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Non-innocent probes in direct sonication: Metal assistance in oxidative radical C—H functionalization

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ABSTRACT

Direct sonication by means of ultrasound horns constitutes a widely used technique in chemical process technology. However, the direct contact between the metal probe and the reaction mixture does not always leave the chemical system unaffected. In this report, we study the *tert*-butyl hydroperoxide-mediated trifluoromethylation of heterocyclic structures, and the influence of sonication thereon. Metal leaching is observed during the process and further examined, showing that several metals can interfere significantly with the chemical reaction under study. Notably, vanadium metal was found to increase the reaction rate exceptionally well, rendering it a useful additive for this type of reactions. Ultimately, some mechanistic considerations are offered, to provide more insight into the nature of the catalytic effect of leached metals.

1. Introduction

Ultrasonic irradiation has proven to be a valuable, non-conventional energy source in organic synthesis [1–4]. By merit of rarefaction-compression cycles and the subsequent formation and implosion of gas-filled or vacuum cavitations, local hot spots are formed with very high local temperatures and pressures (up to 5000 K and >500 atm) [5,6]. These cavitations can serve as microreactors, wherein compounds either react inside the bubble, or on the boundary upon implosion. Especially noteworthy about the cavitation phenomenon is the formation of all kinds of radicals inside the bubble, due to homolytic cleavage of e.g. O—H bonds in water molecules [7,8].

Another benefit of ultrasonication is its ability to replace phase transfer catalysis, as it allows for more efficient micromixing than conventional stirring [9,10]. Also, near solid surfaces, the implosion of a bubble will act as a microjet towards the surface and thus by causing structural defects it will enlarge the specific surface area of the solid [11,12].

From a processing point of view, it was hypothesized by Gogate that ultrasound (US) irradiation can assist chemical reactions in seven ways: (a) reaction time reduction (b) increase in the reaction yield (c) use of less forcing conditions (temperature and pressure) as compared to the conventional routes (d) reduction in the induction period of the desired reaction (e) possible switching of the reaction pathways resulting in increased selectivity (f) increasing the effectiveness of the catalyst used in the reaction (g) initiation of the chemical reaction due to generation of highly reactive free radicals [13].

In its most accessible form, and therefore particularly interesting for lab-scale applications, ultrasound irradiation can be generated with an ultrasound horn. In this user-friendly, compact enough device, a piezoceramic element brings about the acoustic waves incited by a processor, and a cylindrical sonotrode or 'horn' to which it is connected can transmit the vibrations to a certain medium. Vertically positioned, the tip of the horn will usually be immersed between 1 and 3 cm in the fluid, in the center of the vessel. Its ease of use allows the researcher to rapidly assemble a set-up for sonication experiments, without the need for reactor design etc. as one would have to do with indirect sonication methods. As compared to the ubiquitous ultrasonic cleaning baths, which are plagued by low power densities and inho-

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mogeneous US fields, the probe can provide local intensities of several orders of magnitude higher [14].

For these straightforward reasons, organic chemists for whom sonication plays a recurrent role in research projects, will often choose for probe sonication. Despite some drawbacks, like the restriction to a single frequency (usually in the 20–40 kHz range) and to batch conditions, difficulties with atmosphere-sensitive reactions or the general lack of high parameter controllability, direct sonication still proves satisfactory in many cases and remains a popular mode for synthesis projects. Notably, ultrasound has proven useful in heterocycle synthesis [15] and oxidative reactions [12,16–19], and in reactions with solid metals (e.g. cross couplings [20–22], reductions [23–26]) or bases [11,27] (e.g. S_N2 or hydrolysis reactions).

This present study, however, aims to raise a few questions over the imprudent use of ultrasound horns in scientific research. All too often, authors merely mention their methods and suppliers, spending little or no effort to ascertain the absence of potential side effects of the metal surface introduced in the reaction mixture. Although manufacturers do typically warn the user for surface abrasion in their product manuals, not too many publications bother with possible contamination of reaction products. Valuable exceptions are the work by Entezari et al. which reports titanium contamination in X-ray spectra caused by the ultrasound horn [28], and a publication by Betts et al. which expands on issues experienced with direct sonication in nanoparticle synthesis [29]. The study on cycloaddition reactions by Reisse et al. describes an indirect sonochemical effect as well, although the metal influences are excluded in favour of the HCl-generating solvolysis of the dichloromethane solvent [30]. Also, it must not be overlooked that when using US horns for chemical reactions, other effects than merely abrasion can be at play. Under acidic and especially oxidative conditions, corrosion is likely to occur at the surface of the ultrasound probe, to the extent that it can render the equipment out of order in a matter of weeks when used intensively. It is not hard to envisage that especially oxidation reactions which have been studied under influence of probe sonication, might have experienced a certain effect with dissolved metals.

Herein, we report the investigation of the influence of ultrasound irradiation on oxidative radical reactions. As a model reaction, a mild and useful protocol was chosen that allows easy trifluoromethylation and other (fluoro)alkylation of heterocyclic structures [31]. This subtype of Minisci reactions (i.e. radical functionalizations of heteroarenes) uses a trifluoromethanesulfinate salt as the radical precursor, reacting with the *tert*-butyl hydroperoxide (TBHP) oxidant to deliver the CF_3 radical which is capable of adding onto a heteroaromatic ring.

For the first time, the influence of sonication on Minisci type reactions is studied. The discovery of metal leaching from the probe surface is described and consequences thereof are further investigated. From the obtained insights, an explanation for the rate increasing influence is offered. This study therefore aims to describe the chemical effects of the probe metals in one specific model reaction. In extension, we hope to raise awareness for what could be a more general issue in the research field.

