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Acetone: solvent or reagent depending on the addition order in SET-LRP

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Depending on the order of addition to the reaction mixture during the biphasic SET-LRP performed in acetone/water mixtures, acetone can serve as solvent or as reagent being brominated by $CuBr_2$ to provide the electrophilic bromoacetone initiator as well as aldol condensation products.

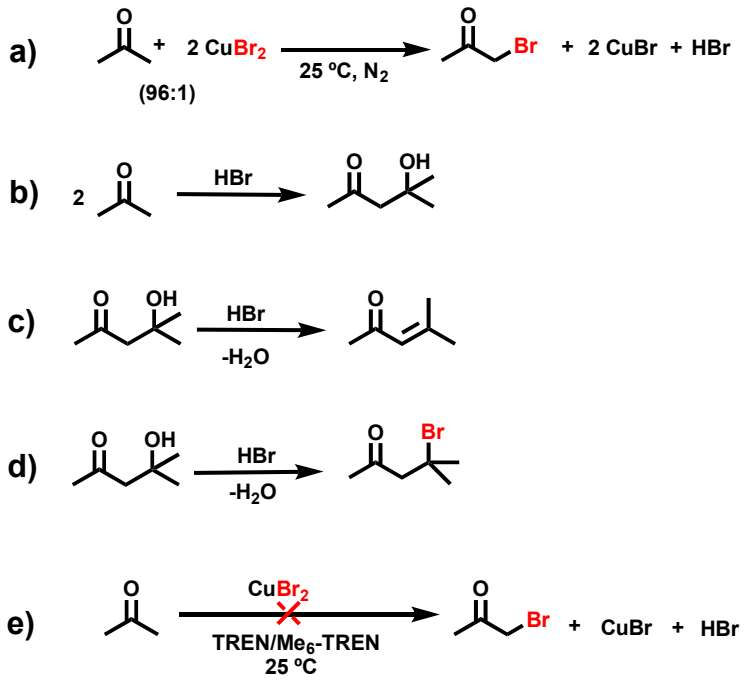
Cu(0)-wire and powder mediated single-electron transfer living radical polymerization (SET-LRP) has been shown to be one of the most robust and versatile polymerization tools to obtain well-defined polymers and more complex architectures in very short reaction times, at room temperature or bellow even in the presence of air.[1] The basic pillar of SET-LRP is the selection of the solvent and ligand. This is because the solvent plays an important role during the polymerization self-regulating the generation of Cu(0) activator and Cu(II)X_2 deactivator *via* the solvent-ligand mediated disproportionation of Cu(I)X species.[2] Water,[3] hydrogenated and fluorinated alcohols,[4] dipolar aprotic and cyclic carbonates[5] and their biphasic mixtures[6] were employed in the past years and are known to mediate an efficient disproportionation of Cu(I)X generated in the presence of *N*-ligands.[7]

Classic non-polar solvents such as toluene or hexane and some polar solvents such as acetonitrile and acetone are poor disproportionating solvents or do not mediate the disproportionation of Cu(I)X and therefore their use in SET-LRP has been limited for a long time.[8] However, our group recently developed a library of "programmed" multiphasic SET-LRP systems based on mixtures of organic solvents with water to overcome this limitation.[6] This approach is sustained by the disproportionation of Cu(I)X species exclusively in the water phase and the simultaneous partitioning of "nascent" Cu(0) species to the organic phase at the same time that the $Cu(II)X_2$ generated remains in the aqueous phase. Thus, the application of this methodology allows the use of classical non-disproportionating solvents with excellent results in terms of molecular weight control and chain end functionality. [6a-d]

In this context, acetone emerged as one of the most appealing solvents to perform SET-LRP due to its very low cost, lack of toxicity and simple recycling. Recently our group reported, the use of acetone-water mixtures as solvent system for the SET-LRP using Cu(0) nano-particles as catalyst generated by *in situ* reduction of $Cu(II)Br_2$ with $NaBH_4$ and non-activated copper wire as catalyst for methyl acrylate and butyl acrylate monomers, resulting in quantitative monomer conversion and high chain end functionality.[6d] Moreover, SET-LRP mediated by tris(2-aminoethyl)amine (TREN) in acetone-water mixtures has also been reported with excellent results for the polymerization of hydrophobic acrylates.[6g] All these results support the use of acetone as a solvent for SET-LRP and others LRP techniques. However, like all other solvents, acetone presents some limitations such as potential side reactions under basic,[9] acidic [10] or redox[11] conditions.

