C result (growing of a new resonance vs. a symmetrical splitting) all spectra could be simulated with identical dynamic parameters. The different appearance as shown in Figures 2 and 3 can be attributed to the large chemical shift difference in ³¹P NMR of 4000 vs. 250 Hz in ¹³C NMR rendering the ³¹P-NMR observation of the equilibrium possible at much higher temperatures, where the equilibrium constant is quite different. As the result of the line-shape calculations for ¹H, ¹³C, and ³¹P for **4e** a medium value of $\Delta G^{\neq}_{(298)} = 44.5 \pm 2$ kJ/mol, $\Delta H^{\neq} = 19 \pm 2$ kJ/mol, and of $\Delta S^{\neq} = -85 \pm 10$ J/mol was obtained. From an evaluation of the temperature-dependent ³¹P-NMR integrals we could calculate $\Delta H^0 = -45.2 \pm 2$ kJ/mol and $\Delta S^0 = -254 \pm 10$ kJ/mol for the reaction. The remarkable negative activation entropy clearly points to an *intermolecular* process which is in accordance with the observation, that lithium salts are required for the appearance of the dynamic NMR process.

D. ¹⁷O and ⁶Li Observations

Since ring opening of the oxaphosphetane as the source of the dynamic equilibrium could be excluded, and an intramolecular conformational process is unlikely[15] due to the large negative activation entropy determined by complete line-shape analysis and the observed lithium salt dependence, we discussed the dimerization of the oxaphosphetanes under lithium salt complexation or ring opening conditions and immediate formation of an eight-membered ring system. However, the ¹³C-NMR spectra of such species should show several diastereomers which were not observed. Furthermore, dimeric structures require the formation of mixed aggregates, if two different oxaphosphetanes are present in solution.This was checked by a ³¹P-NMR cross-over experiment with oxaphosphetanes **4e** and **4c**, where the two exchange species could be observed simultaneously, whereas the oxaphosphetanes form only one combined signal. ³¹P-EXSY[16] spectroscopy confirmed the exchange between the oxaphosphetane signal and both signals of the exchange species. However, no additional signals of a mixed species were detected.

We therefore propose the formation of a lithium adduct of the oxaphosphetane, as shown by formula **6**. The for-

mation of **6** would be in accordance with all experiments discussed above. However, it should also lead to additional observations. One should obtain temperature-dependent ⁶Li-NMR spectra, and ¹H,⁶Li-HOESY[17] spectra should reveal a contact between ⁶Li and the hydrogen atoms of the oxaphosphetane. Furthermore, a spin-spin coupling between ¹⁷O and ⁶Li might be observed.

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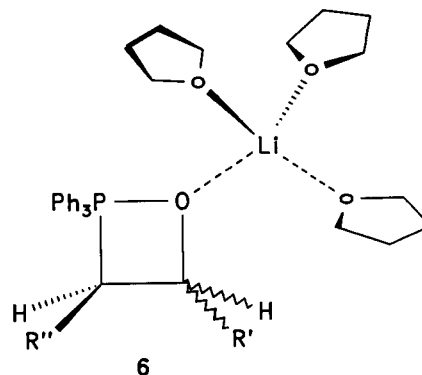
Thus, ylide **3e** was prepared by treatment with ⁶Li-labeled *n*-butyllithium, and the corresponding oxaphosphetane was synthesized. Temperature-dependent ⁶Li-NMR spectra showed a considerable upfield shift and line broadening towards lower temperatures, however two separate signals could not be detected. We succeeded in detecting weak HOESY contacts between ⁶Li and the aromatic hydrogens of **4e** at 183 K. Finally, [¹⁷O]-**4e** was prepared from [¹⁷O]benzaldehyde. To our knowledge, the first ¹⁷O-NMR spectrum of an oxaphosphetane was recorded which displays a very broad signal ($\Delta v_{1/2} = 5000$ Hz) at $\delta = 200$. Clearly, the observation of an ⁶Li,¹⁷O spin coupling is not possible. The signal broadens further at lower temperatures and is no more observable in the exchange region, probably due to the difficulty to observe broad quadrupolar signals at very low temperatures.

Additional proof in favor of structure **6** was sought in a molecular weight determination by low-temperature cryoscopy[18]. Due to the complexity of the system, reliable quantitative results were not obtained. The data only reveal that contrary to the use of salt-free conditions, higher aggregates should be present in solution.

