UNIVERSITAT ROVIRA i VIRGILI

Mechanistic study proposal of the trimethylsilylation of terminal alkynes using $TMSCF_3$ and DMPU

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Arnau Rodríguez Sugranyes

Supervisor: Prof Guy C. Lloyd-Jones FRS

Academic tutor: Prof Elena Fernández Gutiérrez

Abbreviations

List of molecules abbreviations used in the text:

CF_3^- – trifluoromethyl anion

CsF – caesium fluoride

DMI – 1,3-dimethyl-2-imidazolidinone

DMSO – dimethyl sulfoxide

DMPU – 1,3-dimethyl-1,3-diazinan-2-one; N,N’-dimethylpropyleneurea

HCl – hydrochloric acid

KF – potassium fluoride

NHC – N-heterocyclic carbene

RbF – rubidium fluoride

TBAF – tetrabutylammonium fluoride

TMAF – tetramethylammonium fluoride

TMS – tetramethylsilane

$TMSCF_3$ – trifluoromethyltrimethylsilane; Ruppert’s reagent

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1. Summary

En català

Els alquins terminals poden experimentar una reacció de trimetilsililació en presència de $TMSCF_3$ amb DMPU com a dissolvent. A data d'avui, cap estudi mecanístic s'ha centrat en aquesta transformació. Les tècniques de seguiment de reacció permeten dur a terme experiments orientats a desentranyar el mecanisme d'aquesta reacció. Des d'una gràfica de Hammett a la mesura dels efectes isotòpics cinètics, es descriuen algunes tècniques i se n'explica l'aplicació en aquest cas en concret. Una proposta d'un conjunt d'experiments, amb exemples on s'han fet servir anteriorment i explicacions de quina informació poden aportar, es proporciona en aquest text.

In English

Terminal alkynes are known to undergo trimethylsilylation in the presence of $TMSCF_3$ with DMPU as solvent. No mechanistic studies whatsoever have been focused in this transformation so far. Reaction monitoring techniques allow experiments aimed at shedding light on the mechanistic pathway of this reaction. From a Hammett plot to the measurement of kinetic isotope effects, several techniques are described and their application to this particular case explained. A proposal of a set of experiments, with examples where they have been previously used and with explanation of which information they can provide, can be found in this text.

2. Objective

The main objective of the present work is to propose experiments aimed at shedding light on the mechanism behind the trimethylsilylation of terminal alkynes using $TMSCF_3$ and DMPU. Each experiment should be able to provide information about the reaction mechanism. This work aims to be a blueprint for the mechanistic study of this reaction by interpreting how different experiment results might point to different mechanistic features and by explaining how to carry out the experiments and what difficulties might be encountered experimentally. It is also an objective of this work to provide the readers with references of how the proposed techniques have been used in the past in illustrative examples.

3. Introduction

Trifluoromethyltrimethylsilane ($TMSCF_3$), also known as Ruppert's reagent, is a versatile organic reagent that is widely used in the trifluoromethylation of carbonyl groups.[1] Mechanistic studies have shown that the trifluoromethyl anion (CF_3^-), which is released from $TMSCF_3$ in the presence of a fluoride source, acts as the nucleophile.[2]

Nevertheless, in transition-metal-free conditions $TMSCF_3$ is not exclusively used in nucleophilic additions. It has been reported that formal bimolecular nucleophilic substitutions (S_N2) of benzyl bromides,[3] and of sulphur and selenium species (such as disulfides, sulphurcyanates and their selenium equivalents and sulfenyl chlorides)[4,5] take place when using $TMSCF_3$ and a fluoride source.

In some cases, the CF_3^- anion or an equivalent species can act as a base to abstract a proton of a pro-nucleophile. This pro-nucleophile, which becomes a nucleophile, can then react with the appropriate electrophile.

In 1998, when using $TMSCF_3$ and a fluoride source in acetonitrile, the Adams group demonstrated that acetonitrile was deprotonated.[6] In 2013, it was reported that, instead of trifluoromethylation, dichloromethylation and cyanomethylation of nitrones took place when using dichloromethane and acetonitrile as solvents, respectively.[7] In both these cases, the CF_3^- anion does not itself act as a nucleophile, but as a base.

To the best of my knowledge, in 2000 it was the first time that $TMSCF_3$ was reported to trimethylsilylate instead of trifluoromethylate. The reaction was that of a terminal alkyne with $TMSCF_3$, which afforded the corresponding trimethylsilylation product.[8] Alkynylsilanes have many useful synthetic applications, including in the Hiyama cross-coupling, in cycloaddition reactions, and as a protecting group.[9] This transformation has been reported using different additional species such as fluoride sources, NHC and DMPU.[10–12]

More recently, the Kondo group reported that an acidic aromatic position could undergo trimethylsilylation with $TMSCF_3$ and a fluoride source.[13,14]

The reaction of terminal alkynes in the presence of $TMSCF_3$ and DMPU is the one that will be studied here. The trimethylsilylation of terminal alkynes was chosen because I believe it is the one which has more potential to be studied and no thorough mechanistic study has been or is expected to be published.

Knowledge of reaction mechanisms can provide useful information to tune reaction conditions in a rational rather than an empirical way to improve the reaction. Improvements such as higher yields, lower reaction times, suppression of side reactions and use of less extreme conditions are amongst the most desired both in research and industry and they can be achieved by unveiling the true nature of reaction mechanisms.

4. Bibliographic search

In this section, some techniques used to decipher mechanisms are explained and, in some cases, examples are provided about their use in other reactions which might bear some resemblance with the reaction under study. What information these techniques might provide in the reaction under study is also discussed.

Each of the sections in this chapter have a corresponding section in chapter 5. The reader can either first read this chapter and then the following one or alternate both to combine both literature and proposal.

4.1. Reaction under study

The reaction under study is that of $TMSCF_3$ and DMPU (N,N'-Dimethylpropyleneurea) with a terminal alkyne to yield its trimethylsilylated analogue. This reaction was first reported in 2017 by the Kondo group.[12] In figure 1, a reaction scheme with all the reagents drawn is provided. This section is a summary of all the information that was thought important about the article.

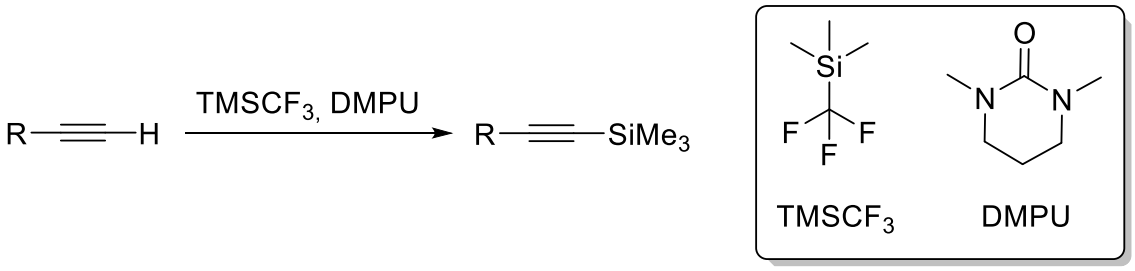

Figure 1. Reaction scheme of the reaction under study and molecular structure of $TMSCF_3$ and DMPU.

The reaction is performed by stirring a mixture of the alkyne, $TMSCF_3$ (1.2 eq.) in DMPU for 24 hours at 40ºC. After that, the mixture is quenched with a saturated chloride ammonium aqueous solution. The product is extracted with diethyl ether and then this ethereal solution is washed with water, and brine; dried with magnesium sulphate and concentrated using a rotary evaporator. The residue is purified using column chromatography.[12]

The scope of this reaction is limited to terminal alkynes with a neighbouring aryl or ester group. The trimethylsilylation of other substrates, such as alkyl substituted terminal alkynes has not been tested. The reaction conditions are tolerant of several different functional groups. These include ether, amine, halogen, nitrile, nitro, ester, and ketone groups. In some instances ketones can undergo trifluoromethylation under these conditions. Substituents in the ortho, meta and para positions of the phenyl ring are tolerated as well as heteroaromatic rings such as pyridinyl and thiophenyl.[12]

Reduced yields were obtained with DMI or DMSO as solvents (and activators). The addition of a fluoride source (CsF or RbF) in DMPU resulted in reduced yields, which is explained by the formation of the unstable pentacoordinate silicon species which decomposes to difluorocarbene. Unlike in other cases where other activators are used (see section 4.2), trimethylsilylation is faster than trifluoromethylation of aldehydes, ketones and esters.[12] The reactions conducted in toluene, dichloromethane, and THF did not lead to any product formation. Raising the temperature to 40ºC did not lead to a significant improvement in yields but to full conversion.

With a keto-1-alkyne molecule, the desired product was the main product (92% yield) when using 1 eq. of $TMSCF_3$. When 3 eq. of $TMSCF_3$ were used, the yield was reduced to 85% and some trifluoromethylation of the ketone occurred (10% yield). When a fluoride source is used to activate $TMSCF_3$, the chemoselectivity is not the same and trifluoromethylation is more favoured. This change in reactivity is attributed to the lack of an alkali cation, which would increase carbonyl electrophilicity, or to the formation of a pentacoordinate species with DMPU. When using TMAF (tetramethylammonium fluoride), which has a bulky cation, the ketone moiety was not trifluoromethylated.[12]

The proposed mechanism, shown in figure 2, consists of two steps: deprotonation of the alkyne and silylation. It involves the generation of a CF_3^- equivalent species from $TMSCF_3$ and DMPU that deprotonates the alkyne before coupling with a silyl source, which is not specified. A naked alkynyl anion is the proposed intermediate. The proposal does not show the silylating agent or how $TMSCF_3$ and DMPU are involved in the deprotonation step.[12]

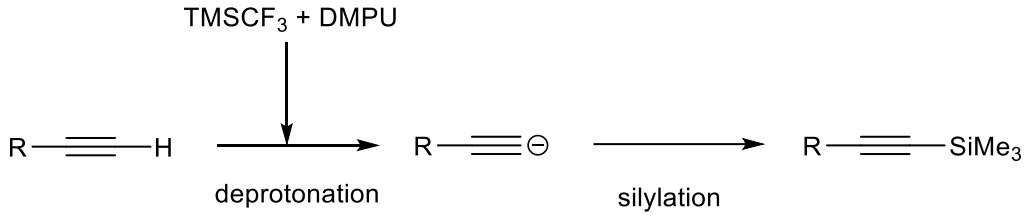

Figure 2. Mechanistic proposal of the reaction of terminal alkynes with $TMSCF_3$ and DMPU (Kondo group).

Although it is not shown in the mechanistic proposal, fluoroform release, as in the similar reactions, is confirmed by ^{19}F NMR. The reaction mixture is diluted in deuterated THF and the doublet appears in the same chemical shift as fluoroform bubbled into a deuterated THF solution.[12]

No experiments have been conducted to support this proposal.

4.2. Other trimethylsilylation reactions of terminal alkynes

The transition-metal-free reaction under study is not the only one that has been reported to trimethylsilylate terminal alkynes using $TMSCF_3$. Three other examples have been found in the literature, which need different reaction conditions. It is important to look at these reactions to see how changing reagents affects reactivity and gather information from it. Each article includes a mechanistic proposal albeit no thorough mechanistic studies on them have been reported so far.

In 2000, the Ishizaki group reported that, when $TMSCF_3$ and CsF were added, a keto-1-alkyne underwent alkyne trimethylsilylation as well as nucleophilic addition to the carbonyl, which was the desired reaction. To the best of my knowledge, this is the first time that such reactivity has been reported using $TMSCF_3$ and a fluoride source. As it can be seen in figure 3, a mixture of three products was obtained.[8]

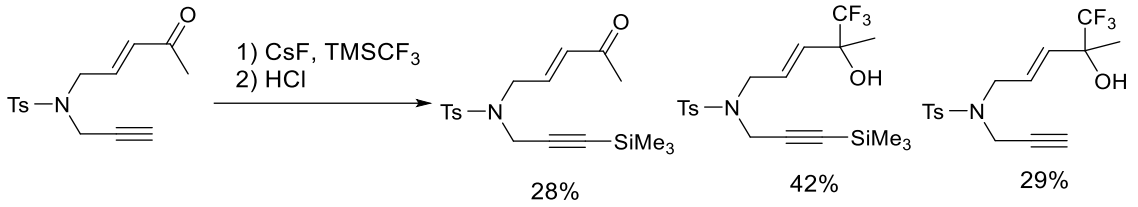

Figure 3. First example of the transition-metal-free terminal alkyne trimethylsilylation using $TMSCF_3$ and a fluoride source.