The typical experimental procedure for SET-LRP and biphasic SET-LRP involves the preparation of the polymerization mixture by sequentially addition of monomer, solvent,

ligand, initiator and finally Cu(II)Br_2 for monophasic SET-LRP and monomer, organic solvent, water containing N-ligand, $CuBr_2$ and initiator for biphasic SET-LRP, in this specific order before the deoxygenation step and the incorporation of the Cu(0) catalyst.[1b] If $CuBr_2$ is added before the ligand, bromination of the monomer occurs.[6d] Here we report that the alteration of the order from above to acrylate monomer, acetone and Cu(II)Br_2 leads to an extremely fast Cu(II)Br_2-mediated bromination of acetone, occurring under non-stoichiometric conditions, to yield bromoacetone, Cu(I)Br and HBr (Scheme 1a). Note, that the stoichiometric bromination of ketones in the presence of Cu(II)Br_2 has been previously investigated and reported in different solvents such as water,[12] alcohols[13] and dipolar aprotic solvents.[14,15] The HBr resulted from this reaction catalyzes the aldol condensation of acetone to form diacetone alcohol (DAA) (Scheme 1b). Finally the HBr-mediated dehydration of DAA resulted in the formation of mesityl oxide (Scheme 1c). Note, that the alteration of the order of addition of reagents from that described above can also lead to the Cu(II)Br_2-mediated dibromination of acrylate monomers as was reported in a previous publication.[16]



Scheme 1. (a) Non-stoichiometric Cu(II)Br_2-mediated bromination of acetone at 25ºC, (b) HBr-catalyzed aldol condensation of acetone, (c) HBr-mediated dehydration of DAA, (d) HBr-mediated bromination of DAA. (e) The not observed Cu(II)Br_2-mediated bromination of acetone in the presence of TREN or hexamethylated tris(2-aminoethyl)amine (Me_6-TREN).

First, we investigated the Cu(II)Br_2-mediated bromination of acetone at room temperature using a large excess of commercially available acetone to mimic SET-LRP conditions in which Cu(II)Br_2 is catalytically present with respect to the organic solvent. This reaction was monitored for 4 hours by ^{1}H-NMR (Fig. 1).

