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Fluoride-mediated Rearrangement of Phenylfluorosilanes

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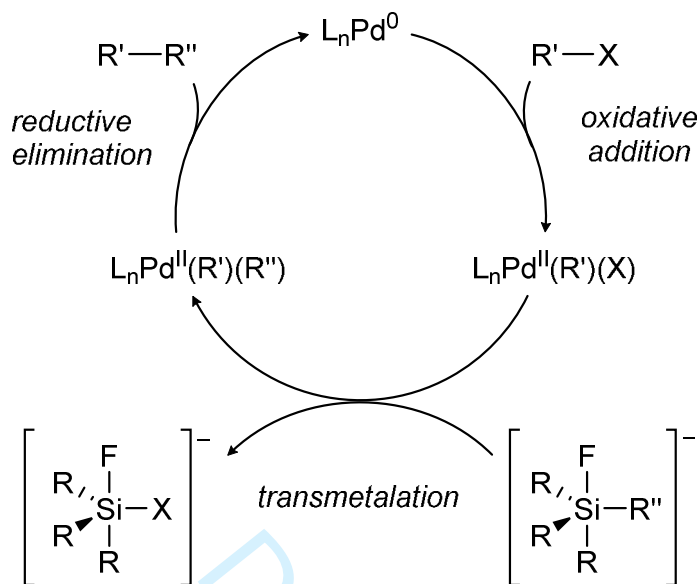
Abstract

Combining Ph_3SiF and fluoride ion under conditions used for the Hiyama coupling causes rapid formation of the expected $[\text{Ph}_3\text{SiF}_2]^-$, but real-time electrospray mass spectrometric analysis reveals that phenyl-fluoride exchange occurs concomitantly, also producing substantial quantities of $[\text{Ph}_n\text{SiF}_{5-n}]^-$ ($n = 0-2$). The exchange process is verified using ^{19}F NMR spectroscopy. This observation may have implications for Hiyama reaction protocols, which use transmetalation from triaryldifluorosilicates as a key step in cross-coupling.

Keywords: mass spectrometry, electrospray ionization, fluorine NMR, fluoride, silane/silicate, exchange

The palladium-catalyzed cross-coupling reaction of organosilicon reagents with organohalides, also known as the Hiyama coupling reaction, is a useful synthetic tool for the formation of carbon-carbon bonds. Relative to other organometallic compounds used in cross-coupling reactions (eg. SnR_3 , Stille-Migita-Kosugi; $\text{B}(\text{OR})_3$, Suzuki-Miyaura; $\text{Zn}(\text{R})(\text{X})$, Negishi), organosilicon compounds are weak nucleophiles as a result of the low polarization of the Si-C bond. The markedly inert character of these compounds is advantageous in synthesis, as they tolerate a wide variety of functional groups; however, their chemical stability makes them poor cross-coupling partners. Early work by Hiyama showed that activation of organosilicon reagents can be achieved through use of a fluoride salt, such as NBu_4F (tetrabutylammonium fluoride, TBAF) or $[(\text{Me}_2\text{N})_3\text{S}]^+[\text{F}_2\text{SiMe}_3]^-$ (Tris(dimethylamino)sulfonium difluorotrimethylsilicate, TASF), resulting in a competent coupling reagent.¹ Hiyama proposed that fluoride activation of the organosilicon reagent allows for the *in situ* formation of a pentavalent organosilicon anion whose labile carbon-silicon bond is essential for the facilitation of transmetalation in the catalytic cycle (Figure 1).²⁻⁴ Following this discovery, an abundance of diversely functionalized organosilicon

reagents have been developed and reaction conditions have been modified to drastically increase the scope and efficiency of the reaction.^{5,6}



While the mechanism of more well-established palladium-catalysed cross-coupling reactions (eg. Suzuki, Stille, etc) have been extensively studied, there have only been a few detailed studies on the mechanism of the Hiyama reaction.⁷⁻¹⁰ The absence of experimentally supported information about the details of the Hiyama coupling mechanism, especially regarding the transmetalation step and the pentacoordinate silicon intermediate, leaves many important questions unanswered. Elucidation of the mechanism through use of experimental techniques is difficult due to short-lived intermediates which are difficult to detect. Previous studies demonstrate the complexity of transmetalation, indicating that rates of coupling are dictated by substituents, catalyst and/or ligand.¹¹ We've developed methodologies - in particular, real-time monitoring of reactions via pressurized sample infusion (PSI)¹² coupled with electrospray ionization mass spectrometry (ESI-MS)¹³⁻¹⁵ - that allow mechanistic studies on difficult problems, and we attempted to apply these methods to the Hiyama cross-coupling

reaction of organosilicon reagents with aryl halides. Initially, our attention was attracted by the presence of anionic pentacoordinate silicon as the reactive species in transmetalation, because charged species are easy to detect and measure using ESI-MS. This manuscript deals with just one component of the overall reaction: an examination of the reactivity between the fluoride source and the neutral triphenylfluorosilane. It proved to be considerably more complicated than anticipated, and the results are very much a cautionary tale.