2. Materials and methods

2.1. Chemicals & equipment

All reagents were obtained from commercially available sources and were used as purchased without further purification. Caffeine was purchased from Roth, sodium trifluoromethanesulfinate from J&K Scientific and *tert*-butyl hydroperoxide (70% aq.) from Alfa Aesar. Titanium granules (99.9%, ~15 mesh) and Vanadium pieces (99.7%) were purchased from Alfa Aesar, Iron powder (97%, 325 mesh) was acquired from Aldrich, Vanadium powder (99.5%, 325 mesh) was bought from Strem, Vanadium granules were produced by flaking of above mentioned pieces (~15 mesh). Technical grade solvents were used for reactions and purification. Reactions were magnetically stirred and monitored using pre-coated silica gel 60 F254 (250 μm) glass-supported TLC plates. Compounds were visualized by UV irradiation (254 nm). Flash column chromatography was performed on a Büchi MPLC set-up (Büchi SepacoreTM flash apparatus, consisting of a C-660 Büchi fraction collector, C-615 Pump manager, C-635 UV-photometer, two C-605 pump modules) connected to a Knauer K2501 UV detector and using manually packed silica gel (220–440 mesh) columns. Solvents were evaporated with a rotary evaporator at a temperature of 50 °C.

Experiments with ultrasonic probe were performed with a Hielscher UP50H ultrasonic homogenizer, with a default frequency of 30 kHz. For 2.5 mmol scale reactions (in 10 mL of solvent) the MS7 tip was connected. The material of the tip was Titanium Grade 5 alloy (Ti6Al4V). The sonotrode was coated by an external partner with multiple PFA layers.

^{1}H-NMR spectra were recorded on Bruker 300 Avance (300 MHz) and Bruker 400 Avance (400 MHz) with tetramethylsilane as internal standard in $CDCl_3$ or d^6-DMSO. ^{13}C-NMR spectra were recorded on Bruker 300 Avance (working at 75 MHz) and Bruker 400 Avance (working at 101 MHz) with the deuterated solvent as internal standard ($CDCl_3$: 77.16 ppm, triplet; DMSO: 39.52 ppm, quintet). The δ-values are expressed in ppm.

GC analyses were performed with a Shimadzu gas chromatographer using a CP Sil 5 column, GC–MS was run on a Thermo Fisher ITQ 900 EI-MS. ICP-OES measurements were performed with a PerkinElmer Optima 8300 Spectrometer and UV/Vis spectra were recorded with a Varian Cary 5000 spectrophotometer.

2.2. Power calibration of the set-ups used

In order to quantify the actual power transmitted by the US horn into the reaction mixture, we used temperature measurements in function of input power, to identify the calorimetric power P_{cal}. The value for P_{cal} [W] follows the formula $P_{cal} = \frac{dT}{dt} c_p m$ with $\frac{dT}{dt} = q$ being the temperature gradient [$K.s^{-1}$], c_p the specific heat [$J.g^{-1}.K^{-1}$] and m the mass of solvent [g]. The US probe with MS7 tip was immersed in reaction tube containing 10 mL of H_2O, and for several values of input power P_{in} (ranging from 10 to 100% of the maximum nominal input power of the probe, being 50 W), the temperature profile in function of time was logged for 20 s of sonication (while stirring at 300 rpm). The slopes of the obtained curves yield the values for q, from which P_{cal} can be calculated. These values can be plotted against P_{in} to find a linear relationship. The coated probe seems to dissipate more heat into the medium than the original specimen. Explanations for this may be sought in acoustic impedance or other properties of the coating layer Fig. 1.

2.3. General method for the trifluoromethylation of caffeine under silent conditions

A 25 mL two-necked flask was charged with caffeine (485 mg, 2.5 mmol) and sodium trifluoromethanesulfinate (975 mg, 6.25 mmol, 2.5 equiv.) in DCM (7 mL) and water (3 mL). The

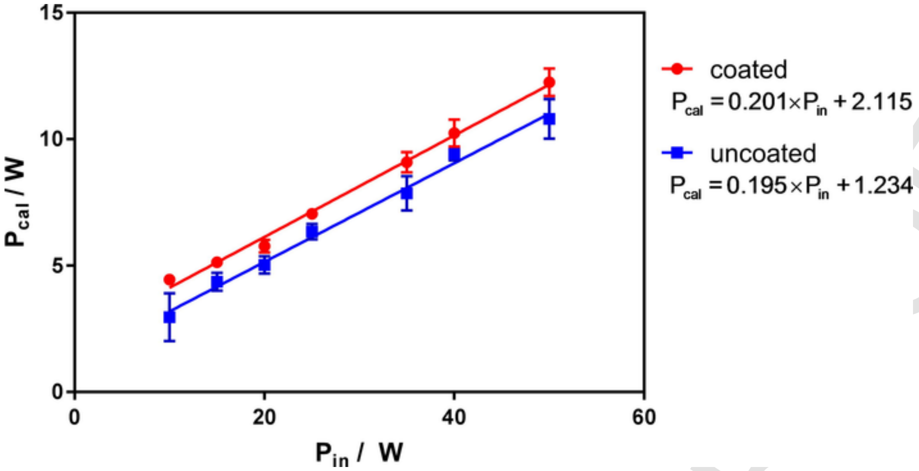


Fig. 1. Calorimetric power calibration of original and coated probe (average over three measurements).

flask was provided with a stirring bar and sealed with a septum that was pierced with a needle to make the system open to air. Next, TBHP (70% aq., 1.71 mL, 12.5 mmol, 5 equiv.) was added dropwise over 20 min while the flask was stirred at 0 °C. After addition, the flask was placed in a water bath at room temperature and further stirred for 2 days. At regular intervals, samples were taken for GC analysis by transferring approx. 0.1 mL of the organic layer into a 2 mL screw cap vial together with 0.2 mL NaS_2O_3 (10% aq. solution) and 1.5 mL of EtOAc. All data correspond to single-point measurements.