They showed that with a non-fluoride catalyst, such as caesium chloride or caesium hydroxide, or with no catalyst whatsoever the reaction does not take place. Only the use of CsF in THF and KF in DMF gave full conversion. A small amount of water in TBAF (tetrabutylammonium fluoride) was the presumed reason why it did not catalyse the reaction.[8]

Several substrates were explored. In the presence of a hydroxide group, this is preferably silylated and only with higher amounts of $TMSCF_3$ is it silylated at the alkyne position as well. A 1,3-diester resulted in a complex reaction mixture. Amines and amides required longer times and higher amounts of $TMSCF_3$. In the presence of an aldehyde, using KF in DMF, the desired product was obtained with a 26% yield (as compared with a 59% for trifluoromethylated and alkyne silylated product). With the use of CsF in THF, no desired product was obtained. At 0ºC, ketones are only trifluoromethylated with a 16% yield (whereas the yield is 72% for the desired product) using CsF in THF. Triethylsilylation was also possible, although it demanded longer reaction times and a higher catalyst loading.[8]

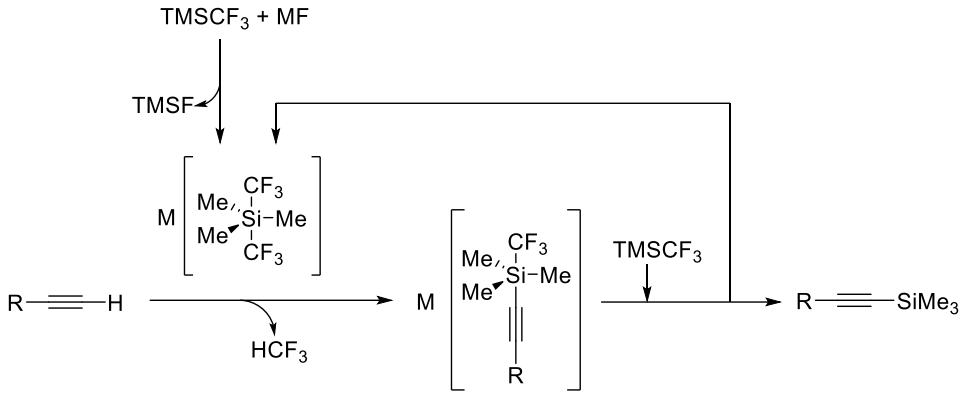

Figure 4. Mechanistic proposal of the reaction of terminal alkynes with $TMSCF_3$ and a fluoride source (Ishizaki group).

Figure 4 is a depiction of the proposed mechanism. The reaction is initiated by $TMSCF_3$ and a fluoride source to form the catalytic species, the pentacoordinate silicon complex, and fluorotrimethylsilane. After initiation, only $TMSCF_3$ is involved. Fluoroform is released.[8]

In 2001, the same reaction was reported using TBAF (tetrabutylammonium fluoride) as the fluoride source. They also report that under these conditions, acetylenic selenides, but not its sulphur analogue, can be converted to silylated acetylenes (strong bases convert acetylenic selenides to acetylides). The presence of a ketone, ester or amide group did not lead to significant desired product formation, if any product formation at all. A mechanism (see figure 5) involving a naked trifluoromethanide anion as the catalytic species is proposed. This anion is first formed by $TMSCF_3$ and tetrabutylammonium fluoride. Fluoroform gas release is proposed (they reported a vigorous and fast gas formation).[10]

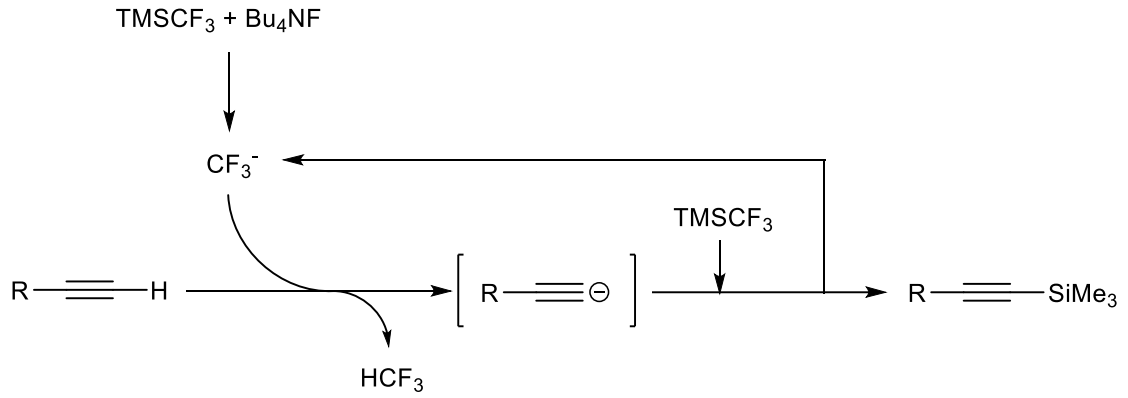

Figure 5. Mechanistic proposal of the reaction of terminal alkynes with $TMSCF_3$ and tetrabutylammonium fluoride (Yoshimatsu group).

In 2014, the Anand group published that the use of NHC (N-heterocyclic carbenes) instead of a fluoride source gave good results. The reaction proceeded faster without any solvent and it did not happen when either the base or NHC precursor were removed.

Other silyl pronucleophiles failed to give the desired product. The reaction went faster with alkynes bearing electron-withdrawing groups. Ester groups were compatible with these reaction conditions. They confirm that fluoroform is released in the reaction. In the same paper, the chemoselective N-silylation of indoles is reported using the same conditions.[11]

Their mechanistic proposal is shown in figure 6. A CF_3^- anion is generated from the pentacoordinate silicon species formed from $TMSCF_3$ and NHC. This is basic enough to deprotonate the alkyne. The alkynyl anion reacts with the electrophilic silicon centre to regenerate the NHC and form the silylated alkyne.[11]

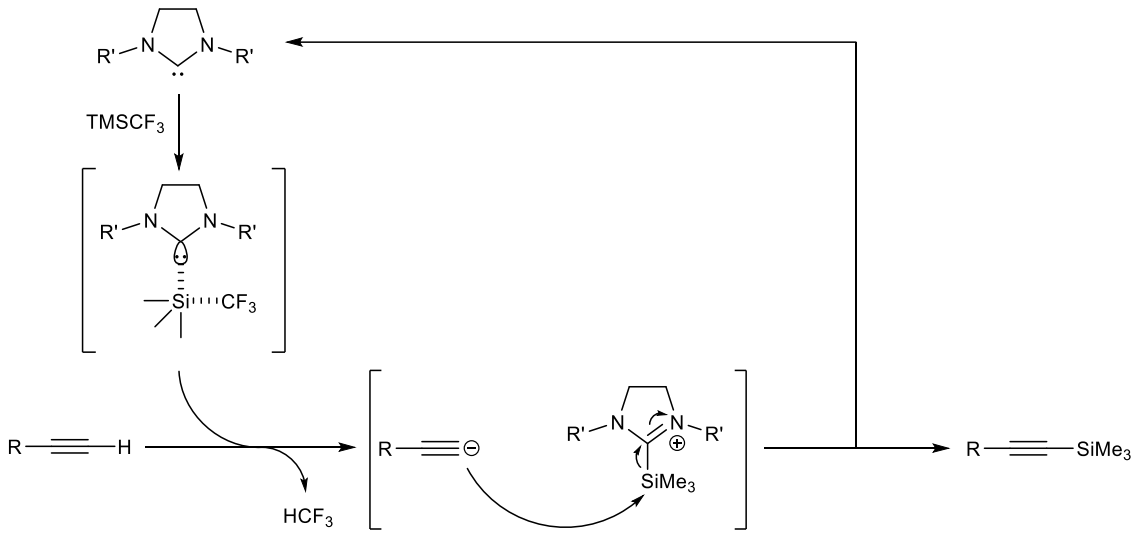

Figure 6. Mechanistic proposal of the reaction of terminal alkynes with $TMSCF_3$ and a NHC (Anand group).

None of these mechanistic proposals are exactly the same. In table 1, some features of each mechanistic proposal are compared. All of them involve fluoroform release. However, they do not propose the same regenerated species, alkyne intermediates or silylating agents.

Table 1. Comparison of the mechanistic proposals

Feature	Mechanistic proposal		
	1st	2nd	3rd
Fluoroform release	Yes	Yes	Yes
Regenerated species	Pentacoordinated silicon species	Trifluoromethyl anion	NHC
Alkyne intermediate	Pentacoordinated silicon species	Alkynyl anion	Alkynyl anion
Silylating agent	$TMSCF_3$	$TMSCF_3$	NHC-$TMSCF_3$

Bearing in mind that these reactions are not the same between them and that their mechanistic proposals do not have experiments to support them, they can still be useful to this present work.

4.3. Reaction monitoring

Before looking at different techniques to study the mechanism and at experiments to gather mechanistic information, it is necessary to analyse how the reaction will be monitored. It is not enough to just take the measurements once the reaction is over, data points must be collected over time, which limits the usable techniques. In this section, a bibliographic search has been carried out to see if it would be possible to monitor the reaction using the most common reaction monitoring techniques (NMR and IR).

^{1}H NMR

The consumption of the terminal alkyne could be easily monitored by the signal of the alkynyl proton in ^{1}H NMR. However, the product could prove more challenging to detect since, apart from the signals of the methyl protons, the other proton signals should be rather similar to those of the terminal alkyne. For example, if phenylacetylene was used as the model substrate, it would give rise to signals at 3.08 ppm (alkynyl proton), and at 7.32-7.35 ppm and 7.48-7.51 ppm (aromatic protons).[15] The product, 1-phenyl-2-(trimethylsilyl)acetylene, has signals at 0.25 ppm (methyl protons), and 7.29-7.31 ppm and 7.45-7.48 ppm (aromatic protons).[15] These spectra are recorded in deuterated chloroform with tetramethylsilane (TMS) as internal standard. Seemingly, the terminal alkyne could be monitored by its alkynyl proton signal and the product, by its methyl proton signal. The aromatic protons of both species are close to each other in chemical shifts and it is likely that their signals would overlap. Fluoroform appears at 6.88 ppm as a quadruplet.[13]

We should not lose sight of the fact that there is also DMPU and $TMSCF_3$ present in the reaction, which will be visible in the NMR spectra. $TMSCF_3$ has a chemical shift of 0.26 ppm in deuterated chloroform using TMS as internal standard.[16] This signal would overlap with that of the methyl protons in the product so it would not be possible to quantify the product by its methyl proton signal. However, DMPU has signals at 1.93-2.01, 2.92 and 3.22-3.26 ppm in the same conditions.[17] In this spectrum, DMPU is not used as a solvent, so it is present in a much lower concentration. Since in the reaction under study DMPU is used as a solvent, it is not unreasonable to think that the peaks will be much more intense and broader and the alkynyl proton will not be detectable, and it will not be possible to monitor the reaction at all. However, there are other options to detect the terminal alkyne.

There are solvent suppression techniques that suppress the solvent signal and even its carbon satellite peaks. For example, the signals due to the protonated solvent in spectra

recorded in 90:10 mixtures of protonated and deuterated solvents such as THF or can be erased while maintaining nearby signals.[18] The use of deuterated solvents, even in small quantities, is cost prohibitive in industrial flow processes. The receiver gain, which is set to maximise signal to noise ratio, must be reduced owing to the intense solvent signals. Solvent suppression can be achieved by using a pulse sequence that supresses the solvent signal before the acquisition. Commonly used solvent suppression techniques such as presaturation do not give quantitative NMR spectra. In most cases, solvent signals can only be reduced but not entirely suppressed, which can make close signals not useful for quantitative purposes. Peak deconvolution is possible by fitting the peaks to a Lorentz-Gauss function.[19]

Deuterated solvents are used to record ^{1}H NMR spectra to significantly reduce solvent peaks. The use of deuterated DMPU (d_{12}-DMPU), which would only show small peaks due to the residual non-deuterated DMPU, would solve the problem. It would allow monitoring of the terminal alkyne and fluoroform but not of the other components since its signals would overlap (*vide supra*). Unfortunately, DMPU is not a much-used solvent and it is not commercially available in its deuterated form. A synthetic route to obtain d_{12}-DMPU is shown in pages 22-23. Deuterated compounds are usually expensive and the synthetic route to obtain d_{12}-DMPU has many steps and requires a considerable amount of time.

Propargyl benzene, which is a similar compound, has the two benzylic protons, which appear at 3.61 ppm as a doublet in deuterated chloroform.[20] The product would appear at 3.66 ppm.[21] The signals of the terminal alkyne and of the product are too close to each other.