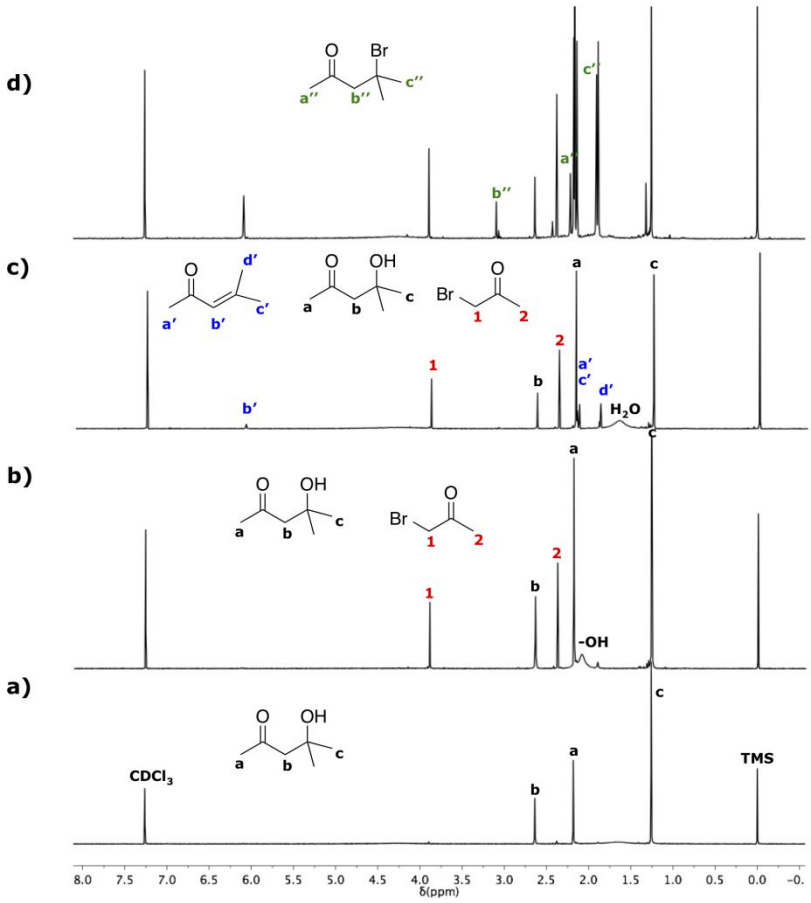


Figure 1. ^{1}H-NMR spectra recorded during the Cu(II)Br_2-mediated bromination of commercial acetone: (**a**) 4 minutes, (**b**) 10 minutes, (**c**) 30 minutes, (**d**) 4 hours.

Shortly after mixing acetone and Cu(II)Br_2 the three characteristic singlets of DAA were detected (Fig. 1a). Next, we observed the formation of bromoacetone after 10 min through the appearance of the characteristic signal **1** corresponding to methylene protons adjacent to the bromo position at 3.8 ppm (Fig. 1b). The ratio between both products was determined to be 30:70 bromoacetone: DAA (Fig. 2a).