2.4. *General method for the trifluoromethylation of caffeine under ultrasound irradiation*

A 25 mL two-necked flask was charged with caffeine (485 mg, 2.5 mmol) and sodium trifluoromethanesulfinate (975 mg, 6.25 mmol, 2.5 equiv.) in DCM (7 mL) and water (3 mL). The flask was provided with a stirring bar, one regular septum (pierced with a needle to open the system to air) and one wide-hole septum, through which the MS7 tip of the UP50H processor was lowered to ensure a tight fit while being immersed approx. 1 cm into the liquid. The US probe was switched on (unless stated otherwise, settings were full cycle and 40% amplitude) and TBHP (70% aq., 1.71 mL, 12.5 mmol, 5 equiv.) was added dropwise over 20 min while the flask was sonicated and stirred at 0 °C. After addition, the flask was placed in a room temperature water bath and was further sonicated and stirred for up to 5 h. At regular intervals, samples were taken for GC analysis by transferring approx. 0.1 mL of the emulsion into a 2 mL screw cap vial together with 0.2 mL NaS_2O_3 10% soln. and 1.5 mL EtOAc. All data correspond to single-point measurements.

2.5. *Phosphine quenching experiments*

The general procedure for the trifluoromethylation of caffeine under silent conditions, as described above, was carried out. At regular time intervals, an aliquot of 100 μL was taken from the reaction mixture and quenched with 0.5 mL of a 0.4 M solution of triphenylphosphine (PPh_3) in methyl *tert*-butyl ether (MTBE). The formation of triphenylphosphine oxide ($P(O)pH_3$) was followed over time by GC analysis, which was converted to the residual concentration of TBHP present in the mixture.

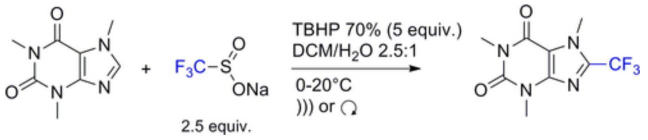
3. Results and discussion

3.1. *Initial findings*

A model reaction was selected based on a series of publications by the group of Baran [31–38]. These studies form an expansion on their initial finding, that sulfinate salts could be engaged, more specifically the Langlois reagent (sodium trifluoromethanesulfinate), as a radical precursor to add alkyl groups directly onto heteroarenes [31]. Using TBHP as a simple oxidant, this elegant reaction is transition metal free and is typically performed in a chlorinated solvent/water biphasic system (Scheme 1).

Within our original intention to study the influence of ultrasound irradiation on this type of reactions, we devised a plan which comprised running the procedure described in Ref. [31], whereby an ultrasound horn was inserted into the reaction mixture. Caffeine was chosen here as a model substrate, although we expect other xanthines, azoles or azines to give similar trends. The progress of the reaction was followed and compared to the silent counterpart (originally reported to complete only after 40 h). Gratifyingly, the sonicated experiment took merely 2 h to reach full conversion in 80% selectivity (Fig. 2).

At this point, it could not be stated with certainty that sonication alone accounts for this rate enhancement. To examine thermal effects, the temperature profile of a representative sonicated reaction was recorded, as shown in Fig. 3A. Noticing that the equilibrium temperature ends in the 30–35 °C range, a silent control experiment (in absence of an ultrasound horn) was run at 35 °C to determine the temperature influence. As can be seen in Fig. 3B, these conditions enabled the reaction to set off quite rapidly, yet subsequently leading to more attenuated progress to full conversion. Although it is possible that acoustic irradiation is exerting a sonocatalytic effect on this reaction, this claim could not be made at present, as thermal effects cannot be ruled out to play the more dominant role.



Scheme 1. General reaction scheme for the trifluoromethylation of caffeine.

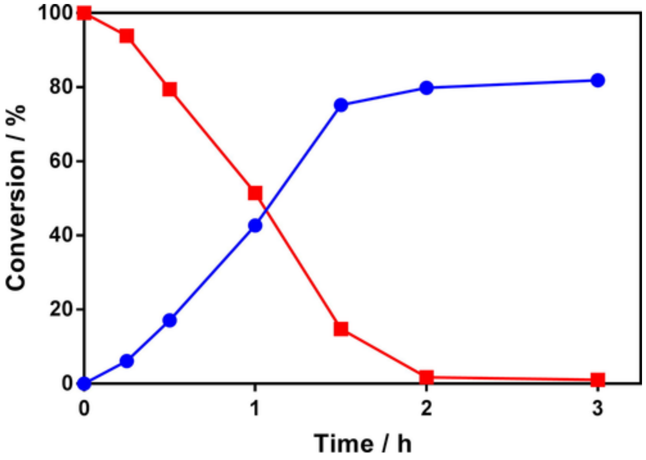


Fig. 2. Reaction profile of trifluoromethylation of caffeine under influence of direct US irradiation (?red curve (■) corresponds to depletion of initial reactant, blue curve (●) to the product formation, yields based on GC analysis).

Similarly, the observation of surface corrosion at the probe tip required further investigation. Approximately two months of frequent experimentation rendered the equipment non-functional, as the sonotrode had thinned out in such a way that it was out of resonance with the piezoceramic element. In order not to consume these tips in a sacrificial manner, a more durable solution was sought. A chemically inert barrier was needed to prevent this decay from happening, and a multi-layered fluoropolymer coating was chosen to allow maximum protection and minimum attenuation.

A coating was applied onto the tip, consisting of a primer and two PFA layers. By calorimetric calibration, it was established that the actual power transmission into the medium was not hampered by the coating. The rate of the reaction, however, was significantly lower when irradiating with the coated horn as opposed to the uncoated specimen (Fig. 2 vs. Fig. 4A, *vide infra*). This result convinced us of the non-innocent role the ultrasound probe was playing in the reaction, and led us to investigate more in depth the extent of metal interference.

3.2. Influence of titanium alloy

First, the extent was determined to which direct contact between US probe and reaction mixture made a difference in the reaction rate. A fourfold experiment was designed for this goal: each time the same reaction was carried out, but either with or without sonication (utilizing a coated probe) and either in the presence or absence of a titanium rod, of the same composition as the uncoated US probe (Grade 5 Ti alloy).