Methods

All manipulations were performed under an inert atmosphere (N_2), using oven-dried glassware where appropriate. ACS grade DMF (Caledon) was dried and stored over 4Å molecular sieves, and sparged with nitrogen for 15 minutes before use. Commercially obtained Ph_3SiF (TCI Chemicals, >97.0%) and $[CH_3(CH_2)_3]_4NF \cdot 3H_2O$ (Sigma-Aldrich, >97.0%) were used without further purification and stored under nitrogen.

NMR spectra were acquired on a Bruker AV 360 MHz spectrometer in d_6 -DMSO ($^{19}F\{^1H\}$, ^{29}Si) or in DMF with a d_6 -acetone coaxial insert (^{19}F) at room temperature. All chemical shifts (δ) are quoted in parts per million (ppm), the coupling constants (J) are expressed in hertz (Hz).

ESI-MS spectra were collected using either a (i) Micromass Q-ToF *micro* hybrid quadrupole/time-of-flight mass spectrometer (QtoF) or a (ii) Waters Acquity triple quadrupole detector with a Z-spray ionization source (TQD) in the negative mode using pneumatically-assisted electrospray ionization. Capillary voltage: 3000 V. Cone voltage: 15V. Source temperature: 110°C. Desolvation temperature: 220°C. Cone gas flow: 200 L h⁻¹. Desolvation gas flow: 200 L h⁻¹. Collision Energy: 2 V. MCP Voltage (QToF): 2400V. Phosphor detector gain (TQD): 470 V. MSMS experiments were performed with a collision energy between 2-30 V with an Argon collision gas flow rate of 0.1 mL/hr.

The general reaction procedure for the PSI-ESI-MS experiments is as follows: a solution of tetrabutylammonium fluoride trihydrate (0.0158 g, 0.05 mmol) was dissolved in 4.5 mL *n,n*-dimethylformamide in the specially designated PSI reaction flasks. The reaction mixture was heated to 110°C (regulated using a thermocouple) and stirred for the course of the reaction. A solution of fluoro(triphenyl)silane (0.0070 g, 0.025 mmol) in 0.5mL *N,N*-dimethylformamide (DMF) was then added to the reaction flask via syringe.

Results and Discussion

Electrospray Ionization Mass-Spectrometry

Before embarking on a full study of the Hiyama reaction, we needed to establish parameters for the conditions employed. Hiyama reactions are generally carried out at high temperature (>100 °C) and in strongly coordinating solvents (e.g. DMF),^{2,5} and we had not previously employed such forcing conditions nor such a high boiling point solvent in PSI-ESI-MS studies. However, with appropriate source conditions (see experimental section), DMF proved to be a well-behaved solvent for electrospray ionization (befitting a polar albeit high-boiling point solvent), and the high temperature of the reaction flask is not an issue for the PSI analysis as the solvent is rapidly cooled on exit into the capillary tubing leading to the mass spectrometer.

The most commonly used fluoride activator for the Hiyama reaction is TBAF, which is only commercially available in hydrate form due to the instability of anhydrous tetraalkylammonium fluoride salts.¹⁶ Two equivalents with respect to the triaryl fluoride are added to the reaction mixture, as per the conventional experimental protocol.³

When Ph_3SiF and two equivalents of $[\text{NBu}_4]\text{F}$ are combined in room temperature DMF, the pentacoordinate silicate $[\text{Ph}_3\text{SiF}_2]^-$ immediately appears in the negative ion mode in the mass spectrum, and its intensity stays stable over an extended period. Its MS/MS product ion spectrum (Figure 1) exhibits unimolecular decomposition at high collision voltages only,

breaking down by rearrangement to eliminate benzene or by heterolytic bond cleavage of a Si-C bond.