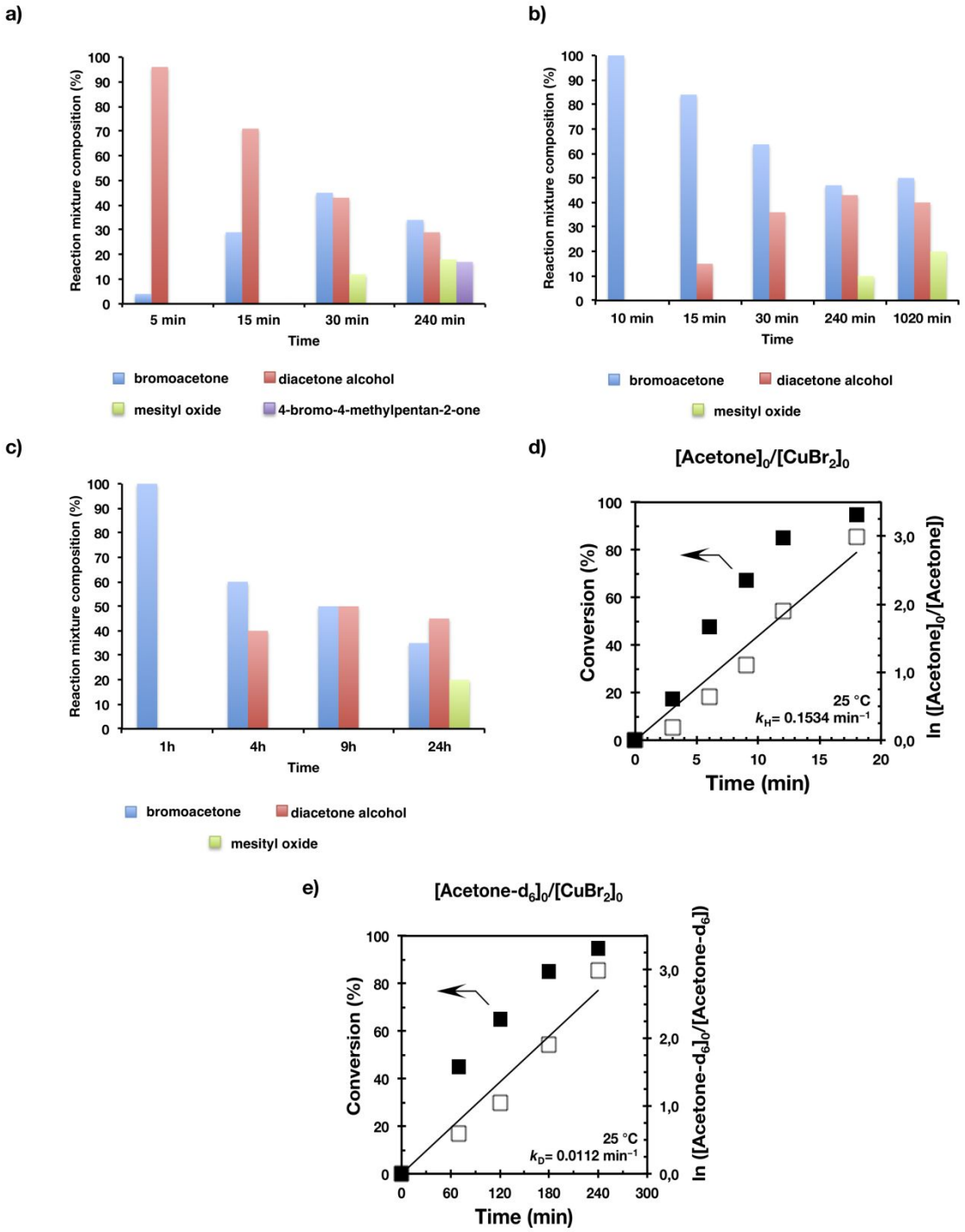


Figure 2. Reaction mixture composition *vs* time for the Cu(II)Br_2-mediated bromination of acetone using: (a) commercially available acetone (b) freshly distilled acetone and (c) freshly distilled deuterated acetone. (d) Kinetic plot for the bromination of freshly distilled acetone. (e) Kinetic plot for the bromination of freshly distilled deuterated acetone.

The visualization of the reaction mixture at this point showed the precipitation of the white Cu(I)Br powder (Fig. 3b). After 30 minutes, the ratio of bromoacetone: DAA increased to 50:50. Meanwhile mesityl oxide was also detected in the reaction mixture was also confirmed by the appearance of the signal **b'** at 6.0 ppm corresponding to the olefinic proton (Fig. 1c). Notice, that at longer reaction times, we also detected the formation of 4-bromo-4-methylpentan-2-one, the halogenation product of DAA (Scheme 1d), by the appearance of the characteristics signals **a''**, **b''** and **c''** (Fig. 1d) in a ratio of 45:20 bromoacetone: 4-bromo-4-methylpentan-2-one (Fig. 2a). Moreover, the increase of the ratio to 40:20 bromoacetone: mesityl oxide and the decrease of the ratio bromoacetone: DAA to 40:30 was observed and was attributed to the dehydration of DAA to form mesityl oxide (Fig. 2a).

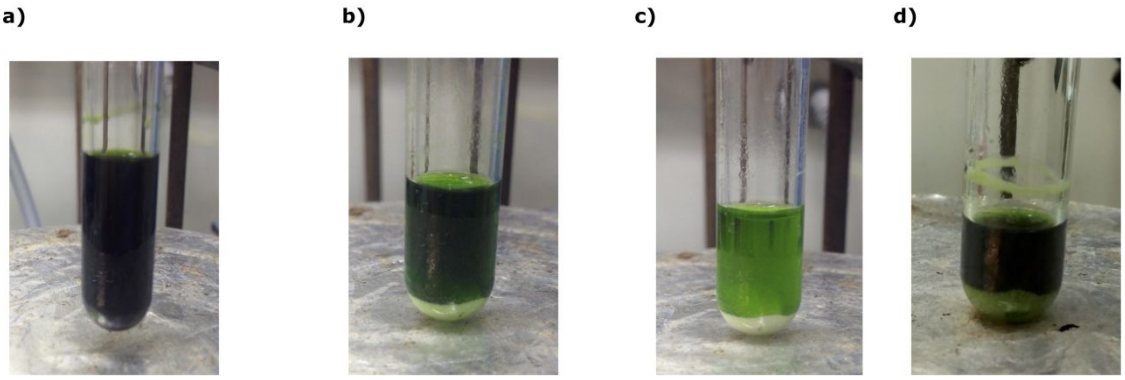


Figure 3. Visualization of Cu(II)Br_2-mediated bromination of commercial acetone after (a) 4 minutes, (b) 10 minutes, (c) 1 hour and (d) 10 minutes in presence of Me_6-TREN.