Fig. 4A shows the profile of the reaction under ultrasound irradiation, utilizing a coated tip and in the absence of any metals. The coated tip makes sure that metal effects can be excluded. As usual when performing this reaction, there is a certain induction time after which the conversion gains more speed. This can possibly be explained by gradual acidification due to sulfuric acid, which might be formed as a side product *via* hydration and further oxidation of the expelled SO_2 gas.

Fig. 4B is the profile of the unassisted reaction, performed as reported in literature [31]. It was reported by Baran et al. that the reaction for this particular substrate takes 40 h to reach completion, and also in our case it was noticed that it typically took more than one day to reach full conversion.

A comparison between Fig. 4A and B shows that sonication does indeed accelerate this oxidative radical reaction, which was our starting hypothesis. The rationale is provided by the foreknowledge that ultrasound irradiation can enhance electron transfer steps in chemical reactions. Given that this C—H functionalization happens *via* a radical chain mechanism, the ultrasound assistance can take place on the level of the initiation, in one of the propagation steps, or in all of these simultaneously. However, as expanded upon above, it cannot be excluded that mere thermal effects are responsible for the distinct conversion rate.

Fig. 4C then shows the same reaction, not only mediated by acoustic irradiation but also in the presence of a titanium metal rod. This outcome is comparable to the results obtained in Fig. 2, yielding a much quicker reaction (full conversion after 1.5 h) than its metal-free counterpart (Fig. 4A).

For exhaustiveness sake, an experiment was included to isolate the effects of metals in silent conditions (Fig. 4D). With conversion reaching about 50% after 3 h, the increase of reaction rate due to metals present was clearly observable. This finding also discredits the hypothesis that the coating is interfering with the reaction system.

These results make quite clear that we were dealing with a cumulative effect of both ultrasound irradiation and metal effects. However, we are still in the dark about how exactly the metal of the probe was enhancing our reaction.

In order to substantiate our presumptions that the coating on the probe is indeed withholding any metal from going into solution, the concentration of trace metals was determined in the reaction mixtures. Titanium, aluminium and vanadium, being the three major constituents of the alloy, were measured, as well as iron, since it can be a trace element in this material for up to

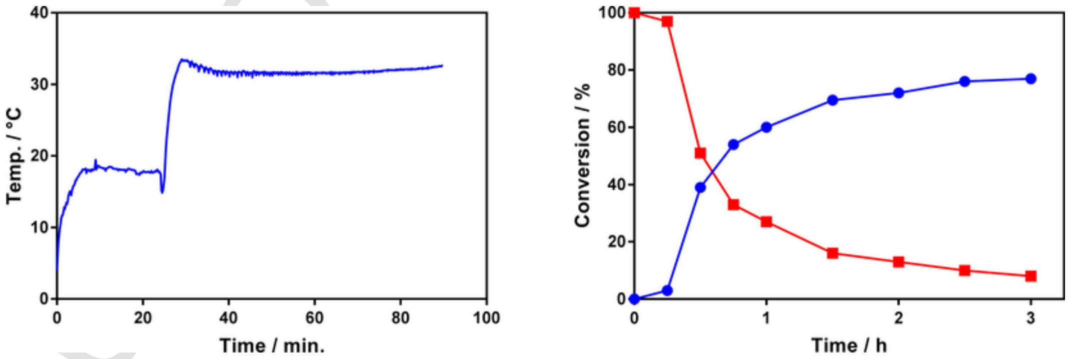


Fig. 3. (A) Temperature profile of typical US irradiated reaction (initially in 0 °C ice bath, after 20 min. changed to room temp. water bath) (B) Silent reaction performed at 35 °C (red curve (■) corresponds to starting material depletion, blue curve (●) to the product formation, yields based on GC analysis).