However, the same experiment conducted at typical Hiyama reaction temperatures (110°C) results in dramatically different behavior. Redistribution of the aryl groups is immediately initiated and the temporal evolution of the observed species is shown in Figure 2. The most prominent signal shows the appearance and decay of m/z 297, readily assigned as $[\text{Ph}_3\text{SiF}_2]^-$. The reaction between F^- and Ph_3SiF is extremely fast ($t_{1/2} < 45$ seconds), given the near-vertical ascent of the line immediately following combination of reagents. The exchange reaction that consumes it is slower, with a half-life of approximately five minutes. Three other anionic pentavalent silicon species were observed as products: $[\text{Ph}_2\text{SiF}_3]^-$ (m/z 239), $[\text{PhSiF}_4]^-$ (m/z 181), and $[\text{SiF}_5]^-$ (m/z 123), whose identities were confirmed through the use of MS/MS experiments and isotope pattern analysis (Figs. S1-S2). A fifth prominent species is also observed at m/z 320, which was identified as the aggregate species $[(\text{NBu}_4)(\text{HF}_2)_2]^-$ based on isotope pattern and MS/MS data (Fig S3).

The traces shown in Figure 3 are averages of three replicates, as we observed variability in the relative intensities of the observed species when repeating the experiment (error bar plots are provided in the supporting information, Figs. S4-S7). Qualitatively, the reaction behaved very similarly, in that the $[\text{Ph}_3\text{SiF}_2]^-$ always formed very quickly and disappeared with a consistent half-life of about 5 ± 2 minutes; however, the relative abundance of the product species was considerably more variable. This variability from experiment to experiment we attribute to the reaction itself rather than any inherent erratic behavior in the PSI-ESI-MS methodology, which regularly produces traces with high reproducibility in other contexts.¹⁷⁻¹⁹ One possible cause is the solvent, *N,N'*-dimethylformamide, whose hydrolysis into dimethylamine and formic acid occurs without catalyst at room temperature.²⁰ These decomposition products, even if present in only small amounts, may dramatically influence the rate and/or success of the reaction, especially if the exchange reaction is acid-catalyzed.

Unfortunately, commercial TBAF cannot be obtained free of water, therefore the presence of water cannot be completely eliminated from the reaction mixture.²¹ Nonetheless, the overall trend is clear in all experiments: within about 20 minutes, very little $[\text{Ph}_3\text{SiF}_2]^-$ remains in solution and the spectrum is dominated instead by fluorine rich silicate species. Note that no $[\text{Ph}_4\text{SiF}]^-$ or $[\text{Ph}_5\text{Si}]^-$ is observed, so the mass balance of Ph is not preserved. It is possible that formation of tetraphenylfluorosilicates is disfavored on steric grounds, given that reaction of PhLi with Ph_3SiF produced a 4:3 mixture of Ph_4Si and $[\text{Ph}_3\text{SiF}_2]^-$, rather than the intended $[\text{Ph}_4\text{SiF}]^-$.²² As such, we investigated whether neutral Ph_4Si is the invisible (to ESI-MS) sink for the “missing” phenyl groups. An authentic sample of Ph_4Si reacted with two equivalents of NBu_4F at the same elevated temperature in DMF resulted in the same rapid disappearance of phenyl groups (Fig. S8), indicating that Ph_4Si is not a secure reservoir of Ph groups. GC-MS analysis was unfortunately not revealing; the quenched mixture of products after the reaction was completed showed a complex chromatogram (see supporting information), dominated by the expected DMF peak, and containing some unreacted Ph_3SiF but with no evidence for potential phenyl reservoirs such as Ph_4Si or biphenyl.

Multinuclear NMR

The phenyl group is not an informative handle for either proton nor carbon NMR, and so we turned to $^{19}\text{F}\{^1\text{H}\}$ and ^{29}Si NMR to provide additional insights. However, even through the use of distortionless enhancement by polarization transfer (DEPT), ^{29}Si NMR spectra were not able to be obtained for the reaction mixture. The lack of detectable signal can be attributed to the mixture of products lowering the signal-to-noise and the signal being distributed across complex multiplets ($[\text{SiF}_5]^-$ would be a sextet, for example). Despite the lack of results from the ^{29}Si NMR experiments, spectra were successfully obtained using ^{19}F NMR, though given the low time

resolution of the technique the reaction was carried out at room temperature rather than at the elevated temperatures used for ESI-MS. NMR Reference spectra (Figs. S9-S11) were obtained for both Ph_3SiF ($^{19}\text{F}\{^1\text{H}\}$: δ -169 (d, $^1J_{\text{F-Si}} = 281$ Hz), ^{29}Si : δ -4.37 (d, $^1J_{\text{Si-F}} = 281$ Hz)) and $\text{TBAF} \cdot 3\text{H}_2\text{O}$ ($^{19}\text{F}\{^1\text{H}\}$: δ -143, -105).^{21,23,24}