^{13}C and ^{29}Si NMR

Other nuclei such as carbon and silicon can be detected by NMR. The problem with the former is that ^{13}C NMR needs long acquisition times, which makes it not feasible, and it is not quantitative when it is proton decoupled. However, ^{13}C NMR would allow all the different species to be differentiated.[15] The problem with the latter is that ^{29}Si NMR requires longer acquisition times than ^{1}H NMR, although not as those of ^{13}C NMR, and the terminal alkyne would not be detected but the solvent would not be detected either.[22,23]

Infrared spectroscopy

There is also the possibility of monitoring the reaction through infrared spectroscopy. IR spectroscopy has already been used before to monitor reactions involving terminal alkynes.[24] Its main disadvantage is the need to use a calibration for each component to obtain its absolute concentration and the broadness of the bands, which are almost always broader than the peaks in an NMR spectrum. The main condition that must be met is that reactants and product do not have band overlapping. The most characteristic bands are the stretching bands of the C(sp)-H and C≡C bonds. The former is usually in

the 3,300 cm^{-1} region and the latter, in the 2,100-2,250 cm^{-1} region.[25] The first signal is only seen in terminal alkynes, so its decay should represent the consumption of the terminal alkyne and it should not have any overlapping with the product bands. This might be a problem for the carbon-carbon triple bond vibration. For phenylacetylene these two bands would appear at 3,290 and 2,108 cm^{-1}.[26] For 1-phenyl-2-(trimethylsilyl)acetylene, a band at 2,160 cm^{-1} is expected,[27] as well as a band at 1,249 cm^{-1}, which is in the Si-CH_3 bond band region.[25] DMPU does not have bands in the alkyne regions but it has a band at 1,252 cm^{-1}.[28] Only a gas IR spectrum of $TMSCF_3$ is reported, with no strong bands in the alkyne regions and with a strong band at 1,227 and 1,265 cm^{-1}.[29]

The azide-alkyne cycloaddition, one of the landmark reactions of "click" chemistry, was monitored using real time infrared spectroscopy. In this reaction, a terminal alkyne and an azide react to form a triazole ring. Spectra of an equimolar ratio of the reactants were recorded after solvent spectrum subtraction and baseline correction. The azide, alkyne and triazole could be monitored by measuring the absorbance of its characteristic peak over time. They also used a principal component analysis and a bidimensional correlation analysis to gather more information.[24]

^{19}F NMR

Another option would be the use of ^{19}F NMR. Fluorine has a high gyromagnetic constant and it has only one natural occurring isotope, which make it a good nucleus to monitor chemical reactions. ^{19}F NMR covers a wider range of chemical shifts than ^{1}H NMR and that reduces the likelihood of signal overlap.[30] It is within reason to argue that a fluorine would have a different chemical shift in the starting material and in the final product. Thus, the use of a fluorinated molecule as substrate would allow the monitoring of the terminal alkyne, the product and $TMSCF_3$. The signal of $TMSCF_3$ appears at -66.8 ppm as a singlet.[16] Unfortunately, the ^{19}F spectra of 1-(fluorophenyl)-2-trimethylsilylacetylenes, the silylated analogue of fluorophenylacetylenes, have not been reported. Trifluoromethyl substituents in the phenyl ring are not a good idea since their chemical shifts, both in their trimethylsilylated and protonated alkyne form are close to one another and with that of $TMSCF_3$.[31] ^{19}F NMR spectra of the pentafluorophenylacetylene and its trimethylsilylated analogue are reported in the literature. Their signals are quite similar, and the most differing peak is that corresponding to the *para*-fluoro, which has a chemical shift of 75.8 ppm in the starting material and one of 76.3 ppm in the product.[32] Even if these two signals did not overlap, the fact that they are still close in chemical shift does not guarantee that ^{19}F NMR would prove useful for reaction monitoring in this case.

What could be easily monitored through ^{19}F NMR is the formation of fluoroform. Fluoroform appears as a doublet at around -78 ppm.[33]

Fast kinetic techniques

When reactions stall or achieve full conversion in a short time span, it is necessary to resort to techniques such as stopped flow (SF), which allow measurements in the first stages of the reaction. In stopped flow, reactions with half-lives (time to consume half of the limiting reagent) in the millisecond scale can be monitored. The reactants flow from different tubes and are mixed close to the detection region, which reduces the dead time considerably.[34] Once the detection region has been filled with the flowing solution, the flow is stopped (otherwise the residence time would be too fleeting) and the spectra are recorded. The dead time, the time for the first spectrum to be acquired after the beginning of the reaction, is in the few milliseconds scale.[35]

4.4. Kinetic isotope effects

Isotope labelling has many applications in reaction mechanism studies. It can be used to "track" atoms from the beginning to the end of a reaction. Moreover, isotope labelling is used to calculate kinetic isotope effects (KIE), which provide information about bond formation and/or cleavage at the transition state (TS), and to perform crossover experiments, which determine if reactions are intermolecular or intramolecular.[36]

As stated above, KIEs provide insight into bond formation and/or cleavage in the rate-limiting step. The rate-limiting step is usually the step of a reaction that presents the highest energy barrier and the one that determines the rate of product formation.[37] KIEs are defined as the ratio of rate constant of the light isotope labelled compound over the rate constant of the heavy isotope labelled compound. KIEs arise from differences in the frequency of the vibrational modes. The zero-point energy of a bond is lower when a heavier isotope is involved.[38]

H/D kinetic isotope effect

Hydrogen and deuterium are the most used nuclei to measure KIEs since their relative mass difference is the largest. Primary KIEs are observed when a bond involving the labelled atom is broken or created in the rate-limiting step. Primary KIEs can have values as large as 6.5 but this value gets smaller if the transition state is non-linear. Secondary KIEs, which have values close to 1 (either larger or smaller), are observed when the carbon next to the proton changes hybridisation. Isotope effects can also perturbate equilibria since the heavy isotope prefers the bond with the largest force constant.[38]

In the case of the reaction under study, a bibliographic search has been made to see if the deuterium labelled compounds are obtainable and also if they could be distinguished through spectroscopic techniques.

The deuterated compound in the alkynyl position is rather expensive, so it is better to synthesise it in-house. Treatment of phenylacetylene with butyllithium in ether for 1 hour at 0ºC followed by addition of heavy water affords the deuterated phenylacetylene.[39] The monitoring of this reaction through ^{19}F NMR would afford the

detection of a triplet at around -79 ppm from deuterated fluoroform.[33] Fluoroform appears as a doublet at around -78 ppm.[33]

Heavy atoms isotope effect

Apart from hydrogen KIEs, heavier atoms, such as carbon, oxygen, nitrogen, and chlorine, can also be used to measure KIEs, although their values are much smaller than those of hydrogen. If the KIEs are higher than 1, a bond involving that atom is formed or broken.[38]

In 1995, Daniel Singleton published a paper with an innovative way to measure both hydrogen and carbon KIEs at natural abundance. This technique requires that the reaction be irreversible (see the proposed experiment in the section 5.4), the mechanism remains the same throughout the reaction and that the reaction be scalable. The reaction is left reacting under almost full completion. The unreacted starting material is recovered and analysed through ^{2}H and ^{13}C NMR. Atoms with a KIE larger than 1 will have more a higher proportion of the heavy isotope than at the start. The change in isotope composition is calculated by assuming that some atom, afar from the reaction centre, is unaffected by the reaction and it still maintains a natural isotope distribution. The following formula is used to calculate the KIE, where F is conversion and R/R_0 is the proportion of the recovered minor isotope compared to that at the start (fresh reagent).[40]

$$KIE = \frac{\ln(1-F)}{\ln\left[(1-F)\frac{R}{R_0}\right]}$$

The KIE of other nuclei such as oxygen and nitrogen can also be measured by using isotope ratio mass spectrometry (IRMS). The molecule whose oxygen or nitrogen KIE wants to be measured is recovered and isolated. The isotopic composition of a gas obtained from the molecule, such as CO_2 or N_2, is measured and the KIE is then determined. In the case of a carbonyl group, both oxygen and carbon KIEs can be determined concomitantly.[41]

4.5. Hammett plot

The Hammett plot is derived from the Hammett equation, which relates how a change in the electron density of a given substrate alters reactivity.[42] A Hammett plot can discern if a naked acetylide is involved in the reaction and which is the rate-limiting step of the reaction.

The electron density of the substrate can be tuned by attaching a phenyl group with different substituents close to the reaction centre. Each substituent has a different sigma value (σ), with higher values corresponding to more electron-withdrawing groups (EWGs). If the phenyl ring has multiple substituents, the sigma values of each are added up. Substituents in the ortho position are not used due to potential steric effects. If a

positive or negative charge is delocalized in the phenyl ring, a different set of sigma values is used (σ^+ or σ^-, respectively).[42]

The change in reactivity is usually measured by the ratio of rate constants of substrates with a substituted phenyl ring versus substrates with an unsubstituted phenyl ring.[42]

$$\log\frac{k_X}{k_H} = \rho \cdot \sigma$$

The Hammett equation is the basis for the Hammett plot. The slope of the Hammett plot, which if the rho value (ρ) indicates how much charge is built up in the transition state. Positive values indicate that EWGs speed up the reaction whereas negative values indicate that EWGs slow down the reaction. A Hammett plot is usually linear, but non-linear plots are obtained when there is a change in reaction mechanism or when the rate-limiting step changes.[42]

Apart from the sign of the rho value, its magnitude also carries information. For example, deprotonation can proceed stepwise or in a concerted manner. In the case of nucleophilic aromatic substitutions, which can also occur in a stepwise or concerted manner, the rho value is used to distinguish both mechanisms.[43]

4.6. Kinetics

Kinetics establish a quantitative relationship between the concentration of reactants and/or products and the reaction rate. By changing the concentration of one of the species and keeping every other concentration and variable constant, the dependence of the reaction rate on the concentration of that species can be determined. Kinetic studies are useful to gather information of the steps before and at the rate-limiting step, but no information about the steps after the rate-limiting step can be collected.[44]

Reactants can be zero-order if increasing their concentration has no effect in the reaction rate, which could mean that they are involved in a step after the rate-limiting step. An inverse order, that is a negative order, means that that reactant inhibits the reaction. A fractional order is indicative of the existence of intermediates in the reaction, meaning that there is more than one step. A reagent can have different orders at different concentrations, for example if the reaction saturates.[45]

From the Hammett plot, the rate determining step might have already been identified. For each of the three possible scenarios, in which the rate-limiting step can be either the deprotonation, the silylation or the silylation after a reversible deprotonation. Kinetics must fit the proposed mechanism for it to be valid.

In classical kinetic analysis, the experiments are performed by adding a high excess (tenfold at least) of all the reagents but one. The decay of this reagent over time can provide information as to which order this reagent is. Each reaction order has a different

integrated expression that somehow relates the concentration of the reagent to time. The best linear correlation indicates the order of the reagent. The order of the other reagents can be obtained by changing the concentration of those other reagents in more than one experiment. A logarithmic plot of the reaction rate versus the concentration has a slope that equals the reaction order in this other component. This method is mainly used for simple systems where the first step is the rate-limiting step.[46]

If a more complicated system is encountered, the steady-state approximation, which states that the intermediate is highly reactive, is used when the first step is reversible. Another approximation, the pre-equilibrium approximation, states that there is a rapid equilibrium between the reagent and an intermediate.[46]

4.7. Release of the trifluoromethyl anion

In the original paper, the trifluoromethyl anion is presumed to be released by a species formed by $TMSCF_3$ and DMPU.[12]

In a mechanistic study, some calculations were done to investigate how $TMSCF_3$ can transfer the CF_3 group to a ketone group when using a fluoride source as activator. There are apparently two possible ways that such anion can be released: direct transfer or dissociative transfer. Direct transfer is not possible since inversion of the CF_3^- anion presents a too high energy barrier. Thus, dissociative transfer is the only remaining possibility.[2]

Therefore, before the trifluoromethyl anion can be released some sort of complex must be formed since $TMSCF_3$ by itself cannot release CF_3^-. It is plausible that a complex of $TMSCF_3$ and DMPU is formed before CF_3^- is released.

In the literature some proposals of complexes of $TMSCF_3$ and some solvent such as DMSO or NMP are reported.[47,48] However, no studies of these possible complexes have been reported up to this date to the best of my knowledge.

Some experiments were carried out to determine the existence of interactions between $TMSCF_3$ and DMF in the context of a trifluoromethylation reaction.[49]

Carbonyl compounds such as aldehydes, ketones and esters undergo trifluoromethylation using $TMSCF_3$ with a catalytic amount of magnesium dichloride using a solvent such as DMF or DMPU. Magnesium dichloride is used to enhance carbonyl electrophilicity. They argue that the amide-type solvents (DMF and DMPU) interact with the silicon in $TMSCF_3$ to increase its nucleophilicity. The yields are multiplied fourfold when using these solvents as compared with acetonitrile as solvent. The existence of an interaction between $TMSCF_3$ and DMF is determined by measuring the ^1H and ^{13}C NMR spectra of both components separately and mixed together. The DMF protons experience an upfield shift (less shielding) and the $TMSCF_3$ protons experience a downfield shift (more shielding), which is in accordance with an interaction

from the electron donating DMF to $TMSCF_3$. The same is true when ^{13}C NMR spectra are recorded.[49] Nevertheless, the difference in chemical shift may not be due to complexation but to solvation.