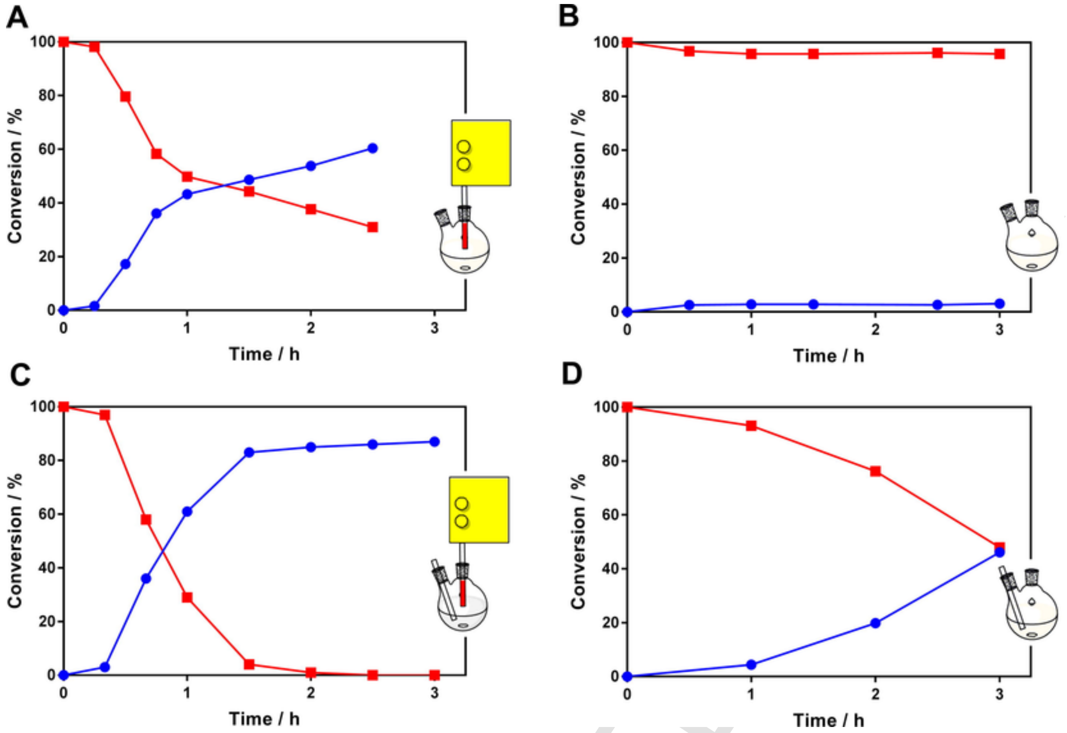


Fig. 4. Reaction profiles of model reaction in presence or absence of titanium rod, with or without sonication (red curve (■) corresponds to starting material depletion, blue curve (●) to product formation). In the graphics, the red colour depicts PFA coating on the US probe, a white bar represents the titanium rod inserted.

0.25 wt%. Moreover, iron is known to assist reactions involving peroxides (Fenton type conditions in particular) [39].

In a first experiment, the reaction with caffeine was performed while sonicated with the coated probe. A second experiment was executed similarly, but with a coated probe that possessed clear defects in the coating, therefore with the metal probe being in direct contact with the reaction mixture.

In the former case (Fig. 5A), concentration of various metals remained below 25 ppm in a 3 h range, whereas the latter experiment (Fig. 5B) showed a startling value of 20,000 ppm titanium dissolved after this time, and Al and V concentrations in the 1500–2500 ppm range.

We considered it therefore safe to say, that 1) the PFA coating formed a sufficiently inert barrier, and 2) the extent of metal leaching for uncoated probe sonication was significant under the studied conditions.

3.3. Role of individual metals

In an effort to elucidate which metal exactly plays the most important role, the model reaction was performed in the presence of each metal individually in the metallic state (in the shape and size as was available from commercial sources). More specifically, we were interested in the influence of titanium, vanadium and iron, but less so in aluminium, as it is not a first row transition metal and therefore deemed less prone to partake in this oxidative chemistry. In addition, some salts or oxides of the concerned metals were tested.

Being the most abundant metal by far in solution, titanium was studied first, by adding Ti granules (10 wt%) to the mixture and keeping the rest of the conditions constant. The resulting reaction profile (Fig. 6) proved to be quite similar in terms of conversion rate to the results that were found when the Ti rod was added. However, the outcome seemed to be less clean, with only 60% selectivity towards the desired trifluoromethylated product.

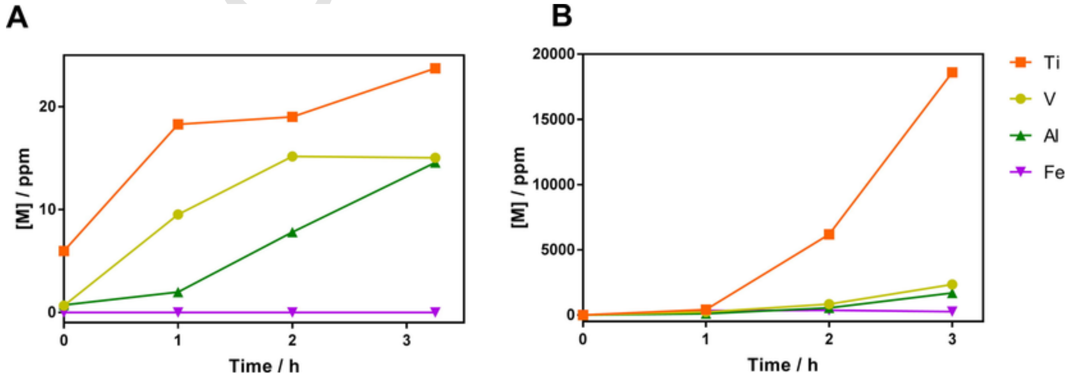


Fig. 5. Concentrations of metals in the aqueous phase, (A) reaction with coated probe, (B) reaction with direct contact between probe and mixture.

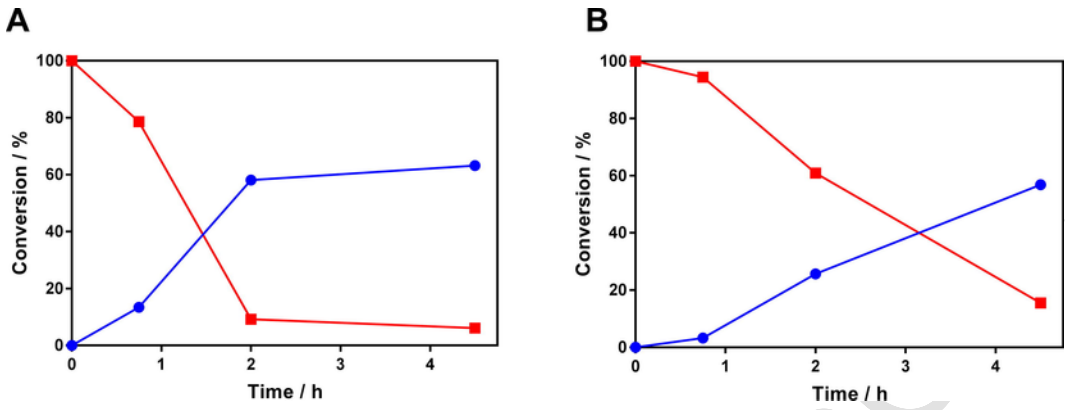


Fig. 6. Influence of 10 wt% metallic Ti granules on reaction profile, under (A) ultrasound irradiation, and (B) silent conditions (red curve (■) corresponds to starting material depletion, blue curve (●) to product formation).

Iron is a known catalyst for oxidative radical chemistry, the first-rate example being Fenton conditions for oxidative degradation of organic pollutants [39]. Also, the treatment of alkyl iodides under Fenton conditions can yield radicals that react towards heterocycles in a Minisci fashion [40]. The presence of iron in the probe (up to 0.25 wt% of the alloy) means it could be present in the liquid medium and therefore serve as a mediator for the radical formation.