Combining the two reagents together at room temperature (Figure 4) led to the appearance of a new peak at -97.5 ppm, consistent with the mass spectrometric observation of rapid formation of $[\text{Ph}_3\text{SiF}_2]^-$. The doublet at -143 ppm arises because the spectrum is not proton decoupled and so coupling to the H of $[\text{HF}_2]^-$ occurs. At room temperature, further change was slow (consistent with MS results at room temperature). A few small new peaks had grown in after 16 hours, and after 72 hours they had become appreciable and some were more abundant than the initial $[\text{Ph}_3\text{SiF}_2]^-$ species (Figure 4). The doublet at -143 had almost disappeared and a singlet at -144 grew in. This can be attributed to disappearance of the $[\text{HF}_2]^-$ and replacement by F^- , consistent with the growth of the signal at -105 ppm.

Literature values for the chemical shifts of some anionic silicon fluoride species are available, albeit in different solvents. $[\text{Ph}_3\text{SiF}_2]^-$ has been reported at -95 ppm (close to our observed value),²⁵ and $[\text{SiF}_6]^{2-}$ appears at -127 ppm (a possible candidate for the peak at -125 ppm) and $[\text{SiF}_5]^-$ at -136 ppm²⁶ (we observe no peaks in that region). The outstanding peaks at -112 and -119 ppm can be assigned to $[\text{Ph}_2\text{SiF}_3]^-$ and $[\text{PhSiF}_4]^-$, based on literature values for the methyl analogues.²⁷

Conclusions

The application of real-time ESI-MS to a high temperature reaction of Ph_3SiF and fluoride revealed rearrangement of the rapidly (<10 s) formed $[\text{Ph}_3\text{SiF}_2]^-$ ion to generate a range of more highly fluorinated silicate ions of the form $[\text{Ph}_n\text{SiF}_{5-n}]^-$ ($n = 0-2$) over a period of minutes.

Confirmation of the rearrangement came from room temperature ^{19}F NMR studies. Neither of these techniques, nor ^{29}Si NMR or ^1H NMR or GC-MS were informative as far as the fate of the “missing” phenyl groups was concerned. The observation of rearrangement itself is significant insofar as reactions that utilize $[\text{Ph}_3\text{SiF}_2]^-$ ions (most notably the Hiyama reaction) is concerned, because the rearrangement leads to lower availability of Ph for cross-coupling. Further elucidation of the details of the rearrangement will likely require the use of a triarylfluorosilane with a good ^1H NMR handle (e.g. the *para*-tolyl analogue).

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Figure 1. Literature catalytic cycle for the Hiyama reaction.

Figure 2. MS/MS product ion spectrum of $[\text{Ph}_3\text{SiF}_2]^-$. Inset: isotope pattern of the precursor ion (line experimental data, bars calculated).

Figure 3. Temporal evolution of $[\text{Ph}_{(3-n)}\text{SiF}_n]^-$ and $[\text{HF}_2]^-$ during the addition of Ph_3SiF to two equivalents of TBAF in dimethylformamide at 110°C . Traces are averages of three replicates. Inset: expansion of lower abundance species.

Figure 4. ^{19}F NMR of $\text{Ph}_3\text{SiF} + 2\text{eq TBAF} \cdot 3\text{H}_2\text{O}$ in DMF acquired at 0, 16, and 72 hours after mixing at room temperature.