From density functional theory (DFT) calculations, they show which of the possible interactions of DMF and $TMSCF_3$ is more favourable by calculating the Mulliken charge of the trifluoromethyl moiety. If the nitrogen atom is the one interacting with the silicon centre, the $-CF_3$ has a higher negative charge than if the coordination is through the oxygen. The interaction of a chloride anion (from magnesium dichloride) with the silicon centre is also studied, as well as the interaction of the alkoxide anion generated after trifluoromethylation. The former is found much less preferable than coordination with the DMF, but the latter is the most preferable of all.[49]

In a mechanistic study of the trifluoromethylation of aldehydes with $TMSCF_3$ in DMF using potassium carbonate in catalytic amounts, some interesting complexes between $TMSCF_3$ and the carbonate anion are proposed. Surprisingly, they find that the reaction works in solvents such as DMSO or DMF but not in THF, but the solvent plays no role in their mechanistic proposal. They argue that the high dielectric constants of these solvents are the reason they stabilise the transition state. They propose a hexavalent silicon intermediate, possible due to a low-lying empty d orbital of silicon, where the carbonate is interacting with $TMSCF_3$ through two oxygens. They also propose a disilicon intermediate in which the two silicon centres are bonded to one oxygen of the same carbonate anion. These two intermediates were found possible by DFT calculations.[50]

The authors of the paper stated that "Currently [in 2017], an NMR study is conducted to monitor these species", referring to the species formed from DMPU and $TMSCF_3$.[12] Three years after the publication of the paper, no study has been reported on this species.

As shown above, ^{1}H and ^{13}C NMR can potentially indicate that $TMSCF_3$ and DMF can form a complex. However, this information is not conclusive to affirm through which atom or atoms these complexes are formed.

In this case it might be useful to resort to a nucleus that it is not normally used in NMR, nitrogen. Nitrogen has two natural occurring isotopes that are magnetically active, and which can therefore be detected using NMR experiments. The most abundant nitrogen isotope (^{14}N) is not usually used for NMR experiments because its quadrupolar properties lead to broad lines in the spectra. However, ^{15}N NMR, which is only 0.37% abundant in natural samples, can be used to detect small changes in its environment. Nitrogen-15 is not especially sensitive, and it has long relaxation times. A relaxation agent, such as chromium tris(acetylacetonate), is usually added to reduce the relaxation time, which allows more spectra to be recorded by time unit, but it also broadens the signals. Apart from direct detection of the ^{15}N nuclei, it is also possible to perform a ^{1}H-

^{15}N HMBC experiment. HMBC stands for heteronuclear multiple bond correlation, which is a two-dimensional NMR experiment that correlates proton and nitrogen atoms that have long range (multiple bond) interactions. Usually, two and three bond coupling constants range from 0.3 to 16 Hz, whereas four bond coupling constants do not exceed 1.5 Hz. This sort of experiment has previously been used to elucidate the structures of complex molecules.[51]

^{15}N NMR has been previously used in transition metal complexes with ligands such as pyridine, which are coordinated to the metal through a nitrogen atom.[52] There is a difference in chemical shift when the ligand is free and when it is coordinated to the metal. It is not unreasonable to think that if a DMPU molecule is coordinated through its nitrogen atom to the silicon centre, there would be a coordination shift.

In the case of trimethylsilyl anilines, there is a scalar coupling constant of 1.1 Hz between the nitrogen and the methyl protons.[53] In the proton spectrum, the methyl proton doublet becomes a singlet when it is irradiated at the right frequency. If there is bonding, an irradiation at the right frequency makes the ^{1}H signal sharper.[54] They do not show the nitrogen NMR spectra of this compound so it is not sure if the three-bond coupling would be visible.

The change in the environment of a given nucleus gives rise to a dynamic process, which affects the NMR spectrum. If there is a chemical equilibrium, the coupling will only be observed if there is slow or no exchange. Only if the complex has a long enough lifetime, will the coupling be observed (and hence the correlation in the bidimensional spectrum). The exchange constant can change with temperature, with lower temperatures enabling the distinction of signals and couplings.[55]

The main advantage of using nitrogen NMR is that only DMPU has nitrogen atoms in the reaction mixture, so any other signal that might arise could be attributed to the complex. The main problem is that ^{15}N is not an extremely sensitive nucleus for NMR experiments. Even if a complex is formed in detectable amounts, it might not be detected through nitrogen NMR since only a fraction of the actual complex might be detected. This difficulty could be overcome using ^{15}N labelling in DMPU but, unfortunately, it is not commercially available. Other ^{15}N labelled compounds can be bought, albeit the prices are high. An alternative route to synthesise DMPU from one of these compounds could be designed. The route that has been found (see pages 24-25) is similar to the one presented to obtain deuterated DMPU but in this case the interest is introducing the ^{15}N label using a commercially available reagent, ammonia or ammonium chloride.

Unfortunately, no ^{15}N or ^{14}N NMR spectra have been reported for DMPU. However, there have been a ^{15}N spectra reported for urea compounds, which have a similar structure to that of DMPU, which is a cyclic urea. Tetramethyl urea has a chemical shift

of -311.5 ppm and tetrabutyl urea has one of -295.8 ppm.[56] DMPU should have a chemical shift close to these values.

Another nucleus that is rarely used in NMR is oxygen. The ^{17}O isotope is the only naturally occurring oxygen isotope that has a non-zero magnetic spin and, in contrast with ^{16}O and ^{18}O, it can be detected by NMR. It has a low gyromagnetic constant, a natural abundance of just 0.04% and a low sensitivity, which make it a difficult nucleus for NMR experiments. Nevertheless, it has a wide chemical shift range.[57]

A recent survey of the ^{17}O spectra of more than a hundred organic compounds included DMPU. Each spectrum took approximately twenty minutes and no enrichment was needed. The reported chemical shift of DMPU is 234.7 ppm when deuterated water is used as the reference (0 ppm).[58]

As in the case of nitrogen, this active isotope could be used to detect if a complex bonded or coordinated through the DMPU oxygen is formed. The low natural abundance of oxygen-17 poses a big problem. DMPU with ^{17}O is not readily available and that makes it more difficult to detect the potential complex. A synthetic route to give access to the oxygen-17 enriched DMPU can greatly help in the detection of the silicon-oxygen interaction between DMPU and $TMSCF_3$ (see page 25). ^{17}O labelled compounds are extremely expensive.

It is also possible to detect a stretching frequency in the infrared region due to the Si-N bond, which would point to Si-N bonding. In the case of trimethylsilyl aniline this frequency is of 890 cm^{-1} for ^{15}N and of 899 cm^{-1} for ^{14}N.[54] The problem is that this infrared region, known as the fingerprint region, has a lot of bands which might difficult its right characterisation.

4.8. Silylating agent

In the original paper, there is no proposal as to what silicon source acts as the silylating agent. There are several potential silylating agents that could be involved, as can be seen from other trimethylsilylation reactions using other initiators, namely $TMSCF_3$ itself or a $TMSCF_3$ complex involving the NHC.

In the previous section some structures inspired by the literature are proposed as potential trifluoromethyl anion sources. After the trifluoromethyl anion release, the complex involved might in turn act as the silylating agent, as suggested in the mechanism proposal of Anand for the trimethylsilylation with NHC.[11]

In a mechanistic study of the trifluoromethylation of ketones carried out by the Lloyd-Jones group they use $TMSCF_3$ and other trialkyltrifluoromethylsilanes to explore how they affect the rate and selectivity of the reaction. $TESCF_3$ and $TIPSCF_3$, which have ethyl and isopropyl alkyl groups, respectively, are the other silyl reagents tested. In an experiment where $TMSCF_3$ and $TESCF_3$ are used in an equimolar ratio, they find that

$TMSCF_3$ reacts first but when $TESCF_3$ starts reacting it accelerates the turnover. They also study how KIEs vary when using these different silyl reagents. Using computation methods, they were able to determine the energy of the transition state for the silylation step.[2]

4.9. Chemoselectivity

To study the chemoselectivity of the reaction, a competition experiment was performed between 1-ethynylnaphtalene and 1-naphthaldehyde. When DMPU is used as solvent, the yields are 40% and 3% for the silylation and the addition product, respectively. The yields go up to 83% and 17%, respectively, when $TMSCF_3$ is used in 2 eq. (and not 1 eq.). Therefore, the ratio of the trimethylsilylation and trifluoromethylation decreases from 13:1 to 5:1 when doubling the concentration of $TMSCF_3$ from 1 to 2 equivalents. The use of CsF as activator (0.1 eq.) gave a 72% yield for the addition product.[12]

The authors attribute this to the fact that there are no alkaline cations in the solution. When caesium fluoride is used to trimethylsilylate terminal alkynes, if a carbonyl group is present either in the alkyne-containing molecule or in a separate molecule trifluoromethylation also occurs. It is reported that when DMPU is used instead of a fluoride source, trimethylsilylation of the terminal alkyne is more favoured. Tetrabutylammonium fluoride (Bu_4NF) is used as a fluoride source instead of caesium fluoride to see if the cation exerts no effect whatsoever in the reaction. This is not the case, since trifluoromethylation is less favoured when using Bu_4NF. In the article they consider two possibilities for this change in chemoselectivity. One is the coordination of the cation, which is a Lewis acid, to the carbonyl, with the corresponding increase in its electrophilicity; or that the species generated in the reaction influence the chemoselectivity.[12]

4.10. Synthesis of isotopically enriched compounds

In this section, the synthesis of isotopically enriched compounds that have been mentioned during this chapter and that will be used in chapter 5 is described.

d_{12}-DMPU

There is not a reported route to synthesise d_{12}-DMPU and the ones reported for DMPU synthesis cannot be used using deuterated compounds that are commercially available. DMPU can be synthesised from N,N'-dimethyl-1,3-propanediamine,[28,59] which is not available in its deuterated form either. In figure 7, two possible pathways are outlined. In the upper one, a high pressure is needed; whereas in the lower one, less pressure is needed, and the yield is higher. The main problem with the lower path is that selenium is toxic, and the yield drops from 94% to 23% if the catalytic method is applied.

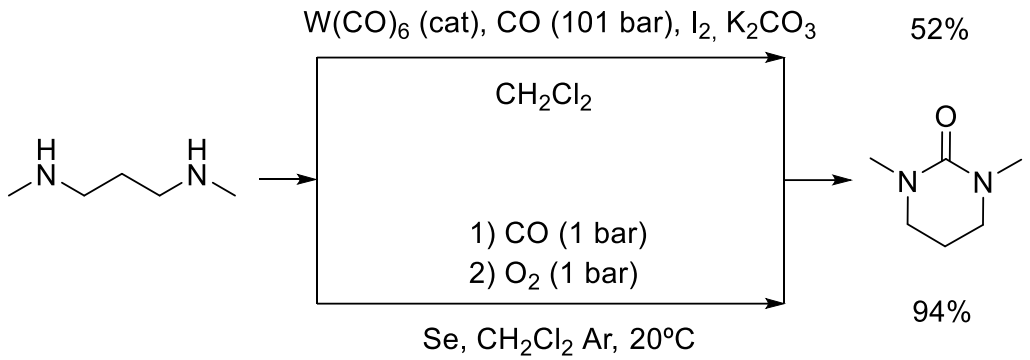

Figure 7. Reaction scheme of the synthesis of DMPU from N,N'-dimethyl-1,3-propanediamine.

N,N'-dimethyl-1,3-propanediamine can be synthesised from 1,3-bromopropane and methylamine, both of which are commercially available in their deuterated forms. A mixture of 1,3-dibromopropane treated with a solution of methylamine at 120-130ºC for 8 hours yields the desired amine in a low yield after treatment with acid, evaporation, treatment with base, extraction with ether and fractioned distillation. The formation of other bases is the main reason for the low yield, which is not specified.[60]

Since deuterated compounds are expensive and should not be wasted, another route that gives a better yield must be found. A similar compound, N,N'-dimethylethylenediamine, has previously been synthesised in its deuterated form from commercially available deuterated reagents. A series of steps, shown in figure 8, allow the synthesis of the deuterated diamine compound starting from potassium phthalimide and 1,2-bromoethane. The needed deuterated reagents are 1,2-bromoethane and methyl iodide.[61] The first step would also work if 1,3-bromopropane is used instead of 1,2-bromoethane.[62]

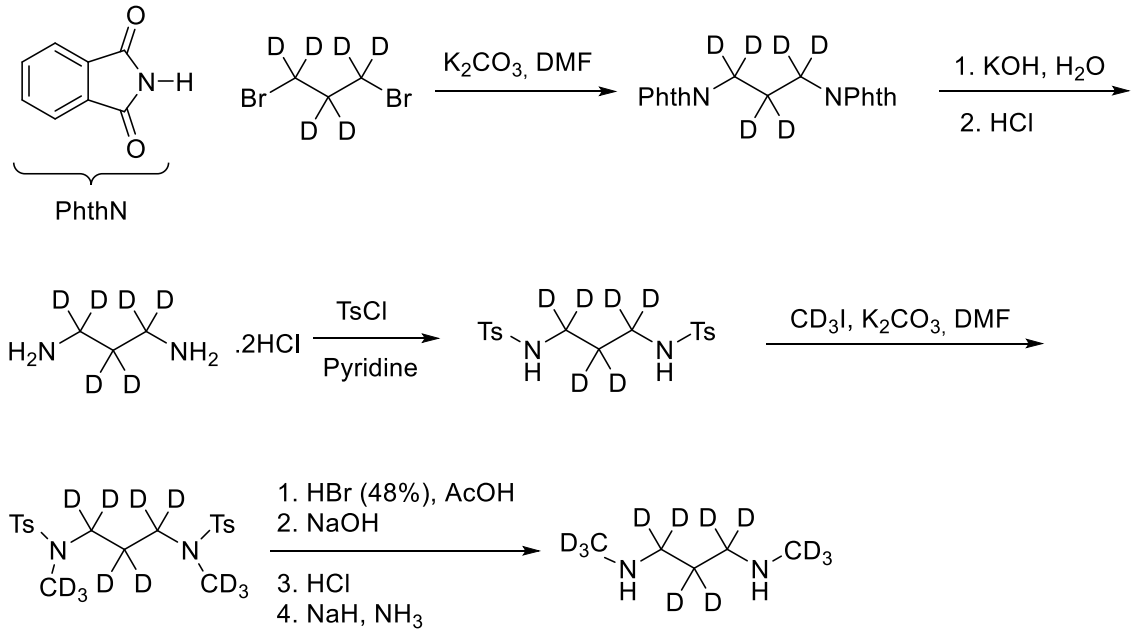

Figure 8. Reaction scheme for d_{12}-N,N'-dimethyl-1,3-propanediamine synthesis.