Finally, it was of interest to prove, whether the stereochemical outcome of the Wittig reaction depends on the new exchange phenomenon described in this work. As expected, however, this was not the case, since **6** was formed at temperatures far below the start of the olefin forming reaction. Thus, the Z/E ratio determined from isolated olefins **5** was not significantly different if the reaction mixture was cooled intermediately down to 173 K. In addition, quenching of the reaction at this temperature by pouring the oxaphosphetanes into boiling THF did not give significantly different Z/E ratios compared with the normal preparation.

Conclusion

We have shown in this work that even with the RI-NMR technology no new intermediates of the Wittig reaction can

be determined. However, by very low-temperature NMR spectroscopy we found a new dynamic equilibrium for oxaphosphetanes, the occurrence of which is restricted to the presence of lithium salts. By the application of a large variety of methods we could exclude several structural proposals and suggest a lithium salt-dependent complexation of the oxaphosphetanes under these conditions.

Experimental

1. *RI-NMR Measurements* were performed with a Bruker AM-400 spectrometer equipped with a 10-mm multinuclear probe head and a RI apparatus as described earlier[7,19]. The probe head was precooled to temperatures between 173 and 213 K, and the spinner air was replaced by dry nitrogen. The solution of the ylides was prepared as described below and placed in an open 10-mm NMR tube into the magnet. Aliquots of benzaldehyde were put into the syringe of the RI apparatus; subsequently the apparatus was mounted on the magnet. The reaction was started by pneunomatical injection of the contents of the syringe and parallel acquisition processing using a optoelectronic device. ^{31}P pulses with a small flip angle (18°) were used to minimize saturation effects, the acquisition time for a single free induction decay was set to 90 ms in order to acquire 10 single scan spectra per second. A special microprogram was written to store these spectra in the RAM of the ASPECT-3000 computer, since disk write routines would have been too long for this purpose. The intensities of the RI-NMR spectra were corrected for saturation effects due to the rapid pulsing.

2. *Dynamic NMR Measurements:* Low-temperature ^{1}H, ^{6}Li, ^{13}C, and ^{17}O measurements were performed partly with a Bruker AMX-500 NMR spectrometer and with a Bruker AM 400 NMR spectrometer using a 5-mm multinuclear probe head under standard measurement conditions. For ^{31}P-NMR measurements a 10-mm probe head was used. ^{1}H,^{6}Li-HOESY spectra were recorded as described earlier[20].

3. *Synthesis:* The required triphenylphosphonium iodides were prepared from the corresponding aryl or alkyl iodides and triphenylphosphane under standard literature conditions. A typical preparation of a 0.2 M ylide solution for the NMR measurement proceeded as follows:

In a dried and argon-flushed flask equipped with a rubber septum was dissolved 0.2 mmol of triphenylphosphonium iodide in 1 ml of THF (purified and dried with Na/K), and the solution was cooled to −78 °C (acetone/CO₂). 0.2 mmol of n-BuLi was added dropwise. After stirring for 15 min the solution was placed into a syringe and transferred to a precooled and argon-flushed NMR tube equipped with a rubber septum. The addition of the ketone or aldehyde was performed either within the NMR magnet during the RI measurements as described above or at the site of the NMR spectrometer for normal dynamic NMR mesurements. In several control exper-

iments *tert*-butyllithium, $NaNH_2$, or KHMDS were used instead of nBuLi.

4. *Labeled Compounds:* In general, labeling procedures were performed as described in ref.[21] $^{13}CO_2$ was generated from 98% ^{13}C-labeled $BaCO_3$ and allowed to react with methylmagnesium iodide or phenylmagnesium bromide to form either acetic acid or benzoic acid. [1-^{13}C]Acetic acid was isolated as the sodium salt and converted into acetyl chloride which was reduced to [1-^{13}C]ethanol. The labeled ethanol was converted into ethyl iodide from which the corresponding triphenylphosphonium salt was prepared. Benzoic acid was reduced to benzyl alcohol which was oxidized to [α-^{13}C]benzaldehyde according to the Swern method.

To prepare ^{17}O-labeled benzaldehyde, O_2 containing 30% of $^{17}O_2$ was condensed into a solution of benzylmagnesium bromide. The isolated [1-^{17}O]benzyl alcohol was oxidized with PCC to benzaldehyde.

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