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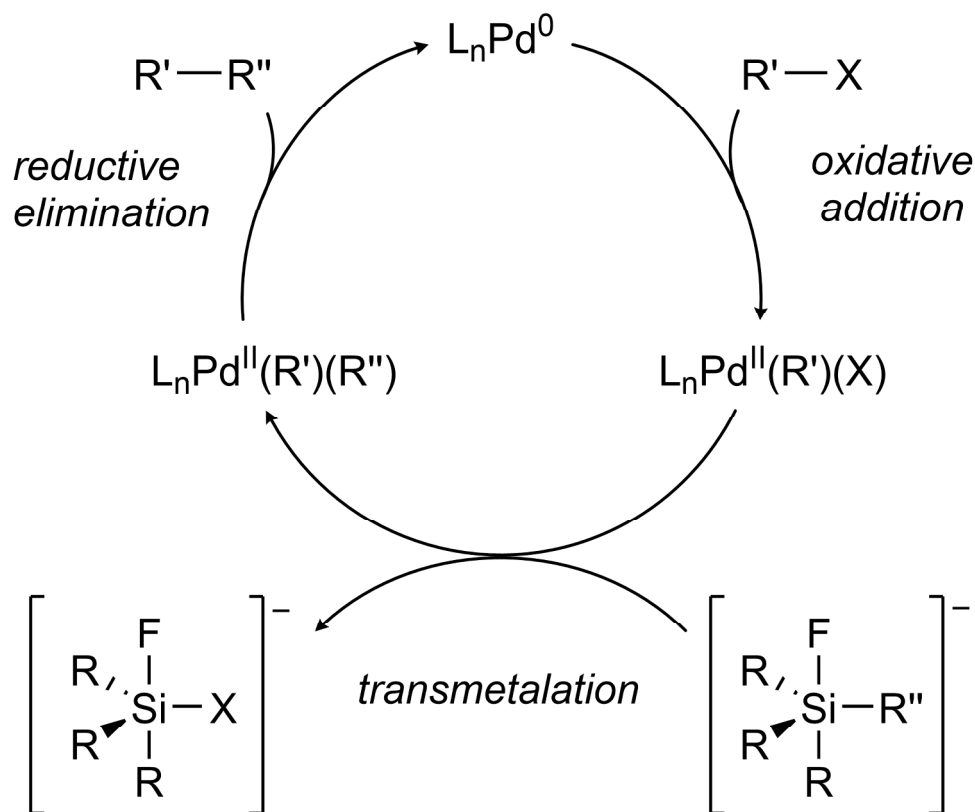