[2-^{13}C]-phenylacetylene

[2-^{13}C]-phenylacetylene can be synthesised in three steps from N-methoxy-N-methylbenzamide (see figure 9),[63] which is a cheaper way than buying the expensive commercially available compound. First, a ^{13}C labelled iodomethane is added to an ether solution with magnesium to form methylmagnesium iodide. This solution is then added to a solution of N-methoxy-N-methylbenzamide in THF at 0ºC, followed by extractions and flash-column chromatography to yield the labelled acetophenone. A solution of acetophenone is added at 78ºC to a previously prepared solution of diisopropylamine and n-butyllithium. Diethylchlorophosphate is added to the solution and then a solution of lithium diisopropylamide (prepared from diisopropylamine and n-butyllithium) is added. After extraction, drying, filtration and Kugelrohr distillation, [2-^{13}C]-phenylacetylene is obtained.

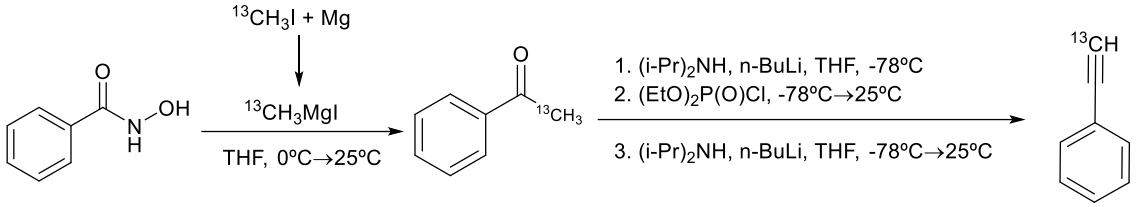

Figure 9. Reaction scheme for [2-^{13}C]-phenylacetylene synthesis.

^{15}N labelled DMPU

The synthetic route represented in figure 10 is the one that can be applied to obtain the ^{15}N labelled compound. It consists on a Gabriel synthesis to generate the primary amine followed by an alkylation reaction. When the secondary diamine compound is obtained, the same procedures shown in figure 7 can be used to obtain DMPU.

Treatment of phthalic anhydride with labelled ammonium chloride with sodium hydroxide in methanol affords the ^{15}N labelled phthalimide.[64] Phthalimide reacts with 1,3-dibromopropane and potassium carbonate in dry dimethylformamide with molecular sieves to give 1,3-diphthalimidopropane.[65] This in turn reacts with potassium hydroxide in water before being distilled into a solution of hydrochloric acid and then distilled with water and methanol to yield the hydrochloride salt of 1,3-diaminopropane.[64] The free 1,3-diaminopropane is the desired product and not its hydrochloride salt, so the distillation with hydrochloric acid is not needed. If distillation with hydrochloric acid was unavoidable, the free diamine could be obtained by stirring the solution with sodium in methanol.[65] To methylate the amino groups avoiding polyalkylation, a different path from the one used in the deuterated DMPU synthesis will be used. It was not proposed in the synthesis of deuterated DMPU because it is not sure that deuteration would work in this step. 2,2-dimethylpropane-1,3-diamine can react with ethylformate and then with lithium aluminium hydride in THF under an argon atmosphere at 0ºC to yield the secondary diamine.[66] The same procedure would work

with 1,3-diaminopropane since it is not significantly different than its 2,2-disubstituted analogue.

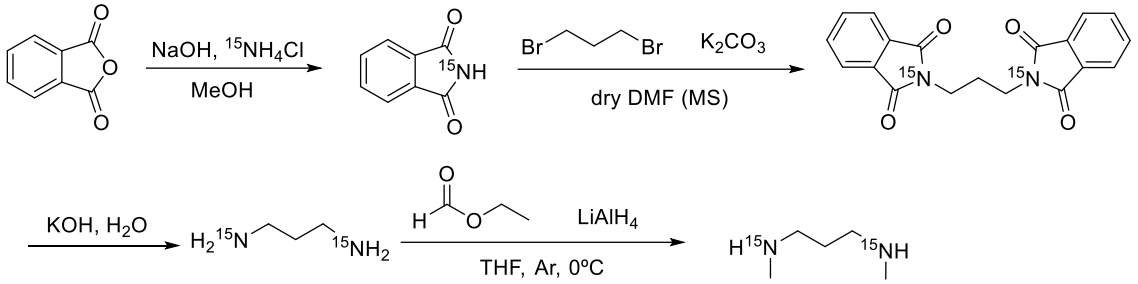

Figure 10. Reaction scheme for ^{15}N labelled N,N'-dimethyl-1,3-diaminopropane, precursor to DMPU, synthesis.

^{17}O labelled DMPU

1,3-dichloropropane and an aqueous solution of methylamine (40%) can react with carbon dioxide gas during 2 hours at 120ºC to yield DMPU with a 64% yield. A side reaction gives 3-methyl-1,3-oxazinan-2-one as a product in a 15% yield.[67] Carbamates and urea derivatives can be separated using high performance liquid chromatography (HPLC).[68] A mixture of DMPU and other side products could potentially be separated using HPLC. It is possible to buy oxygen-17 enriched carbon dioxide at 45 and 60 % isotopic purity at Sigma Aldrich although the cost is not specified. This procedure requires the use of a special pressure vessel. The synthetic route to obtain this compound is shown in figure 11.

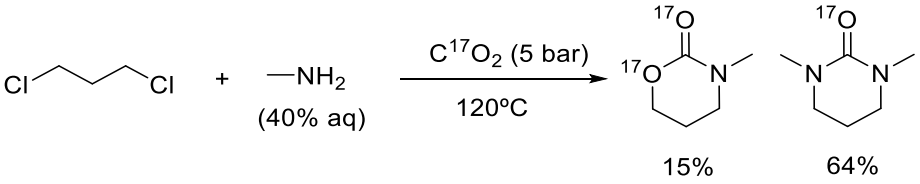

Figure 11. Reaction scheme for ^{17}O labelled DMPU synthesis

This route can also be used to obtain the ^{18}O labelled compound.

5. Project proposal

In the previous chapter, some techniques that can help elucidate the reaction mechanism have been presented. In some cases, how they have been used in past mechanistic studies and their suitability for this particular reaction has also been explained. In the present chapter, some experiments are proposed based on the techniques previously described. The experiments are presented in the chronological order in which I think they should be performed. Some of the experiments are not based in any technique nor in any particular previously reported study but have also been added in this chapter.

In mechanistic studies, as well as in other studies in chemistry and science in general, new questions might arise from the information obtained from some experiments about the nature of the mechanism and provide inspiration to design new experiments. This will not be the case in this proposal since there is no actual data.

5.1. First things first

Before starting the mechanistic study, a thorough search of the literature must be carried out. Some experiments must be proposed to help elucidate the mechanism. The feasibility of the experiments must also be checked before carrying them out. This is what has been done in chapter 4.

5.2. First step: Choosing a monitoring technique

There is one point that needs to be given careful consideration. This reaction releases a gas, fluoroform, meaning that the amount of alkyne and $TMSCF_3$ will be kept at levels that are not as high as to generate too much pressure inside the reaction vessel. If the reaction vessel is not sealed or if it has a balloon this does not have to be an issue. However, in techniques such as NMR reaction monitoring it is not possible to introduce an NMR tube without a cap, since its contents would spill all over. The use of a Young NMR tube would partially overcome this problem by allowing some pressure to build up in a controlled manner.[69] Before any actual reaction monitoring inside the NMR spectrometer, some experiments can be carried out using different concentrations of the alkyne, which is the limiting reactant, to ensure that there is no significant overpressure (the NMR tube cap does not pop out).

The experiments will be carried out at room temperature, since warming up the reaction to 40ºC does not have a significant impact in the yield and it also simplifies the experimental procedure for each reaction.

The fitness of each monitoring technique will depend on the requirements of each experiment. Some require the monitoring of only the starting material and some other require the monitoring of both starting material and product.

From the search in the literature, it seems that using IR reaction monitoring to study the reaction with DMPU as solvent would be possible. Monitoring the reaction through ^{1}H NMR using non-deuterated or deuterated DMPU as solvent does not seem feasible. Using a solvent that does not intervene in the reaction can be another option although it is not certain that this option might be feasible. ^{19}F NMR could potentially be a good technique to monitor the reaction. It should be borne in mind that it would be possible to study the reaction using another solvent, such as DMSO, in which the reaction is possible and where the reaction could be followed through ^{1}H NMR or IR spectroscopy.

I think that the best monitoring technique available for this reaction is ^{19}F NMR, since both reagents and products in the reaction (but for DMPU) can be detected. Using this technique would require no alteration of the solvent system. Some experiments with model substrates such as 4-fluorobenzeneacetylene or 3-fluorobenzeneacetylene can be carried out to confirm if the terminal alkyne and the product can be distinguished.

If this were not the case, ^{1}H NMR could be used to monitoring the reaction. A solvent suppression technique that still makes quantitative analysis of the signals near the solvent, for example that of the terminal alkyne proton, would need to be found. Some pulse sequences that suppress the solvent signal before acquisition might make this possible. To confirm this, samples of terminal alkyne in DMPU at known concentrations would need to be used. If the solvent suppression technique does not affect the signal of the terminal alkyne, its concentration should be accurate when using an internal standard at a known concentration, which would need to have its signals afar from the solvent signal. The real concentration of the terminal alkyne can be independently calculated by using a terminal alkyne with a fluorine and measuring a ^{19}F NMR spectrum in the presence of an internal standard of a known concentration.

Using deuterated DMPU would be expensive and time-consuming since the solvent would need to be synthesised in many steps and using deuterated reagents, which are expensive. Using deuterated DMPU would allow the monitoring of the reaction using ^{1}H NMR but if there is any kinetic isotope effect involving its hydrogen atoms, the kinetics of the reaction will be compromised.

If this were not the case, IR monitoring would be the next option to investigate. Separate spectra for each compound can be acquired and then several spectra during a reaction run. If the characteristic peaks for each species are clearly distinguishable, a calibration curve for each of the species can be plotted from different spectra with different concentrations of that compound. Then, the concentration of each species at a given point in reaction time can be obtained.

If it were not possible to monitor the reaction with the previous techniques, there is a way that the reaction could be monitored by ^{1}H, ^{13}C and/or ^{29}Si NMR. It would consist in conducting end-point experiments, which means that the reaction would have to be

repeated several times to measure several data points. Each time the reaction would be left reacting for different amounts of time before quenching. In this case, a sealed reaction vessel would not be needed. After quenching the reaction, some work-up might be needed and extraction of all components, followed by evaporation of the solvent. The remaining residue would be diluted in a deuterated solvent such as deuterated chloroform to measure the spectrum of the reaction at the time the reaction was quenched. This, however, would require the calculation of the recovery of each species (except DMPU and fluoroform, which it would not be possible to measure) and checking if there is some degradation over the time gone by from quenching to measuring the spectra. Although this technique is likely to work, it implies a painstaking process to obtain each data point, which requires a lot more time compared to measuring how the components evolve during the reaction in situ. Conditions would be a little bit different for each data point, so the kinetic data will probably not be completely reliable.

In any case where NMR is involved in reaction monitoring, an internal standard needs to be employed. An internal standard is added to the reaction mixture before the reaction starts and it needs to have a different chemical shift from any other reaction species. Moreover, its concentration needs to be precisely known for a correct quantification of the reaction species. The internal standard can also correct any fluctuations during the course of the reaction, since it will also experience them.

5.3. Second step: Reaction time and product identification

Apart from the trimethylsilylated alkyne and fluoroform, which are the expected products, and the reagents, if any other signals are observed in the spectra they should be identified. Side reactions can also provide information about the mechanism and perhaps even common intermediates.