The presence of DAA as the only product at short reaction times led us to think about the possibility of the presence of this compound as an initial impurity in commercial acetone. This was indeed confirmed by ^{1}H-NMR. In order to clarify the order of the formation of the products during the reaction and the possible mechanism, acetone was freshly distilled and

used immediately to carry out the bromination reaction using $CuBr_2$. In this case, bromoacetone was the first identified product (ESI, Fig. 1b). No formation of DAA was observed, while the precipitation of Cu(I)Br was also observed. After 15 minutes, the formation of DAA was clearly observed in a ratio of 90:10 bromoacetone: DAA (Fig. 2b and ESI Fig. 1c). After 30 minutes the ratio of DAA increased to 60:35 bromoacetone: DAA (Fig. 2b) and after 4 hours the formation of the mesityl oxide was determined in a ratio of 50:10 bromoaetone: mesityl oxide (Fig. 2b and ESI, Fig. 1e). ^{1}H NMR spectrum after 17 hours still showed the coexistence of the above mentioned three compounds. (ESI, Fig. 1f). These observations suggest, as expected, that first the bromination of acetone takes place via copper-bound enolate generating bromoacetone, hydrobromic acid and Cu(I)Br (Scheme 1a, I), followed by the acid catalyzed aldol condensation of acetone to yield DAA, which undergoes dehydration to produce mesityl oxide. (Scheme 1b and c)

In order to determine the bromination rate, the above described experiment was carried out in the presence of anisole as internal standard. Fig. 2d shows the evolution of conversion of acetone to bromoacetone in time considering the 100% of conversion of bromoacetone obtained with respect to the stoichiometric amount of $Cu(II)Br_2$ used, since acetone is present in a large excess. Note, that after 6 min more than 60% of acetone was converted to bromoacetone and more interestingly the full conversion of acetone into bromoacetone within 18 min points out to the extremely high rate ($K_H = 0.1534$ min^{-1}) of bromination of acetone even in the presence of a catalytic amount of $Cu(II)Br_2$.

An additional experiment using freshly distilled acetone-D6 was carried out under the conditions described above, in order to determine the bromination rate using deuterated acetone and investigate the potential existence of a kinetic isotopic effect (KIE)[18] (Fig. 2c and Fig. 4). The first important observation is that in this case, the formation of white

Cu(I)Br powder required longer reaction time (45 min) than when non-deuterated acetone was used (10 min). In this case, the reaction was monitored using D-NMR. As can be seen in Fig. 4a, no products were detected by NMR after 30 minutes. Note that when using non-deuterated acetone, bromoacetone was already detected after 10 min (Fig. 1b and ESI, Fig. 1b). After 1 h, signals **1** and **2** corresponding to bromoacetone-D5 were already observed (Fig. 4b). After that, the D-NMR analysis of the aliquot corresponding to 4 h reveal the formation of the DAA-D12 with the characteristic signals of the product **a**, **b**, **c** (Fig. 4c) in a ratio of 60:40 bromoacetone-D5: DAA-D12 (Fig. 2c) Finally, the formation of mesityl oxide-D10 was only detected at long reaction times. Fig. 4e shows the D-NMR spectrum after 17 h where the characteristic signals of bromoacetone-D5 and DAA-D12 coexist with the signals of the mesityl oxide-D10, (**a'**, **b'**, **c'**, **d'**). Note that mesityl oxide was detected in the previous experiment already after only 1 hour.