When the mixture was treated with Fe powder (10 wt%) we obtained the results shown in Fig. 7. In this case, US irradiation didn't seem to make much of a difference, since both reactions were terminated within 2 h. Despite the obvious acceleration by the presence of Fe, both cases showed an inferior selectivity of 60%.

We then also checked whether similar results would be found with an iron (II) source, thus the mixture was treated with 5 mol% of $FeSO_4 \cdot 7H_2O$ (a relevant quantity compared to Fe(II)/peroxide-mediated literature examples). Here, sonication still provided a faster reaction (Fig. 8), although for unclear reasons the reaction remained rather incomplete after 3 h. The silent reaction reached 50% conversion after about 3.5 h.

Finally, vanadium metal was tested for its role in reaction acceleration, although it comprises only 4 wt% of the alloy. A vanadium plate (15 × 9 × 2 mm, approx. 3 g) was added to the mix-

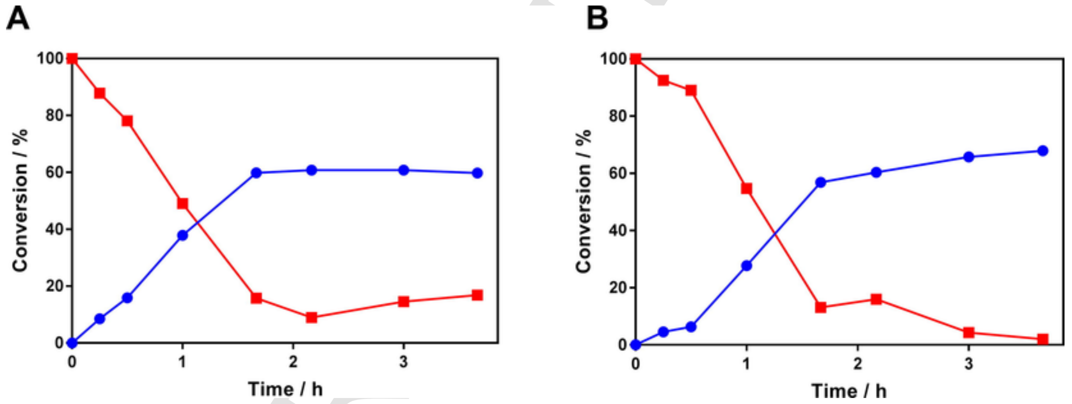


Fig. 7. Influence of 10 wt% metallic Fe powder on reaction profile, under (A) ultrasound irradiation, and (B) silent conditions (red curve (■) corresponds to starting material depletion, blue curve (●) to product formation).

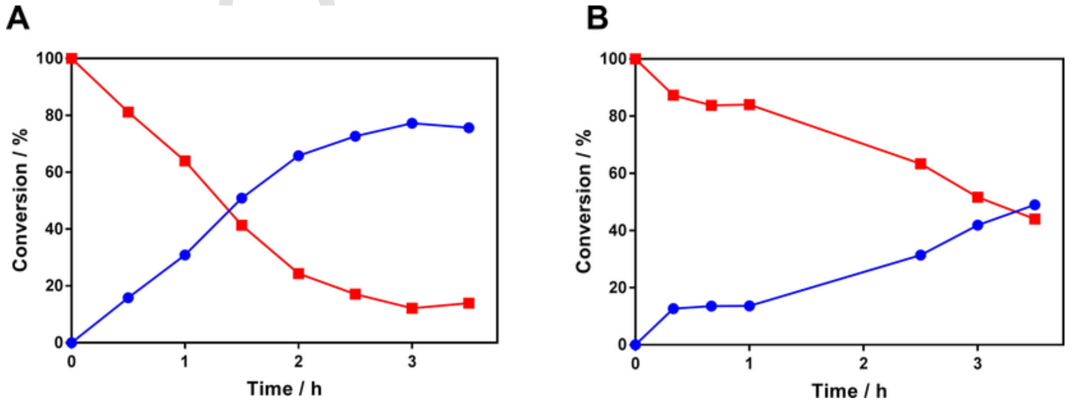


Fig. 8. Influence of $FeSO_4$ salt (5 mol%) on reaction outcome, under (A) ultrasound irradiation, and (B) silent conditions (red curve (■) corresponds to starting material depletion, blue curve (●) to product formation).

ture and allowed to react as usual. Fig. 9 shows the surprising result of these experiments, where the ultrasound reached plateau conversion after 1 h already with excellent selectivity (90%). The stirred counterpart also greatly benefited from the presence of vanadium metal, reaching completion after an unprecedented 3 h. In these reaction mixtures, the typical blueish colour invariably appeared in the aqueous phase after ±1.5 h, probably owing to the vanadyl (VO^{2+}) cation in solution [41]. A similar colour could be seen when performing US-assisted reactions with the uncoated probe, albeit after reacting more than 4 h.

In order to confirm that vanadium is indeed a more capable promoter of this reaction, not just because the amount of added metal was higher in the above experiment, we also performed the reaction in presence of 10 wt% V granules or powder (325 mesh) to directly compare with Ti or Fe, respectively (see supporting information, Figs. S1 and S2). In each case, vanadium metal gave rise to more rapid conversion. Interestingly, the amount of leached ions was seen to be significantly lower for vanadium than for iron or titanium. Subsequently, these three shapes of metallic vanadium (plate, granules, powder) were examined in the same quantity (Fig. S3) to probe for any correlation between available surface area and reaction rate. The powder form indeed enhanced the initial conversion most and the plate form least, although the smaller particle sizes afforded much more side product formation. Also, in the case of the powder form, conversion halted after 1 h, probably because of too rapid, nonproductive decomposition of the oxidant by the highly available vanadium. Low surface to volume ratios are therefore deemed superior in the mediation of this reaction, also because it was seen that metal leaching remained relatively low in this case (220 ppm) compared to other shapes or other metals (>4000 ppm).