If there are no side reactions, the amount of fluoroform released should equal that of alkyne and $TMSCF_3$ consumption and product formation. Nevertheless, side reactions which might have fluoroform as product would mean that fluoroform formation is not equivalent to product formation or starting material depletion. Since the same amount of $TMSCF_3$ that is consumed in these reactions is released in fluoroform, a plot of the concentration of both species is expected to be linear. There is no way of measuring how much fluoroform is produced from the terminal alkyne deprotonation with non-deuterated substrates. Using a deuterated terminal alkyne, the deuterated fluoroform released would equal the amount of terminal alkyne consumed, whereas non-deuterated fluoroform would come from other side reactions. A plot of the concentration of deuterated fluoroform against the concentration of $TMSCF_3$ would intercept at 0 if no side reaction occurred, meaning that if no deuterated fluoroform is released no $TMSCF_3$ is consumed. A non-zero intercept value of n would indicate that some $TMSCF_3$ (concentration n) has been consumed in a reaction or reactions other than the one under study.

Surprisingly, no reaction time optimisation is reported for this reaction and the reaction is left reacting for 24 hours. It is important to know how long this reaction takes to reach full conversion. Once this reaction is monitored, the time needed to achieve full conversion will be established and with it the time that each reaction will approximately take. The reaction time can be established by measuring fluoroform through ^{19}F NMR; once no fluoroform is released at all, the reaction is over.

If the reaction takes indeed around a day to get to completion, there would be no need to use the fast kinetics techniques since it is highly likely that most of the reaction takes place after the dead time of a standard NMR reaction monitoring experiment (1-2 minutes). However, this still poses the problem of taking too much time to monitor the reaction. It could still be possible to just take the measurements every hour to free instrument time, but the best option would be to optimise the reaction conditions.

The reaction could be optimised by changing the concentrations of $TMSCF_3$ and terminal alkyne and monitoring the reaction to see how this impacts reaction time. Apart from just reaction time, more information could be obtained from such experiments, namely reaction rates and kinetic data from changing the concentrations of the different components.

5.4. Third step: Kinetic isotope effects

In this reaction, by labelling the alkynyl proton with deuterium, it is expected that deuterated fluoroform will be released because CF_3^- is the presumed base. Deuterated fluoroform can only be released if the CF_3^- equivalent species abstracts it from the terminal alkyne, as shown in figure 12.

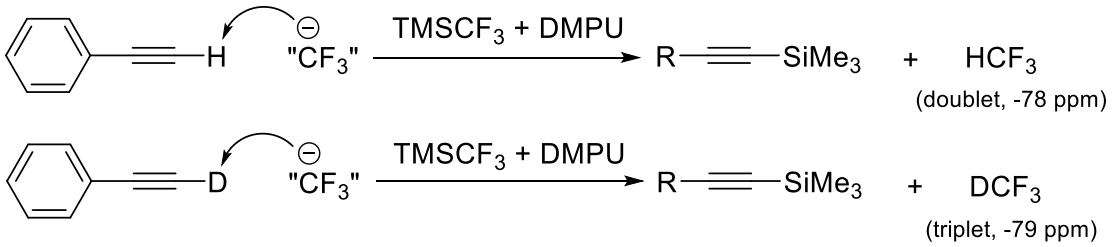

Figure 12. Reaction scheme of phenylacetylene and d_1-phenylacetylene with $TMSCF_3$ and DMPU.

There are two ways that the H/D KIE can be calculated: either by measuring fluoroform formation or terminal alkyne depletion. Fluoroform formation is easier to measure since there will be no solvent signals. Two separate experiments will have to be perfomed: one with the non-deuterated alkyne and another one with its deuterated form. The ratio of the two reaction rates is the KIE. It is important that the reaction conditions are kept the same for both experiments. For this reaction, the reaction rate is calculated by measuring the change in concentration of a given chemical species over time.

The carbon KIE for the alkyne terminal carbon can be obtained using the Singleton technique. The reaction can be carried out in large amounts of starting material, with the due precautions to avoid any overpressure (use of a ballon or non-sealed reaction vessel). When the reaction is almost complete, which can be estimated by reaction time experiments or when fluoroform release is not as strong (no strong bubbling), the reaction can be quenched with ammonium chloride, extracted possibly with ether, and evaporated using a rotary evaporator. After dilution with a deuterated solvent, a quantitative ^{13}C spectrum can be recorded using an internal standard. It can be assumed that the isotopic composition of one of the aromatic carbons does not change during the reaction. With ^{2}H NMR, it may be possible to calculate the hydrogen KIE for the alkynyl proton by assuming that the proton in the para position to the alkyne maintains its isotopic distribution. This can be a good way to check if the results agree with those of the previous experiments and also to see if there is any KIE for the aromatic protons, which is unlikely. However, since deuterium is less abundant than carbon-13, a higher amount of starting material would probably be needed.

The KIE of other nuclei such as nitrogen and oxygen in DMPU cannot be calculated in the usual way. It is not confirmed that DMPU is consumed during the reaction and there is no indication that it is in a significant way. Thus, even if it was consumed, the effect would be so small that it would not be detectable. The only way to measure the KIE for these nuclei is by measuring the kinetics and not the isotope ratio through isotope ratio mass spectrometry (IRMS). The kinetics of the process, which can be extracted from the alkyne consumption, can indicate if the different nitrogen and oxygen isotopes have any impact on the reaction rate. The synthesis of labelled DMPU compounds is possible, albeit expensive, and it has been explained in section 4.11. These synthesis can give access to DMPU with ^{15}N, and ^{18}O labels by using the right reagents. The ratio of the rate constant using non-labelled DMPU, which has ^{14}N and ^{16}O at natural abundance (>99%), and the rate constant using the synthetically labelled DMPU gives the kinetic isotope effect. It is important that the reaction is carried out using the same experimental conditions.

5.5. Fourth step: Hammett plot

It is necessary that the reaction is not reversible overall for the Hammett plot to be valid. This condition can be checked by introducing the expected product of the reaction but with some sort of isotopic label or by using an isotopic label in the starting material in the presence of the non-labelled expected product. If the reaction is reversible, the label will be found in both reactant and product whereas if the reaction is irreversible, the label will be present in the reactant or in the product, but not in both.

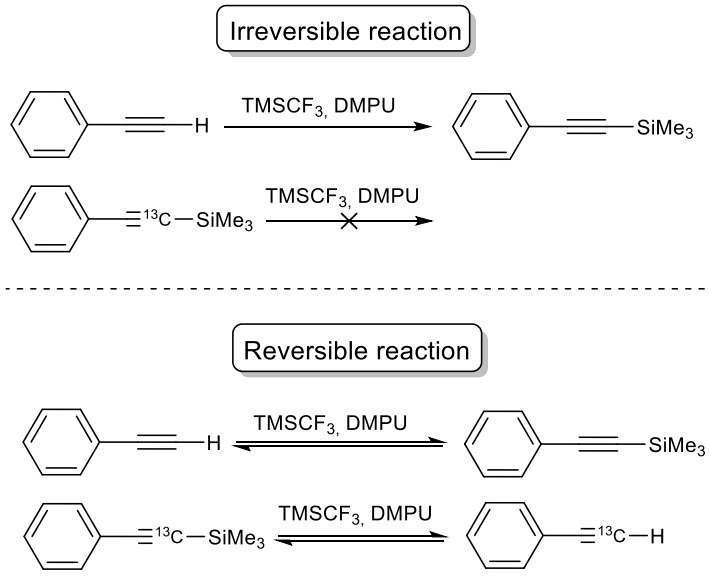

Figure 13. Scheme of the mixture of products and starting material in case of irreversability and reversability

As is shown in figure 13, this experiment can determine if the reaction is reversible overall. The labelled compound can be synthesised according to the procedure in page 24.

The terminal alkyne is a non-labelled phenylacetylene and a labelled product is introduced in the reaction mixture, in this case with a ^{13}C label in the sp carbon next to the silicon. If the reaction is reversible, a ^{13}C-labelled terminal alkyne will appear in the reaction mixture. But if the reaction is irreversible, the ^{13}C label will only be present in the product.

The alkynyl proton of the labelled terminal alkyne appears as a doublet at 2.5 and 3.8 ppm with a coupling constant of 251 Hz,[70] whereas the non-labelled compound's alkynyl protons appears as a singlet at 3.1 ppm. If this doublet ascribed to the alkynyl proton appears at the ^{1}H spectrum of the reaction mixture (recorded in a deuterated solvent, not in DMPU) and its integral value does not correspond to 1.13% (natural abundance of carbon-13), which could then be attributed to a carbon satellite signal, the reaction is reversible.

It is intuitive that this reaction has two steps: deprotonation and silylation. In the case of this reaction, there are three different scenarios that might be encountered involving a naked alkynyl anion, which are outlined in figure 14. The first one is a slow deprotonation step that is the rate-limiting step, which would give a positive rho value. Electron-withdrawing substituents would favour this step by making the alkynyl proton more acidic. The second proposal is a fast deprotonation followed by a slow (and rate-determinating) silylation. This would imply a negative rho value since electron-donating substituents speed up the silylation step by making the anion more reactive (more charge density). The third and last proposal would be the existence of an equilibrium of

the protonated terminal alkyne and its anion followed by slow silylation step. The rho value would be close to zero in this scenario. Electron-withdrawing substituents would shift the equilibrium towards the anion but the silylation step would then be disfavoured. In turn, electron-donating substituents would disfavour the formation of the alkynyl anion while at the same time favour the silylation step. The reaction rate would stay pretty much constant regardless of the aromatic ring substituents. It is important to emphasise that in this case it is only the deprotonation step that is reversible and not the overall reaction, so the Hammett plot is still valid in this case.

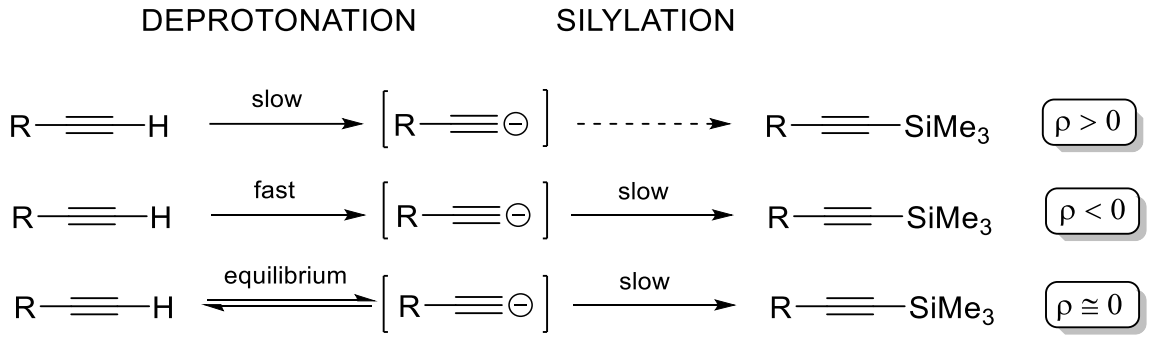

Figure 14. Rho values for different mechanistic scenarios.

In the previous scenarios, it is assumed that a naked alkynyl anion is formed, which gives rise to large positive and negative values in the first two scenarios. However, if the reaction does not proceed in a stepwise but in a concerted manner, the resulting rho values would be close to zero. In figure 15, the stepwise and concerted pathways if the deprotonation is the rate-limiting step are shown with their presumed rho values. In the case of silylation being the rate-limiting step, its stepwise pathway would result in a large negative rho value. In the case of a concerted mechanism, the rho value will depend on which bond is first formed in the transition state. If it is the silicon-carbon bond, the rho value would be slightly negative; whereas if it is the carbon-proton bond formation to form fluoroform, the rho value would be slightly positive.

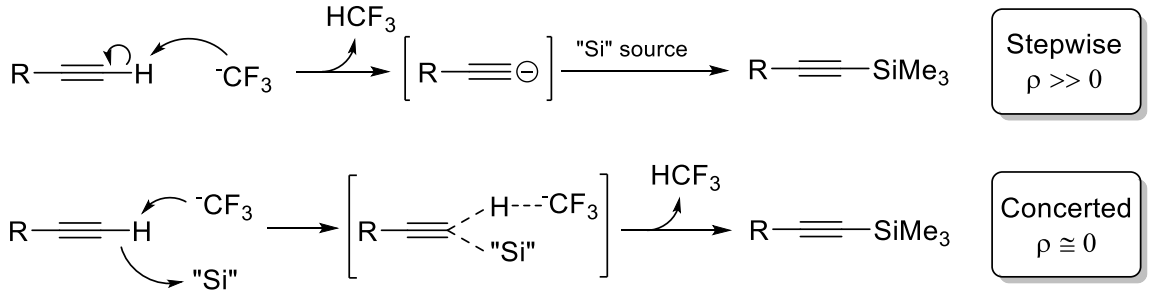

Figure 15. Magnitude of the rho values for different mechanistic scenarios if deprotonation is the rate-determining step.

In table 2, a list of substrates is proposed to carry out the Hammett plot. The Hammett plot can be built from measuring the rate constant for each of the substrates in table 2.

The substrates can be monitored by the decay of the alkynyl proton NMR shift or C(sp)-H stretching frequency. Which of those technique will be used will depend on the previously proposed exploration experiments (see section 5.2).