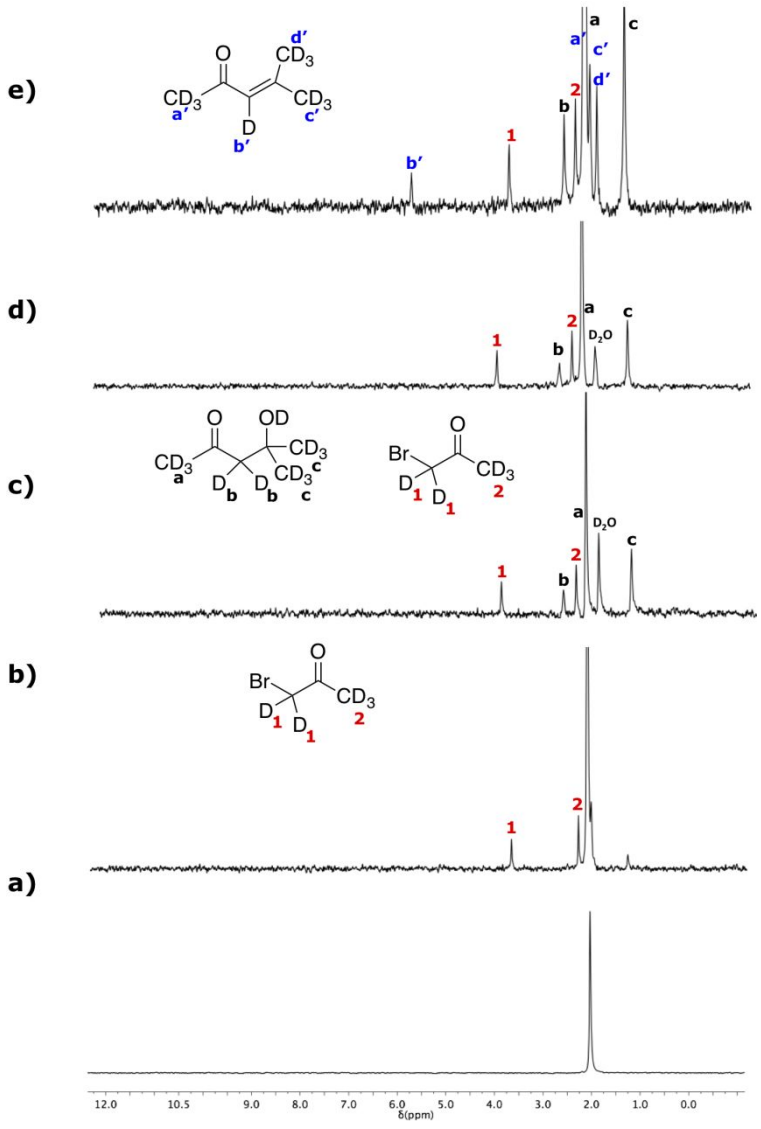


Figure 4. D-NMR spectra recorded during the Cu(II)Br_2-mediated bromination of freshly distilled acetone-D6: (**a**) 45 minutes (**b**) 4 hours, (**c**) 9 hours, (**d**) 12 hours and (**e**) 17 hours.

These observations suggest, as expected, that the reaction mechanism follows the same reaction pathways as when non-deuterated acetone was used.[18] However, the much longer reaction time when using acetone-D6 (K_D= 0.0112 min^{-1}, Fig. 2, e) in comparison to when non-deuterated acetone was used (K_H= 0.1534 min^{-1}, Fig. 2, d) supports the existence of the KIE derived from the lower mobility and increased stability from the higher dissociation energies of heavier isotopes (D) when compared to compounds containing lighter isotopes

(H). Note, that the difference in rate (K_H/K_D = 14) indicates the presence of a primary kinetic isotopic effect, which is associated to the labelled bond, is made or broken in the rate determining step.[17]