It was clear that every metal under study invariably afforded an increase in conversion rate. This result is not surprising in itself, since first-row transition metals are known to catalyze several types of oxidation chemistry, due to their ability to give or accept d-shell electrons. For example, iron salts are often combined with *tert*-butyl hydroperoxide or other peroxides in oxidation reactions [42]. In these cases, Fe^{3+} typically functions as the active oxidant and is constantly regenerated by TBHP. However, since all the investigated metals seem to react in more or less the same way in this study, it seems implausible that the metal is acting here as the terminal oxidant, which abstracts an electron from the sulfinate species.

The other hypothesis then, is that the metal is exerting its influence in the initiation step. The term initiation is appropriate here, since the original report by the Baran group proposes a radical chain mechanism for this trifluoromethylation protocol (Scheme 2). They suggest the *tert*-butyl hydroperoxide activation to be initiated by trace metals, i.e. reduced to hydroxide and a *tert*-butoxyl radical. The latter species then sets in motion a sequence of single electron transfer with the sulfinate salt, SO_2 extrusion, radical addition and reoxidation by another TBHP molecule regenerating the original radical. If higher amounts of metals account for more frequent initiation steps, it is not hard to envisage that the overall reaction time could be shortened as well.

3.4. Role of vanadium

From this point on, we decided to dedicate our attention to vanadium in particular, because of its superiority in terms of selectivity and reaction time. The goal was to specify what part is played mechanistically, by the vanadium metal that had leached from the probe surface.

The colour change made clear that V was going into solution as a cationic species. To verify whether or not it is the oxidized, ionic form of the metal, and therefore a homogeneous catalyst, which assures this improvement, several vanadium oxides or salts were tested for their reactivity (10 mol% added each). Fig. 10 summarizes the results of this screening, showing the V^{4+} species $VO(acac)_2$ to yield the fastest reaction. However, the V metal plate still proved far superior over any of its oxidized forms. For unclear reasons, the reaction rarely reached more than 50% conversion with any of the tested salts. No correlation could be seen between rate and either solubility or oxidation state of the V species.

These data seem to support our misgivings that any vanadium species could be acting as a terminal oxidant. There are of course many examples described where vanadyl complexes are engaged as oxidation catalysts [43–47], even in combination with TBHP as an oxidant [48]. Mechanistically, however, these oxidations are typically dominated by high oxidation states of vanadium (+4 or more often +5). Considering that metallic vanadium impacts the reaction most significantly, it is not inconceivable that vanadium is acting as a reductant rather than as an oxidant.

V^{2+} has been described to serve as a reductant [45], for example reacting as an initiator for radical additions of CCl_3X to olefins [49]. Barton et al. describe the role of low oxidation states (2+ and 3+) of V as reducing agents, capable of transforming TBHP cleanly into the *tert*-butoxy radical (in much the same way as Fe^{2+}) [50]. Considering the potentials of some low valence vanadium redox pairs ($E^0(V/V^{2+}) = -1.18$ V and $E^0(V^{2+}/V^{3+}) = -0.26$ V), it is not hard to envisage that vana-

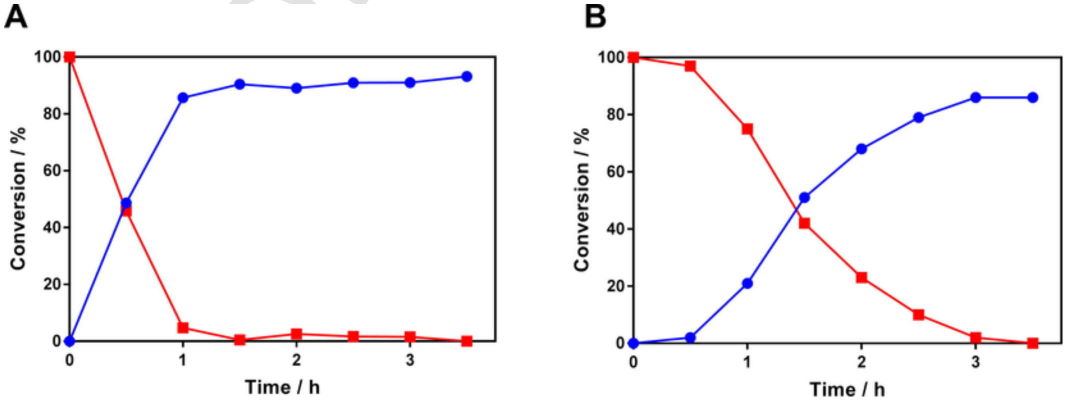
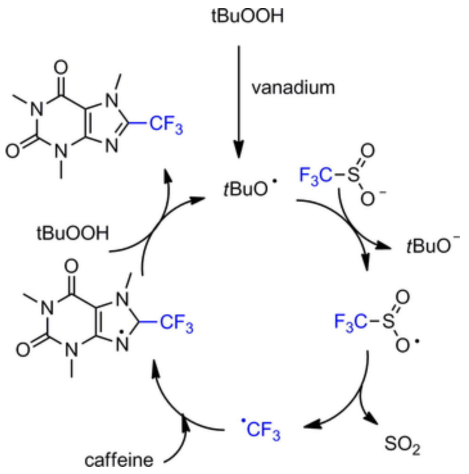


Fig. 9. Influence of a 2.3 g metallic V plate on reaction profile, under (A) ultrasound irradiation, and (B) silent conditions (red curve (■) corresponds to starting material depletion, blue curve (●) to product formation).



Scheme 2. Plausible mechanism of the trifluoromethylation reaction of caffeine.

dium metal is capable of reducing the O—O bond in TBHP. If this would indeed be its function in the concerned reaction system, the previously mentioned hypothesis of more frequent initiation could indeed explain why conversion is so substantially accelerated in the presence of vanadium.