Table 2. Hammett plot substrates with their sigma values and characterisation data

Substrate	Substituent	Sigma value[71]	^{1}H NMR chemical shift[a]	IR C(sp)-H stretching frequency
Phenylacetylene	H	0.00	3.07[15]	3292[15]
4-methoxyphenylacetylene	4-OMe	-0.27	3.00[15]	3290[15]
4-methylphenylacetylene	4-Me	-0.17	3.03[15]	3290[15]
4-fluorophenylacetylene	4-F	0.06	3.04[72]	3295[73]
4-chlorophenylacetylene	4-Cl	0.23	3.10[15]	3293[15]
3-fluorophenylacetylene	3-F	0.34	3.09[74]	3300[73]
3-chlorophenylacetylene	3-Cl	0.37	3.12[75]	3294[76]
3-cyanophenylacetylene	3-CN	0.56	3.19[15]	3293[15]
4-nitrophenylacetylene	4-NO_2	0.78	3.36[15]	3253[15]

[a] Using deuterated chloroform as solvent and trimethylsilane (TMS) as internal standard.

The rate constants obtained from the measurement of the terminal alkyne decay can then be divided by the one obtained for phenylacetylene. The same conditions (concentration, temperature, solvent, etc.) must be used for all the substrates. Different temperatures and concentrations would lead to incomparable rate constants.

There is also another option if ^{1}H NMR proved to be unhelpful to monitor the decay of two terminal alkynes, and that is ^{19}F NMR. A fluorine atom could be added to each molecule (either a fluoro or a trifluoro group in the meta or para positions). The problem with this is that the range of covered sigma values would be significantly reduced, and the more negative sigma values would not be accessible. There is also the limitation that there can be no acidic position in the phenyl ring (for example two fluorine in meta to each other) since then there could be deprotonation and silylation at that position.[14] Alternative, the model substrate could be 2-fluorophenylacetylene since fluorine is not a bulky atom and then a wider range of sigma value would be accessible (although the substrates would be more electron-withdrawing than using phenylacetylene as the model substrate).

^{19}F NMR is not guaranteed to work since, as shown in section 4.3, the difference in fluorine chemical shift of the terminal alkyne and the product is close and overlapping is likely. I was not able to find any 3,4; 4,4; or 3,3,4 substituted phenylacetylenes with both chemical shifts for the starting material and the product to discard signal overlap.

If the other possibilities became unfeasible, the ^{19}F NMR spectra of both terminal alkyne and product would need to be recorded to see if monitoring the decay of terminal alkynes through ^{19}F NMR is possible.

5.6. Fifth step: Kinetics

In this reaction there are three species present at the start: the terminal alkyne, $TMSCF_3$ and DMPU. The role of DMPU is unclear because since it is used as solvent, it is not known if it is required in stoichiometric amounts or in catalytic amounts, which would mean that it regenerates. If even reducing its amount to substoichiometric quantities (compared to the terminal alkyne), the reaction still takes places in a significant yield (or the product is obtained in a higher concentration than that of initial DMPU), DMPU is then needed in catalytic amounts.

Whether DMPU is needed in stoichiometric or catalytic amounts will influence both the kinetics of the reaction as well as the determination of the complexes of $TMSCF_3$ and DMPU to release the trifluoromethyl anion, and the silylating reagent. Either way, the use of a mixed solvent system, that is mixing DMPU with other solvents such as THF, toluene or hexane still raises some issues. DMPU needs to be significantly reduced from its high concentration (solvent) to smaller amounts which allow the measurement of its consumption over time, if there is any. Thus, the role of DMPU will change from solvent to co-solvent.

After determining if DMPU is a catalyst or not, the reaction order of the other compounds implicated in the reaction can be studied. The concentration of all reactants but one can be increased in the case of the alkyne or $TMSCF_3$ as long as the other one is in a concentration low enough to avoid any overpressure. Depending on the rate-limiting step, which can be found using the Hammett plot, and the role of DMPU, different approaches can be taken. For example, in the case of the first step being the rate-determining one, a classical kinetic analysis can be used, as described in section 4.6. If the first step is found to be reversible, a steady-state approximation can be used for the alkynyl anion (naked or not) intermediate.

Kinetics must fit the proposed mechanism. Therefore, kinetics will not be used to discover the mechanism but rather to back it up. Since there are many unknowns, not every possibility can be analysed in this work. However, some mechanisms and the rate laws that would support them can be given. If the complex formation between $TMSCF_3$ and DMPU were the rate-limiting step, the reaction would be first order in $TMSCF_3$ and DMPU, and zero order in the alkyne. If complex formation were an equilibrium process and deprotonation were the rate-limiting step, the reaction would be first order in all the components. In contrast, if the rate-limiting step were the silylation, the reaction would be first order in $TMSCF_3$ but zero order in DMPU.

Apart from the kinetic experiments done by changing the concentrations of the reactants, other experiments can be done. For example, after the reaction stalls or when it is completed but some of the components remain, the lacking component can be added to see what happens afterwards in terms of reaction rate.

5.7. Sixth step: Release of the trifluoromethyl anion

A set of complexes involving DMPU and $TMSCF_3$ are pictured in figures 16-18. The interactions of these complexes in a 1:1 or other ratios can be studied using computational tools. A simulation of the bonding or coordination of each of the proposals should be able to furnish the energy levels of each of the components and their energy barriers.

In figure 16, four different complexes of DMPU and $TMSCF_3$ that could be formed before releasing the trifluoromethyl anion are proposed. A DMPU molecule could be coordinated through the oxygen or nitrogen atom to the silicon centre (A and C in figure 16, respectively). The DMPU molecule could be bonded through the oxygen or nitrogen atoms to the silicon centre (B and D in figure 16, respectively).

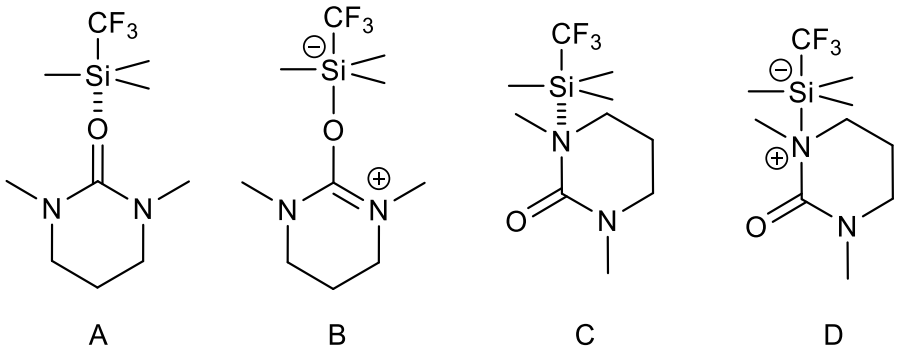

Figure 16. Representation of four possible DMPU and $TMSCF_3$ complexes

As shown in figure 17, a hexavalent silicon species and a disilicon species could also be the species involved in the CF_3^- anion release. In the case of the reaction under study, both the oxygen and the nitrogen of DMPU could interact with the silicon of $TMSCF_3$ (compounds A in figure 17) and one DMPU molecule could interact with two $TMSCF_3$ molecules, through the oxygen with one, through the nitrogen with the other (compounds B in figure 17). In both cases, as shown in the right-hand side representations of A and B, the nitrogen lone pair of electrons can delocalise to the oxygen atom.

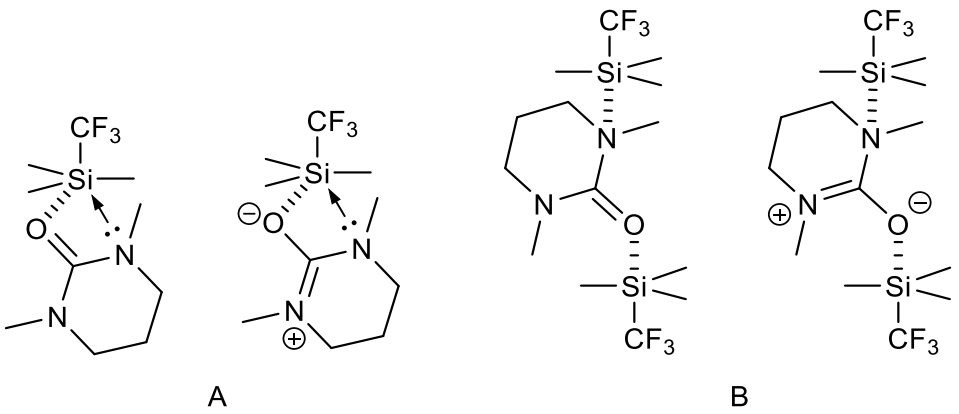

Figure 17. Representation of a hexavalent, and a disilicon species of $TMSCF_3$ and DMPU

It is worth noting that DMPU has three potential coordination sites, two of which are equivalent (the nitrogen atoms). Some other possibilities are represented in figure 18. For instance, the hexavalent silicon species could involve the interaction of the two nitrogen atoms of DMPU (A in figure 18). Moreover, the disilicon species could also involve the nitrogen atoms of both DMPU molecules involved (B in figure 18). To complete the picture, a combination of both a hexavalent and disilicon species could occur (C in figure 18). One of the silicon centres could be interacting with an oxygen and nitrogen of the DMPU, which would increase the electron density at that $TMSCF_3$ molecule, and the other silicon centre could be interacting with the other nitrogen atom in DMPU.

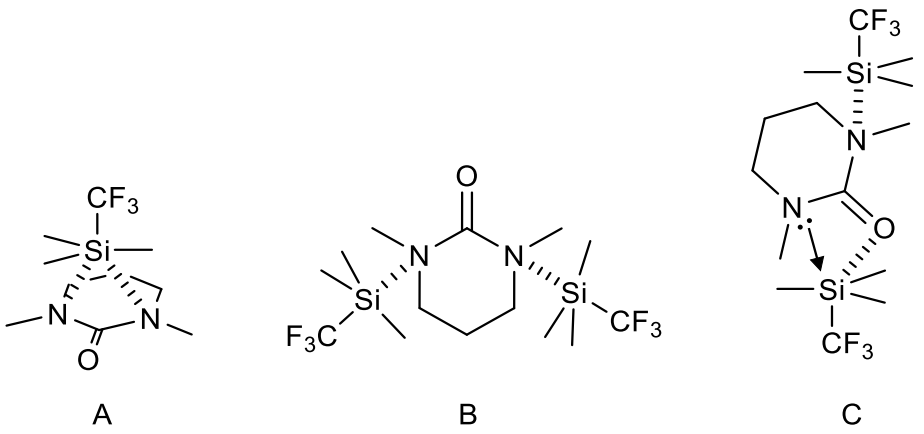

Figure 18. Representation of a hexavalent, and two disilicon species of $TMSCF_3$ and DMPU

I would like to point out that figures 16-18 are representations of possible interactions between DMPU and $TMSCF_3$ but these species might have different geometries, bond lengths, bond angles, among other things.

Examples in the literature have been found of the use of ^{1}H and ^{13}C NMR to detect if complexes are formed, although the shift can be due to solvation and not coordination. I would expect a downfield shift in the case of coordination of DMPU with $TMSCF_3$ since

less electron density would surround the nuclei if these atoms were coordinated with $TMSCF_3$. In this case, ^{15}N and ^{17}O NMR would be the most useful techniques to detect if a complex has been formed involving DMPU, since coordination would be through these two nuclei. Correlation spectra can prove useful to detect multiple bond correlations between nuclei of the two molecules. In case the natural abundance of these nuclei is not enough, it is possible to synthesise the isotopically labelled analogues. In the same way, ^{29}Si NMR could also be used to detect any change in silicon environment.

From the NMR experiments mentioned above, information can be obtained as to the formation of a complex between DMPU and $TMSCF_3$. However, computational studies are a useful tool to complete the picture. Computational studies might tell if bonding of DMPU to $TMSCF_3$ through the oxygen, nitrogen or both is favoured and if the more complex structures (disilicon complexes) are also possible. A combination of computational chemistry calculations and heteronuclear NMR can provide useful information to identify the most likely candidates for the species that releases the trifluoromethyl anion.

Even if one of the above-mentioned complexes is detected, that does not mean that this complex will be involved in the reaction. This experiment would only demonstrate that such a complex can exist when $TMSCF_3$ is mixed with DMPU.

5.8. Seventh step: Silylating agent

Proposing experiments to determine which silylating agent is involved in this reaction is more difficult since there is no way to isolate the potential candidates. Taking this into account, a computation study of the energy barriers for the silylation step would at least discart some possibilities if the energy barriers are insurmountable. The Hammett plot will have provided information about the nature of the intermediate. Depending on the results of the Hammett plot, at the starting point there could be a naked alkynyl anion or not (see figure 15). If the mechanism is stepwise, the computational study will be much more easy since only the alkynyl anion and the silyl source will have to be taken into account. Otherwise, the trifluoromethylanion would also have to be included.