It is important to point out that when the reaction was conducted by dissolving the Cu(II)Br_2 in acetone containing an equimolar amount of *N*-ligand such as TREN or Me_6-TREN as the most common ligands for SET-LRP (Scheme 1e), no bromination reaction was observed even after long reaction times (24 hours). Note, that the formation of green acetone-insoluble crystals of Cu(II)Br_2/ligand complex was observed in 10 minutes (Fig. 3, d). These results indicate on the importance of the order of addition of reactants to the reaction mixture using acetone as solvent for SET-LRP and other LRP techniques. To avoid the formation of bromoacetone during the SET-LRP set-up is of crucial importance because it is a highly electrophile reagent that can act as alkylating agent towards the classical *N*-ligands used in SET-LRP such as TREN or Me_6-TREN as well as an alternative alkyl initiator during the polymerization process. In addition, mesityl oxide is well known to undergo a wide variety of simple nucleophilic additions at the double bond including amines. Consequently, the addition of N-ligand to mesityl oxide is a non-desirable side reaction that needs to be taken into account and avoided.[18] The bromination of acetone and other ketones mediated by $CuBr_2$ has been reported during the past years, with the attractive interest of use the brominated analogous ketones to access more complex molecules through the inherent reactivity of α-brominated position.[19] However, this reaction has never been studied under conditions that can be relevant to SET-LRP or ATRP. The experiments reported here indicate and set-up a new and necessary protocol for

the addition order of reagents for SET-LRP[6dg,20] and most probably also for ATRP[21] when acetone is used as solvent in order to practice a clean and efficient process.

In order to estimate the role of the order of addition of reagents to ATRP experiments performed in the presence of $CuBr_2$ two literature experiments in which the order of addition of the reagents to acetone solvent was incorrect,[21a,b] and their initiation step were reinvestigated. In the first case when CuBr, $CuBr_2$, monomer, initiator and ligand was the order of addition 20% bromoacetone was obtained after 3 min and 45% was obtained after 6 min.[21a] In the second case[21b] 27% bromoacetone was obtained after 4 min and 57% after 6 min.[21b] These simply demonstrate that under incorrect reaction conditions bromoacetone initiator is generated and acts as co-initiator for the polymerization while the $CuBr_2$ becomes CuBr and acts as supplementary activator rather than deactivator. This demonstrates the extremely important role of the order of addition of reagents to metal catalyzed living polymerizations performed in acetone.

Conclusions

Cu(II)Br_2 brominates acetone at 25 ºC yielding bromoacetone in few minutes and a mixture of DAA and mesityl oxide. This bromination reaction can be suppressed in the presence of *N*-ligands such as TREN or Me_6-TREN. Bromoacetone is known to be a reactive electrophile that acts as an *N*-alkylating agent towards primary amino groups at room temperature or even below and also a good initiator for all metal catalyzed radical polymerizations. This side reaction together with the additional side reactions recently

reported from our laboratory[16], must be taken into account during the practice of current SET-LRP and other metal-catalyzed LRP's using acetone as a solvent.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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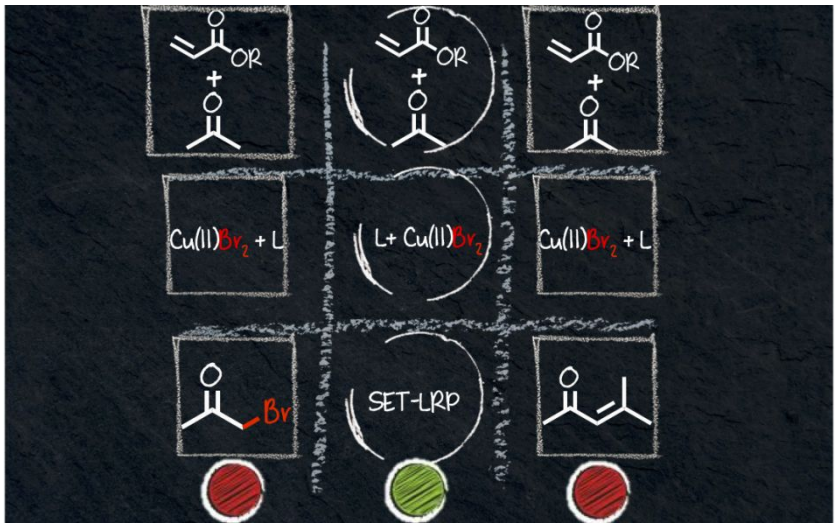

The importance of reagents order in biphasic SET-LRP in acetone/water mixtures