Figure 1

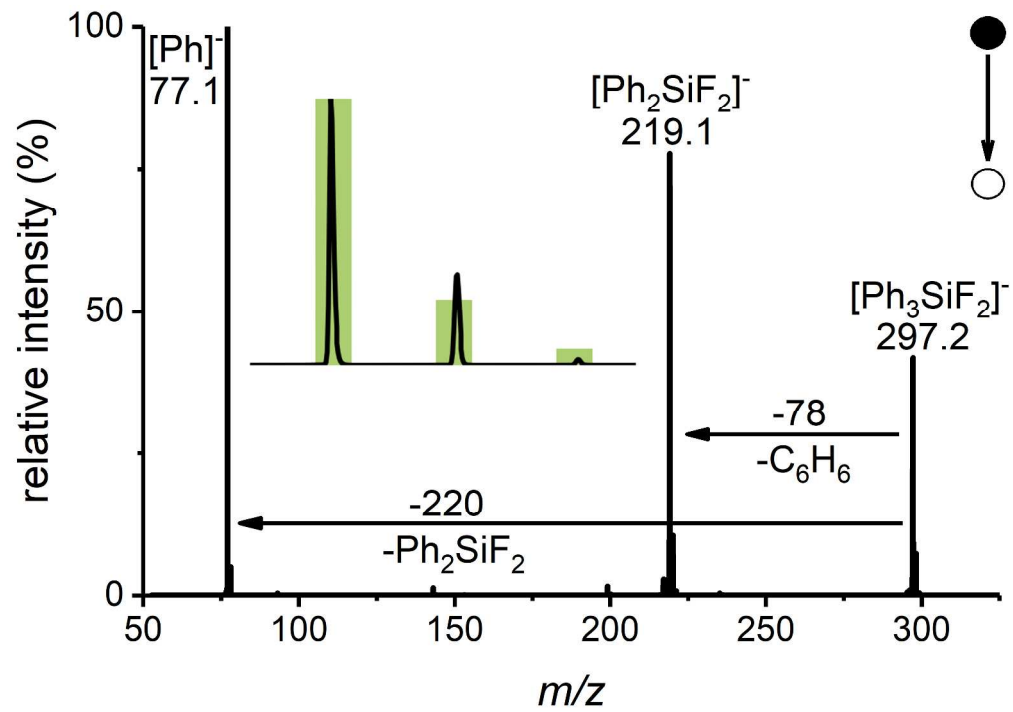


Figure 2

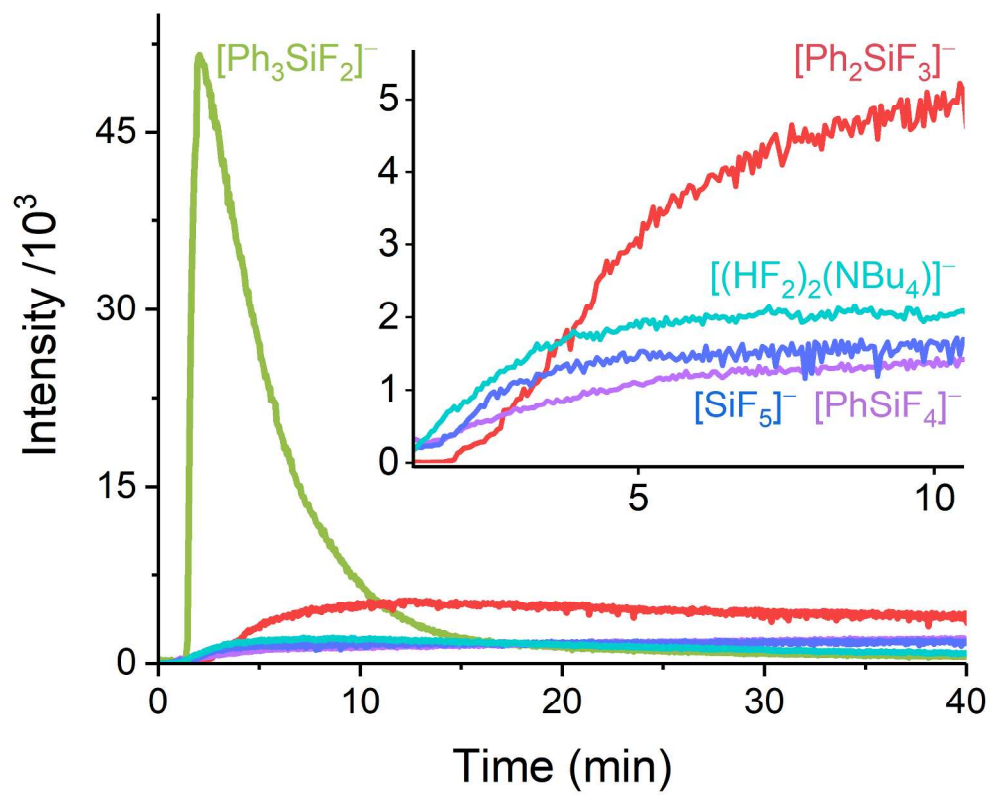


Figure 3

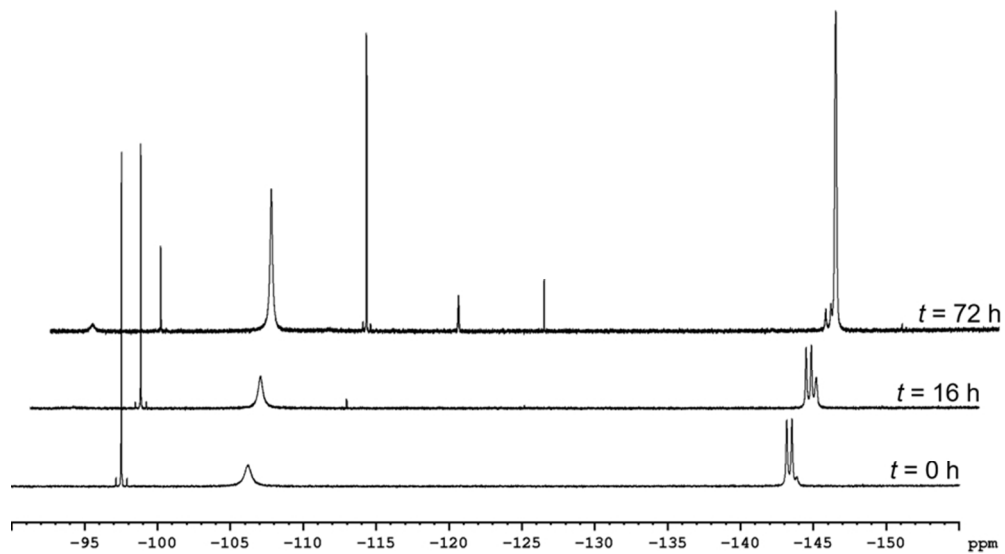


Figure 4