Apart from trying to envision the silyl source of the reaction, experiments using other trialkyltrifluorosilanes can be carried out. Changing the alkyl chains from methyl to ethyl or isopropyl groups can give information about the nature of the mechanism. However, changing these substituents not only alters the silylation step, but the formation of the complex to release the trifluoromethyl anion. Both will have to be taken into account when analysing how using the other silyl reagents changes the rate of the reactions. Experiments proposed in previous sections, such as a Hammett plot, calculating the KIEs and studying the kinetics can also be done for the alternative silyl reagents. Fewer substrates could be used in the Hammett plot and fewer experiments when studying the kinetics to save time in case the results resemble that of the previous one with

$TMSCF_3$. A Hammett plot with similar rho values for each silyl reagent, similar KIEs and the same kinetic dependences would strongly point to the same mechanism for each of the three silyl sources. Discrepancies might point to slightly different mechanisms or completely diferent mechanisms altogether.

5.9. Eight step: Chemoselectivity

As shown in section 4.9, the chemoselectivity is not the same when using a fluoride source instead of DMPU. If a Lewis acid is the reason for this change in chemoselectivity, an inert salt could be added to the reaction mixture to increase the electrophilicity of the carbon. If there is a change in chemoselectivity, the cation plays a role in changing the chemoselectivity. The only requirements for this inert salt would be that its cation is a Lewis acid. For example, an alkali metal would be a good Lewis acid and it is also caesium (alkali metal) the one used in the examples where carbonyl trifluoromethylation is preferred. Moreover, the salt should also not intervene in any fashion with the trifluoromethyl anion equivalent release or with the silylation. For example, if the salt has a fluoride as the anion it would interact with $TMSCF_3$.

A soluble inert salt must be found. In a previous paper, caesium chloride is used to activate $TMSCF_3$ to no avail. It can be assumed that caesium chloride does not promote at any measure the trimethylsilylation of terminal alkynes. Since using a chloride instead of a fluoride source seems not to promote the reaction, a chloride salt could be a good candidate. A study showed that potassium chloride is soluble in DMPU. This solubility is attributed to the metal alkali ions' ability to weakly interact with the solvent, that is DMPU.[77] However, it should be borne in mind that DMPU has a carbonyl group as well since it is a cyclic urea derivate, which favours the solubility of the salt but might affect the ability of the alkali cation to activate just the carbonyl group of the substrate.

In this kind of experiment, it is not mandatory to monitor the reaction until completion or stalling since chemoselectivity can be studied at the end point. Monitoring would give information about a change in chemoselectivity, if there is any chance at all, throughout the reaction.

To confirm that the alkali cation acts as a Lewis base and coordinates to the carbonyl of the substrate, a ^{13}C NMR spectrum of a mixture of the substrate in DMPU could be recorded. If the cation is coordinated to the carbonyl of the substrate, a decrease in the chemical shift is expected since the carbonyl carbon would be less shielded. Furthermore, the DMPU carbonyl would also experience a downward shift (deshielding) if the cation coordinates with it.

It would also be interesting to check if in the presence of this chloride salt anything happens with $TMSCF_3$. A ^{19}F NMR spectrum would help discern if there is any kind of interaction of either the cation or the anion with $TMSCF_3$ by a chemical shift change. Any fluoroform release would point to an interaction of the salt's components with $TMSCF_3$

that release a trifluoromethyl anion equivalent. Alternatively, ^{29}Si and ^{13}C NMR could be used to detect if there is any interaction of $TMSCF_3$ with the salt by checking if there is a change in the chemical shift of the $TMSCF_3$ silicon, and methyl carbons, respectively.

To confirm that the salt cannot trigger the reaction, an experiment with all the components but for the DMPU is in order. In this case, another solvent that cannot promote the reaction might be needed. In case solubility allows it, THF would be a good option.

Moreover, a more electrophilic carbonyl such as trifluoroacetaldehyde could also be added to see if the trifluoromethyl anion shows any more preference for nucleophilic addition to this more electrophilic carbonyl than for alkyne deprotonation.

Another experiment that could be useful would be adding a crown ether when caesium fluoride is used as fluoride source to prevent the caesium cation from interacting with the carbonyl. Crown ethers have been shown to form complexes with caesium cations.[78] If the chemoselectivity using CsF and a crown ether were to favour deprotonation over nucleophilic addition, as is the case when using DMPU, the difference in chemoselectivity would indeed be due to the cation. If that is not the case, the reason for this chemoselectivity difference will probably have to do with the formed complexes between $TMSCF_3$ and DMPU.

5.10. Ninth step: Other solvents

In the paper, other solvents such as DMI and DMSO are used to promote the reaction. DMI gives a 53% yield whereas DMSO gives a 71% yield when studying the reaction parameters.[12] DMI is the most structurally similar to DMPU since it is also an N-methylated cyclic urea but with a five-membered ring instead of a six-membered ring. DMSO has a more different structure compared to DMPU since it is a sulfoxide, and the only thing in common is the presence of methyl groups and more importantly their potentially coordinating oxygen.

Depending on the results of the previous experiments, some further experiments could be done to compare these two solvents with DMPU. DMI has the same issue as DMPU in regards with its deuterated form not being commercially available, so its reaction monitoring would be similar to the one employed with DMPU. DMSO is commercially available in its deuterated form, so monitoring through ^{1}H NMR would be possible although, if there is any hydrogen KIE with the solvent, it would affect the kinetics.

Moreover, other solvents with a similar structure to DMPU and DMSO could be screened to see if they also allow the reaction to take place. Solvents with acidic protons cannot be used since they will be deprotonated (the trifluoromethyl anion is known the deprotonate acetonitrile and dichloromethane, for example). Another urea derivate, such as tetramethylurea, could be a good candidate since it still has the urea group but

no acidic protons. If tetramethylurea failed to promote the reaction, it could be plausible to say that the cyclic ring in the urea derivative stabilises the complex with $TMSCF_3$.

Depending on the results obtained as to how DMPU interacts with $TMSCF_3$ to release the trifluoromethyl anion, other solvents which can mimic its structure can be screened to confirm that these interactions are extrapolative to slightly different solvents. For example, the carbonyl fraction is maintained in other solvents with a ketone or aldehyde group such as acetone or formaldehyde. However, these solvents may not be inert to the reaction conditions since they are prone to undergo trifluoromethylation, specially if they are used as solvents (much higher concentration).

5.11. Looking at the bigger picture

Once all these experiments have been carried out, and probably many more to dig deeper and shed more light on the mechanism, more information about the mechanism will have been obtained. Many other experiments which have not been explained here, such as an Eyring plot and radical clock experiments, could also be carried out. A proposal about the mechanism of this reaction will have to be supported by each and every one of the collected data. If any experiment fails to support the mechanism, it means that the mechanism is not valid and is therefore disproved. If even after all the experiments, more than one mechanism fits all the data, new experiments will have to be designed with the aim of disproving them. Nevertheless, we must not lose sight of the premise of mechanistic studies: a mechanism cannot be completely proven.

6. Conclusions

En català

La reacció de trimetilsililació d'alquins terminals estudiada no és l'única on hi participen $TMSCF_3$ i un altre reactiu hi intervenen. Se n'han trobat altres exemples on, en comptes de DMPU, es fa servir una font de fluorurs o NHC.

S'ha explorat el seguiment de reacció, que és la base de molts dels experiments proposats, per a trobat tècniques que puguins ser útils per aquesta reacció. La RMN de ^{19}F és la que donaria més informació si és possible distinguir l'alquí terminal del producte, cosa que no s'ha pogut demostrar. La RMN de ^{1}H també donaria informació, encara que hi ha problemes relacionats amb els senyals del dissolvent que són dificils de resoldre sense canviar el sistema de dissolvent. El seguiment per IR també és una altra possibilitat encara que no és tan diàfana com la RMN. Sempre hi ha l'opció de realitzar els experiments de punt final, que són molt més tediosos.

Els efectes isotòpics cinètics i la gràfica de Hammett són tècniques comunes en estudis de mecanismes. S'ha descrit com podrien ser utilitzades per obtenir informació sobre aquest mecanisme en concret. Els efectes isotòpics cinètics poden ajudar a elucidar l'estructura de l'estat de transició mentre que la gràfica de Hammett pot determinar l'etapa determinant de la velocitat i si un anió alquinil està involucrat com a intermedi o no (mecanisme per passos o concertat). S'han trobat exemples de com els efectes isotòpics cinètics s'han mesurat en experiments previs i altres casos on la gràfica de Hammett s'ha utilitzat per deteminar la natura del mecanisme (per passos o concertat)

S'han descrit els punts principals sobre la cinètica. Tanmateix, l'ampli reguitzell de possibilitats i incògnites sense dades experimentals fa massa complicat analitzar cada possibilitat. La cinètica es pot emprar per comprovar els results dels experiments previs i la cinètica ha de concordar amb les dades obtingudes d'aquests.

Després d'aquestes tècniques més comunes, s'han explorat altres experiments més fets a mida per aquesta reacció. La RMN pot ser una eina útil per explorar el complex o complexos que es poden formar entre DMPU i $TMSCF_3$, que probablement hi juguen un paper. S'han descrit estudis previs de RMN orientats a detectar complexos similars, així com la RMN d'altres nuclis menys comuns en RMN. Els estudis computacionals també poden ser útils en àrees on l'experimental no hi arriba.

L'etapa de sililació és més complicada d'estudiar. Calen estudis computacionals per a determinar la natura del reactiu de sililació. Nogensmenys, es poden dur a terme experiments emprant diferents reactius sililants amb grups alquil diferents als de $TMSCF_3$, cosa que s'ha fet en altres estudis.

Tambe s'ha de parar especial atenció al paper del dissolvent. Altres dissolvents amb parts estructurals similars es poden estudiar per comprovar quines característiques del DMPU són necessaris perquè aquesta reacció funcioni.

La principal particularitat d'aquesta reacció és la seva quimioselectivitat, que afavoreix els alquins per sobre de cetones o aldehids. Es proposen experiments per a determinar l'origen d'aquesta quimioselectivitat, principalment centrats en explorar el paper de les fonts de fluoror amb contracations alcalins, que mostren la quimioselectivitat inversa.

Després de tots aquests experiments, depenent de les característiques descobertes de la reacció la combinació de $TMSCF_3$ i DMPU podria ser útil en reaccions similars.

A tall de cloenda, aquest document conté una proposta que cobreix diverses tècniques emprades normalment que poden ser útils en estudis de mecanismes i experiments més específics per aquesta reacció. Crec que després de dur a terme aquests experiments, el mecanisme de reacció podrà ser establert amb una bona certesa.

In English

The trimethylsilylation reaction of terminal alkynes under study is not the only one where $TMSCF_3$ and another reagent are involved. Other examples where, instead of DMPU, a fluoride source or an NHC are used have also been found in the literature.

Reaction monitoring, which is the basis for many of the proposed experiments, has been explored to find which techniques might be the most useful to this reaction. ^{19}F NMR is the one that would provide the most information if both terminal alkyne and product can be distinguished, which has not been proved. ^{1}H NMR would also give information, although there are problems related with the solvent signals that are difficult to overcome without changing the solvent system. IR monitoring is also another available option although it is not as straightforward as NMR. There is always the possibility of conducting the much more painstaking end-point experiments.

Kinetic isotope effects and the Hammett plot are commonly employed techniques in mechanistic studies. It has been described how they could be used to extract information about this very reaction mechanism. Kinetic isotope effects can help elucidate the structure of the transition state whereas the Hammett plot can determine the rate-determining step and if a naked alkynyl anion is involved as intermediate or not (stepwise or concerted mechanism). Examples of how KIEs have been measured in past experiments and other cases where a Hammett plot is used to determine the nature of a mechanism (stepwise or concerted) have also been found.

The main points about kinetics have been described. However, the wide variety of possibilities and unknowns without experimental data makes it too intricate to analyse

every possibility. Kinetics can be used to check the results of the previous experiments and kinetics must fit the data obtained from those experiments.

After these more well-established techniques, other experiments more tailor-made for this reaction are explored. NMR can be a useful tool to explore the complex or complexes that may form between DMPU and $TMSCF_3$, which are likely to play a role. Past studies showing NMR studies aimed at detecting similar complexes are described and the more uncommon nuclei NMR are briefly described. Computational studies can also prove useful in areas that experimental data cannot reach.

The silylation step is more cumbersome to study. To determine the nature of the silylation reagent, computational studies need to be used. However, experiments can be carried out using other silyl reagents with different alkyl groups in $TMSCF_3$, which has been done in other studies.

The role of the solvent also needs to be given special attention. Other solvents with similar structural motifs can be screened to check which DMPU characteristics are necessary for this reaction to work.

The main particularity of this reaction is its chemoselectivity, that favours alkynes over ketones or aldehydes. Experiments are proposed to determine which is the root of this observed chemoselectivity, mainly focused on exploring the role of fluoride sources with alkali countercations, which have the inverse chemoselectivity.

After all these experiments, depending on the discovered features of the reaction the combination of $TMSCF_3$ and DMPU could be used for other similar reactions.

In conclusion, a proposal covering several commonly used techniques that can prove useful for mechanistic studies, and more specific experiments for this reaction is laid out in this document. I believe that after carrying out these experiments, the mechanism for this reaction can be established with good confidence.

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