An experiment was thus needed to follow the decomposition of aq. TBHP over time, in order to establish whether or not the presence of vanadium is affecting this rate. Terephthalic acid or potassium iodide dosimetry proved ill-suited to follow *tert*-butoxy radical formation. Quenching experiments with triphenylphosphine (PPh_3), however, provided an immediate reaction which could easily be followed using ^{31}P NMR or GC analysis. It was reasoned that when decomposition of the peroxide happens more efficiently or faster in the presence of vanadium metal, the oxidation of PPh_3 to $P(O)Ph_3$ should also gain higher conversions in shorter times.

Fig. 11 shows the difference between the vanadium mediated and the unassisted reaction. While after 2.5 h the metal-assisted version reaches almost 50% conversion, the metal-free reaction mixture still contains over 90% of the initially added TBHP. These profiles results match with the reaction profiles obtained earlier, where the V metal additive gave rise to full conversion in approximately 3 h.

We propose therefore, considering its substantial benefit in our reaction system, that vanadium metal is an active agent in radical generation from TBHP, but that it doesn't do so in the most effective way. This more controlled initiation is believed to be the crucial advantage over other metals, which presumably decompose the oxidant too fast and uncontrollably, giving rise to more side reactions.

The idea of controlled radical generation finds support in a follow-up study by Baran et al., where the TBHP-mediated trifluoromethylation is described under electrochemical control [38]. Their findings are that challenging substrates can be functionalized in higher yields and with lower amounts of reagents, due to a stable current delivering a more constant radical formation. We consider it therefore reasonable that the presence of a metal like vanadium provides an equally controlled environment for the oxidation of the sulfinate salt, ensuring a progressive conversion, but also preventing it from reacting with the oxidant too quickly.

4. Conclusion

In summary, we have studied the TBHP-mediated trifluoromethylation of caffeine by sodium trifluoromethanesulfinate under direct acoustic irradiation. The surface of the ultrasound horn was found to corrode under these circumstances, and leaching of metals was significant as confirmed by ICP analysis. We established that the reaction benefited both of ultrasonication and of the presence of metals. The influence of some of the Ti alloy components was investigated separately, and although rate enhancement could be seen in every case, vanadium metal proved to be superior in terms of selectivity and acceleration. Further experiments were conducted to elucidate the role of this metal. We presently believe that vanadium is exerting its influence on the initiation step of the reaction by reducing the oxidant to the *tert*-butoxy radical, in an optimal way so that a steady radical formation is realized but in a relatively controlled fashion.

The observation that surface leaching of the ultrasound horn gave rise to substantial differences in reaction outcome, was an unexpected result and is here put forward as a warning sign to the scientific community. In addition, we propose the use of vanadium metal in the TBHP-mediated sulfinate-Minisci reaction as an interesting modification of the procedure, affording shorter reaction times and possibly less side product formation.

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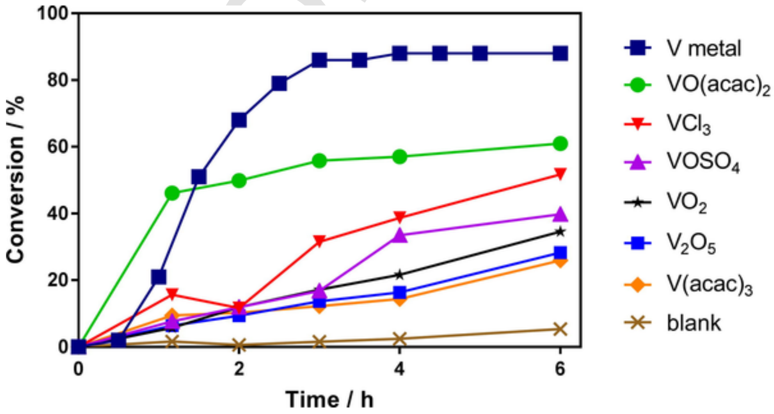

V source	Solub. (H_2O) g.L^{-1}
$VO(acac)_2$	<1
VCl_3	decomp.
$VOSO_4$	sol.
VO_2	<1
V_2O_5	0.8
$V(acac)_3$	<1

Fig. 10. Left: Product formation over time, when performing the usual reaction with 10 mol% of [V] species added. Stagnation was seen after 6 h. Right: Solubilities in H_2O of V sources.

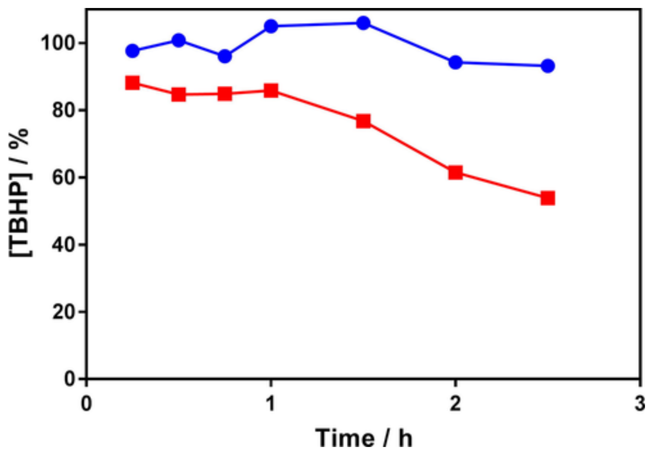

Fig. 11. Concentration of oxidant over time, expressed as fraction of original concentration. Determined via GC analysis. Blue curve (●) corresponds to metal-free reaction, red curve (■) to vanadium-catalysed reaction. TBHP = *tert*-butyl hydroperoxide.

application of PFA coatings. Michèle Vanroelen is thanked for the ICP-OES measurements. Our gratitude goes to Prof. Dirk De Vos for the usage of GC equipment.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ultsonch.2017.09.027.

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